Tetrahedron Letters 55 (2014) 6721–6725

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of cyclobuteniminium salts derived from aldo-keteniminium salts and study of their reactivity in Diels–Alder reaction

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ARTICLE INFO

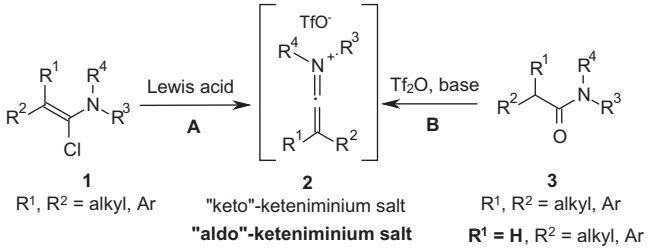
Article history:
Received 2 September 2014
Revised 30 September 2014
Accepted 3 October 2014
Available online 30 October 2014

Keywords:
'Aldo'-keteniminium salts
Cyclobuteniminiums
[2+2] cycloaddition
Diels–Alder reaction
Cyclobutenone
DFT calculations

ABSTRACT

The synthesis of broad scope of novel monosubstituted cyclobuteniminium salts derived from aldo-keteniminium salts and acetylene or 1-propyne is described. The reactivity of cyclobuteniminium salts in Diels–Alder reactions has been studied in detail by DFT calculations and by performing competition reaction with cyclobutenone derivatives.

Since the first report by Ghosez in 1972,[1] the [2+2] cycloaddition reaction between a keteniminium salt **2** and an olefin has been intensively studied[2] and applied to the synthesis of various functionalized cyclobutanones,[3] γ-lactones,[4] prostanoid scaffolds,[5] and natural products.[6] While 'keto'-keteniminium salts **2** (R^1, $R^2 \neq H$) were prepared from the corresponding α-chloroenamines **1**[1] (pathway **A**, Scheme 1) or tertiary amides **3**[7] (pathway **B**, Scheme 1), only the latter route was compatible with aldo-keteniminium salts **2** ($R^1 = H$) owing to their very high reactivity.[7] Indeed, they react faster with α-chloroenamine from which they are formed than with the olefin. Surprisingly, much less attention has been devoted to the [2+2] cycloaddition reaction with alkynes[7,8] and even less with aldo-keteniminium salts **2**.[7,8b] We recently demonstrated that building blocks **6** can be efficiently prepared via a one-pot [2+2]/[4+2] sequence (Scheme 2).[9] In this work, a broad range of novel cyclobuteniminium salts **4** were prepared by [2+2] cycloaddition reaction between keto-keteniminium salts **2** (R^1, R^2 = alkyl, *c*-alkyl) and acetylene or 1-propyne. Iminium salts **4** were then used as dienophiles in Diels–Alder reactions with various functionalized dienes leading to **6** in good yields (Scheme 2). In order to extend



Scheme 1. Access to keteniminium salts **2** from α-chloroenamine **1** and tertiary amide **3**.

the scope of our methodology, we report herein the synthesis of various cyclobuteniminium salts **4** ($R^1 = H$) derived from aldo-keteniminium salts **2** as well as their use as dienophiles.

We started our investigation with *N*,*N*-dimethylpropanamide **3a** and acetylene as alkyne partner. Using the optimized conditions found for [2+2] cycloaddition with keto-keteniminium salts (*sym*-collidine, Tf_2O, and $CH(D)Cl_3$),[7–9] strong precipitation occurred and a very complex mixture with only trace of [2+2] adduct **4a** was observed by ^1H NMR (Scheme 3).[10] No improvement was obtained with higher dilution ($c = 0.05$ M) or using a more hindered base such as 2,6-di-tert-butylpyridine. Since a

