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Cycloaddition of keteniminium with terminal alkynes toward cyclobuteniminium and their use in Diels–Alder reactions

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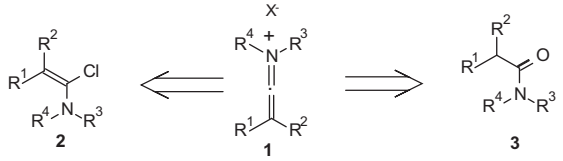
ABSTRACT

An efficient access to cyclobutanone derivatives has been developed via a 'one-pot' [2+2]/[4+2] sequence involving keteniminium and cyclobuteniminium salts as key intermediates. A broad range of novel cyclobuteniminium salts have been prepared via [2+2] cycloaddition of keteniminium salts and alkynes. The resulting [2+2] adducts were then further transformed by Diels–Alder reaction with various dienes to afford cyclobutanone derivatives in good yields. A density functional theory (DFT) based computational study has been performed to obtain insight into the nature of the cycloaddition reactions and to investigate the difference in reactivity of cyclobuteniminium salts. Finally, the usefulness of cyclobutanone derivatives has been demonstrated by ring expansion reactions affording lactone, lactame, and cyclopentanone derivatives.

Keteniminium salts **1**, which can be defined as nitrogen analogues of ketenes, are heterocumulenes with an arrangement of an iminium and an olefin (Scheme 1).[1] They are easily formed in situ from the corresponding α-chloro enamines **2**[2] or directly from amides **3**[3] using Ghosez's methodologies (Scheme 1) as well as by protonation of ynamides or ynamines.[4]

Although ketene intermediates have been extensively employed in various reactions which show the importance of such intermediates in organic synthesis,[1b,5] the use of keteniminium salts in [2+2] cycloadditions with unsaturated substrates has drawn considerable interest since they have shown higher reactivity, stability, and regioselectivity than the homologous ketenes.[1] Other reactions include [4+2] cycloadditions,[6] Pictet–Spengler cyclization,[7] and nucleophilic additions of ether oxygen or aryl sulfoxides followed by 'Claisen-like' rearrangements.[8] Another major advantage of keteniminium salts is the possibility to easily develop asymmetric variants by using chiral auxiliaries on the nitrogen atom (R^3, R^4, Scheme 1) such as chiral pyrrolidines.[1c,9] Among the different substrates used in [2+2] cycloaddition reactions, functionalized terminal or internal alkenes have been the most widely used substrates. A large number of intermolecular as well as intramolecular reactions have been reported to lead to



Scheme 1. Possible access to keteniminium salts.

functionalized cyclobutanones after hydrolysis of the corresponding iminium salts **4** (Scheme 2).[1,9,10] Other unsaturated substrates have been investigated, including dienes,[2] imines,[11] and in some rare examples allenes[1a] and alkyne[12] derivatives. The last class of substrates is highly interesting since cyclobuteniminium salts **5** are formed which can be further elaborated by Diels–Alder reactions to afford, after hydrolysis, versatile building blocks **6**.[13,14] Herein, we disclose the synthesis of a broad range of structurally diverse cyclobuteniminium salts, which were further used as dienophiles in Diels–Alder reactions with functionalized dienes.[15]

We first looked at the preparation of various dienophile intermediates **5** via [2+2] cycloadditions of keteniminium salts with acetylene or terminal alkynes and we were able to monitor these reactions by ^{1}H NMR spectroscopy. Keteniminium salts **1** were generated from the corresponding easily prepared amides using Ghosez's procedure.[3] Optimized conditions were found using 2,4,6-trimethyl pyridine (collidine) as the base and

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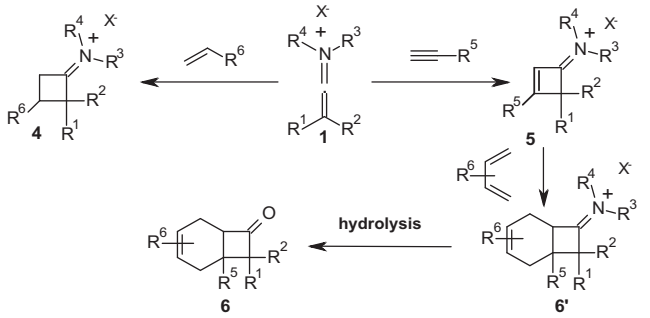
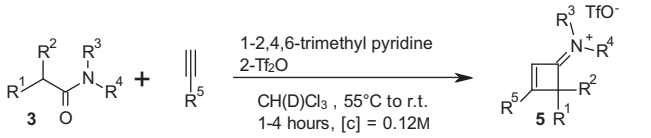


