Abstract: This review presents the recent progress in the chemistry of dimethyl acetylenedicarboxylate (DMAD). The interest in and applications of this powerful reagent with more than 135 years of history have greatly increased in the last 10 years, further proving its versatility. Undoubtedly, DMAD can be a multi-tool in the quest of molecular complexity and diversity. The extreme structural diversity of the products described in this review illustrates the powerful potential of DMAD as a building block in organic synthesis.

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Key words: DMAD, dimethyl acetylenedicarboxylate, Michael reactions, cycloadditions, multicomponent reactions

1 Introduction

Dimethyl acetylenedicarboxylate, commonly abbreviated as DMAD, is an electro-deficient alkyne diester. This ester, which exists as a liquid (density: 1,156 g/mL, 25 °C) at room temperature (boiling point: 95–98 °C), is highly electrophilic. As such, DMAD is used as a dienophile and a dipolarophile in cycloaddition reactions. Today, it is being used increasingly in chemical synthesis as it has proven useful in carbon–carbon bond formations. DMAD is an extremely versatile tool for organic chemists and completely new avenues have been explored for its use in combinatorial and multicomponent chemistry and heterocyclic synthesis. Following the pioneering discovery by Diels and Alder, the reactions of dimethyl acetylenedicarboxylate with heterocyclic compounds have been the subject of a great number of publications. This treatise assembles and presents the fundamental characteristics of DMAD chemistry, as well as current developments thereof. The focus is placed on Michael reactions, cycloadditions (Diels–Alder, 1,3-dipolar and [2+2] cycloadditions), and, of course, multicomponent reactions by generation of zwitterions (Scheme 1). Recent literature examples that are both illustrative of the power of this reagent in the construction of complex heterocyclic molecules and pivotal for the design of synthetic strategies toward natural or designed targets are discussed herein. This review seeks to highlight the 'power of DMAD' by examining selected examples of its elegant applications.

DMAD is inexpensive and widely available, or it can be prepared from maleic acid (1) via a bromination–dehydrohalogenation sequence to furnish acetylene dicarboxylic acid (4), which upon esterification with methanol using sulfuric acid gives the desired dimethyl acetylenedicarboxylate (5). It is noteworthy that DMAD is still synthesized in exactly the same way as it was originally obtained (Scheme 2).

2 Michael Reactions

DMAD is a powerful Michael acceptor and can take up various nucleophiles, most commonly sulfur and nitrogen...
(Scheme 3). A common strategy is to use it in an initial reaction as a Michael acceptor and then carry out a cyclization, usually through loss of –OMe or –CO$_2$Me. The majority of reactions have been carried out on heteroaromatic systems, such as pyridines, quinolines, isoquinolines, thiazoles, imidazoles, phenanthridines, quinoxalines, pyridazines and their substituted derivatives, with DMAD being used as a cyclizing agent.

Scheme 3

2.1 Sulfur as Nucleophile

2.1.1 Reactions with Thiourea, Thioamide and Thiosemicarbazide Derivatives

Thiazole, thiazolidines, thiazolidinones and thiazinones are very important groups of heterocyclic compounds covering a broad spectrum of biological activity. The reaction between thioamides, thiosemicarbazides and thiourea derivatives 7 with DMAD is known to be a convenient and effective method for the preparation of the aforementioned heterocycles depending on the reaction conditions. Generally, the sulfur attacks the triple bond, resulting in the formation of thiolactam intermediate 8, followed by the aminolysis of an ester group (Scheme 4), thus leading to the formation of either 1,3-thiazolidin-4-ones 9 or 1,3-thiazin-4-ones 10.

Ahmadi et al. 9 developed a general strategy based on the reaction of thiourea derivatives 11 with DMAD (Scheme 5) to prepare 4-thiazolidinone derivatives 12. Furthermore, various thiosemicarbazone derivatives 13 (furfural, benzophenone, butanal, p-methoxybenzaldehyde, etc.) and DMAD reacted in ethyl acetate to give compounds 14 as the only products, although from the reaction in anhydrous methanol only compounds 15 were formed. It is noteworthy that the adducts 14 could be converted into products 15 by refluxing the reaction mixture in anhydrous methanol (Scheme 6). 10

Biographical Sketches

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In a more characteristic example, compounds 16, upon reaction with DMAD, yielded the 1,3-thiazol-4-ones 17 as the major products (Scheme 7) rather than the 1,3-thiazin-4-ones 18. Likewise, an acridine reactant with a bulky substituent on N-1, such as 19, produced the thiazolidinone 21 upon cyclization with DMAD (Scheme 8).

Moreover, reactions of DMAD with the N-imidoylthioureas 22 in acetic acid afforded the thiadiazepines 23 in 65–84% yield (Scheme 9).

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In recent decades, ferrocenes (Fc) have attracted attention because of their wide utility in materials science and catalysis. Therefore, the DMAD-mediated cyclization of 1,5-bis(ferrocenylmethylene)thiocarbono hydrazide (24) and its S-methyl derivative 25 were studied, leading to the preparation of biologically promising sulfur heterocycles 26 and 27, and the methylthio-substituted nitrogen heterocycles 28 and 29, respectively (Scheme 10). In addition, by treatment of the ferrocenyl thiosemicarbazone derivatives 30 with DMAD in refluxing acetonitrile, three types of cyclic products (31, 32 and 33) were isolated in moderate to good yields. The methylthio derivatives 34, obtained by selective alkylation of 30, were also allowed to react with DMAD under the same conditions, thereby affording complex mixtures of methylthio-substituted products including pyrimidones 35, imidazolones 36 and fumarates 37 (Scheme 11). Reaction of DMAD with dithizone (2:1 molar ratio) in methanol resulted in the formation of thiadiazine 39 through a Michael-type addition and a Diels–Alder [4+2]-cycloaddition reaction. In contrast, the reaction of DMAD with dithizone (1:1 molar ratio) in methanol gave compound 40 (Scheme 12). Thiadiazine derivatives are widely used as nematicides, fungicides, herbicides and insecticides. In addition, some thiadiazine derivatives show activity against tripanosoma cruzi amastigotes.

Scheme 9

Scheme 10

Scheme 11
2.1.2 Reaction with Thiones and Thiols

An example of the ‘DMAD strategy’ for the synthesis of heterocycles was described by Neochoritis et al. It is well known that Michael-type amine and thione addition to acetylenic esters leads to E/Z isomeric mixtures. The reaction of DMAD with 1-arylaminoimidazole-2-thiones in the presence of a base through a Michael reaction afforded imidazolothiazoles. However, in the reaction of 41 with DMAD in the absence of a base, only the S-substituted products 42 were formed as an E/Z mixture. A thorough investigation of this thio-Michael-type addition of DMAD and an explanation of the reaction’s stereospecificity were reported (Scheme 13).

A systematic study of the reactions of DMAD with 5-mercaptoazoles, 44, 47, 49 and pyridine-2-thiones 52 was also carried out and, as a result, a number of novel imidazothiazinones 45, imidazothiazolones 46, triazoles 48, pyrazolothiazinones 51 and thiazolopyridines 53 were obtained. The size of the ring, formed in the reactions of cyclic thioamides with DMAD, was found to be dependent on the size of the starting heterocycle. Thus, a five-membered thiazolidine ring condenses onto the pyridine ring whereas a six-membered thiazine ring is fused onto a five-memberedazole ring (Scheme 14).
Furthermore, the reaction of quinazoline derivatives 54 with DMAD affording compounds 56 was investigated within a study of the varying reactivity of nitrogen and sulfur as nucleophiles with an electron-deficient ester (Scheme 15).

Scheme 15

The reaction of DMAD with thiols 57 in water was reported to lead to E/Z isomeric mixtures of 58 in quantitative yield (Scheme 16).

Scheme 16

In 2008, DMAD was used in the synthesis of 3-substituted thieno[3,2-b]furan derivatives 61. The Michael reaction between methyl thioglycolate and DMAD, followed by in situ intramolecular cyclization, afforded the 3-hydroxythiophene 60 in 85% yield (Scheme 17).

The reaction of DMAD with arylidenemalononitriles 62, in the presence of potassium isothiocyanate in acetonitrile, led to a mixture of cyanothiophene 63 and dicyanocyclopenta-1,3-diene derivatives 64. It was proposed that this multicomponent reaction could have been started with the addition of isothiocyanate ion to DMAD (Michael reaction) followed by addition of 62 (Scheme 18).

Scheme 17

Scheme 18

2.2 Nitrogen as Nucleophile

2.2.1 Reactions with Tertiary Amines and Heterocycles

In recent years, there has been considerable interest in investigations of the reactivity of nitrogen-containing heterocycles with DMAD affording a wide range of products. For example, benzothiazines and benzothiazepines 65 and 68 were allowed to react with DMAD in methanol, affording the corresponding pyrrolo- and oxazolo-benzothiazines and benzothiazepines 67 and 70. It was suggested that the products were formed by the addition of one molecule of DMAD to one molecule of benzothiazine or benzothiazepine, with elimination of one molecule of methanol (Scheme 19).
Fodor et al.\textsuperscript{23} reported that benzothiazines 71 reacted with DMAD in acetonitrile at room temperature, affording the regioisomeric ring systems 1,5-thiazocines 73 and 75 in a ratio of approximately 1:1. DMAD was found to attack either the nitrogen or sulfur atom of 71. The key intermediates in the formation of 5,6-dihydro-2H-1,5-benzothiazocines 73 were most probably the zwitterions 72, whereas the unexpected formation of 5,6-dihydro-4H-1,5-benzothiazocines 75 was explained by invoking intermediates 74 (Scheme 20).

