

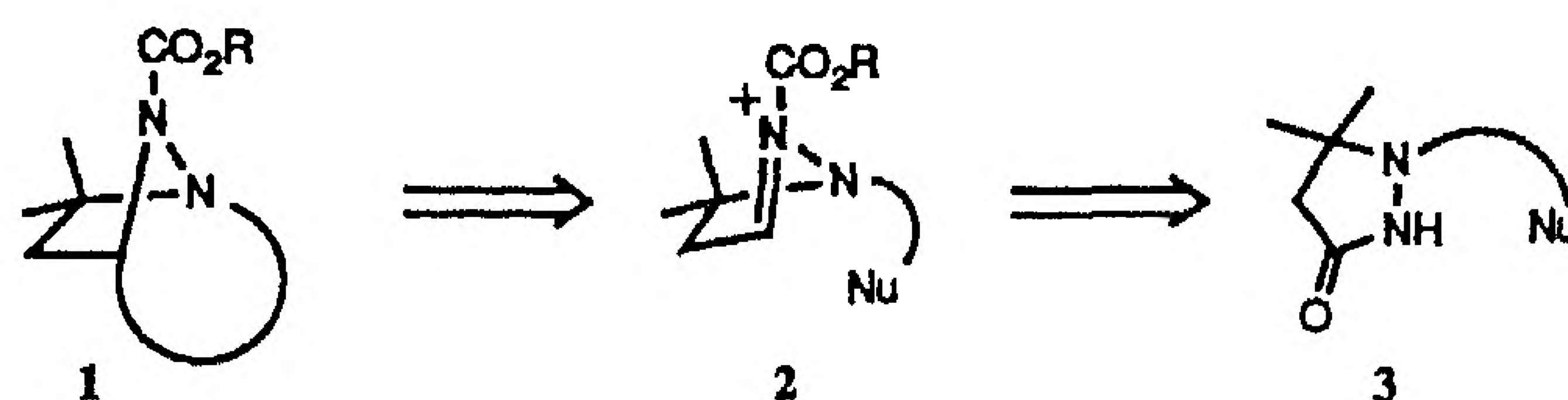
SYNTHESIS OF BRIDGED BICYCLIC HYDRAZINES VIA CYCLIC *N*-ACYLHYDRAZONIUM INTERMEDIATES

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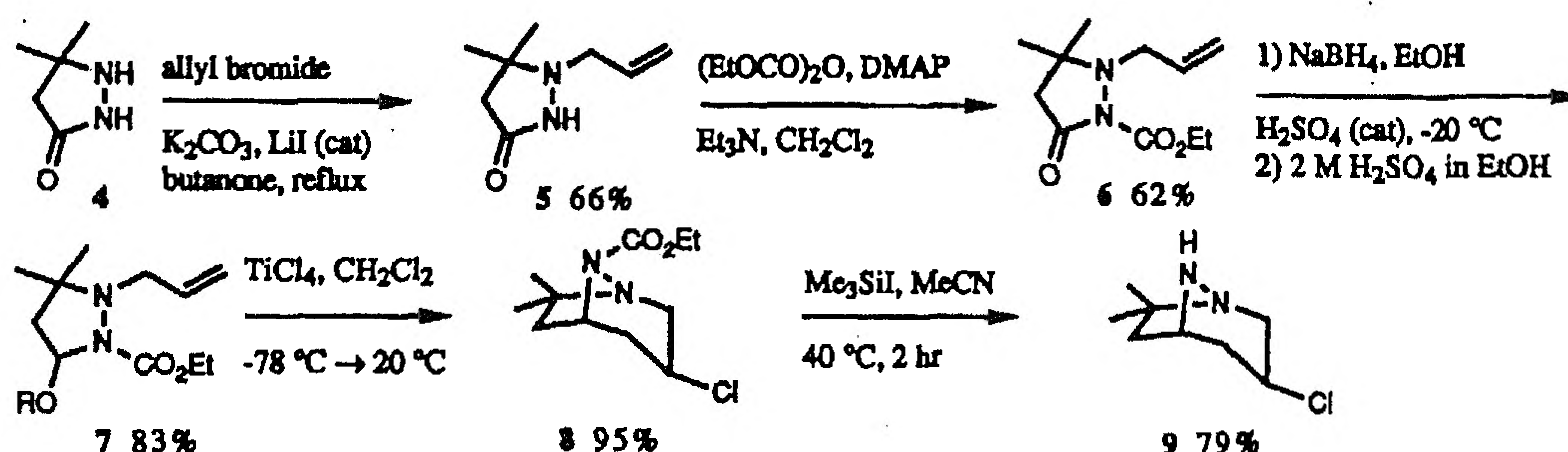
Summary: The efficient preparation of bridged diazabicyclics **1** from pyrazolidones **3** by cationic ring closure of endocyclic hydrazoneium electrophiles **2** is described.

