SYNLETT
Spotlight 208

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Dimethyl Acetylene Dicarboxylate

Compiled by Manoj Kumar Sahoo

Manoj Kumar Sahoo obtained his B.Sc. (Govt. College, Angul, Orissa) and M.Sc. (Utkal University Chemistry Department, India). After qualifying via the CSIR-National eligibility test (NET) for a research fellowship, he joined the research group of Dr. N. P. Argade for a Ph.D. at National Chemical Laboratory, Pune. In 2004, he passed the DRDO-Scientist Eligibility Test (SET) and moved to Defence Research and Development Establishment, Gwalior where he is currently working under the supervision of Dr. R. C. Malhotra. His research interests include total synthesis of bioactive natural products, development of new methodologies, decontamination of chemical warfare agents and medicinal chemistry.

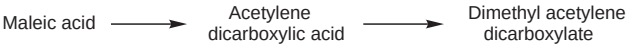
Process Technology Development Division, Defence Research and Development Establishment, Jhansi Road, Gwalior, 474002 (MP) India
E-mail: mks9@rediffmail.com

Dedicated to Dr. N. P. Argade, OCS Division, NCL, Pune

Introduction

Dimethyl acetylene dicarboxylate (DMAD) is an electron-deficient alkyne diester widely used as dienophile and dipolarophile in cycloaddition reactions. It is used as a standard in Diels–Alder reactions to check the efficiency of various dienes. It can undergo [2+2] cycloaddition reactions,[1] 1,3-dipolar cycloaddition with 1,3-dipoles, for example azides,[2] diazoalkanes, nitrile oxide, carbonyl ylides,[3] and azomethine ylides. Besides it is also a powerful Michael acceptor and can accept various nucleophiles, for example nitrogen, oxygen, carbon, sulfur, and phosphorus.

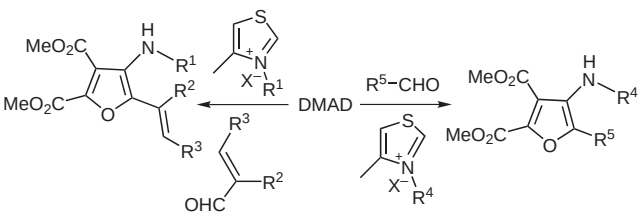
DMAD is inexpensively available, and it can be prepared from maleic acid via a bromination–dehydrohalogenation sequence to furnish acetylene dicarboxylic acid,[4] which, upon esterification with methanol using sulfuric acid, gives dimethyl acetylene dicarboxylate.[5]



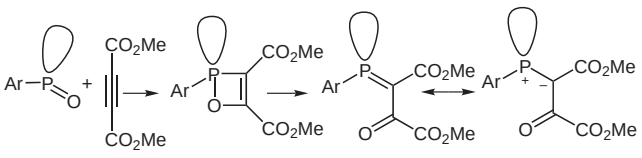
Scheme 1

Abstracts

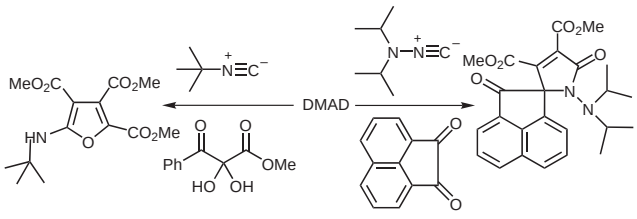
(A) N-Heterocyclic carbenes undergo multicomponent reactions with DMAD and different types of aldehydes (aromatic, α,β-unsaturated) to produce substituted furans.[6] The nature of the product depends on the nature of the N-heterocyclic carbene used and on the type of aldehyde.



(B) An inverse Wittig-reaction-type protocol was demonstrated where cyclic 2,4,6-trialkylphenyl phosphineoxides undergo [2+2] cycloaddition with DMAD to furnish spirocyclic oxaphosphate intermediates which afford a stabilized phosphonium ylide.[7]

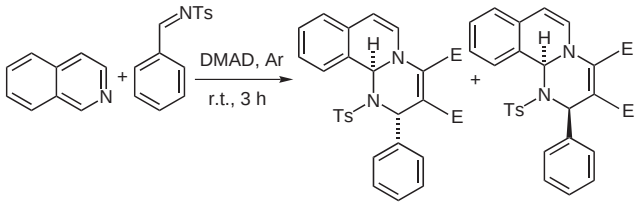


(C) Diisopropylamino isocyanide reacts with DMAD to generate zwitter ions which react with a variety of dicarbonyl and vicinal tricarbonyl compounds affording substituted 1-aminopyrrolin-2-ones and tetrasubstituted furans under mild conditions.[8]

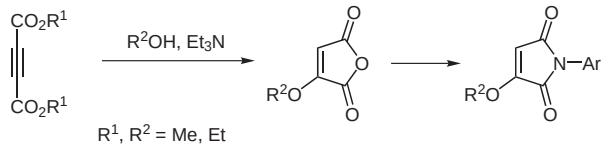


SYNLETT 2007, No. 13, pp 2142–2143
Advanced online publication: 12.07.2007
DOI: 10.1055/s-2007-984894; Art ID: V21107ST