The reaction of pyrrolopyrimidine 76 with DMAD afforded, depending on the reaction conditions, the trifluoroacetylpyroles 79 and 80 through the zwitterionic intermediates 77 and 78 (Scheme 21).\textsuperscript{24}

Tetrahydropyrrolopyridines 81 and tetrahydropyridindoles 86 underwent piperidine ring opening under the action of DMAD in acetonitrile, alcohols or aqueous dioxane, providing substituted pyroles 82–85 and 87, respectively (Scheme 22).\textsuperscript{25,26}

In 2008, reactions of quinoline derivatives with DMAD were reported. The reaction began with a Michael addition of the tertiary amine in benzonaphthyridines 88 to the triple bond of the alkyne. The intermediate zwitterion 89 was further transformed by two pathways, A and B. Pathway A was conditioned by the acidic character of the CH$_2$ group and led to ylide 90, which, by Stevens rearrangement (characteristic of ylides), was transformed into acryloyl-substituted naphthyridines 92. The implementation of pathway B was caused by the nucleophilic attack of the zwitterion on the nitrile group. The intermediate 91 was converted into succinate 93. Naphthyridines 94 (R$^1$ = Bn, R$^2$ = H and R$^1$ = Pr, R$^2$ = Br) did not react with DMAD in methanol at room temperature, whereas reflux led to the elimination of benzyl or isopropyl substituents and the formation of N-substituted derivatives 95 (Scheme 23).\textsuperscript{27}
Tetrahydropyridines, [c]-condensed with π-excessive pyrrole, indole, and thiophene units or with a benzene ring, were converted to either condensed azocines or azonines under the influence of DMAD. However, in the case of tetrahydropyridines, the reaction most probably begins with the addition of the nitrogen atom of the tetrahydropyridine moiety of 96 to the triple bond of DMAD, resulting in the formation of an ammonium zwitterion leading, finally, to compounds 97, 98 and 99 (Scheme 24).

Analogous opening of the tetrahydropyridine ring was observed by the reaction of thiazolo- and thiazolido-condensed pyridopyrimidines 100 and 102 with DMAD in methanol, at temperatures from –15 to –20 °C. These reactions led to the 5-vinyl-substituted thiazolopyrimidines 101 in 56–95% yields and to the thiadiazolo-pyridopyrimidines 103 in 20–60% yields, respectively (Scheme 25).
In 2012, the synthesis of various highly functionalized thiazolopyridines 105, along with the open chain products 106, was accomplished by the reactions of keto–enol tautomeric pairs of heterocycles 104 with DMAD (Scheme 26).30

It was reported that the parent Tröger base 107 reacted with DMAD in the presence of boron trifluoride–diethyl etherate to give compound 108 in 60% yield (Scheme 27).31

Hydrogenated γ-carbolines 109 underwent tandem piperidine ring cleavage on treatment with DMAD in the presence of alcohols, producing 3-alkoxymethyl-substituted indoles 112 in good yields. These compounds were cyclized to tetrahydroazocino[4,5-b]indoles 113 in the presence of aluminum trichloride (Scheme 28).32

González-Gómez et al.33 reported novel domino reactions in β-carbolines with DMAD. Vinlypyrrolo-[2,1-a]-β-carbolines 114 gave different products upon reaction with dienophiles as, with DMAD, a novel domino process took place, involving Michael attack and rearrangement, affording complex polycycles like 115, 116 and 117.

In addition, the reaction of 2-allyl-1-vinyl-β-carboline 118 with DMAD gave a mixture of products 119 and 120 in a 1:3 ratio, 120 being an unstable product. These products resulted from the same rearrangement reaction. The reaction began with the nucleophilic attack on DMAD, behaving as a Michael acceptor, followed by nucleophilic attack on one unsaturated carbon which led to new polycycles with an increase in skeletal complexity (Scheme 29).

2.2.2 Reactions with Primary and Secondary Amines

Zewge et al.34 described a mild and efficient synthesis of the quinoline derivatives 122 through a Michael reaction of commercially available aryl amines with DMAD in alcoholic solvents (Scheme 30).
The reaction of primary and secondary aliphatic amines 123 and 125 with DMAD, for less than two hours, in aqueous medium afforded compounds 124 and 126, respectively (Scheme 31).

Scheme 30

The reaction of 1,2-diaminocyclohexane (127) with DMAD gave quinoxaline derivatives 128 and/or 129, depending on the molar ratio of the starting materials (Scheme 32).

Scheme 31

Reaction of 1,2-diaminocyclohexane (127) with DMAD gave quinoxaline derivatives 128 and/or 129, depending on the molar ratio of the starting materials (Scheme 32). The reaction of diamine 130 with DMAD afforded the nitrogen-bridgehead pyrido-triazepine 131 (Scheme 33). In the next example, the initial Michael reaction on nitrogen (amine group) was followed by a reaction with a third component. Ramesh et al.37 described a simple and efficient three-component protocol for the synthesis of highly substituted pyrroles 134 by using amines 132, DMAD and glyoxal (133), with DABCO as a catalyst (Scheme 34). Highly functionalized pyrroles were also synthesized by using amines, DMAD, triphenylphosphine and arylglyoxals.

Scheme 32

The reaction of diamine 130 with DMAD afforded the nitrogen-bridgehead pyrido-triazepine 131 (Scheme 33). In the next example, the initial Michael reaction on nitrogen (amine group) was followed by a reaction with a third component. Ramesh et al.37 described a simple and efficient three-component protocol for the synthesis of highly substituted pyrroles 134 by using amines 132, DMAD and glyoxal (133), with DABCO as a catalyst (Scheme 34). Highly functionalized pyrroles were also synthesized by using amines, DMAD, triphenylphosphine and arylglyoxals.
In 2011, three-component reactions involving 3-amino-carbazoles 135, DMAD and aromatic or aliphatic aldehydes affording carboline derivatives 137 and 138 were described (Scheme 35). Although the reaction of thiosemicarbazones with DMAD was used for the synthesis of thiazolidinones9 (Scheme 5), Vijesh et al.40 reported the synthesis of imidazole derivatives 141, containing a substituted pyrazole moiety, by reflux of the thiosemicarbazones 140 with DMAD in methanol (Scheme 36).

Moreover, reaction of thiosemicarbazide 142 with DMAD, either in hot methanol or in a solventless system under microwave irradiation (Scheme 37), afforded the triazine derivative 143.41

The reaction of DMAD with guanidines 144 yielding the five-membered imidazolin-4-ones 145 was also reported (Scheme 38).42

The biological activity of 1,4-diazepine derivatives has been widely explored. Zaleska et al.43 studied the formation of new tricyclic ring systems of fused 1,4-diazepines. They found that reaction of the zwitterionic compound 146 with DMAD led to the formation of diazepine 149, in 57% yield, through a Michael reaction (Scheme 39).

Scheme 35

Scheme 36

Scheme 37

Scheme 38

Scheme 39
2.3 Oxygen as Nucleophile

Humphrey et al. reported that Michael reaction of oxime afforded, through oxygen, a Z/E mixture of adducts (Scheme 40). The final target of this synthesis was an HIV integrase inhibitor.

Furthermore, a gold-catalyzed approach for the regioselective synthesis of highly substituted pyrroles directly from oximes and DMAD was recently developed (Scheme 41).

2.4 Addition to Carbon–Carbon Double Bonds

Nitrogen heterocycles containing phosphorus functional groups are compounds of interest in many areas of industrial chemistry such as the textile, pharmaceutical, and agricultural fields. A useful strategy for the preparation of such compounds is based on the cyclization of functionalized enamines. β-Enamine phosphine oxides were prepared by a one-pot process involving the sequential reaction of triphenylphosphine oxide with methyllithium and then with alkyl and aryl nitriles. The enamines added regioselectively, through the β-carbon, to the carbon–carbon triple bond of DMAD with a stereoselectivity that depended on the substituent of the enamine. Heating the phosphoryl enamines afforded phosphorus-substituted 2-pyridones and 2-pyrrolidones in good to excellent yields (Scheme 42).

A general and versatile high-yielding method for the divergent and diastereoselective synthesis of polyhydroxylated indolizidines such as has been established using DMAD. At ambient temperature, the reaction of with DMAD proceeded rapidly to form a yellow-colored compound, which was isolated and identified as the adduct (Scheme 43). In warm methanol, was converted into 5-indolizinone-7,8-dicarboxylate in 88% yield; this was then itself converted into the polyhydroxylated indolizidine in good yield through practical hydrogenation and reduction reactions.

Indigotin is the major chemical constituent of indigo, which has been used as a dyestuff for at least 4000 years. The reduced monomeric unit of indigotin, 3-hydroxyindole, is much less studied owing to its easy oxidative dimerization to indigotin. The pyrrolone de-
derivative 168, a monomeric unit of indigotin 166 with the benzene ring being replaced by a heterocyclic ring, underwent a Michael reaction with DMAD, giving 169 (30%) as a single isomer. Reactions of 1-substituted pyrrol-3(2H)-ones with DMAD could also take place at the corresponding 2-position, though the tautomeric nature of the product was different (Scheme 45).\(^50\)

### 3 Cycloaddition Reactions

As previously stated, DMAD is a powerful dienophile widely used in cycloaddition reactions. The most important examples of cycloadditions are the Diels–Alder reactions, in which very often DMAD is used as a standard to check the efficiency of various dienes, and also the 1,3-dipolar cycloaddition reactions. Moreover, [2+2] cycloadditions involving DMAD are also reported. There are also some examples of other cycloadditions, such as [8+2], involving this useful alkyne diester (Scheme 46).