The recent interest in the biological¹ and physical² properties of cyclic hydrazine derivatives sharply contrasts with the relative paucity of methods for preparing this compound class. The major route for the construction of bridged hydrazines **1** is the 1,3-dipolar cycloaddition reaction³ requiring the availability of functional open chain hydrazines. An attractive novel pathway would make use of the endocyclic ring closure of pyrazolidinium intermediate **2**, the latter to be generated from the pyrazolidone **3**. In view of the ready availability⁴ of the precursor of **3** such a sequence would open a varied field of applications. In this communication we report the successful realization of our plans as exemplified in Scheme I.



Thus, pyrazolidone **4**⁵ was alkylated at the N-1 position with allyl bromide using potassium carbonate as base in the presence of lithium iodide to afford **5**. Introduction of the alkoxy carbonyl substituent at N-2, necessary for activation of the ring oxo function,⁶ was achieved by treatment of **5** with diethyl dicarbonate (2 equiv) in presence of triethylamine (1 equiv) and 4-dimethylaminopyridine (DMAP, 1 equiv) to give the desired **6** in 62% yield (82% if corrected for recovered starting material). The sodium borohydride reduction⁶ proceeded smoothly and produced an almost quantitative yield of hydroxy derivative **7** (R = H). Upon brief treatment with acidic ethanol the corresponding ethoxy compound **7** (R = Et) was obtained, already indicating the intermediacy of the cationic entity. The latter electrophile **2** would be expected to form less easily compared with the well-investigated *N*-acyliminium ion⁷ due to the presence of the second nitrogen.