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A new entry to the synthesis of substituted azetidines: [2+2] cycloaddition reaction of four-membered endocyclic enamides to ketenes

Antonio Carlos B. Burtoloso and Carlos Roque D. Correia*

Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, CEP. 13083-970, Campinas, São Paulo, Brazil

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Abstract—The first example of a [2+2] cycloaddition reaction of a four-membered endocyclic enamide (2-azetine) to dichloroketene is described and constitutes a new entry to the synthesis of substituted azetidines. Preliminary studies concerning the Baeyer–Villiger oxidation of the [2+2] cycloadduct revealed an unusual regioselectivity. The synthesis of a new azetidine-3-carboxylic acid derivative from the [2+2] cycloadduct is also presented.

Azetidines are an interesting class of four-membered nitrogen-containing heterocycles which have been receiving much attention from the chemical community recently. Some of the reasons for this increasing interest are the applications of azetidines in biological chemistry and in the field of chiral ligands (Fig. 1).[1,2]

Despite this interest, azetidines still do not have the deserved attention regarding the development of synthetic methodologies. This scenario can be attributed mainly to the scarcity of natural azetidines when compared to other cyclic amines such as pyrrolidines and piperidines. Although the literature reports a reasonable number of studies on the synthesis of azetidines,[1,2] most of these studies are based on an intramolecular nucleophilic substitution for the construction of the four-membered ring. Therefore, new protocols are necessary and desirable.

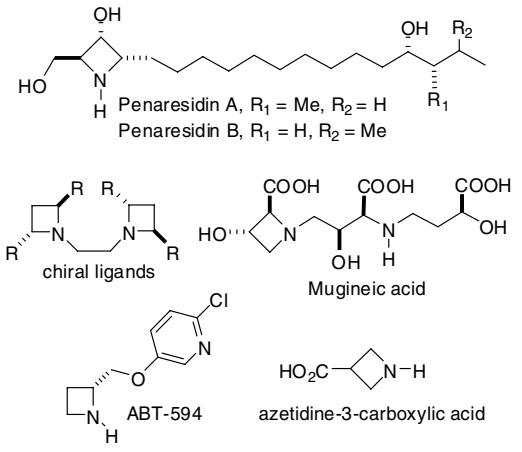
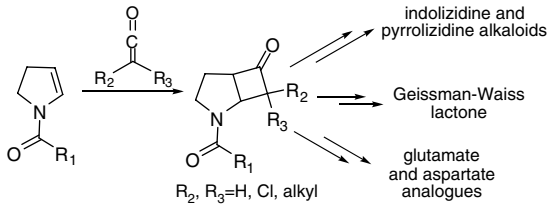


Figure 1. Some examples of natural and synthetic azetidines.[2]

During the last few years, we have been involved with the development of different methodologies for the synthesis of 4, 5 and 6-membered nitrogen and oxygen heterocycles.[3] Of these, the [2+2] cycloaddition reaction of five-membered endocyclic enecarbamates and enamides with ketenes has been particularly effective (Scheme 1). Employing this [2+2] cycloaddition methodology, we accomplished the synthesis of many nitrogen heterocycles such as the Geissman–Waiss lactone, indolizidine and pyrrolizidine alkaloids and conformationally restricted analogues of aspartic and glutamic acids.[3d–g]



Scheme 1. [2+2] cycloaddition of five-membered enecarbamates with ketenes.

* Corresponding author. Tel.: +55 19 37883114; e-mail: roque@iqm.unicamp.br

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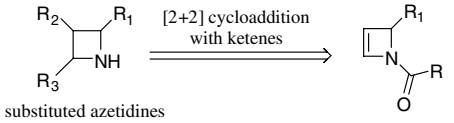
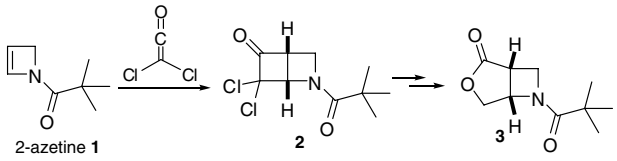
The [2+2] cycloaddition of five-membered enamides and enecarbamates with ketenes has shown great applicability. However, the same reaction involving strained four-membered nitrogen analogues constitutes a considerable challenge.[4] A successful cycloaddition would potentially open a new entry for the synthesis of substituted azetidines (Scheme 2).