The reaction of 176 with DMAD afforded a new Diels–Alder adduct 177 in 58% isolated yield (Scheme 49). However, when the reaction was carried out with 1,1,2,2-tetracyanoethylene (TCNE) under the same reaction conditions, no reaction was observed.\(^54\)

Dendralenes are cross-conjugated hydrocarbons that quickly became attractive starting materials for organic synthesis. The following example shows a diene-transmissive Diels–Alder addition of DMAD to dendralene 178. The process could be stopped at the mono adduct stage 179, but it could also be performed, under harsher conditions, to yield directly the 2:1 adduct 180 (Scheme 50).\(^55\)

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**Scheme 45**

**Scheme 46**

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**Scheme 47**

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**Scheme 48**
Ferrocenophane 181, obtained by the ene–yne metathesis method, possessing a conjugated diene functionality in the bridging side chain could be further modified via a Diels–Alder cycloaddition with DMAD, in a highly diastereoselective fashion, affording compound 182 (Scheme 51).

Nair et al. reported the facile Diels–Alder reaction of compound 183 with DMAD affording a hexasubstituted benzene derivative 184 (Scheme 52).

Sher et al. showed that the reaction of compound 192 with DMAD, in the presence of a catalytic amount of p-toluene sulfonic acid (PTSA; 5 mol%), afforded 193 (Scheme 54).

DMAD is often used in natural product synthesis in key transformation steps. A recent example presenting a stereoselective synthesis of marine sesterterpenes 188 and 189 included a Diels–Alder addition with DMAD (Scheme 53).
The Diels–Alder reaction of α-tropolone 194 with DMAD, promoted by triethylamine or silica gel, yielded adduct 195 as reported by Okamura et al. (Scheme 55).\textsuperscript{61}

Scheme 55

The synthesis of 198 commenced with 1,6-methano[10]annulene 196, which added DMAD via its ring-closed bis-norcaradiene valence isomer (Scheme 56).\textsuperscript{62}

Scheme 56

DMAD has also been employed in materials synthesis. Recently, a Diels–Alder reaction of compound 199 with DMAD affording compound 200, a useful intermediate for the synthesis of photoalignment layers for liquid crystals, was reported (Scheme 57).\textsuperscript{53}

Scheme 57

Allenic, by virtue of their reactive and cumulative double bonds, are excellent partners for both [4+2] and [2+2] cycloadditions. Allenylphosphonates (phosphorylated allenes) and allenylphosphine oxides constitute a class of compounds that are more readily accessible (and inexpensive) than most of the other allenes.\textsuperscript{64,65} Allenes 201 (R = Ph, p-tolyl, bromophenyl, p-anisyl) with a terminal =CH\textsubscript{2} group gave products 202–204. Even more interesting was the reaction of vinyl allenes 205 with three equivalents of DMAD that led to products 206–209 (Scheme 58).\textsuperscript{66}

DMAD was also used recently in a transition-metal-mediated annulation in which polyfunctionalized arenes were constructed. This strategy is based on an enyne metathesis followed by Diels–Alder cycloaddition and oxidation. Treatment of diphenylacetylene (210) with the second-generation Grubbs catalyst and DMAD, in the absence of additives, gave a mixture of 211, resulting from enyne metathesis, and the non-metathesis product 212 (Scheme 59).\textsuperscript{67}
3.1.2 Reactions with o-Quinodimethanes

The elusive intermediate o-quinodimethane, also named o-xylene, has attracted much attention from both theoretical and synthetic chemists over the past 30 years. As cis-dienes, o-quinodimethanes have a remarkable Diels–Alder reactivity and are often used as building blocks in the syntheses of cyclic organic compounds by inter-or intramolecular [4+2] trapping.

As an example, the efficient procedure for the generation of the imidazole-4,5-quinodimethane intermediate 214, from imidazole derivative 213 and its first-time capture by DMAD to afford the corresponding Diels–Alder benzimidazole adducts 215 and 216, was reported (Scheme 60).68

Bicyclic o-quinodimethanes were also prepared from the tricyclic sulfones 217. However, reactions had to be carried out by heating the sulfones with an excess amount of DMAD, in the absence of solvent at 250–320 °C, in order to afford the corresponding cycloadduct 219 (Scheme 61).69

Benzopentathiepins 220 reacted slowly with DMAD to give the benzodithiins 221 as the only reaction products, with the reaction being greatly accelerated by the addition of triphenylphosphine. The pentathiepin 222 also reacted with DMAD in the presence of triphenylphosphine in dichloromethane, at room temperature, to give the 1,4-dithiin 223 in 78% yield. Triphenylphosphine presumably initiates the reaction by nucleophilic attack on sulfur, opening the pentathiepin ring 220 and removing sulfur atoms, possibly to give intermediate 224,70 which is intercepted by DMAD (Scheme 62).71

3.1.3 Heterocycles as Dienes

Functionalized arenes 227 were also synthesized through substituted α-pyrones 226, which have been used as important synthetic intermediates72 and are found in a wide variety of biologically interesting natural substances (Scheme 63).73
Narayan and Sarpong\textsuperscript{74} reported the reaction of DMAD with indolizinone\textsuperscript{228}, a nitrogen heterocycle recently reported in the literature as a very useful precursor to indolizidine natural products, pharmaceutical agents and new materials. It was supposed to give the product\textsuperscript{229}; this, however, proved to be unstable and afforded instead the retro-Diels–Alder product\textsuperscript{230} (Scheme 64).

\begin{scheme}
\centering
\includegraphics[scale=0.5]{Scheme_64}
\end{scheme}

It has been known for a long time that the reaction of alkyynes with heterocyclic dienes, such as furans, results in the formation of bridged oxacycles, which can be transformed into functionalized benzene derivatives by acidic hydrolysis. Diels–Alder reactions of 4-substituted 2-(2-furyl)-, 2-styryl-, and 2-crotyl-3-chlorofurans such as\textsuperscript{231} with DMAD occurred exclusively on the chlorofuran diene moiety and not on the non-chlorinated furano diene or the chlorinated exocyclic diene alternatives, demonstrating the predominance of the halogen effect in the furan Diels–Alder reaction as shown by Ram and Kumar.\textsuperscript{75,76} For example, chlorobifuryl, having a chlorofuran ring and a non-halogenated furan ring, on heating with DMAD gave exclusively the corresponding furylchlorophenol\textsuperscript{233} in 74\% yield by cycloaddition to the chlorofuran ring (Scheme 65).

\begin{scheme}
\centering
\includegraphics[scale=0.5]{Scheme_65}
\end{scheme}

Moreover, Diels–Alder reactions of furano derivatives such as\textsuperscript{234} with DMAD affording functionalized phenols\textsuperscript{236} (Scheme 66) have been reported.\textsuperscript{77}

\begin{scheme}
\centering
\includegraphics[scale=0.5]{Scheme_66}
\end{scheme}

Furthermore, the reaction of DMAD at the furan fragment of 3,4-fused 2-furyltetrahydroquinoline derivatives\textsuperscript{237} according to the [4+2] cycloaddition pattern was studied. The reaction proved not to be stereoselective, yielding two diastereoisomeric 7-oxabicyclo[2.2.1]hepta-2,5-diienes\textsuperscript{238a,b} in 32–88\% total yield (Scheme 67).\textsuperscript{78}

\begin{scheme}
\centering
\includegraphics[scale=0.5]{Scheme_67}
\end{scheme}

Reactions of DMAD with pyrroles have been studied extensively. The 4\,\pi\,2\,\pi\, cycloaddition between pyrroles and dienophiles has been shown to be a general method for the synthesis of 7-azabicyclo[2.2.1]hepta-2,5-diene and 7-azabicyclo[2.2.1]hept-2-ene derivatives. However, pyrrole is a poor diene for the [4+2] cycloaddition and usually reacts with DMAD to give Michael addition products. Moreover, when a pyrrole nitrogen atom bears an electron-withdrawing group, the aromatic ring was found to be more reactive as a diene toward DMAD.\textsuperscript{26} Nevertheless, application of ultrasound to the reaction of pyrrole with DMAD in an aqueous solution resulted in the cycloaddition adduct\textsuperscript{240} in 60\% yield without the formation of Michael-type products (Scheme 68).\textsuperscript{79}

\begin{scheme}
\centering
\includegraphics[scale=0.5]{Scheme_68}
\end{scheme}

The 4\,\pi\,2\,\pi\, cycloaddition of 1-(alkylamino)pyrroles or 1-(alkoxycarbonylamino)pyrroles with electron-deficient alkyynes was shown to follow a predictable pathway and provide a remarkably simple route for the preparation of substituted benzenes. Upon heating\textsuperscript{241} with three equivalents of DMAD, benzene derivatives\textsuperscript{243} were obtained in good yields (50–90\%; Scheme 69).\textsuperscript{79}

\begin{scheme}
\centering
\includegraphics[scale=0.5]{Scheme_69}
\end{scheme}
Pyrrolo[3,4-b]pyrrole 244 afforded the cycloadduct 245 on treatment with DMAD. Oxidation of the latter with m-chloroperbenzoic acid, followed by thermolysis, gave the indole derivative 246 (Scheme 70).80

3.1.4 Heterocycles with an Exocyclic Double Bond

Ikeuchi et al.81 described a ‘Cp2Zr’-mediated reaction and subsequent copper(I)-catalyzed carbon–carbon bond formation for the construction of biologically attractive molecules such as compounds 250. In order to examine the reaction’s utility, preliminary reactions of the latter compounds to obtain polycyclic heterocyclic systems were examined (Scheme 71). To this end, the reaction of the allylation product 248 gave the unstable diene 249 in good yield, through intramolecular enyne metathesis82 using the second-generation Grubbs catalyst (ambient temperature for 15 hours); 249 was then used directly for the subsequent Diels–Alder reaction with DMAD at ambient temperature for 10 hours leading to compound 250 as a major product (250/251 = 24:1 in the case of X = NMe).

