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# Communications

## New Synthesis of 2-Azetines and 1-Azabutadienes and the Use of the Latter in Diels–Alder Reactions: Total Synthesis of (±)-δ-Coniceine[1]

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*Summary:* An efficient synthesis of 1-acyl-2-azetines, their thermal electrocyclic ring opening to 1-acyl-1-azabutadienes, and intra- and intermolecular Diels–Alder reactions of the resultant azadienes are described. A total synthesis of (±)-δ-coniceine has been carried out by this route.

The synthesis of indolizidine and quinolizidine alkaloids would be facilitated if Diels–Alder reactions between 1-azabutadienes and various dienophiles could be carried out efficiently.[3] However for years Diels–Alder reactions of systems containing a 1-azabutadiene unit were capricious at best.[4] Recently several groups,[5-8] especially those of Fowler,[5] Ghosez,[6] and Boger,[7] have greatly expanded the utility of this process. We report here a completely different approach for the preparation of 1-acyl-1-azabutadienes, namely, the thermal electrocyclic ring opening of 1-acyl-2-azetines, and subsequent Diels–Alder reactions of the dienes.

**Table I. Preparation of 1-Acyl-3-(mesyloxy)azetidines 6a–f and 1-Acyl-2-azetines 7a–f**

| compd | R | yield of 6 (%) | yield of 7 (%) |
|---|---|---|---|
| a | $CH_3$ | 98 | 74 |
| b | $C_6H_5$ | 98 | 88 |
| c | $4\text{-}CH_3C_6H_4$ | 88 | 93 |
| d | $CH_2CH_2CH_2CH{=}CH_2$ | 87 | 72 |
| e | $CH_2CH_2CH{=}CH_2$ | 95 | 89 |
| f | $C(CH_3)_3$ | 54 | 62 |

By analogy to the cyclobutene to butadiene isomerization, we reasoned that 2-azetines on heating would undergo electrocyclic ring opening to generate 1-azabutadienes. If this process could be accomplished, it might be an ideal way of producing 1-azabutadienes since no other products are formed and no other reagents are necessary. However, this method would only be of value if a simple high-yielding preparation of 2-azetines were available. The only applicable azetine synthesis, that of Warrener,[9] required several steps and proceeded in fairly low overall yield. Therefore we developed the following very efficient route to 1-acyl-2-azetines. Stirring epichlorohydrin (1) and benzhydrylamine (2) in methanol (25 °C/7 d, 50 °C/7 d, then 25 °C/18 d) gave the azetidinol 3 in 51% yield.[10]

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(2) UCLA Mentorship Awardee, 1989–90.
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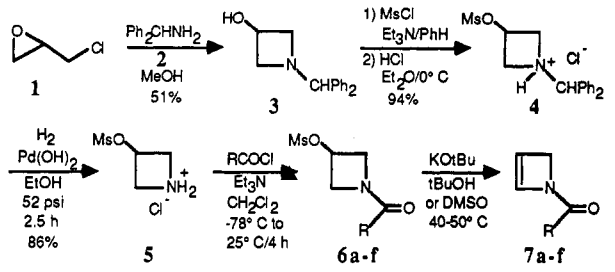
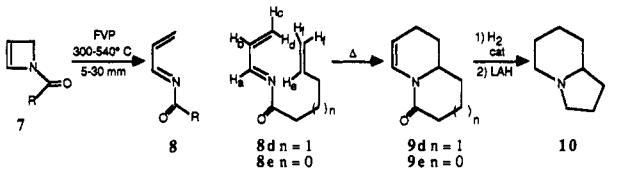



Mesylation[11] and protonation gave, in 94% yield, the salt **4**, which was reduced[11b] over palladium hydroxide in ethanol to give the 3-(mesyloxy)azetidinium salt **5** in 86% yield. Acylation of this salt with a series of acid chlorides produced the 1-acyl-3-(mesyloxy)azetidines **6a–f** in good yield (Table I). Simple base-catalyzed $\beta$-elimination afforded the desired 1-acyl-2-azetines **7a–f** in high yields. The corresponding *N*-tosyl-2-azetine **7** could also be prepared by this route, albeit in low yield (20%); its spectral data matched those reported for the same compound by Warrener.[9] However, similar treatment of the *N*-carbomethoxy analogue of **6** did not give the desired azetine **7**, perhaps due to the decreased acidity of the methylene protons. The $^1$H NMR spectra of **7a–f** in toluene-$d_8$ showed two sets of resonances for all of the azetine protons, thus indicating a slow rotation about the amide N–CO bond; warming to 80 °C caused these signals to coalesce.