Herein, we describe our preliminary study of the [2+2] cycloaddition reaction of four-membered endocyclic enamides and enecarbamates with ketenes and the successful synthesis of azabicyclic cyclobutanone **2** from the four-membered endocyclic enamide **1** (Scheme 3). We also investigated the Baeyer–Villiger oxidation of the highly strained azabicyclic system **2** by converting it to the lactone **3**, an advanced precursor of substituted azetidine-3-carboxylic acids. The β-amino acid azetidine-3-carboxylic acid and its analogues possess interesting pharmacological properties in peptidomimetics.[5] Azetidine-3-carboxylic acid has been used by the Merck Research Laboratories for the preparation of many pharmacologically active compounds, including tryptase inhibitors, procollagen C-proteinase inhibitors and growth hormone secretagogues, among others.[6]

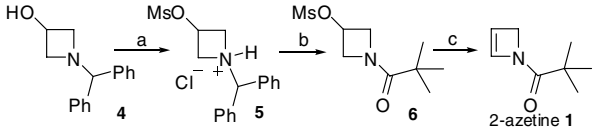
We started the investigation of the [2+2] cycloaddition reaction by preparing the non-substituted 2-azetine **1** from azetidin-3-ol **4** (Scheme 4) using protocols described in the literature.[7] Azetidin-3-ol **4** was prepared by the reaction of benzhydrylamine and epichloridrine[7a] and was subsequently converted to the mesylate **5** in quantitative yield.[7b] Next, the benzhydryl group in mesylate **5** was removed by hydrogenolysis[7b,c] and the nitrogen atom protected in the presence of pivaloyl chloride in 86–91% overall yield.[7d] The synthesis of the 2-azetine **1** was then concluded by the addition of potassium *tert*-butoxide in a hot solution of the *N*-pivaloyl mesylate **6** in *tert*-butanol.[7d]



Scheme 2. Synthesis of substituted azetidines.



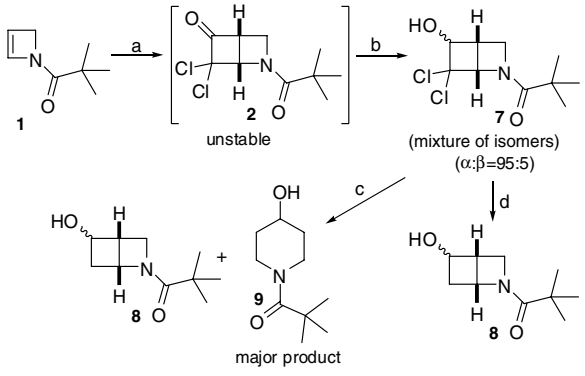
Scheme 3. Application of the [2+2] cycloaddition reaction.



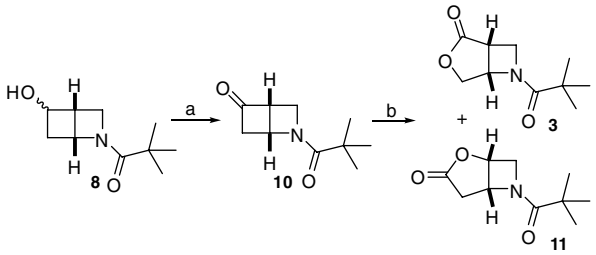
Scheme 4. Synthesis of 2-azetine **1** from 3-azetidinol **4**. Reagents and conditions: (a) Et_3N, MsCl, C_6H_6, 0 °C-rt, 3 h. Then, HCl/Et_2O 0 °C, 100%. (b) $Pd(OH)_2$, H_2, 55 psi, 3,5 h. Then, Et_3N, CH_2Cl_2, PivCl, −78 °C-rt, 4 h, 86–91%. (c) *t*-BuO$^-$K$^+$/*t*-BuOH, 60 °C, 6 h, quantitative.