Interaction of pyrrole 252 with DMAD afforded, after exposing adduct 253 to air, the hydroxyindole 254 and the bis-adduct 7-vinylindole 255 (Scheme 72). The latter compound was formed as a result of the 1,2-addition of the primary cycloadduct 253 to a second DMAD molecule followed by elimination of trimethylsilanol. When the reaction was performed without solvent, under an oxygen atmosphere, indole 254 was mainly formed (254/255 = 72:28).83

Indoles 257 and 259 were obtained, in 17% and 27% yield respectively, by reaction of 3-vinylpyrroles 256 and 258 with DMAD (Scheme 73).83c

2-Vinylpyrrolo[2,3-b]pyridine 261 afforded, upon reaction with 1.5 equivalents of DMAD, compound 262, the unexpected derivative 263, and trace amounts of an aromatized derivative from 262. Attempts to carry out the cycloaddition reaction under atmospheric pressure gave solely 262 in 30% yield. Cycloaddition of 261 to DMAD (5 equiv) led to compound 263, in low yield, due to the decreased reactivity of the diene (22% of the starting material was recovered) and the formation of cyclodimer 264, resulting from an intermolecular hetero-Diels–Alder reaction.

Scheme 70

Scheme 71

Scheme 72
Dimethyl Acetylenedicarboxylate

**Scheme 74**

**Scheme 75**

**Scheme 76**

**Scheme 77**

The reaction of equimolar amounts of enamiones with DMAD resulted to the formation of a variety of pyran and pyrrole-3-ylidene derivatives and having pharmacological and medicinal significance. The mechanism concerning pyran derivatives involves an initial [4+2] cycloaddition followed by a 1,3-hydride shift, whereas for an initial enamine-type nucleophilic attack of the α-carbon of 267 at the acetylenic carbon of DMAD is proposed.

The reaction of thiazoles with DMAD gave pyridines through a hetero-Diels–Alder reaction and further sulfur extrusion, although, in this case, extremely harsh conditions were required. The activating effect of the amino functionality in the reaction of 2-(dimethylamino)thiazole toward electron-poor reagents, such as DMAD, tosylisocyanate, and ketenes has been also demonstrated. Nevertheless, no cycloadducts were formed in these reactions, but only Michael-type products resulting from the functionalization at the 5-position of the thiazole ring. This activating effect was evident when 2-amino-4-methylthiazole was allowed to react with DMAD. From this reaction, conducted at room temperature, a new adduct was isolated in 42% yield, along with the thiazolopyrimidinone formed in 30% yield. The formation of 277 was explained as the result of a [4+2] cycloaddition in which the heterocycle acts as heterodiene (Scheme 77).
3.2 1,3-Dipolar Reactions ([3+2] Cycloadditions)

Although 1,3-dipoles have been known for more than a century, their cycloaddition reactions are nowadays powerful synthetic tools, providing access to highly functionalized oxygen-, sulfur- and nitrogen-containing heterocycles. The synthetic utility of these cycloadditions has been further enhanced by the development of tandem processes that allow the preparation of complex molecules starting from relatively simple materials.

3.2.1 Azomethine Ylides

Azomethine ylides have become one of the most investigated classes of 1,3-dipoles. The substituted pyroles were obtained by a one-pot reaction between quinazolinium bromides and DMAD in 1,2-epoxybutane as the reaction medium and acid acceptor (Scheme 78).

Scheme 77

Bridgehead nitrogen heterocycles are important natural products. Among them, indolizines have received much attention in recent years owing to both their intriguing molecular structures featuring 10 π-delocalized electrons and their important biological activities. These molecules have been used in various pharmaceutical applications. The synthesis of indolizine in 53% yield, via the 1,3-dipolar cycloaddition between pyridinium bromide and DMAD, using Amberlite IRA-402 (OH) ion-exchange resin as a base, was recently described (Scheme 79).

Scheme 78

1,3-Dipolar cycloaddition of with DMAD as dipolarophile yielded the pyrazole derivative in low yield. Attempts to improve the yield by insertion of a spacer yielded pyrazoles and as a result of overreaction in a Michael fashion with DMAD. The polymer-supported azomethine imines which were generated from polymer-supported silylnitrosoamides by a 1,4-silatropic shift gave pyrazole derivatives. A feature of this reaction is that no cleavage operations are required after the cycloaddition. Thus, azomethine imine, which was generated via a 1,4-silatropic shift of the silyl group onto the oxygen of the nitroso group, underwent 1,3-dipolar cycloaddition with DMAD to give the five-membered-ring adduct.

It is interesting that the acyl group was spontaneously eliminated as a silyl ester and N-unsubstituted pyrazoles were obtained after aromatization. If a polymer is attached to the acyl group of , the versatility of the reaction is greatly enhanced (Scheme 80).
3.2.2 Nitrones

Mlostoń et al.\(^9\) described a new method for the preparation of 1,4,5-trisubstituted (imidazol-2-yl)acetates \(^{296}\), based on the reaction of the corresponding imidazole 3-oxides \(^{293}\) with DMAD. Formation of the products was rationalized by a formal 1,3-dipolar cycloaddition and subsequent oxaloyl cleavage (Scheme 81).

![Scheme 81](image)

Chakraborty and Luitel\(^9\) reported the cycloaddition of \(N\)-benzyl fluoro nitrones \(^{298}\) with DMAD, accelerated by ionic liquids, to afford novel isoxazoline and isoxazolidine derivatives \(^{299}\) in a one-pot reaction process (Scheme 82).

![Scheme 82](image)

3.2.3 Azides

The 1,3-dipolar cycloaddition reaction between alkynes and azides, developed by Huisgen,\(^9\) is one of the most popular reactions because of the resulting five-membered substituted 1,2,3-triazole heterocyclic ring. It was found to have a wide range of industrial applications such as for dyes, photostabilizers and agrochemicals and also in the designing of new drugs. Adducts of azidomethylamines \(^{300}\) and \(^{302}\) with DMAD afforded compounds \(^{301}\) and \(^{303}\), respectively (Scheme 83).

![Scheme 83](image)

Kumar and Rode\(^10\) reported the first general approach for the synthesis of fused 1,2,3-triazolo-\(\delta\)-lactams \(^{309}\) using a Huisgen [3+2]-dipolar cycloaddition reaction in water, between activated alkynes and azides such as \(^{307}\) derived from different amino acids, this ‘click’ reaction was followed by cyclization (Scheme 85).

![Scheme 85](image)

Semakin et al.\(^1\) reported that \(\alpha\)-azidooximes, readily obtained from aliphatic nitro compounds, were cleanly converted into previously unknown pyrazinones \(^{313}\). Here, oximes \(^{310}\) reacted with DMAD via [3+2] cycloaddition at room temperature affording triazolones \(^{311}\). However, the cycloaddition was accompanied by partial hydrolysis of the oximino group leading to carbonyl derivatives \(^{312}\). This side process could be avoided by carrying out the [3+2] cycloaddition of \(^{310}\) with DMAD in toluene. Oximes \(^{311}\) were readily reduced with Raney nickel when \(R^1\) was not an ester giving the target heterocycles \(^{313}\) (Scheme 86).
3.2.4 Nitriloxides

Tandem electrophilic cyclization, [3+2] cycloaddition and rearrangement reactions of 2-alkynylbenzaldoximes 314 (R1 = H, F; R2 = Ph, 4-MeOC₆H₄, etc.), DMAD and bromine afforded the unexpected isoquinoline-based azomethine ylides 315 in good to excellent yields. The products could be further worked upon via palladium-catalyzed cross-coupling reactions to generate highly functionalized isoquinoline-based stable azomethine ylides (Scheme 87).102

Scheme 87

3.2.5 Diazoalkanes

In the last ten years, the range of indazole derivatives with valuable biological activities increased substantially. Among them, agonists of estrogen receptors and dopamine D₃ receptors, HIV protease inhibitors and new anti-inflammatory substances have been discovered. Strakova et al.103 described the [3+2] cycloadditions of a series of tetrahydroindazoles 316 with DMAD that gave the spiro derivatives 317 (Scheme 88).