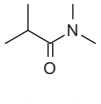
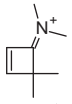
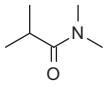
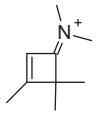
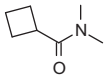
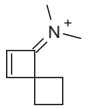
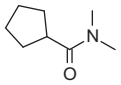
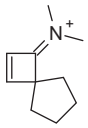
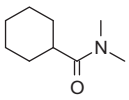
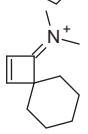
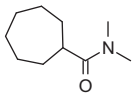
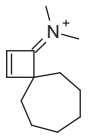
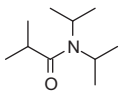
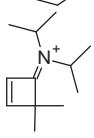
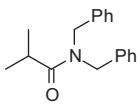
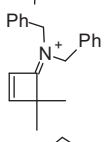
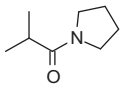
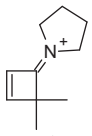
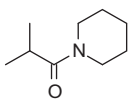
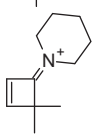
Scheme 2. [2+2] Cycloaddition of keteniminium salts with terminal alkenes or terminal alkynes followed by Diels–Alder.

trifluoromethanesulfonic anhydride in $CH(D)Cl_3$ with a concentration of 0.12 M in order to prevent a significant precipitation of the keteniminium salt. Reaction of the keteniminium salt derived from *N*,*N*-dimethyl isobutyramide with acetylene and 1-propyne afforded cyclobuteniminiums **5a** and **5b** cleanly with excellent conversion (95% and 68%, entries 1 and 2, Table 1) and good regioselectivity (3:1, entry 2, Table 1).[12] To our delight, amides with a cycloalkane (4-6-membered) in the α position (Table 1, entries 3–5) reacted smoothly with acetylene to give access to novel cyclobuteniminium salts **5c–e** bearing a spiro-center. The seven-membered ring derivative **5f** was obtained with lower conversion (45%, entry 6, Table 1), which can be explained by an important steric hindrance induced by the higher conformational flexibility of the cycloheptane compared to smaller ring sizes. To the best of our knowledge, it is the first time that spiro-cyclobuteniminium salts have been reported. Surprisingly, with the exception of piperidine derivative **5j** (Table 1, entry 10), other nitrogen substituents gave poor results and only traces of cycloadducts were formed (Table 1, entries 7–9). Subsequent Diels–Alder reactions with various dienes were directly performed using a solution of cyclobuteniminiums **5** (Table 2) in $CH(D)Cl_3$ without any purification step. Reaction of **5a** with highly reactive cyclopentadiene (Table 2, entry 1) proceeds smoothly at room temperature in 2 h and **6a** was isolated in good yield with perfect *exo* selectivity after hydrolysis of the iminium salt intermediate with aqueous NaOH solution (62%, over three steps, entry 1, Table 2).[12a,15,14d] It is noteworthy to mention that this methodology is a convenient three step 'one-pot' procedure.[16] Unfortunately, the reaction with substituted cyclobuteniminium salt **5b** did not afford cycloadduct **6b** even at higher temperature (Table 2, entry 2). Reaction between **5a** and less reactive 1,3-butadiene derivatives furnished the corresponding bicycles **6c–g** in good yields (53–66%, entries 3–6, Table 2) with very high regio- and stereoselectivities (Table 2, entries 4–6). However, 1-methyl-1,3-butadiene, 1,3-butadiene, and 3-ethyl-1,3-butadiene required a higher temperature (80 °C, sealed tube). To our delight, furan as well as 3-bromofurane reacted at 80 °C and cycloadducts **6h** and **6i** were isolated in very good yield (64 and 68%, entries 7 and 8, Table 2). We were also pleased to obtain complex building blocks **6j–l** (Table 2, entries 9–11) from spiro cyclobuteniminium **5c**/**5d** (Table 1) and cyclopentadiene or 2,3-dimethyl-1,3-butadiene. Only complex mixtures were observed when using six and seven-membered ring derivatives **5e** and **5f** (Table 1) probably due to unfavorable steric repulsions. It should be noted that using cyclobuteniminium as dienophiles, no external activation (e.g., Lewis acids) was required for all reactions described unlike previous reports involving cyclobutenones as reaction partners.[14]

A density functional theory (DFT) based computational study was performed to obtain insight into the nature of the

Table 1
Access to cyclobuteniminium salts **5** via [2+2] cycloaddition between keteniminium salts and terminal alkynes



Entry	Amides	Alkynes[a]	Products		Conv[b] (%)
1				**5a**	95[c]
2				**5b**	68[d]
3				**5c**	90
4				**5d**	98
5				**5e**	85
6				**5f**	45
7				**5g**	<5
8				**5h**	–[e]
9				**5i**	<5
10				**5j**	95

[a] Acetylene was used at atmospheric pressure.
[b] The reaction was monitored by ^{1}H NMR and the conversion was determined by integration of the ethylenic signals in the ^{1}H NMR (compare to starting amide).
[c] A slight precipitate was observed in the reaction mixture.
[d] A 3:1 mixture of regioisomers was obtained (major product represented in Table 1).
[e] No trace of product was detected in the ^{1}H NMR spectra.

cycloaddition reactions of cyclobuteniminiums and to investigate the difference in reactivity of cyclobuteniminiums **5a** and **5b** toward cyclopentadiene (Table 2, entries 1 and 2). Cycloaddition reactions were modeled using the Gaussian 09 program package,[17]