With the 2-azetine **1** in hand, we started our study of its [2+2] cycloaddition reaction with dichloroketene. After some experimentation, we found that best results for the cycloaddition reaction can be obtained with the slow addition of dichloroketene to a solution of 2-azetine **1** in a mixture of cyclohexane and benzene (10:1 ratio) (Scheme 5). In view of its great instability, the cycloaddition adduct **2** could not be purified and handled properly. After many fruitless attempts to convert the crude cycloaddition product into a stable derivative,[8] we discovered that the immediate reduction of cyclobutanone **2** with $NaBH_4$ in THF was the best choice.[9] Using these conditions, cyclobutanol **7** could be prepared in 54% yield after two steps from 2-azetine **1**.[10]

Next, we investigated the removal of the chlorine atoms by employing a mild dechlorination procedure (H_2, Pd/C, 45 psi) described in the literature.[11] Interestingly, together with the desired dechlorinated alcohol **8**, we also observed the formation of piperidine **9** as the major reduction product. Piperidine **9** was probably formed from a very facile hydrogenolysis of the strained azabicyclic cyclobutanol **7**. The use of more mild conditions such as lower temperatures and lower pressures did not suppress the formation of piperidine **9**. However, the use of the classic radical dechlorination procedure using *n*-Bu_3SnH/AIBN[12] circumvented this hydrogenolysis problem and provided the desired azabicyclo [2.2.0] hexanol **8** in 65–85% yields, which was smoothly oxidized to cyclobutanone **10** with PCC.[13] We then carried out the Baeyer–Villiger (BV) oxidation of azabicyclic cyclobutanone **10** (Scheme 6). Unfortunately, Baeyer–Villiger oxidation of ketone **10** with *m*-CPBA in CH_2Cl_2 consistently furnished low yields of a mixture of lactones **3** and **11**. After some attempts to improve yields, we found that sequential addition of PCC and *m*-CPBA to a CH_2Cl_2 solution of cyclobutanol **8**, at 0 °C in basic medium, was the best experimental condition to generate the BV adducts. In this case, lactones **3**



Scheme 5. Synthesis of cyclobutanol **8** from enamide **1**. Reagents and conditions: (a) Cl_2CCO, C_6H_{12}/C_6H_6, 2 h, rt. (b) $NaBH_4$, MeOH, −21 °C, 5 min, 54% over two steps. (c) H_2, Pd/C, MeOH, K_2CO_3, 2 h, 70% (**8** + **9**). (d) AIBN, *n*-Bu_3SnH, C_6H_6, reflux, 24 h, 65–85%.



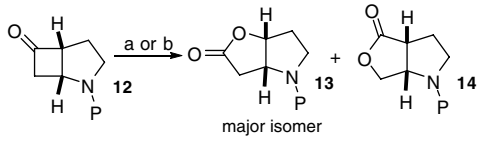
Scheme 6. Baeyer–Villiger oxidation of cyclobutanone **10**. Reagents and conditions: (a) PCC, CH_2Cl_2, NaOAc, molecular sieves, 0 °C, 1 h. (b) *m*-CPBA, $NaHCO_3$, 0 °C, 15 min, 45–55% over two steps.

and **11** were isolated in 45–55% yields over the two steps as a 3:1 regioisomeric mixture. Recrystallization of this mixture increased the ratio to 5:1.

