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Received: 30.07.2014 
Accepted after revision: 09.10.2014 
Published online: 10.11.2014 

Abstract The (3+2)-cycloaddition reaction involving oxyallyl cations has proven to be a versatile and efficient approach for the construction of five-membered carbo- and heterocycles, which are prevalent frameworks in natural products and pharmaceuticals. The following article will provide a brief summary of recent disclosures on this process featuring chemo-, regio- and diastereoselective oxyallyl cycloadditions with both electron-rich and electron-deficient 2π partners.

1 Introduction

The chemistry of oxyallyl cations has been a fertile ground for the design and development of powerful reaction processes. Cycloaddition reactions, in particular, are highly valued for their synthetic utility. This one-step process represents a facile approach to construct a variety of ring types and increase molecular complexity.1 Both (4+3)- and (3+2)-cycloaddition modes of oxyallyl cations are known under thermal conditions and have been investigated for decades.2 As shown in Scheme 1, the (4+3) cycloadditions with dienes provide access to seven-membered carbocycles and have been incorporated in a number of elegant syntheses of natural products.3

The (3+2) cycloaddition of oxyallyl cations with a 2π partner, although less intensively investigated compared to the (4+3) counterpart, remains an attractive research topic. In this [2π+2π] process (Scheme 1), orbital symmetry considerations indicate that a concerted mechanism is not allowed under thermal conditions. Instead, the reaction can proceed via a step-wise pathway, which makes it reasonable to regard this process as a formal cycloaddition. Generally, the reaction would start with electrophilic bond formation of the oxyallyl cation with one atom of the 2π partner to give a zwitterionic intermediate. The cation on the other atom of the 2π partner may then be captured by either the O or C atom on the oxyallyl moiety to furnish five-membered rings (e.g., cyclopentanones), which are ubiquitous in nature as well as useful building blocks.4,5

The (3+2) cycloaddition possesses several different features relative to the (4+3) process. First, the (4+3) cycloaddition typically provides carbocycles with the formation of two C–C bonds. In the case of (3+2) annulations, the oxygen
2 Heteroatom-Substituted Oxyallyl Cations

Heteroatom-substituted oxyallyl cations have been extensively studied to participate in dipolar cycloadditions since the last century.\textsuperscript{10} Although they are commonly utilized in (4+3) cycloadditions, Kuwajima demonstrated a highly regio- and stereoselective (3+2) cyclopentannulation by employing sulfur-substituted oxyallyl cations.\textsuperscript{11,12}

As shown in Scheme 2, the 3-(alkylthio)-2-siloxyallyl cation \textit{7}, which was generated from allyl acetate \textit{6} by the treatment of EtAlCl\textsubscript{2} or AlCl\textsubscript{3}, was able to react with various kinds of olefins including enol ethers, vinyl sulfides, styrenes, and trialkylolens to afford the corresponding cyclopentanones in good yields (e.g., \textit{9-12}). Notably, these reactions proceeded in almost complete regioselectivity by forming the sterically more hindered isomers as the predominant product in every case. Moreover, surprisingly high stereoselectivity was observed in the reaction of \textit{6} with vinyl sulfides. As shown in Scheme 3 (a), both the \textit{E}- and the \textit{Z}-isomers of 2-(benzylthio)but-2-ene (\textit{13}) afforded the same diastereomer \textit{14} as the major product. This may be due to the rapid geometric isomerization between (\textit{E})-\textit{13} and (\textit{Z})-\textit{13} under the influence of EtAlCl\textsubscript{2} (Scheme 3, b). To further rationalize the origin of diastereoselectivity, chair-like six-membered transition-state models \textit{TS-1} and \textit{TS-2} were also proposed, which featured the orbital interaction between the sulfur atom of the vinyl sulfide and the \(\alpha\)-carbon of the oxyallyl cation (Scheme 3, b). Since \textit{TS-2} contains a 1,3-diaxial steric repulsion between the \(\beta\)-methyl group of (\textit{Z})-\textit{13} and the siloxy group of the oxyallyl cation, this cycloaddition would be slower than that of (\textit{E})-\textit{13}. The authors propose that the cycloaddition reactions of both (\textit{E})-\textit{13} and (\textit{Z})-\textit{13} proceed through \textit{TS-1} in a step-wise manner to first form the C–C bond distal to both sulfur atoms. This generates an intermediate that proceeds to forge the second C–C bond without further bond rotation to give \textit{14} as the major product.
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Scheme 3 (a) Stereoselective cycloaddition using vinyl sulfides (E)-13 and (Z)-13. Reagents and conditions: CH2Cl2, –45 °C. (b) Proposed transition-state model resulting in high stereoselectivity.

