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Efficient access to functionalized cyclobutanone derivatives using cyclobuteniminium salts as highly reactive Michael acceptors

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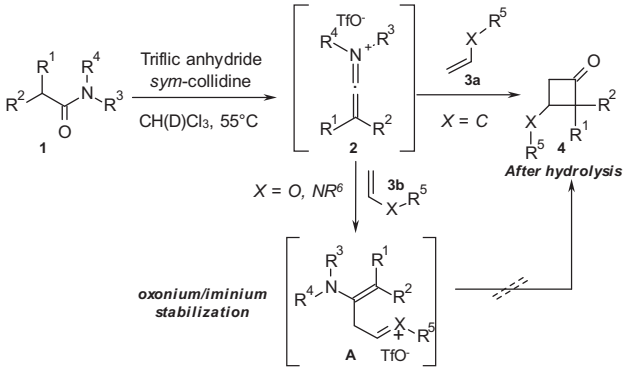
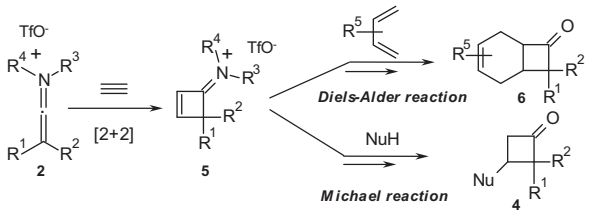
ABSTRACT

A new efficient access to β-substituted cyclobutanones via Michael addition using cyclobuteniminium salts is described. Competition reactions have been performed in order to demonstrate the higher reactivity of cyclobuteniminium salts compared to their cyclobutenone analogs and the results have been rationalized by DFT calculation. Michael adducts have also been efficiently functionalized demonstrating the utility of such building blocks in organic synthesis.

Cyclobutanone derivatives are remarkably versatile building blocks in organic synthesis.[1] Amongst the different methods reported for their synthesis,[1,2] [2+2] cycloaddition reactions between an olefin and a ketene[1,3] or a keteniminium salt[1,4] **2** have been the most widely used (Scheme 1). The keteniminium chemistry is however more attractive since **2** does not undergo side-reactions such as dimerization/oligomerization and can be easily prepared in situ from tertiary amide **1** using Ghosez's procedure (Scheme 1).[5] However, a drawback of this methodology compared to the one based on ketene is that it does not apply to vinyl ethers and enamines, probably due to the stepwise mechanism of the cycloaddition and the important stabilization of the cationic intermediate by the heteroatom (**A**, Scheme 1).[6] We recently reported an efficient access to cyclobutanone derivatives **6** via a one-pot [2+2]/[4+2] sequence (Scheme 2).[7] Next, we aimed to further elaborate cyclobuteniminium salts **5** by Michael addition (Scheme 2). Indeed, the one-pot [2+2]/(hetero)-Michael reaction sequence would be an attractive alternative to the cycloaddition with ketenes[1b] or keteniminium salts (Scheme 1) since it would avoid the sometimes delicate and/or hazardous synthesis of vinyl precursors **3**. Herein, we disclose the first general access to β-substituted cyclobutanone derivatives via Michael addition of *O*-, *N*-, *S*-, *Se*-, and *C*-nucleophiles to in situ prepared



Scheme 1. Access to keteniminium salts **2** from amide **1** followed by [2+2] with alkene derivatives **3**.



Scheme 2. Diels-Alder and Michael reactions with cyclobuteniminium salts **5**.

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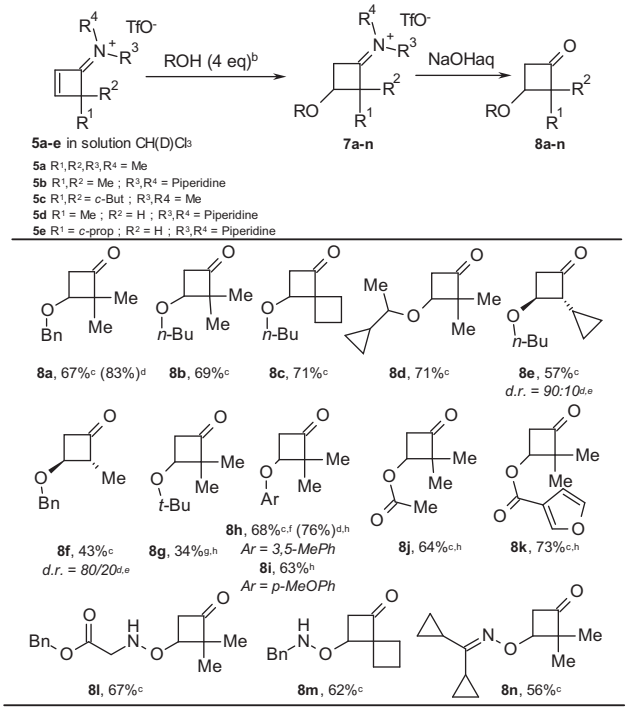
0040-4039/