⁸ Furthermore, the latter atom may be protonated by the added acid obstructing the formation of the derived iminium species. Ring closure of **7** (R = Et) under the influence of TiCl₄ (2 equiv) took place in almost quantitative yield to the bridged compound **8**. Stirring of **7** in formic acid did not lead to cyclization (*vide infra*). Dealkoxycarbonylation of **8** gave the free hydrazine **9** as a crystalline compound⁹ (mp 44.5-45 °C). Its stereochemistry was established by using NOE-difference ¹H NMR. Irradiation of one of the methyl signals gave a strong enhancement of the signal of the hydrogen atom adjacent to chlorine. The appearance of the latter signal (4.20 ppm, tt, *J* = 11.1 and 6.3 Hz) points to an axial hydrogen in a chair-like six-membered ring. This stereochemistry is in agreement with the usual mechanism for cationic olefin cyclization featuring equatorial attack of the nucleophile in a chair-like transition state⁷ (see Scheme II, R = H).

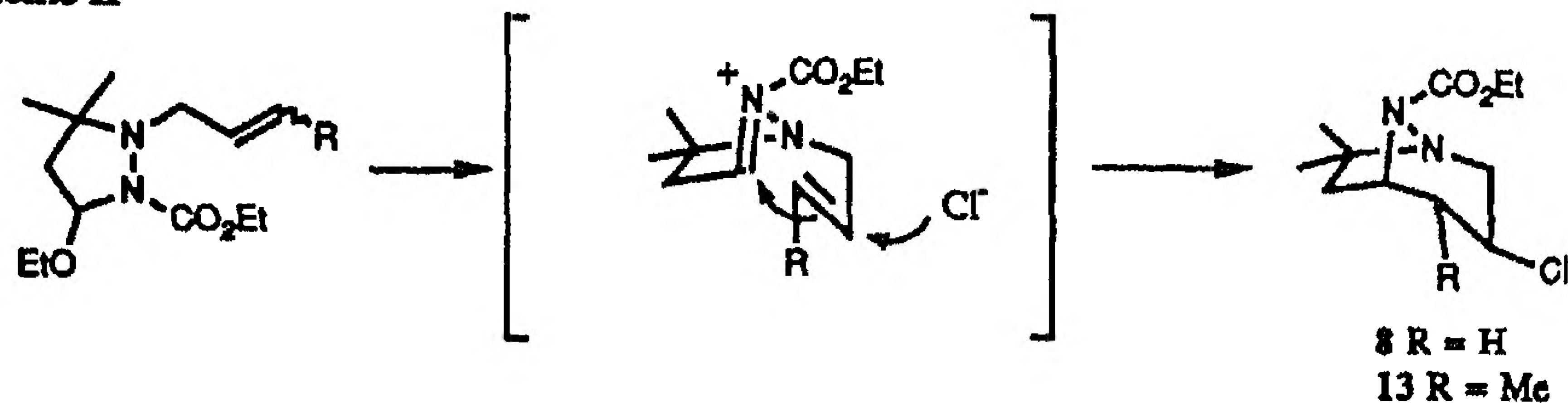
Scheme I



The results on seven other examples, collected in the Table, demonstrate the usefulness of this new procedure. The alkylation at N-1 proceeded in moderate to good yield with activated alkyl halides.¹⁰ Introduction of the alkoxycarbonyl moiety was achieved via one of the following three methods: (A) reaction with diethyl dicarbonate as described above, (B) deprotonation with NaH in THF, followed by acylation with ethyl or methyl chloroformate, and (C) deprotonation with LDA in THF at $-78\text{ }^{\circ}\text{C}$, followed by acylation with methyl cyanofornate.