Due to its wide range of applicability, as well as the high selectivity, the above (3+2)-cycloaddition strategy was successfully incorporated in the total synthesis of (–)-coriolin in a following report by the same group.13,14 As shown in Scheme 4, the ABC triquinane ring system of coriolin was constructed via two successive (3+2)-cycloaddition reactions. Treatment of benzyl ether 16 with vinyl sulfide 6 in the presence of EtAlCl2 provided a 1:1 mixture of annulated products 17 and 18 in diastereomERICally pure forms. The crude mixture was then subjected to a desulfurization-hydrogenation sequence to give bicyclic ketone 19 in a yield of 73% for three steps. The use of ethanethiol and chlorotrimethylsilane transformed 19 to vinyl sulfide 20. Subsequently, 20 underwent a second (3+2) cycloaddition with 21 to install the A-ring unit of (–)-coriolin, which was followed by the TBAF-mediated β-elimination of ethanethiol to give enone 23, which was eventually taken on to (–)-coriolin.

The heteroaromatic oxidopyrylium species, which are widely used in (5+2) dipolar cycloadditions,15 may also act as stabilized oxyallyl cations. For example, Porco and co-workers demonstrated that the oxidopyrylium betaine 25 or 26 derived from excited-state intramolecular proton transfer (ESIPT) of 3-hydroxyflavone 24 could undergo (3+2) cycloaddition with electron-deficient methyl cinnamate (27) (Scheme 5, a).16 The resulting (3+2)-cycloadduct 28 could be further transformed into methyl rocaglate with an α-ketol rearrangement/reduction sequence. The (3+2) photocycloaddition of 24 and 27 may also proceed enantioselectively by using functionalized TADDOL derivative 29 as chiral Brønsted acids (Scheme 5, b).17 As a result, (–)-methyl rocaglate was obtained in 94% ee with a similar strategy as mentioned above. It was proposed that the hydrogen bonding interaction between the phenoxide oxygen of oxidopyrylium 25 or 26 and the free hydroxyl group of TADDOL derivative 29 may play an important role in stabilizing the oxyallyl intermediate, as well as controlling the stereofacial approach of the 2π partner 27. Notably, the above (3+2) photocycloaddition involving oxidopyrylium ions allowed facile access to several other rocaglate natural products including rocaglaol, rocaglamide, silvestrol, episilvestrol, as well as several derivatives (e.g., 30–32) (Figure 1).18
Figure 1 Rocaglate natural products and derivatives synthesized by employing (3+2) photocycloaddition as a key step.
In addition to the above heteroatom-substituted oxallyl cations, Hsung, Houk, Krenske, and co-workers recently reported an unexpected (3+2) cycloaddition of nitrogen-stabilized oxallyl cations with the electron-deficient carbonyl groups of a tethered dienone.20 Despite the fact that other oxallyls like 44 do undergo intramolecular (4+3) cycloadditions (Scheme 7, a),21 the treatment of allene amide 47 with dimethyldioxirane (DMDO) proceeds only through the (3+2) pathway to generate oxabicyclic species 49 (Scheme 7, b). The density functional theory calculations (DFT) on current system indicated a transition state that features simultaneous interactions of the oxallyl LUMO with the carbonyl π and lone-pair orbitals. They termed this process as ‘hemipseudopericyclic’, which is halfway between purely pericyclic and purely pseudopericyclic reactions. Further investigation on (3+2) cycloadditions was conducted theoretically and experimentally by employing various carbonyl sources including aldehydes, ketones, esters, and amides. Only tethered ketones with electron-rich substituents are amenable in this process (e.g., 51–54).

3 Oxyallyl Cations Derived from Substituted Ketones

As mentioned earlier, the use of α,α-dihalo ketones as oxallyl sources has been well established since the 1970s upon the treatment with reducing agents such as Fe$_2$(CO)$_9$, Fe(CO)$_5$, and Zn/Cu couple.22 Other disubstituted ketones, in principle, may also produce oxallyl cations under appropriate reductive conditions. For example, Hardinger showed that bis(sulfonyl) ketone 55 could generate oxallyl intermediate 56 upon treatment with Fe(CO)$_5$, and TiCl$_4$.23 Subsequent (3+2) trapping of 56 with alkenes would furnish the corresponding cyclopentanones (e.g., 59 and 60). Moreover, electron-rich alkynes also turned out to be compatible 2π partners (e.g., 61 and 62) (Scheme 8).
In addition to disubstituted ketones, monosubstituted ones may also act as oxyallyl precursors. Recently, Wu and Hughes reported a regio- and diastereoselective (3+2) annihilation of electron-rich 3-substituted indoles 63 with α-halo ketones 64 (Scheme 9). This method provides easy access to highly functionalized cyclopenta- or cyclohexa-fused indoline compounds 65, which are common structures of many natural products. Impressive regiochemical control was observed in the cycloaddition employing acyclic α-halo ketones (e.g., 68, 69).