Scheme 88

3.2.6 Sulfur Dipoles

Indoles fused with the 1,2-dithiole-3-thione ring, as in compound 318, could be of interest because such compounds have a broad spectrum of biological activity and may be useful synths for many sulfur heterocycles.104 A one-pot synthesis of derivatives 319 and 320 from 318 with DMAD by 1,3-dipolar cycloaddition was reported (Scheme 89).105,106

Scheme 89
In 1979, Cava and co-workers suggested a modification of Hartzler’s procedure by adding a mixture of DMAD and tetrafluoroboric acid etherate, at –65 °C, to tributylphosphine–carbon disulfide complex. The thus-formed ylide was protonated and then trapped as its phosphonium salt 326, which was isolated in 72% yield. This salt proved to be of high synthetic value in 1,3-dithiole and tetrathiafulvalene chemistry, affording compounds such as the derivatives 327 (Scheme 92). This general scheme was extended to the synthesis of diselenadithiafulvalene 330, the first step being a cycloaddition of DMAD to 2-thioxo-1,3-diselenolane 328. It was also used for the synthesis of tetraselenafulvalene from ethylene triselenocarbonate (Scheme 93).111

Microwave-assisted regiospecific [2+2] cycloadditions of DMAD to derivatives 334, resulting in the formation of butadienes 335, were reported in 2008 (Scheme 96).113

Moreover, the microwave-assisted [2+2] cycloaddition of DMAD to imidazolidine-2,4-dione 336a, or to the corresponding thioxo derivative 336b, in acetonitrile, produced the highly functionalized imidazolidine-2,4-dione derivatives 337 and 338 (Scheme 97).114

Reactions of enamines of cyclic ketones with DMAD can be manipulated to achieve ring enlargement by a unit of two carbon atoms. The reactions proceed via [2+2] cycloaddition and subsequent ring opening of the intermediate cyclobutenes (Scheme 94). This becomes a valid strategy for constructing an extended π-conjugated system when applied to cyclic π-conjugated enamines. This method was also successfully used to achieve ring enlargements of thiophenes to thiepines, benzofurans to benzoxepines, indoles to benzazepines and pentalenes to azulenes. Di-pyrrolidinyl-annelene 332 reacted with an excess of DMAD in refluxing toluene to give ring-enlarged annulene 333 (Scheme 95).112

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The reaction of the thiazole derivatives 339 with DMAD led unexpectedly to compounds 341, which resulted from a sequence of reactions initiated by a [2+2] cycloaddition of DMAD to the formal carbon–carbon double bond of the thiazole ring (Scheme 98).115

Scheme 98

Sajna et al.66 described the reaction of allenylphosphonate 342 with DMAD under neat conditions to afford compounds 343, 344 and 345 following a plausible [2+2] cycloaddition (Scheme 99).

Scheme 99

3.4 [8+2] Cycloadditions

Orbital-symmetry-allowed [8+2] cycloadditions between tetraenes 346 and tetraenophiles 348, can in theory provide a straightforward approach for the synthesis of 10-membered-ring compounds. Before the year 2003, however, all of the reported [8+2] cycloadditions were limited to geometrically constrained tetraenes (such as heptafu- venes, tropones, and indolizines), in which the terminal carbons or heteroatoms at positions 1 and 8 were rigidly held in close proximity.116

Kuznetsov et al.117 reported that although 5-bromoindolizine 350 was found to be passive toward nucleophiles, its reaction with DMAD led to cycl[3.2.2]azine 351 in 87% yield, through an [8+2] cycloaddition (with HBr elimination). This [8+2] cycloaddition of dienophiles, across positions 3 and 5, is a well-known type of indolizine reactivity (Scheme 100).

In 2003, it was reported that dienylisobenzofurans 352 could react with DMAD to furnish, as the major products, [8+2] adducts possessing the 11-oxabicyclo[6.2.1]undecane ring system 353.118a It was later noted that dienylfurans 354 could also participate in [8+2] cycloadditions with DMAD, affording compounds 355 (Scheme 101).118b

These [8+2] cycloadditions provided a direct approach for the synthesis of ring skeletons such as eleutherobin, brirellins and other natural products that have anticancer activity. Ten-membered-ring compounds with an oxygen bridge can also be readily synthesized through these [8+2] cycloadditions.

Roy and Ghori119 reported a one-pot three-component coupling of o-alkynylheteroaryl carbonyl derivatives 356.
with α,β-unsaturated Fischer carbene complexes and DMAD, leading to the synthesis of heterocyclic analogues of furanophane derivatives 358 through an [8+2] cycloaddition reaction (Scheme 102).

4 DMAD and the Generation of Zwitterions; Multicomponent Reactions (MCRs)

Zwitterions are transient intermediates formed by the addition of neutral nucleophiles to electrophilic receptors. Zwitterions are a unique tool in organic synthesis leading to a variety of heterocycles. These reactive intermediates can be captured by suitable substrates (e.g., nucleophiles), after a series of transformations. In fact, it was found that in the case of acetylenedicarboxylate, three reaction paths are possible (paths A, B and C). Basically, in both paths A and C the nucleophile is added irreversibly, leading to a multi-component reaction. On the other hand, in path B the nucleophile gets eliminated from the system, and thus plays a catalytic role, conducting a two-component reaction. Path B usually involves nucleophiles, such as phosphines and tertiary amines such as pyridines and quinolines, while paths A and C involve mainly nucleophilic heterocyclic carbenes (NHCs) and isocyanides (Scheme 103).

4.1 Phosphines and Derivatives

The importance of organophosphoric compounds as reagents in organic synthesis and as transition-metal-cat-

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ing benzene, an intramolecular Wittig reaction to produce highly strained spiro compounds 366 which spontaneously underwent ring-opening to produce functionalized 1,3-dienes 367 (Scheme 105).

On the other hand, 3,4-diacetylhexane-2,5-dione (368) in its reaction with DMAD, in the presence of triphenylphosphine, underwent a diastereoselective intramolecular Wittig reaction to produce the cyclopentene derivative 369 in good yield (Scheme 105).

### 4.1.2 Reactions of Triphenylphosphine, DMAD and N–H Acids

Reaction of the reactive 1:1 intermediate adduct of triphenylphosphine and DMAD with 3-chloroindole-2-carbaldehyde (370) led to a vinylphosphonium salt which underwent an intramolecular Wittig reaction to produce the corresponding pyrrole derivative 372 (Scheme 106). Moreover, the reaction of the 1:1 triphenylphosphine–DMAD adduct with some other N–H acids delivered the corresponding pyrrole derivatives via an intramolecular Wittig reaction.

The reaction of arylsulfonamide derivatives of 2-amino-benzaldehyde 373, DMAD and triphenylphosphine produced dihydroquinoline derivatives 375 in excellent yields (Scheme 106).

In addition, the DMAD–triphenylphosphine intermediate was trapped by ethyl 1H-pyrimidine-2-carboxylate 376 to the pyrimidine derivatives 377 and 378 in a nearly 7:1 ratio and overall good yields (Scheme 106).

A series of triazene derivatives 380 with polyfunctional substituents, such as the ylide moiety and ester groups, were synthesized by the reaction of DMAD with 1,3-diallyl-1-triazenes 379 in the presence of triphenylphosphine in ethyl acetate (Scheme 106).

A convenient synthesis of highly functionalized phosphorus ylides was achieved by the reaction of DMAD with N-phenylacetamides 381 in the presence of triphenylphosphine. The intramolecular cyclization of ylide 382 in toluene, at reflux, gave the pyrazole derivative 383 in a high yield (Scheme 106).

### 4.1.3 Reactions of Triphenylphosphine, DMAD and O–H Acids

Johnson and Tebby established the intermediacy of a zwitterion in the reaction of triphenylphosphine with DMAD, which proved to form the basis of a wide variety of later transformations. These zwitterionic species were shown to undergo annulation reactions with electrophiles, such as aldehydes, α-keto nitriles, α-keto esters and N-tosylinines, to provide highly substituted unsaturated γ-lactones and lactams.

Recently, the reaction between DMAD and various aryl aldehydes in the presence of triphenylphosphine was reported, leading to unsaturated γ-butyro lactone derivatives 385 and highly substituted enones 386 in fairly good yields at room temperature (Scheme 107).
The reaction between arylglyoxal monohydrates 387, DMAD and triphenylphosphine led to the dihydrofuran derivatives 389 by a simple and efficient method (Scheme 108).\textsuperscript{133}

The one-pot reaction between ninhydrin 391, amide derivatives 390, DMAD and triphenylphosphine led to oxacyclopenta[\alpha]indene derivatives 392 (Scheme 109).\textsuperscript{134}
Yavari et al.\textsuperscript{135} described a new and operationally convenient approach to the synthesis of 4-carboxymethylcoumarins based on the aromatic electrophilic substitution between the conjugate base of a substituted phenol and a vinyltriphenylphosphonium salt derived from the reaction of DMAD with triphenylphosphine. In this context, 4-carboxyalkyl-8-formyl coumarins\textsuperscript{394} were synthesized from 2-hydroxybenzaldehydes\textsuperscript{393} in good yields via vinyltriphenylphosphonium salt mediated electrophilic aromatic substitution. The salt was generated in situ by protonation of the reactive 1:1 intermediate produced by the reaction of triphenylphosphine and DMAD with the 2-hydroxybenzaldehyde (Scheme 110).\textsuperscript{136}

Scheme 110

Moreover, Symeonidis et al.\textsuperscript{137} reported the synthesis of linear [6,7]-fused coumarins\textsuperscript{396}, along with a minor product\textsuperscript{395}, which were obtained from the reaction of [3,4]-fused phenols\textsuperscript{398} with DMAD and triphenylphosphine (Scheme 110). The synthesis of angular [7,8]-fused coumarins from the reaction of [2,3]-fused phenols with DMAD and triphenylphosphine was also reported.\textsuperscript{137}

Scheme 111

Novel spirocyclic lactones\textsuperscript{399} and\textsuperscript{401} were synthesized by Nair et al.\textsuperscript{131} who carried out a phosphine-mediated reaction of DMAD with\textsuperscript{o-} and\textsuperscript{p-}quinones\textsuperscript{398} and\textsuperscript{400}. The zwitterion, not surprisingly, exhibited a complete preference for the quinone carbonyl group, leaving the enone double bond intact (Scheme 111).