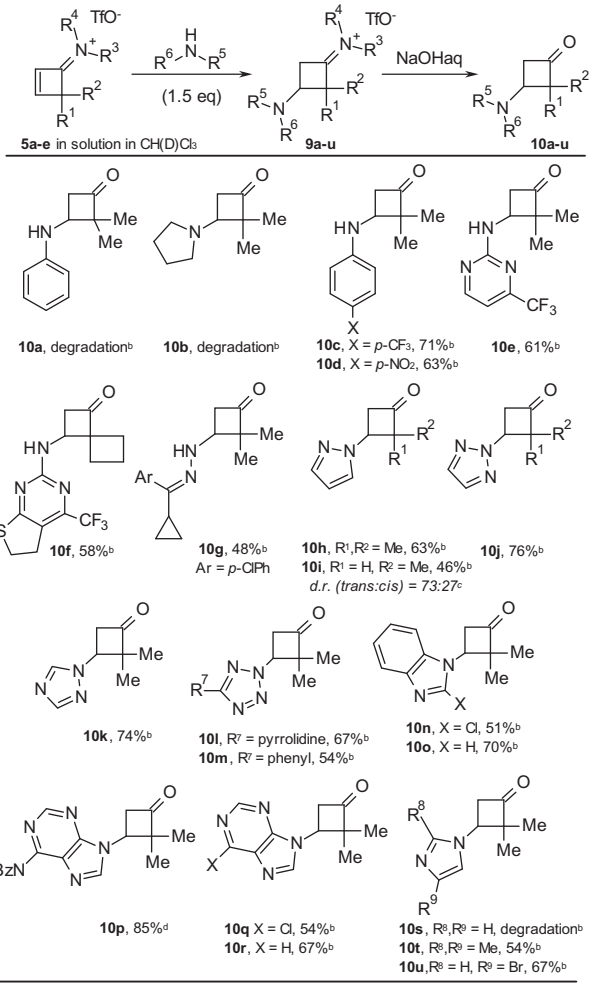
cyclobuteniminium salts.[8] We started our investigation using alcohols[9] as nucleophiles and to our delight the addition of primary and secondary alcohols to cyclobuteniminium **5a–e**[10,11] proceeded at room temperature in 30 min affording β-alkoxycyclobutanone **8a–f** in good overall yields after hydrolysis (43–71%, 4 steps, Scheme 3).[12] Good to high diastereoselectivities (80:20 and 90:10) in favor of *trans*-cyclobutanones **8e** and **8f** were observed when using mono-substituted cyclobuteniminium salt **5d**/**e** as Michael acceptors. Tertiary alcohol functionality (*tert*-butanol, **8g**) was compatible with the methodology although the increased steric hindrance required a higher reaction temperature (60 °C). Phenol derivatives (**8h**/**i**), carboxylic acids (**8j**/**k**), hydroxamic acids (**8l**/**m**) and oxime (**8n**) were also suitable *oxo*-nucleophiles affording functionalized cyclobutanones **8j**/**n** in good yields (56–73%, Scheme 3).

Surprisingly, when attempts were made to use primary and secondary amines such as aniline and pyrrolidine as nucleophiles, no traces of cyclobutanones **10a**/**b** were detected (Scheme 4).[13] NMR monitoring of the reaction showed that complete decomposition of intermediate iminium **9a**/**b** occurred before the hydrolysis step. Based on the work of Matsuo[14] these results can be explained by a fast ring-cleavage of **9** leading to highly reactive cationic intermediates **B** as depicted in Scheme 5. Since no degradation was detected with *oxo*-nucleophiles, this ring-opening reaction would be more favored with **9** than with **7** owing to the better stabilization of the iminium **B** (Scheme 5).

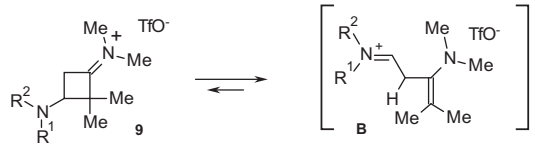
This was further validated by DFT calculations, where the ring opening depicted in Scheme 5 was modeled for **7a** and **9a**. Free energies of activation and reaction are consistent with the experimental observations, indicating both an ease of ring opening for **9a** as well as a thermodynamically more stabilized ring-opened form



Scheme 3. *oxo*-Michael reaction with cyclobuteniminium **5**.[11] [a]Reaction conditions: **5** (10 ml, 0.12 M in $CH(D)Cl_3$), ROH (4.8 mmol), 30 min, room temperature. [b]With 1 equiv of nucleophile, reaction time >24 h. [c]**5a** was used as Michael acceptor. [d]**5b** was used as Michael acceptor. [e]Major diastereoisomer (*trans*) represented. [f]Diastereoisomeric ratio determined by integration in the crude ^1H NMR. [g]15% of cyclobutenone (elimination product) was observed in the crude ^1H NMR after hydrolysis of the iminium salt **7g**. [h]Reaction performed at 60 °C (reflux) during 16 h.



Scheme 4. *Aza*-Michael reaction with cyclobuteniminium **5**.[11] [a]Reaction conditions: **5** (10 ml, 0.12 M in $CH(D)Cl_3$), R^5NHR^6 (4.8 mmol), 5 min, room temperature. [b]**5a** was used as Michael acceptor. [c]d.r. determined by integration of the signals in the crude ^1H NMR. [d]**5b** was used as Michael acceptor.



Scheme 5. Proposed pathway for the decomposition of **9** (via ring-cleavage).

(Fig. 1). In **9a**-open form, bond distances for the positively charged nitrogen illustrate a partial double bond character on both sides of the iminium ion, indicating stabilization thorough electron delocalization from the aromatic ring.

Hypothetically, less donating nitrogen should minimize such side reaction. This hypothesis was confirmed by the addition of anilines bearing strong electron-withdrawing groups (*p*-CF_3 and *p*-NO_2) which afforded cyclobutanones **10c**/**d** in good yields (63/71%, Scheme 4) without any traces of decomposition. The same results were obtained with electron-poor pyrimidines (**10e**/**f**, 61/58%) and the hydrazone derivative (**10g**, 48%). We were also pleased to find that the *aza*-Michael reaction worked also very well and regioselectively with a broad range of heterocycles such as pyrazole (**10h**/**i**), triazole (**10j**,**k**), tetrazole (**10l**/**m**), benzimidazole (**10n**/**o**), adenine (**10p**) and purine (**10q**/**r**) derivatives.[12] However, only degradation was observed with imidazole (**10s**), probably due