Cyclobutenes generally isomerize to butadienes on heating between 100 and 200 °C. Theoretical calculations at the 3-21G level indicated that the activation energy for the ring opening of *N*-formyl-2-azetine was 41.8 kcal/mol (compared to 34.7 kcal/mol for the carbon analogue) and that the formyl group preferred to rotate outward to give the *E* isomer of 1-formyl-1-azabutadiene.[12] However refluxing 1-(5-hexenoyl)-2-azetine (**7d**) in toluene or mesitylene (in the presence or absence of maleic anhydride) gave only polymeric material. This forced us to use flash vacuum pyrolysis to generate the desired 1-azabutadienes. At temperatures of 190 or 210 °C, only the starting azetine was recovered, but above 300 °C the isomerized product could be obtained. The optimum conditions for **7d** are typical, namely, injection via syringe of a 0.02 M solution of **7d** in benzene-$d_6$ into a serum-capped 1.5-cm (i.d.) quartz tube filled with glass helices heated to 440 °C and under a vacuum of 5 mmHg with trapping at −78 °C. Proton NMR (after partial evaporation of the solvent) indicated a very clean conversion[13] to the desired 1-(5-hexenoyl)-1-azabutadiene (**8d**): $^1$H NMR ($C_6D_6$) $\delta$ 7.68 (1 H, d, $J$ = 9.2 Hz, $H_a$), 6.20 (1 H, ddd, $J$ = 17.3, 10.1, 9.3 Hz, $H_b$), 5.64 (1 H, ddt, $J$ = 17.0, 10.2, 6.7 Hz, $H_e$), 5.35 (1 H, bd, $J$ = 10.1 Hz, $H_c$), 5.32 (1 H, bd, $J$ = 17.3 Hz, $H_d$), 4.95 (2 H, m, $H_f$), 2.28 (2 H, t, $J$ = 7.4 Hz), 1.92 (2 H, app q, $J$ = 6.6 Hz), 1.66 (2 H, quintet, $J$ = 7.2 Hz). Presumably the azabutadiene does not spend enough time in the hot zone under these conditions to be able to attain the transition state necessary for the Diels–Alder reaction. This unexpected result allowed us to study the intramolecular cycloaddition of **8d** at various temperatures. Cycloaddition of **8d** to **9d**[5c] was complete in 7 days at 50 °C and in 6 h at 100 °C.[14] The doubling of rate observed with every 10° increase in temperature corresponds to an activation energy of approximately 20–25 kcal/mol. Thus the Diels–Alder cycloaddition of **8d** is not unusual from a kinetic point of view. Raising the pressure to 20–30 mm permitted the direct isolation of the cycloadduct **9d** from **7d** without the intermediate isolation of **8d**, although the overall yield was somewhat lower than the two-step procedure. In a similar manner, pyrolysis of **7e** at 540–50 °C at 5 mmHg followed by refluxing **8e** in benzene for 28 h produced the enamide **9e**[5c] in 46% yield. Hydrogenation of **9e** followed by hydride reduction afforded (±)-$\delta$-coniceine (**10**). Finally, other 1-acyl-1-azabutadienes, e.g., the acetyl and benzyl analogues, **8ab**, could also be obtained by this route.[15]




In summary, we have developed a new synthesis of 1-acyl-2-azetines, subjected them to flash vacuum pyrolysis to generate cleanly 1-acyl-1-azabutadienes, and effected the cycloaddition of these dienes to produce intermediates for the synthesis of quinolizidine and indolizidine alkaloids such as $\delta$-coniceine.[16]

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(13) The yield of the isomerization could not be calculated exactly since complete purification of **8d** was impossible. However the material balance was excellent and the $^1$H NMR spectrum was quite clean indicating a very good conversion.

(14) Intermediate temperatures gave intermediate rates as expected: 90 °C, 12 h; 80 °C, 24 h; 70 °C, 2 d; 60 °C, 3.8 d. The cycloadduct **9d** could be isolated in ~70–80% yield. There was essentially no difference in yield at the different temperatures. A minor byproduct is obtained in these cycloadditions. Its $^1$H NMR is very similar to **8d** (nearly identical couplings but with significant chemical shift differences). We have not yet determined the structure of this compound although it may be the Z isomer of **8d**.

(15) Intermolecular cycloadditions of **8ab** proceeded with ethyl vinyl ether (~10 equiv) and ketene dimethyl acetal (~6 equiv), respectively, although in poor yield. No systematic attempts have been made to try to improve these cycloadditions.

(16) After the chemistry described herein had been largely completed, a report by Yamamoto and co-workers appeared in which he described a one-pot preparation of the Diels-Alder adduct **9d** and similar compounds from acrolein via the trimethylsilylimine. Uyehara, T.; Suzuki, I.; Yamamoto, Y. *Tetrahedron Lett.* **1990**, *31*, 3753.