4.1.4 Reactions of Triphenylphosphine, DMAD and S–H Acids

Stable crystalline phosphorus ylides\textsuperscript{403} were obtained in excellent yields from the 1:1:1 addition reaction between triphenylphosphine and DMAD in the presence of 1-methylymidazole-2-thiol (402). These sulfur-containing phosphoranes\textsuperscript{403} existed in solution as a mixture of two geometrical isomers, owing to restricted rotation around the carbon–carbon double bond resulting from conjugation of the ylide unit with the adjacent carbonyl group (Scheme 112).\textsuperscript{138}

Analogously, the reaction of triphenylphosphine and DMAD in the presence of thiophenol derivatives\textsuperscript{404} proceeded spontaneously, at room temperature, to produce stable phosphorus ylides\textsuperscript{405} (Scheme 112).\textsuperscript{139} The reaction of some other strong S–H acids with DMAD, in the presence of triphenylphosphine, led to the corresponding phosphoranes.\textsuperscript{140}

Crystalline phosphorus ylides\textsuperscript{407} were obtained in excellent yields from the 1:1:1 addition reaction between triphenylphosphine, DMAD and N–H or S–H acids\textsuperscript{406} such as 2-amino-4-phenylthiazole, 2-amino-5-(3-chlorobenzyl)thiadiazole, 3-amino-2-methylquinazolin-4-one and 3-amino-2-mercaptoquinazolin-4-one (Scheme 113).\textsuperscript{141}

Scheme 112
4.1.5 Reactions of Triphenylphosphine, DMAD and Oxa- or Azadienes

Waldmann and co-workers,142 wishing to synthesize compound collections inspired by natural products for chemical biology and medicinal chemistry research, developed an enantioselective triphenylphosphine- or tributylphosphine-organocatalyzed asymmetric [4+2] annulation between electron-deficient heterodienes and acetylene derivatives. By using 3-formylchromones 408, DMAD and triphenylphosphine (up to 30 mol%), tricyclic benzopyrones 409 (X = O) were isolated in high yields; these were further used for an efficient synthesis of tetrahydroindolo[2,3-a]quinolizidines (centrocountins). Analogously, from the reaction of 3-formylchromone N-tosylimines 408 (X = NTs) the tricyclic products 409 (X = NTs) along with the hydroxybenzoylpyridines 410 were formed. Finally, the reaction of acyclic electron-poor oxadienes 411 with DMAD and triphenylphosphine was also studied, whereupon the initially detected [4+2]-annulation products underwent a subsequent Claisen rearrangement to yield dehydropyrans 412 (Scheme 114).

4.1.6 Reactions of Phosphine Derivatives with DMAD

The nucleophilic addition of trialkyl phosphites to electron-deficient triple bonds led to highly reactive zwitterionic intermediates, which could be trapped by various electrophiles. Phosphonate esters are an important class of compounds obtained by the sequential addition reaction of trivalent phosphite with α,β-unsaturated carbonyl molecules in the presence of C–H or N–H acids. Synthesis of phosphonato esters 414 and 415 was accomplished via reaction between DMAD and triphenylphosphite in the presence of biological compounds 413 such as theophylline, 4-hydroxypyrimidine, 2H-3,1-benzoxazine-2,4(1H)-dione, 2-chloroaniline or 3-nitroaniline at ambient temperature (Scheme 115)143,144.

Scheme 113

Scheme 114

Scheme 115

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omatic amine 416 to an arylsulfonyl isocyanate 417, were selectively alkylated to give 418 in excellent yields under neutral and mild conditions by treatment with trialkyl phosphate–DMAD at ambient temperature (Scheme 116).

A three-component reaction between DMAD and trialkyl phosphites in the presence of N-aryl-3-hydroxynaphthalene-2-carboxamide 419 led to dialkyl 2-(dimethoxyphosphoryl)-3-[2-hydroxy-3-(arylcarbamoyl)naphthalen-1-yl] succinates 420 in excellent yields (Scheme 116).146

Protonation of the reactive intermediate produced in the reaction between trialkyl(aryl) phosphites and DMAD by C–H acids such as indane-1,3-dione and N,N′-dimethylbarbituric acid, led to functionalized phosphonates 422 in good yields (Scheme 116).146

Deng et al.147 reported the synthesis of aryl-substituted γ-lactones 425 bearing an α-phosphorus ylide moiety, in moderate to good yields, through the assembly of DMAD, electron-deficient aldehydes 423, and triaryl- or trialkyl-phosphanes (Scheme 117).

A new class of phosphorus-ylide containing conjugate heterocycles was isolated from a mixture of colored products of the reaction of a silylphosphate 426 and DMAD. The indigo-like bis-phosphole structure 427 appeared with a green to blue color because of the low energy gap of the phosphole (Scheme 118).148

The reaction of dihydrophosphate 428 with an excess of DMAD was found to give the ring-expanded product 429 (Scheme 119).149a fully characterized by X-ray crystal structure analysis. A similar rearrangement was proposed in the case of 1-phenyl-3,4-dimethylphosphole (430)149b yielding the ring-expanded product 431. However, fairly recently Duan et al.149c reinvestigated the reaction and established the formation of the stable ylide 432.
4.2 Amines

4.2.1 Reactions of Primary Aromatic or Aliphatic Amines

Although not quite as productive as phosphine catalysis, amines can also initiate various transformations by generating zwitterionic intermediates from activated olefins and acetylenes.

A protocol has been developed for the efficient synthesis of structurally diverse 3,4-dihydropyridin-2(1H)-ones 436 and 3,4-dihydro-2H-pyran 438 via four-component reactions of arylamines 433, DMAD, aromatic aldehydes 434 and cyclic 1,3-diketones 435 and 437, respectively. The selective formation of the very different pyridinone or pyran derivatives was found to depend on the structure of the cyclic 1,3-diketone (Scheme 120).150

In addition, a practical and efficient procedure for the preparation of the polysubstituted dihydropyridines 440 was developed through a unique four-component reaction of aromatic aldehydes, nitriles 439, arylamines and DMAD (Scheme 120).151

A facile and efficient synthesis of tetrasubstituted 1,4- and 1,6-dihydropyridines 443 and 444 was achieved by employing a three-component domino reaction using DMAD, aliphatic amines 441 and α,β-unsaturated aldehydes 442 in the presence of trifluoroacetic acid. Interestingly, regioselectivity in the synthesis of 1,4-dihydropyridines was increased by using triflic acid (Scheme 121).152

The 1,4-dihydropyridines 443 were further used for the synthesis of fused-naphthyridine derivatives 447 and 448 by reaction with aromatic amines 445 and aromatic aldehydes 446 catalyzed by boron trifluoride–diethyl etherate in acetonitrile (Scheme 122).152

Scheme 120

Polystyrene glycol (450) and iron(III) chloride were found to be an inexpensive, non-toxic and effective medi-
um and catalyst, respectively, for the one-pot synthesis of highly functionalized pyrroles using bromides, amines and DMAD. Utilizing this protocol, various pyrrole derivatives were synthesized in excellent yields. Environmental acceptability, low cost, high yields and the recyclability of the polyethylene glycol are the important features of the protocol (Scheme 123).

Scheme 123

The four-component reaction of DMAD, aromatic aldehydes, benzylamines and malononitrile led to polyfunctionalized 1,4-dihydropyridine derivatives (Scheme 124).

Scheme 124

4.2.2 Reactions of Tertiary Amines

Stereoselective reaction of various substituted phenols with DMAD, in the presence of a catalytic amount of an aqueous solution of a trialkylamine in dichloromethane, led to dimethyl 2-phenoxymaleates in good to excellent yields under mild conditions (Scheme 125). The 1,4-dipole derived from 4,5-dimethylthiazole and DMAD was shown to react readily with chromone-3-carboxaldehydes, resulting, after an unusual rearrangement, in the facile synthesis of thiazolopyridine derivatives. In some instances, tetracyclic chromenothiazolopyridines were formed (Scheme 126).

Scheme 125

Scheme 126

Pyridines and quinolines generally deserve special attention owing to the variety of transformations that mediate. Following the observations made by Diels and Alder of the reaction of pyridine with DMAD (affording derivatives and 466), Huisgen was successful in intercepting the 1,4-dipole with phenyl isocyanate, leading to a pyrimidinedione derivative with eventual elimination of pyridine during the course of the reaction (Scheme 127).
The 1,4-zwitterionic intermediate generated from pyridine and DMAD was added to aldehydes in a formal [2+2] manner, resulting in the facile synthesis of 2-oxo-3-benzylidene succinates (Scheme 128). Pyridine catalyzed the reaction of 1,2-diaryl diones with DMAD to afford diaroyl maleates. This unprecedented rearrangement involved a unique benzoyl migration and proceeded with complete stereoselectivity (Scheme 128).

In 2009, an efficient synthesis of the 2H-pyridinyl-2-butenedioate was described via the reaction of dimethyl methoxymalonate and DMAD in the presence of a nitrogen nucleophile (Scheme 128). Maghsoudlou et al. reported a three-component reaction between aromatic ketones and DMAD in the presence of pyridines (Scheme 129).