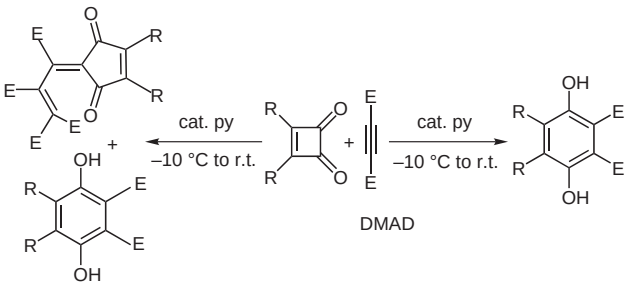
(D) Diastereoselective synthesis of 2*H*-pyrimido[2,1-*a*]isoquinolines is reported through a novel three-component reaction involving DMAD, isoquinoline, and *N*-tosyl imines.[9] 1,4-Dipoles are generated by reaction of isoquinoline with DMAD and react readily with *N*-tosylimine to produce pyrimidoisoquinoline.



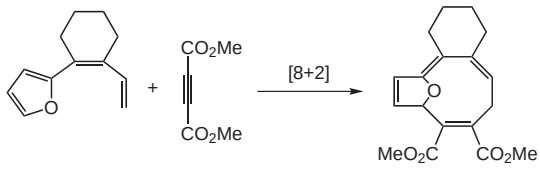
(E) Alkoxy maleimides/maleic anhydrides can be synthesized from DMAD through base-induced oxa-Michael addition of alcohols to DMAD and hydrolysis followed by cyclization.[10] This is a very simple and straightforward method for the synthesis of alkoxy maleic anhydrides as well as maleimides which are important intermediates in organic synthesis.



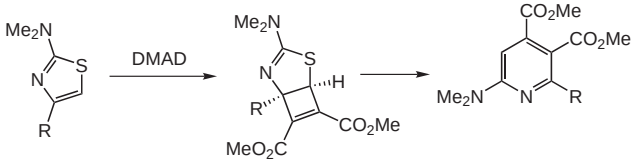
(F) When pyridine reacts with DMAD, zwitterions are generated. Those have been engaged in a novel strategy with cyclobutene diones for the selective synthesis of highly substituted benzene and cyclopentene dione derivatives.[11] The selectivity is merely dependent on the concentration of pyridine.



(G) Couplings of dienyl furans with DMAD proceed via [8+2] cycloaddition to afford furan-bridged 10-membered ring systems as single diastereomers.[12] These [8+2] cycloadducts undergo electrophilic reactions selectively at the enol ether alkene to give substituted 10-membered rings.



(H) Various 2-aminothiazoles undergo [2+2] cycloaddition reactions with DMAD at the C–C double bond of the thiazole ring to generate fused cyclobutene intermediates.[13] Thermal disrotatory ring opening of the cyclobutene intermediates furnished tetrasubstituted pyridines in good yield.



References

(1) Cook, A. G. *Enamines: Synthesis, Structure, and Reactions*, 2nd ed.; Cook, A. G., Ed.; Dekker: New York, **1988**, 384.
(2) Prabhakar, J. K.; Shanmugasundaram, P.; Ananthnarayanan, C.; Ramakrishnan, V. T. *Indian J. Heterocycl. Chem.* **1992**, *1*, 157.
(3) Paquette, L. A.; Shen, C. C. *J. Am. Chem. Soc.* **1990**, *112*, 1159.
(4) Abbot, T. W.; Arnold, R. T.; Thompson, R. B. *Org. Synth., Coll. Vol. II* **1943**, 10.
(5) Huntress, E. H.; Lesslie, T. E.; Bornstein, J. *Org. Synth., Coll. Vol. IV* **1963**, 329.
(6) Ma, C.; Ding, H.; Wu, G.; Yang, Y. *J. Org. Chem.* **2005**, *70*, 8919.
(7) Keglevich, G.; Kortvelyesi, T.; Forintos, H.; Vasko, A. G.; Vladiszlav, I.; Toke, L. *Tetrahedron* **2002**, *58*, 3721.
(8) (a) Nair, V.; Mathen, J. S.; Viji, S.; Srinivas, R.; Nandakumar, M. V.; Varma, L. *Tetrahedron* **2002**, *58*, 8113. (b) Nair, V.; Deepthi, A. *Tetrahedron Lett.* **2006**, *47*, 2037.
(9) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Bhadbhade, M. M.; Gonnade, R. C. *Org. Lett.* **2002**, *4*, 3575.
(10) Sahoo, M. K.; Mhaske, S. B.; Argade, N. P. *Synthesis* **2003**, 346.
(11) Nair, V.; Pillai, A. N.; Beneesh, P. B.; Suresh, E. *Org. Lett.* **2005**, *7*, 4625.
(12) Zhang, L.; Wang, Y.; Buckingham, C.; Herndon, J. W. *Org. Lett.* **2005**, *7*, 1665.
(13) Mateo, A.; Jose, C.; Pastor, A.; Sanchez-Andrada, P.; Bautista, D. *J. Org. Chem.* **2006**, *71*, 5328.