It is also interesting that the regioisomeric, acyclic α-halo ketones 71 and 72 both afforded 73 as the major product with high diastereoselectivity (>20:1) (Scheme 10, a). Notably, a common O-alkylated intermediate 77 was isolated (Scheme 10, b), suggesting that the reactions of α-halo ketones 71 and 72 may proceed via the same hydroxyallyl intermediate 76. As illustrated in their proposed mechanism (Scheme 10, b), the first C–C bond formation between hydroxyallyl 75 and N-benzylskatole (70) generates intermediate 76, which possesses a weak C–OH interaction. Removal of the proton with carbonate base at this point would furnish the observed intermediate 77. Alternatively, the pronated form 77 could re-dissociate and alkylate at carbon to generate the kinetically favored cycloadduct 74, which can then isomerize to the thermodynamically favored product 73. The above rearrangements, as well as the kinetic and thermodynamic properties of 73 and 74 are in accordance with experimental observations and computational studies.
Furthermore, DFT calculations in the above (3+2) cycloaddition did raise the question of whether hydroxyallyl cation 75 or its zwitterionic form is the real reactive species. While other cycloaddition reactions are thought to proceed through zwitterionic oxyallyl cations, DFT studies on the current system predicted that a pathway for the formation of product 74 via hydroxyallyl 75 is a lower-energy route than that emanating from the corresponding zwitterionic form. Harmata and Schreiner have also observed similar divergent reactivity between oxyallyl and hydroxyallyl cations before.

The synthetic potential of this (3+2)-cycloaddition process was demonstrated by a concise synthesis of the core structures of vincorine, isocorymine, and aspidophylline A. As shown in Scheme 11, Baeyer–Villiger oxidation of the (3+2)-cycloadduct 78 afforded tertracyclic lactone 80 in 70% yield. Compound 80 was then subject to a debenzylation–oxidation sequence to give hemiaminal 82. Cleavage of the phthalimide group with MeNH₂ liberated the amine, which spontaneously closed to furnish the pyrrolidine ring of pentacycle 84. Compound 84 maps well to the cores of vincorine and isocorymine. By employing a similar strategy, pentacycle 85 was obtained from (3+2)-cycloadduct 79, which provided a good starting point for the synthesis of aspidophylline A.
4 Oxyallyl Cations from Interrupted Nazarov Cyclizations

The Nazarov cyclization entails the 4π-electrocyclic ring closure of a conjugated pentadienyl cation 87, which is derived from dienone 86 upon treatment with acids or irradiation, to form a cyclopentenyl cation 88 (Scheme 12). Conventionally, a β-elimination of the adjacent proton would furnish cyclopentenone 89. In the interrupted Nazarov reaction, however, the reactive intermediate 88 may be intercepted by a 2π partner (an alkene or alkyne) to undergo a (3+2) cycloaddition at a rate competitive to the normal elimination route.

In 1998, West and co-workers reported the first intramolecular (3+2) cycloaddition of olefins and Nazarov-derived oxyallyls (Scheme 13). As shown in Scheme 13, diquinane 94 was obtained from achiral trienone 93. It was presumed that activation of trienone 93 generated the reactive cyclopentenyl intermediate 95, which underwent intramolecular (3+2) trapping by the proximal olefin to afford tricyclic compound 96. It is noteworthy that the oxygen atom of the oxyallyl moiety preferentially participated in the annulation with the formation of a C–O bond. Upon aqueous workup, the structurally strained enol moiety was hydrolyzed to give hemiketal 94 with selective protonation from the convex face.

Afterwards, the same group found allylsilanes and vinyl sulfides to be amenable in the intermolecular mode of (3+2) cycloaddition involving Nazarov-derived oxyallyls (Figure 2). Complete regioselectivity was observed in the reactions employing allylsilanes as 2π partners (e.g., 97), since allylsilane selectively attacks the least substituted end of unsymmetrically substituted oxyallyl cations. This is in accordance with Noyori’s earlier observation that regioselectivity is predicated on pathways intercepting the more stabilized enolate.

