On the scope of acylnitrilium ion initiated heteroannulations: monocyclizations terminated by unactivated alkenes

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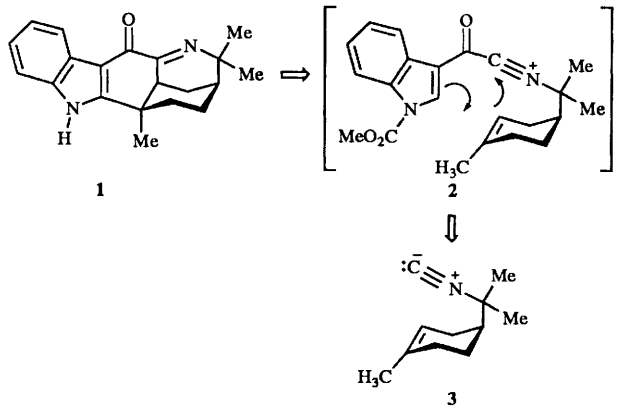
Intramolecular trapping of transient acylnitrilium ions by di- and tri-substituted alkenes has been shown to occur with reasonable efficiency to provide the corresponding 2,3,4,5-tetrahydropyridine and 3,4-dihydro-2*H*-pyrrole derivatives in moderate overall yield.

Annulations initiated by heteroatom-stabilized carbocations have played a prominent role in the synthesis of numerous carbocyclic and heterocyclic natural products.[1-3] The vast majority of cyclizations in this category involve alkene participants that give rise to metastable carbocations which are subsequently trapped by a waiting nucleophile[4] or rapidly transmutated *via* facile molecular reorganization.[5] Efficient cyclizations that proceed under mild conditions *via* relatively long-lived carbocations are comparatively few in number.[6] Our interest in the prospective use of an acylnitrilium ion[7] initiated alkene-cascade cyclization for the synthesis of the *Aristotelia* alkaloid (+)-makonine (**1**)[8] (Scheme 1) prompted our examination of prototypical cyclizations between these cations and simple, unactivated alkenes. Herein we report the results of this study.

The isocyanides employed throughout this investigation were prepared from the corresponding amines by sequential *N*-formylation/dehydration. Accordingly, formylation of the amine **4** (EtOCHO, reflux, 5 h) followed by dehydration ($POCl_3$–Et_3N, THF, 0 °C) furnished the isocyanide **5** in 82% yield after distillation.