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http://dx.doi.org/10.1016/j.tetlet.2014.10.013
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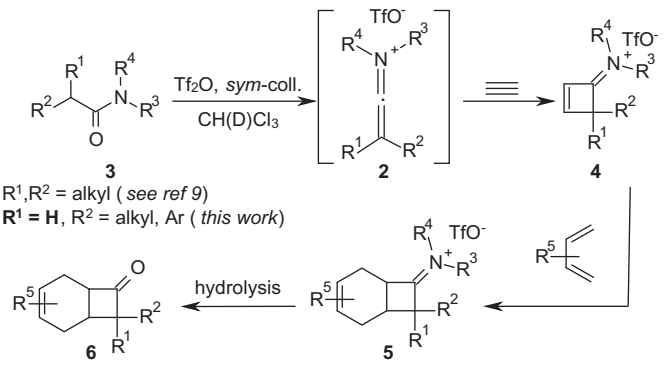
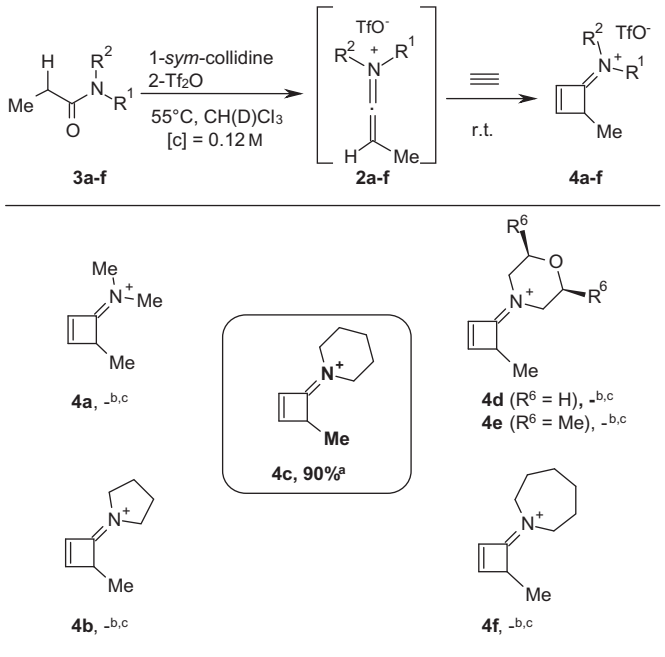


Scheme 2. One-pot [2+2]/[4+2] sequence involving cyclobuteniminium salts **4** as dienophiles.

precipitate was observed during the keteniminium formation, we wondered if increasing the lipophilicity of the nitrogen substituent would improve the solubility of the aldo-keteniminium salt **2a** in $CDCl_3$. While 5-membered ring **4b** (pyrrolidine) gave poor results, piperidine derivative **4c** was obtained cleanly without precipitation (Scheme 3). Although both heterocycles are expected to improve the solubility, the piperidine moiety is geometrically more accommodating for the [2+2] cycloaddition transition state and hence, the formation of keteniminium salt. As seen in Figure 1, the pyrrolidine CH_2 groups are much closer to the attack trajectory and may have a negative impact on the formation of the cyclobuteniminium by sterically blocking the cycloaddition. Very complex mixtures were obtained using propanamides **3d–f** derived from morpholine, *cis*-2,6-dimethylmorpholine, and azepane, respectively (Scheme 3).

The scope and limitation of the [2+2] cycloaddition reaction were then investigated by using various tertiary amides bearing a piperidine moiety. Pleasingly, various alkyl substituents as well as a benzyl chain were well tolerated and the corresponding cyclobuteniminium salts **4g–j** were formed in moderate to good conversion (50–90%, Scheme 4). No isomerization of the double bond was observed by NMR whatever the nature of the side-chain (Scheme 5). DFT calculations show the high energetic demand of the isomerization, confirming its unlikelihood (Fig. 2). A single step proton transfer diagonally across the ring is not possible since the distance is 2.15 Å, hence the isomerization of the cyclobuteniminium double bond is a two step process, which involves two highly energetic transition states ($\Delta G^{\ddagger}$ is 65 and 73 kcal/mol, respectively) and an intermediate with extra strain. Although the isomerization



[a] Conversion determined by ^{1}H NMR spectroscopy.
[b] Conversion not determined.
[c] Complex mixture with only traces of [2+2] cycloadduct **4** observed.

Scheme 3. Influence of the nitrogen substituent on the synthesis of the cyclobuteniminium salt **4**.

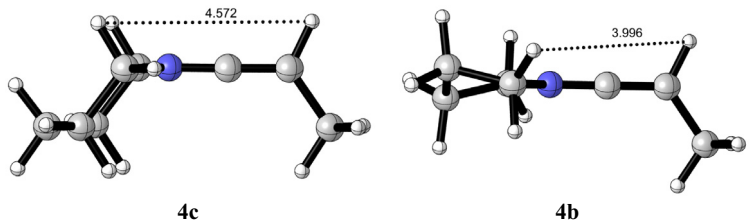


Figure 1. Optimized geometries (M06-2X/6-31+G(d,p)) for cyclobuteniminium salts **4b** and **4c** (side view of piperidine and pyrrolidine).