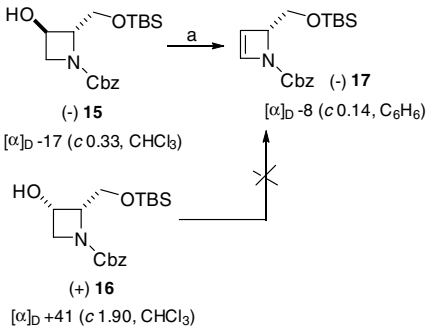
Interestingly, the major isomer **3** was not the expected lactone considering the Baeyer–Villiger oxidation rules. The use of other procedures such as urea hydrogen peroxide complex (UHP)[14] with acetic anhydride and *m*-CPBA in neutral or acid medium did not change this trend of the BV oxidation to furnish lactone **3** as the major product. Another interesting point is the very fast Baeyer–Villiger oxidation of cyclobutanone **10** in the presence of PCC (10 min with PCC and 6 h in the absence of it). We hypothesize that a chromium species is functioning as a Lewis acid or as a peroxide metal complex during the Baeyer–Villiger oxidation step, making it faster. Some efforts are under way in our laboratories to understand not only this apparent catalysis, but also the unusual regioselectivity of this Baeyer–Villiger oxidation.

These results are even more surprising when we compare these BV results with those obtained previously[3e,h] from aza-cyclobutanone **12** (Scheme 7), in which the expected lactone **13** was obtained as the major isomer. Nevertheless, lactone **3** constitutes an interesting intermediate to the synthesis of substituted azetidines. Since the [2+2] cycloaddition reaction furnished satisfactory results with enamide **1**, its employment in the reaction with more complex enamides might constitute a potential route to fully-substituted azetidines.

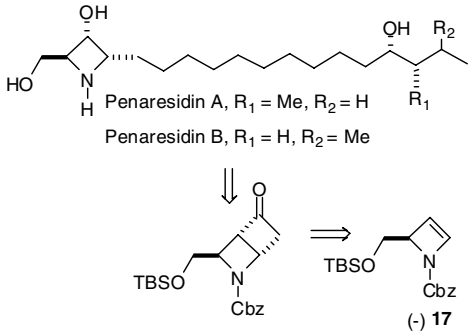
In spite of the fact that there is no report in the literature dealing with the synthesis of more complex four-membered enamides or enecarbamates, we were able to prepare the four-membered chiral enecarbamate **17** from *trans*-3-azetidinol **15**. Curiously, the *trans* relationship between the hydroxyl group and the alkyl substituent is crucial for effective elimination since we could not synthesize **17** from the *cis*-3-azetidinol **16** (Scheme 8). The preparation of chiral enecarbamate **17**, opens a new entry to the synthesis of chiral fully-substituted azetidines as outlined in Scheme 9 (ongoing studies aiming at the synthesis of azetidine alkaloids).



Scheme 7. Baeyer–Villiger oxidation of azabicyclobutanone **12**. Reagents and conditions: (a) (P = Cbz): *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 0,5 h, 90% (**13**:**14** = 1:0). (b) (P = Boc): H_2O_2, AcOH, 0 °C, 3 h, 80% (**13**:**14** = 7:1).



Scheme 8. Synthesis of the chiral endocyclic enecarbamate **17**. Reagents and conditions: (a) Et_3N, CH_2Cl_2, MsCl, reflux, 24 h or $POCl_3$, Et_3N, C_6H_6, 24 h, (~40%).



Scheme 9. Strategy for the synthesis of azetine alkaloids from endocyclic enecarbamate **17**.

In summary, we have demonstrated for the first time the [2+2] cycloaddition reaction between a ketene and a four-membered endocyclic enamide. Baeyer–Villiger reaction on the [2+2] cycloaddition adduct **10** furnished the unusual regioisomeric lactone **3** as the major product. Bicyclic lactone **3** poses as an advanced intermediate for the synthesis of substituted 3-azetidine-carboxylic acids and others substituted azetidines. Furthermore, the synthesis of enecarbamate (−)-**17** opens a new entry to the synthesis of chiral fully substituted azetines.