1 2 3

Scheme 1

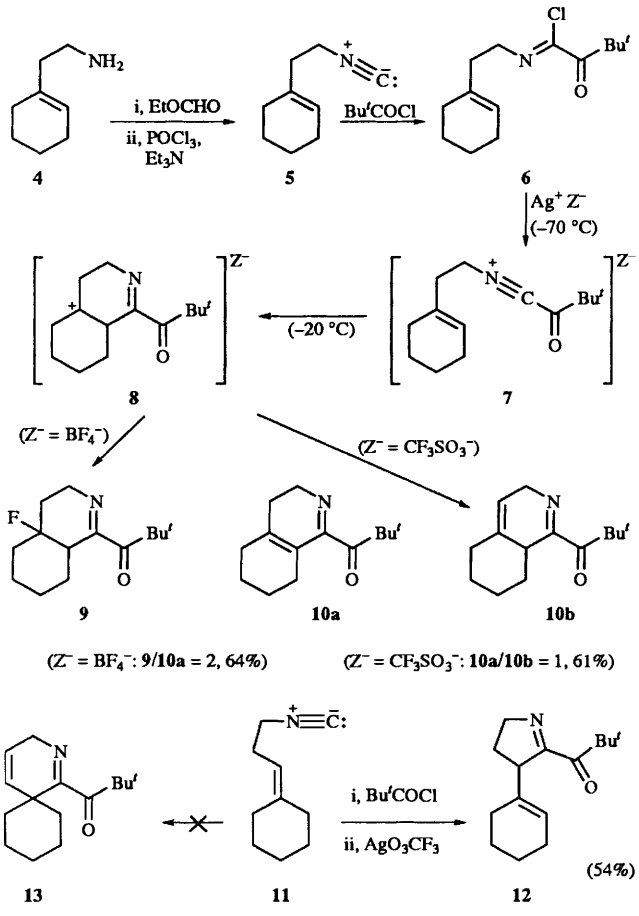
Cyclization studies

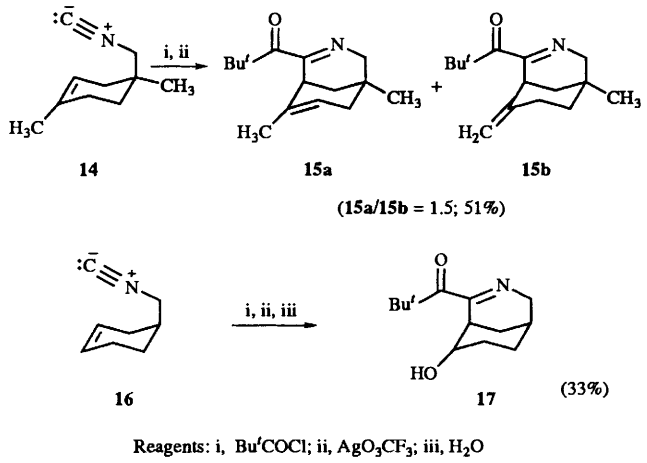
The initial conversion of compound **5** into the corresponding α-keto imidoyl chloride **6** was achieved by treatment with trimethylacetyl chloride (TMAC) (1.05 equiv.) as described previously.[7b] Whereas ionization of **6** could be readily achieved by exposure to $AgBF_4$ (1.10 equiv.) in accord with literature precedent [CH_2Cl_2–$(CH_2Cl)_2$, −70 °C],[7] subsequent cyclization of the resulting acylnitrilium ion **7** took an unexpected course. When the reaction mixture was warmed to −20 °C, cyclization of **7** proceeded by way of the tertiary carbonium ion **8** to provide **9**‡ and **10a** (**9**/**10a** = 2) in 64% isolated yield. The formation of **9** could be completely suppressed by the use of AgO_3SCF_3 for generation of the initial acylnitrilium cation. Accordingly, treatment of **6** with AgO_3SCF_3 (1.10 equiv., CH_2Cl_2, −70 °C→ −40 °C) provided the isomeric hexahydroisoquinolines **10a** and **10b** [**10a**/**10b** = 1 (NMR)] in 61% overall yield from the isocyanide **5**. Exposure of this mixture to silica gel resulted in quantitative conversion of **10b** into **10a** which could be isolated in analytically pure form in 61% yield.§ As expected, the regiochemistry of the foregoing cyclizations (fused *vs.* spiro) would appear to be governed by the relative stabilities of the respective post-cyclization carbocations. A similar outcome was observed in the acylative cyclization of 3-cyclohexylidenepropyl isocyanide **11**.¶ Sequential reaction of **11** with TMAC (1.05 equiv.) followed by ionization/cyclization of the resulting α-keto imidoyl chloride [AgO_3SCF_3 (1.10 equiv.), CH_2Cl_2, −70 °C→ −40 °C] provided the 3,4-dihydro-2*H*-pyrrole **12**§ to the exclusion of the corresponding spirocycle **13** in 54% yield after chromatography. Not surprisingly, conformational restriction of the 3-cyclohex-1-enyl substituent precluded facile isomerization of the nonconjugated alkene within **12** (*vide supra*).

As a prelude to the intended synthesis of (+)-makonine **1**, we next turned our attention to the construction of bridged bicyclic ring systems *via* acylnitrilium ion-alkene cyclizations. Reaction of 4-isocyanomethyl-2,4-dimethylcyclohex-1-ene **14**‖ with TMAC (1.05 equiv.) followed by Ag^+ mediated cyclization [AgO_3SCF_3 (1.10 equiv.), CH_2Cl_2, −70 °C→ −40 °C] secured the azabicyclo[3.3.1]nonanes **15a** and **15b** [**15a**/**15b** = 1.5 (NMR)] in 51% yield after chromatography.** Presumably **15a** and **b** arise as a consequence of divergent proton elimination from a common carbocationic intermediate. In contrast to this result, acylation/cyclization of the 1,2-disubstituted alkene-containing isocyanide **16** (vide supra) furnished the bicyclic alcohol **17** as the only major product after an aqueous quench albeit in low (33%) isolated yield.†† In this instance, a series

† Fellow of the Alexander von Humboldt Foundation, 1993–1995.
‡ The bicyclic fluoride **9** was determined to be stereochemically homogeneous by ^{13}C NMR and GC–mass spectral analysis.
§ All new compounds were fully characterized by IR, ^1H and ^{13}C NMR spectroscopy and possessed satisfactory combustion analyses or an exact mass measurement.