A route towards stereoselective and regioselective halogenated pyrido[2,1-b][1,3]oxazines in high yields was recently described by Asghari et al. The products were isolated in moderate to excellent yields through a three-component reaction involving pyridines, DMAD and different α-halo ketones (Scheme 130).

The pyridine-mediated reaction of DMAD and cyclobutene-1,2-diones afforded selective access to either hexasubstituted benzene derivatives or cyclopentenedione derivatives, depending on the concentration of pyridine (Scheme 131). Terzidis et al. reported an efficient synthesis of functionalized benzophenones, polysubstituted xanthones or pyranochromenes through the reaction of chromones and DMAD catalyzed by a pyridine derivative (Scheme 132). Pyranochromenes were also isolated by using DABCO or β-isooquinidine as organocatalysts.
Quinoline is widely known to form a 1,4-zwitterion with DMAD, which can be trapped by various dipolarophiles such as compounds 489, 491, 493, 495 and 497 to yield a variety of pyridoquinoline and oxazinoquinoline derivatives including 490, 492, 494, 496 and 498 and 499 (Scheme 133).\(^\text{164}\)

The reaction of isoquinoline (500) with two equivalents of DMAD was originally developed by Diels and Alder in 1933. The reaction proceeded through the zwitterionic intermediate 501, which then underwent a domino Michael addition and Mannich reaction with a second equivalent of DMAD to afford benzoquinolizine 502 (Scheme 134).\(^\text{164b}\)

In 1967, Huisgen et al.\(^\text{165}\) reported three multicomponent variations of this reaction in which intermediate 501 was trapped with several different dipolarophiles, including dimethyl azodicarboxylate (503), diethyl mesoxalate (505) and phenyl isocyanate (507), to form the tricyclic scaffolds 504, 506 and 508, respectively (Scheme 134).

Later, some more examples were reported by Nair et al.,\(^\text{166–168}\) who used benzoquinone 509 and arylidenemalononitriles 511 to obtain the spiro-isoquinoline 510 and tetrahydrobenzoquinolizine derivatives 512, respectively (Scheme 134).

More recently, Yavari et al.\(^\text{169}\) reported a new three-component reaction in which intermediate 501 was trapped with aryl nitromethanes 513 to give pyrroloisoquinolines 514 (Scheme 134).\(^\text{170}\)

Multicomponent reactions involving azines [isoquinoline (500; Scheme 135) or phenanthridine (524; Scheme 136)] and DMAD were executed in the presence of heterocyclic N–H compounds (indole, methylindole, 3,6-dibromocarbazole) or 1,3-dicarbonyl compounds (N,N-dimethylbarbituric acid, 1,3-diethyl-2-thiobarbituric acid, acetylacetone, 1,3-diphenylpropane-1,3-dione, cyclopentane-1,3-dione) 515 to generate enamino esters 516 and 526 in good yields.\(^\text{171,172}\)

Isoquinoline reacted smoothly with DMAD in the presence of amides 517 to produce the derivatives 518 (Scheme 135).\(^\text{173}\)

The 1,4-dipole derived from isoquinoline and DMAD was also shown to react readily with N-tosylamines 519, resulting in the diastereoselective synthesis of 2H-pyrimido[2,1-a]isoquinoline derivatives 520 (Scheme 135).\(^\text{167}\)

Moreover, the reaction of isoquinoline 500 and DMAD with benzoquinone 521, at room temperature, afforded the spiro-oxazino isoquinoline derivatives 522 and 523 as a mixture of regioisomers in a 2:1 ratio and 91% yield (Scheme 135).\(^\text{168}\)

Li et al.\(^\text{174}\) described an efficient synthesis of [1,3]oxazino[3,2-f]phenanthridine derivatives 525 via a three-
Scheme 133

Scheme 134
component reaction of phenanthridine 524, DMAD and aromatic aldehydes (Scheme 136).

The reaction of 3-methylisoquinoline (527) with chromone-3-carboxaldehydes 459 and DMAD to produce chromenopyridoisoquinoline dicarboxylates 528 was also studied (Scheme 137).175

Safaei et al.176 reported a novel, facile and environmentally benign one-pot three-component synthesis of pyrazolines 530 from arylaldehydes, hydrazines 529 and DMAD

Scheme 135

Scheme 136

Scheme 137
with excellent yields and diastereoselectivities using a bifunctional Brønsted acidic ionic liquid as a safe, inexpensive and reusable catalyst under solvent-free conditions (Scheme 138).

Scheme 138

4.3 Isocyanides

Hundreds of multicomponent reactions have been described over the years. Isocyanide-based multicomponent reactions (IMCRs) constitute a special subclass. They are particularly interesting because they are more versatile and diverse than the other multicomponent reactions. The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond-forming processes available, their functional group tolerance and the high levels of chemo-, regio- and stereoselectivity often observed. The outstanding position of IMCRs can be traced back to the exceptional reactivity of the functional group of the isocyanides. No other functional group reacts with both nucleophiles and electrophiles on the same atom, leading to the so-called R-adduct. Winterfeldt et al. were the first to describe the reactions of DMAD with isocyanides in their pioneering work published in 1969.177a A large number of IMCRs were described by Dömling in his reviews.177b,c

4.3.1 Synthesis of Five-Membered Heterocycles with One Heteroatom

4.3.1.1 Nitrogen-Containing Heterocycles

The zwitterion generated by the addition of alkyl(aryl) isocyanides 531 to DMAD was trapped by benzoyl chloride (532) to yield functionalized 2,5-dihydro-1H-pyrroles 533 (Scheme 139). However, in the presence of electron-withdrawing groups at the para-position of the benzoyl chloride, tetrasubstituted furans 534 were isolated instead.178

The 1:2 zwitterion, generated by the addition of triphe- nilphosphine to DMAD, was protonated by trifluoroacetic acid and subsequently attacked by isocyanide and water in a pseudo-seven-component diastereoselective reaction giving compounds 535 with three stereogenic centers and a phosphorane group in good yields (Scheme 140).179

Scheme 140

The three-component reaction of the zwitterion generated from DMAD and isocyanides with various quinoneimides such as 536 and 538 afforded the corresponding γ-spiroiminolactams 537 and 539 in good yields (Scheme 141).180

4.3.1.2 Oxygen-Containing Heterocycles

In 2004, the three-component reaction of cyclohexyl isocyanide with DMAD and various aromatic or aliphatic aldehydes 540 was reported to have gone to completion in less than two hours when carried out in ionic liquids, affording the expected heterocycles 542 in high yields.181 Water was reported as a novel reaction medium for the synthesis of highly functionalized 2-amino furan derivatives 542, via the coupling of aldehydes 540, with DMAD and cyclohexyl isocyanide (Scheme 142).182 3-Aromatic aldehydes,183a formylindoles183b and quinoline-3-carbaldehydes183c were also found to undergo smooth condensation with the zwitterions derived from isocyanides and DMAD either in benzene or in acetonitrile to give the corresponding furanyl derivatives in good yields.
In addition, the reaction of 1:1 zwitterionic intermediates generated in situ from either tert-butyl isocyanide or cyclohexyl isocyanide and DMAD with 3-formylchromones was reported to lead to chromenylfurandicarboxylates or to cyclopenta[b]chromenedicarboxylates, depending on the nature of the chromone 6-position substituent (Scheme 143).184

The reaction of alkyl isocyanides with DMAD, in the presence of pyridine-containing carbonyl compounds or or, led to the stable products or in excellent yields (Scheme 144).185

The reaction of DMAD and isocyanides with vicinal tricarbonyl systems and produced highly substituted furan derivatives and respectively, whereas when the diphenyl triketone was used, the pyran derivative was the only reaction product (Scheme 145).186

The zwitterion formed from an alkyl isocyanide and DMAD reacted with acetic anhydride or phthalic anhydride to form methylfurans or benzo-fused spirolactones or in relatively good yields, at room temperature and without using a catalyst (Scheme 145).187

The reaction between alkyl isocyanides and phenanthrene-9,10-dione or dione in the presence of DMAD was found to afford γ-dispiroiminolactones and respectively, in high yields (Scheme 146).188

1,2-Benzoquinones are inert towards isocyanides and electron-deficient alkynes at ambient temperature; however, they readily react with the zwitterions generated from these two. For example, the reaction of cyclohexyl isocyanide and DMAD generated a zwitterion which, on
Scheme 145

Scheme 146
interception with 3,5-di-tert-butyl-1,2-benzoquinone (565), yielded a regiosomeric mixture of spiroiminolactones 566 and 567 reacting exclusively with the carbonyl functionalities of the quinone (Scheme 146). Nair et al. found that DMAD could be induced to add itself to the most electron-deficient carbonyl of various benzoquinones in the presence of some nucleophilic initiator, such as triphenylphosphine or an isonitrile. In particular, benzoquinone 568 underwent cyclization in the presence of cyclohexyl isocyanide and DMAD to afford the iminolactone 569 in 92% yield (Scheme 146). Isocyanides reacted smoothly with DMAD in the presence of hexachloroacetone (570) to produce the furan derivatives 571 in high yields (Scheme 147). Benzoyl chlorides 572 with electron-withdrawing substituents at the para-position led to tetrasubstituted furans 573 (Scheme 147).

A three-component condensation reaction between an isocyanide, DMAD and 2-bromo-1-(4-bromophenyl)ethanone (574) efficiently provided fully substituted iminolactones 575 in high yields in a one-pot condensation reaction without any activation or modification (Scheme 147).