^{6,11} Interestingly, method B gave a considerable amount of O-acylated product in most cases, whereas the other methods did not produce this byproduct. Reduction and ethanolysis occurred in excellent yield in all cases. The ethanolysis was not carried out in the case of entries 6 and 7, in view of the acid lability of the N-1 substituent.

For the cyclization reactions of entries 1-5, both TiCl_4 and SnCl_4 were tried as Lewis acids, but TiCl_4 gave higher yields. The milder acid $\text{BF}_3\cdot\text{OEt}_2$ was successfully used in the case of the more nucleophilic π -systems of entries 6 and 7. Cyclization by simple dissolution of the precursor in formic acid was attempted for all entries and was successful except for entries 2 and 5. Apparently, ring closure with formic acid requires either a trisubstituted olefin or an acetylene.

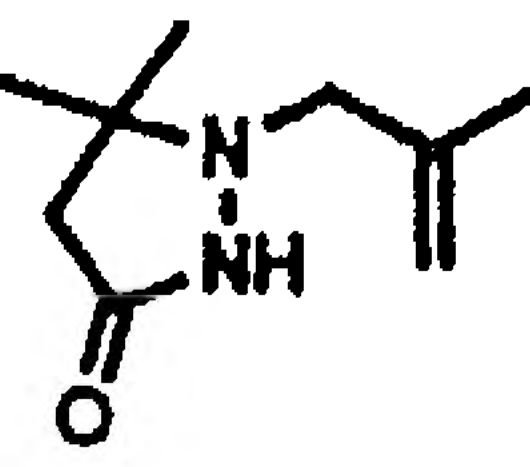