¶ The isonitrile **11** was prepared by the reaction of (2-chloroethylidene)cyclohexane with isocyanomethyllithium.
‖ The isocyanide **14** was prepared by the conversion of 1,4-dimethylcyclohex-3-ene-1-carbaldehyde[9] to the corresponding amine [i, H_2N–OTHP; ii, $LiAlH_4$ (74% overall)] followed by *N*-formylation–dehydration.
** Azabicyclo[3.3.1]nonane **15a** was isolated from this mixture by careful chromatography on silica gel and was fully characterized (see footnote §).
†† The stereochemical disposition of the hydroxy group of **17** has not been determined.





Reagents: i, Bu'COCl; ii, AgO_3CF_3; iii, H_2O

of DEPT and ^1H–^{13}C HETCOR experiments was used to establish unambiguously the connectivity of the core heterocycle and rule out the isomeric [3.2.2] ring system. The regioselectivity of cyclization in the case of **17** is likely a reflection of preferential 6-membered ring formation.

The preceding examples clearly show that even isolated, unactivated alkenes can serve as suitable terminators for cyclizations involving acylnitrilium ions. Although cyclization efficiencies are somewhat lower than in previous examples,[7] these results indicate that isolated alkenes in various settings might serve as effective cationic relay moieties for cascade type annulations.

Experimental

4-Cyclohex-1-enyl-5-trimethylacetyl-3,4-dihydro-2*H*-pyrrole 12
A 50-cm^3 round bottom flask fitted with a magnetic stirrer bar, flame-dried and cooled under a stream of argon, was charged with (3-isocyanopropyl)cyclohexane (149 mg, 1.0 mmol). The system was again flushed with argon, sealed with a septum and an argon balloon was attached to it. Dichloromethane (1.5 cm^3) was added *via* a syringe to the flask followed by trimethylacetyl chloride (127 mg, 1.05 mmol) also added *via* a syringe. The mixture was stirred under argon at room temperature. (A previously performed NMR tube reaction dictated how long this reaction takes.)

When the acylative insertion was complete, the reaction mixture was diluted with dichloromethane (15 cm^3) and the flask was cooled to *ca.* −70 °C in a Pr^iOH–CO_2 bath (NB: −78 °C is too cold!). Silver trifluoromethanesulfonate (283 mg, 1.1 mmol) was added to the reaction mixture as a solid all at once after which the system was sealed and stirred in the range −60 to −70 °C under argon for 1 h (after 10 min a pale precipitate was seen in the flask). The reaction mixture was then allowed to warm slowly to −35 °C over 30 min and was maintained at that temperature overnight (16 h). Water (10 cm^3) was added to the reaction mixture which was then allowed to warm to room temperature with stirring over over 10 min. The mixture was filtered through a pad of wet Celite with dichloromethane (20 cm^3) and the filtrate was transferred to a separatory funnel [with further dichloromethane (10 cm^3)]. The biphasic mixture was shaken, separated and the aqueous layer was extracted with dichloromethane (2 × 10 cm^3). The combined organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (*ca.* 10 × 1.5 cm) by gradient elution with mixtures of ether and hexane (50 cm^3 each of 5, 10, 20, 50 and 100% polar solvent in non-polar as necessary) to provide the title compound **12** as a colourless oil (126 mg, 54%); $\delta_H(CDCl_3)$ 5.38–5.33 (m, 1 H, C=CH), 4.06–4.00 (m, 2 H, CH_2N), 3.71 (m, 1 H, CH), 2.13–1.99 (m, 3 H), 1.81–1.65 (m, 2 H), 1.63–1.45 (m, 4 H) and 1.25 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ 205.9, 174.2, 136.5, 123.3, 61.9, 56.4, 44.1, 28.7, 26.9, 26.8, 25.2, 22.8 and 22.2; ν_{max}(thin film)/cm^{-1} 3042, 2929, 2860, 2837, 1684, 1617, 1481 and 1458; *m/z* 233 (M^+), 218, 177, 148 and 57 (100%) [Found (HRMS): M^+, 233.1769. Calc. for $C_{15}H_{23}NO$: M^+, 233.1780].

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