As mentioned earlier, irradiation may also promote the formation of oxyallyl species. Stephenson and Porco recently demonstrated a tandem dienone photorearrangement-cycloaddition reaction of alkyne-tethered cyclohexadienones (Scheme 14, a) to produce highly complex architectures. It was surmised that photochemical rearrangement of substituted dienone 101 would lead to the formation of...
oxyallyl cation 103 via the Nazarov-type cyclopentenone 102. The reactive 1,3-dipole 103 then underwent intramolecular (3+2) cycloaddition with tethered alkyne to form cycloadduct 104. The resulting strained cyclic alkene 104, which turned out to be unstable during purification, could be further elaborated by either inter- (Scheme 14, a) or intramolecular cycloaddition (Scheme 14, b) with furans or a nitrile oxide (via oxime) to generate polycyclic, bridged frameworks. Impressively, in the reaction to yield compound 112 (Scheme 14, b), four rings and six stereogenic centers were generated in this single process.

While the reactive cyclic oxyallyl cations 88 have usually been derived from dienones 86 in traditional Nazarov reactions, they may also be generated from different sources (Scheme 15). For example, Burnell and co-workers reported in 2010 that treatment of allenyl vinyl ketone 113 with BF₃·OEt₂ could lead to the cyclic oxyallyl cation 114 through Nazarov cyclization. In the presence of appropriate olefins, the reactive intermediate 114 may be captured in the (3+2) cycloadditions. As shown in Scheme 15, electron-rich styrenes reacted smoothly to afford bridged (3+2) cycloadducts 116, 117, and 118 as single diastereomers. When aliphatic dienes were employed, the reaction provided a mixture of (3+2) and (4+3) products regioselectively and diastereoselectively (e.g., 119–122). It was indicated that the proportion of (3+2) to (4+3) products is highly dependent on the diene substituents.

In addition, Yadav and co-workers recently described (3+2) trapping of oxyallyl cations generated from homocyclization of 2-((tert-butylidiphenylsilylmethyl) cyclopropyl vinyl ketones 123 with allylsilanes (Scheme 16). This reaction was proposed to begin with the cleavage of σ C–C bond of the cyclopropyl ring on 123 to generate enolate 124. The positive charge was proposed to be stabilized by the proximal silyl group. Intermediate 124 then underwent ring-closure to give oxyallyl cations 125, which was then captured by allylsilanes in a (3+2) manner. Although the reaction proceeded with only moderate regioselectivity (e.g., 128/129 = 2:1), exclusive exo-cycloaddition was observed.

5 1-Alkylidene-2-oxyallyl Cations

In 2006, Fujita reported that the ring opening of alkylidenecyclopropanone acetal 130 under acidic conditions would produce the 1-alkylidene-2-oxyallyl cation 131 as an intermediate, which then undergoes (3+2) or (4+3) cycloadditions in the presence of olefins or dienes (Scheme 17). While the reaction of 131 with excess furan delivered a mixture of (4+3) cycloadducts and rearranged products from the (3+2) cycloadducts, the reaction with 2,3-benzofuran 132 furnished (3+2) cycloadduct 133 as a single regioisomer in 76% yield.

6 Summary and Outlook

The cycloaddition chemistry of oxyallyl cations represents a versatile process in the rapid generation of molecular diversity and complexity. The (3+2) cycloaddition, in particular, enables efficient construction of five-membered carbo- and heterocycles. As discussed above, a variety of oxyallyl cations are able to participate in this [2π+2π] process including those stabilized by heteroatoms and those
‘unstabilized’ species. Both classes of oxyallyl cations can either be cyclic or acyclic and may be derived from different sources. Due to the electrophilic nature of oxyallyl cations, electron-rich alkenes or alkynes are generally favorable 2π partners. However, electron-deficient 2π partners including α,β-unsaturated ketones (e.g., methyl cinnamate, methyl butynoate), carbonyl groups, and diethyl azodicarboxylate are also amenable in some cases.

The past twenty years have witnessed the development of many chemo-, regio- and diastereoselective oxyallyl (3+2) cycloadditions. Some of them have also been successfully employed in the elegant syntheses of natural products. Despite the impressive progress that has been made in the oxyallyl (3+2) cycloadditions, there is still plenty of room for improvement and further exploration. For example, the development of catalytic and enantioselective processes...
still remains relatively rare. It is our hope that this article will stimulate continued interest in the (3+2) cycladdition of oxallyl cations and make it a prolonged and prominent research area for developing novel methods used for natural product syntheses.

Acknowledgment

The NIH-NIGMS (1R01GM111638-01) and Dartmouth College are gratefully acknowledged for generous support of research in the current area.

References

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