Moreover, a new and efficient method for preparing electron-poor imides 577 and fully substituted furans 578 from triphenylphosphine, 1,1,3,3-tetramethylbutyl isocyanide, DMAD and benzoic acid (576) under neutral conditions has been reported (Scheme 147).

The reaction between alkyl(aryl) isocyanides, DMAD and alkyl cyanoformates 579 under solvent-free conditions led to furan derivatives 580 in high yields (Scheme 147). The highly reactive 1:1 adducts produced from the reaction between DMAD and alkyl isocyanides were trapped by benzoyl cyanide derivatives 581 to afford furan derivatives 582 in good yields (Scheme 147).

### 4.3.2 Synthesis of Six-Membered Heterocycles with One Heteroatom

#### 4.3.2.1 Nitrogen-Containing Heterocycles

A three-component condensation reaction between an isocyanide, DMAD and triphenylphosphonium bromide 583 efficiently provided fully substituted N-alkyl-2-triphenylphosphoranylidene glutarimides 584 in a one-pot reaction without any activation (Scheme 148).
Li et al.\textsuperscript{199} reported a facile, efficient and regioselective synthetic approach for the construction of highly substituted pyridine-2(1\textit{H})-ones 586 and allenyl derivatives 587. Their synthesis involved a one-pot three-component reaction between \textit{N}-arylidene-2-cyanoacetohydrazides 585, DMAD and isocyanides (Scheme 149).

### 4.3.2.2 Oxygen-Containing Heterocycles

Functionalized dihydroindenopyrans 589 were synthesized from the reaction of alkyl(aryl) isocyanides, DMAD and indane-1,3-dione (588; Scheme 150).\textsuperscript{200}
Fused heterocycles were prepared in a one-pot three-component reaction of alkyl isocyanide, DMAD and α-tropolone (590). The reaction proceeded smoothly at room temperature and under neutral conditions to afford tropolone derivatives 591 in good to high yields (Scheme 150).201

Chemoselective reaction of isocyanides with DMAD in the presence of relatively strong cyclic C–H acids 592, such as 4-hydroxy-6-methyl-2H-pyran-2-one or 4-hydroxycoumarin, led to a facile synthesis of highly functionalized chromeno or pyrano derivatives 593, respectively, in good yields (Scheme 150).202

A three-component reaction of an isocyanide, DMAD and tetronic acid (594) in dichloromethane at room temperature afforded 4H-furo[3,4-b]pyran derivatives 595 (Scheme 150).203

The reaction between alkyl or aryl isocyanides and DMAD with 3-hydroxy-1H-phenalene-1-one produced a vinylisonitrilium cation, which subsequently underwent an addition reaction with the conjugate base of the 3-hydroxy-1H-phenalene-1-one to produce biologically interesting compounds 597 in moderate to fairly good yields (Scheme 150).204

The one-pot, three-component condensation reaction of alkyl isocyanides with DMAD in the presence of phthalhydrazide 610 was successfully applied to the synthesis of compounds 611 (Scheme 151).211

### 4.3.3 Synthesis of Six-Membered Heterocycles with Two Heteroatoms

#### 4.3.3.1 Nitrogen-Containing Heterocycles

Reaction of alkyl isocyanides, DMAD and dimethylurea (604) in glucose provided novel 2,6-dioxohexahydropyrimidines 605 (Scheme 151).208

A one-pot, three-component synthesis of pyrimidine derivatives 607, from the reaction of isocyanides, DMAD and N-(2-heteroaryl)amides 606, was also reported (Scheme 151).209

A three-component reaction of isocyanides, DMAD and N-(2-pyridyl)amides 608 led to the synthesis of the corresponding 4H-pyrido[1,2-a]pyrimidines 609 (Scheme 151).210

The one-pot, three-component condensation reaction of alkyl isocyanides with DMAD in the presence of phthalhydrazide 610 was successfully applied to the synthesis of compounds 611 (Scheme 151).211

**Scheme 151**

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4.4 Carbenes

Over the past half-century and specifically ever since Bre-slow’s original demonstration of the role of thiazole car-benes as nucleophilic catalysts in enzymatic reactions,\textsuperscript{212} the intensive studies of N-heterocyclic carbenes (NHCs) as reaction intermediates by Wanzlick\textsuperscript{213} and the first iso-lation of stable diaminocarbene by Arduengo and co-workers in 1991,\textsuperscript{214} these species have attracted consider-able attention. Their role as excellent ligands for transition met-als\textsuperscript{215} and their ability to catalyze various carbon–carbon coupling reactions, namely benzoin condensation, transesterification\textsuperscript{216} and Stetter reaction,\textsuperscript{217} have contrib-uted significantly to the tremendous interest in N-hetero-cyclic carbenes.

A straightforward preparation of 3-aminofuran deriva-tives \textsuperscript{614} via multicomponent reactions of thiazole car-benes \textsuperscript{612}, aldehydes \textsuperscript{613} and DMAD was reported. In this process, the thiazole carbenes, generated in situ from thiazolium salts, reacted with aldehydes and DMAD to af-ford the substituted furans \textsuperscript{614} in moderate to good yields. Eight substituted thiazolium salts were employed as car-bene precursors in the reaction. In addition to aryl alde-hydes, α,β-unsaturated aldehydes \textsuperscript{615} were also investigated and found to be applicable to this reaction (Scheme 152).\textsuperscript{218}

A three-component synthesis of the unique polysubstitut-ed furan-fused 1,4-thiazepines \textsuperscript{618} from thiazolium salts \textsuperscript{612}, 1,1-disubstituted ketenes \textsuperscript{617} and DMAD was also reported (Scheme 152).\textsuperscript{219}

Nair et al.\textsuperscript{220} described the reaction of carbenes \textsuperscript{620} with DMAD and aromatic aldehydes \textsuperscript{619}, which proceeded smoothly to deliver four-component acyclic adducts \textsuperscript{621} in good yields (Scheme 153).

Scheme 153

\begin{align*}
\text{ArCHO} & \xrightarrow{\text{NaH, THF}} \text{ArCHO} \\
\text{ArCHO} & \xrightarrow{\text{NaH, THF}} \text{ArCHO} \\
\text{ArCHO} & \xrightarrow{\text{NaH, THF}} \text{ArCHO} \\
\text{ArCHO} & \xrightarrow{\text{NaH, THF}} \text{ArCHO}
\end{align*}

1-Thiocarbamoylimidazo[1,5-\textit{a}]pyridinium inner salts \textsuperscript{624}, which were obtained readily from the addition of the C,N-substituted heterocyclic carbenes, imidazo[1,5-\textit{a}]pyridin-1-ylidenes \textsuperscript{622}, to isothiocyanates \textsuperscript{623}, are powerful ambident nucleophilic zwitterions. When treat-ed with DMAD, they behaved exclusively as sulfur nu-cleophiles to afford fully substituted thiophenes \textsuperscript{625} in excellent yields, providing an efficient orthogonal synthe-sis of polyfunctionalized thiophenes not easily obtained by other chemical means (Scheme 154).\textsuperscript{221}

Pan et al.\textsuperscript{222} reported a multicomponent reaction using both N-heterocyclic carbenes and substituted phthalalde-hydes. The imidazo[1,5-\textit{a}]pyridine carbenes \textsuperscript{626} reacted with phthalaldehydes \textsuperscript{627} and DMAD to produce diaste-reomeric benzo[\textit{d}]furo[3,2-\textit{b}]azepine derivatives \textsuperscript{628} and \textsuperscript{629}. The carbene underwent a nucleophilic addition to the phthalaldehyde to form a dipolar intermediate which then underwent [3+2] cycloaddition with DMAD (Scheme 155).

Scheme 152
4.5 Miscellaneous Reactions

Chaniyara et al., in continuation of their research into new bifunctional DNA-crosslinking agents for antitumor application, used benzothiazole derivative 630 and DMAD in order to gain access to diesters 631 and ultimately, after two steps, to the bis(alkylcarbamate) derivatives 632 for antitumor studies (Scheme 156).

In 2011, an efficient synthesis of iminothiopyran and isothiochromene derivatives 635 and 637, via one-pot reactions between DMAD, aryl isothiocyanates 633 and enaminoes 634 and 636 in dichloromethane at room temperature, was described (Scheme 157). The zwitterion formed by the reaction of dimethoxycarbene and DMAD added efficiently to one of the carbonyl groups of 1,2-dicarbonyls and anhydrides to generate dihydrofurans and spirodihydrofurans 639–642 in good yields. In many cases, the carbene is inserted into the carbon–carbon bond of the dione to yield masked vicinal tricarbonyl systems (Scheme 158). Ding et al. reported a 1-methylimidazole-catalyzed reaction of DMAD with in situ generated ketenes by the action of Hunig’s base on acyl halides (Scheme 159).
5 Conclusion

In conclusion, we have presented here an overview of the recent progress in the chemistry of DMAD as a unique reagent with significant application in organic synthesis and medicinal chemistry. It also plays a pivotal role in many diverse synthetic pathways. The high synthetic potential of this very accessible reagent has resulted in numerous applications, especially for the synthesis of complex heterocyclic structures. The increasing number of citations clearly shows the great importance of this simple but powerful reagent, and it is believed that additional new and useful DMAD chemistry will be discovered in the future.

References

(1) Sahoo, M. K. Synlett 2007, 2142.