Acknowledgements

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Supplementary data

^{1}H NMR, ^{13}C NMR, IV and MS for all new compounds. The supplementary data are available online

with the paper in ScienceDirect, at doi:10.1016/j.tetlet.2006.06.174.

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8. Attempts to remove the chlorine atoms of cycloadduct **2** employing Zn/Cu, NH_4Cl in MeOH or AIBN, and *n*-Bu_3SnH in C_6H_6 under reflux were fruitless. Also, a direct Baeyer–Villiger oxidation of **2** did not provide the expected dichlorolactone.
9. The use of MeOH as solvent causes ring open of bicyclic cyclobutanone **2** to furnish a methyl ester, together with cyclobutanol **7** (ratio 1:1).
10. Typical experimental procedure for the [2+2] cycloaddition reaction, and reduction of the unstable cyclobutanone **2** to cyclobutanol **7**: 108.5 mg (0.78 mmol) of 2-azetine **1** was dissolved in a dry mixture of 10:1 cyclohexane/benzene (5.5 mL), under argon. Next, 0.38 mL (2.74 mmol) of dry Et_3N was added under vigorous stirring, followed by the slow addition (3 mL/h) of the ketene precursor (1.95 mmol of dichloroacetyl chloride dissolved in 3.3 mL of a 10:1 mixture of cyclohexane/benzene). After the addition of ~2.0 mL, most of 2-azetine **1** had already been consumed, as indicated by TLC analysis ($KMnO_4$ stain). The reaction mixture was filtered to remove Et_3NHCl, which was washed a few times with a 1:1 mixture of cyclohexane/benzene. The combined organic layers were washed with cold water (eliminate some remaining Et_3NHCl), dried over Na_2SO_4 and evaporated in vacuo to furnish the crude cyclobutanone **2** as an yellowish oil. (^1H NMR (300 MHz, benzene-d_6): $\delta = 4.73$ (br s, 1H), 3.65 (dd, $J = 8.8$, 2.9 Hz, 1H), 3.55 (t, $J = 8.8$ Hz, 1H), 3.08 (ddd, $J = 8.8$, 4.4, 2.9 Hz, 1H), 0.98 (s, 9H). IR (cm^{-1}): 2974, 1810, 1642. MS-ESI: 254 (M+1, 2 ^{37}Cl), 252 (M+1, ^{37}Cl + ^{35}Cl), 250 (M+1, 2 ^{35}Cl), 57, 55). Cyclobutanone **2** was immediately dissolved in 20 mL of THF and cooled to −21 °C. Next, 150 mg of $NaBH_4$ (5 equiv) was added to this solution and after 15 min of stirring, saturated ammonium chloride was added. The organic solvent was removed in vacuo, and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The resulting oil was purified by *flash* column chromatography to give 106 mg of cyclobutanol **7** (54% yield) as a white solid. ^1H NMR (major isomer) (300 MHz, tetrachloroethane-d_2, 100 °C): $\delta = 4.96$ (m, 1H), 4.70 (d, $J = 6.6$ Hz, 1H), 4.56 (dd, $J = 8.5$, 1.9 Hz, 1H), 4.30 (t, $J = 8.5$ Hz, 1H), 3.36 (m, 1H), 3.02 (br s, 1H, OH), 1.25 (s, 9H). IR (cm^{-1}): 3299, 2969, 2925, 1608, 1480, 1425, 1365, 1149, 782. MS-ESI: 256 (M+1, 2 ^{37}Cl), 254 (M+1, ^{37}Cl + ^{35}Cl), 252 (M+1, 2 ^{35}Cl), 200, 198, 196, 57. TLC: $R_f = 0.51$, AcOEt. HRMS *m/z* calcd for $C_{10}H_{15}Cl_2NO_2$ 251.04798, found 251.04898.
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