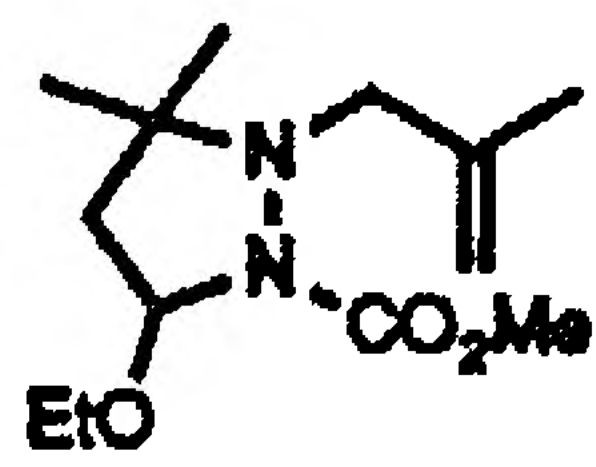
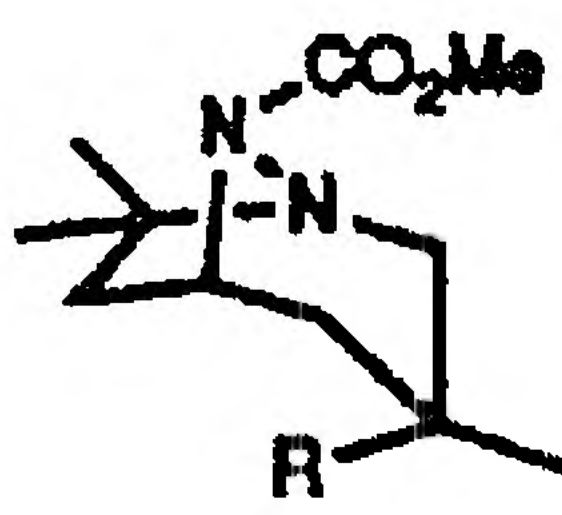
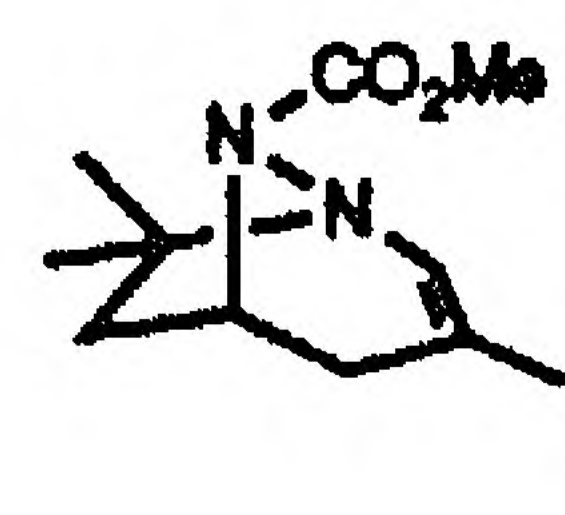
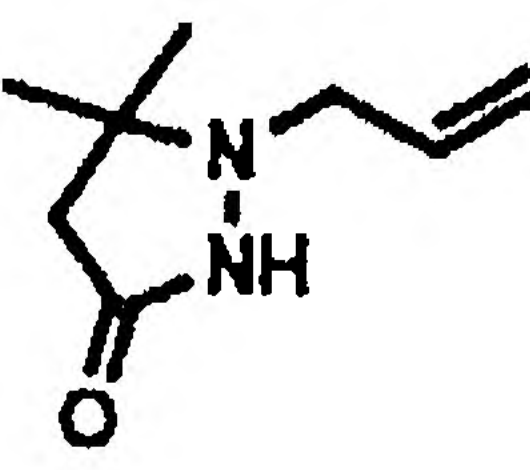
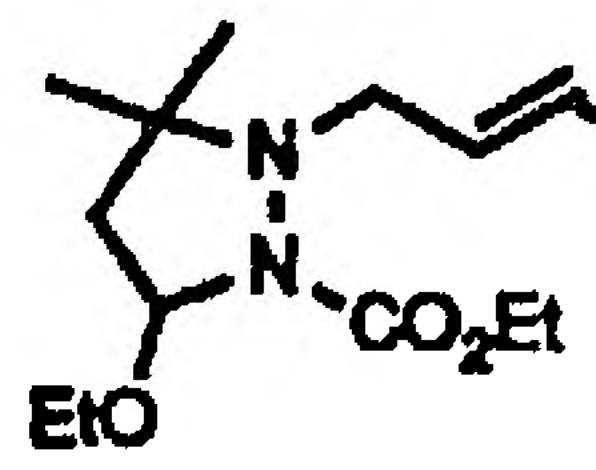
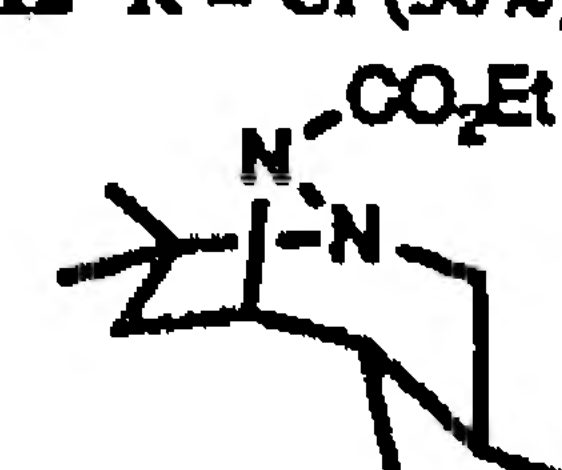
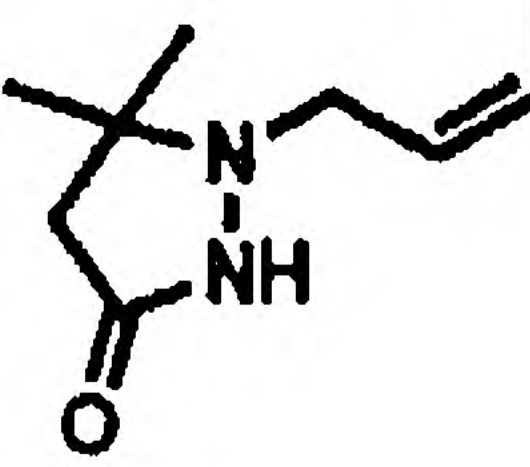
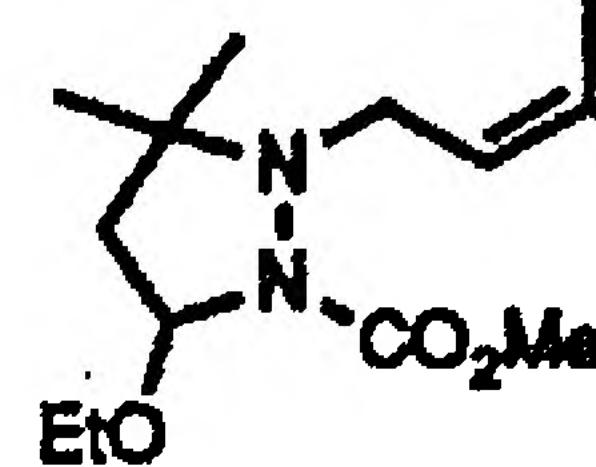
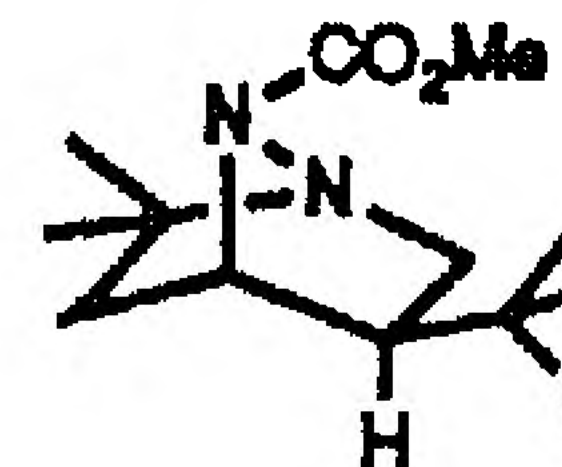

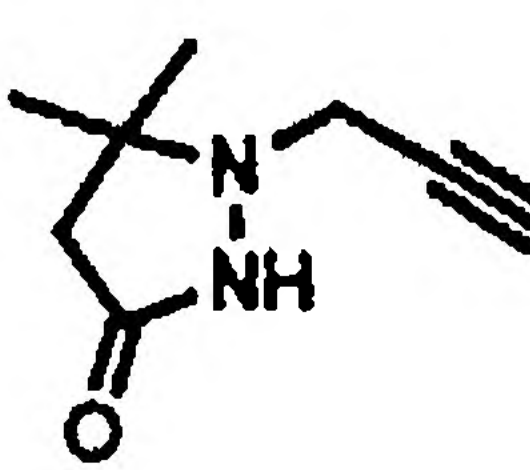
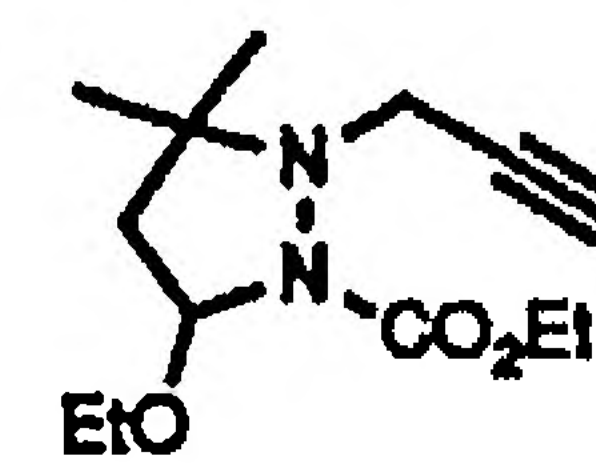
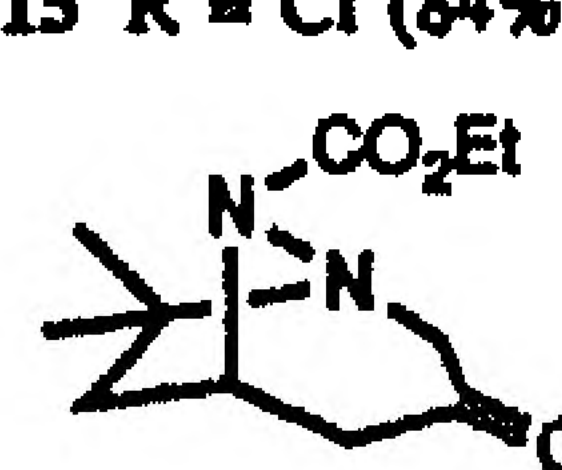
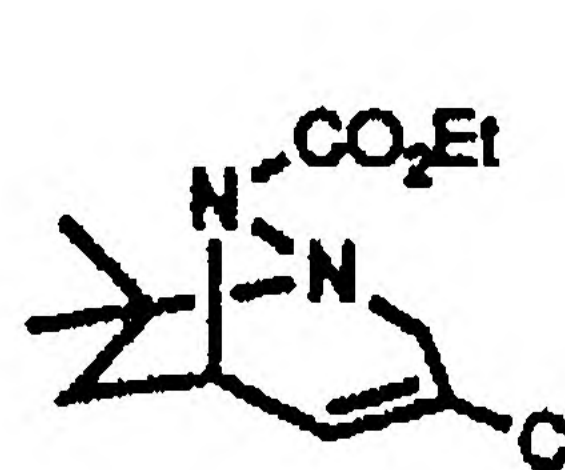
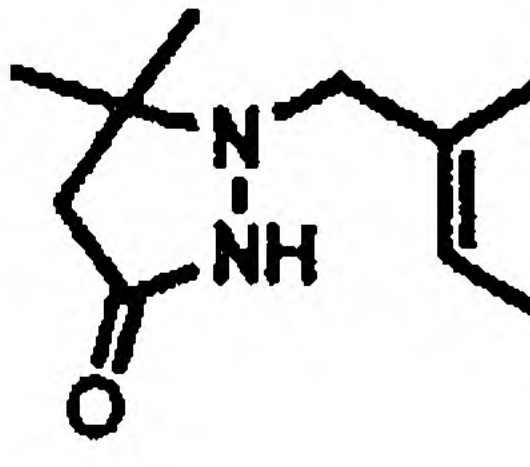
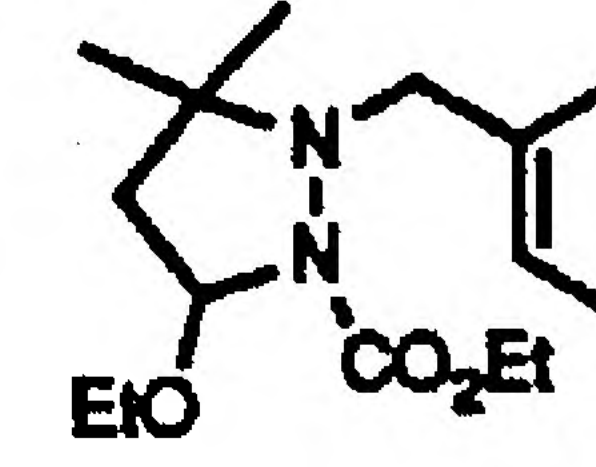
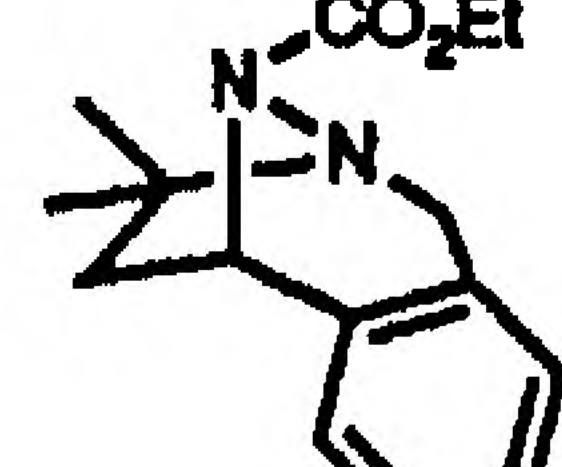
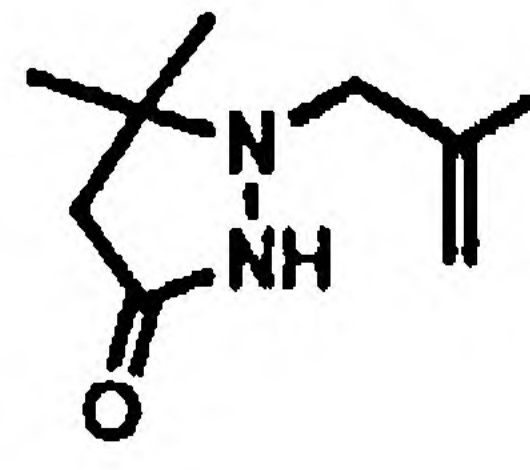
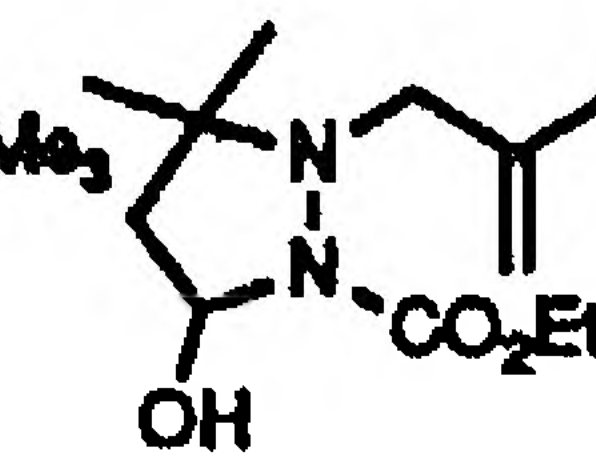
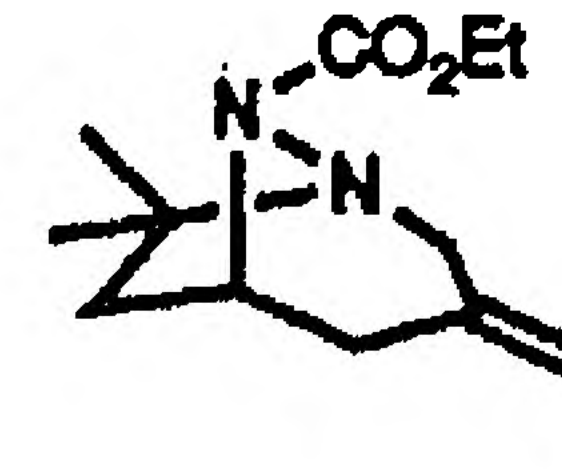
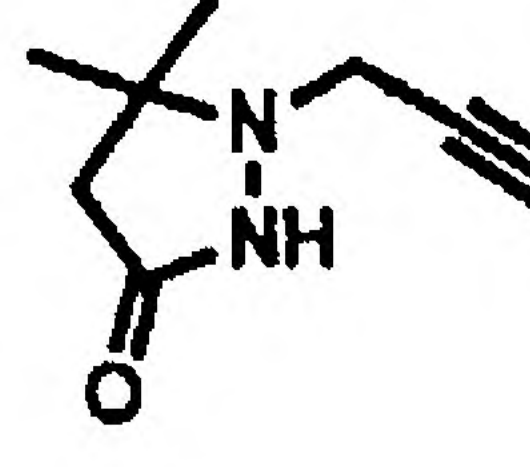
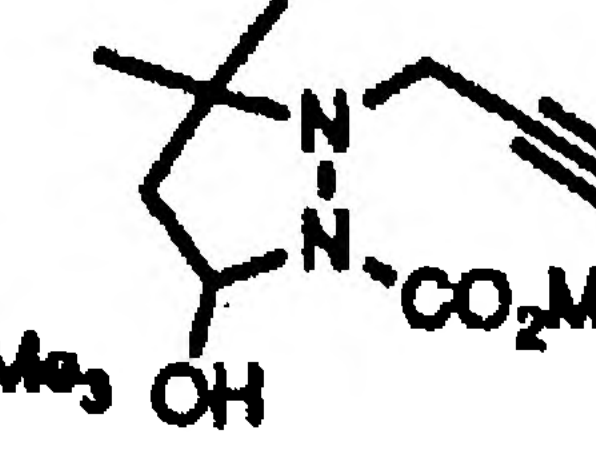
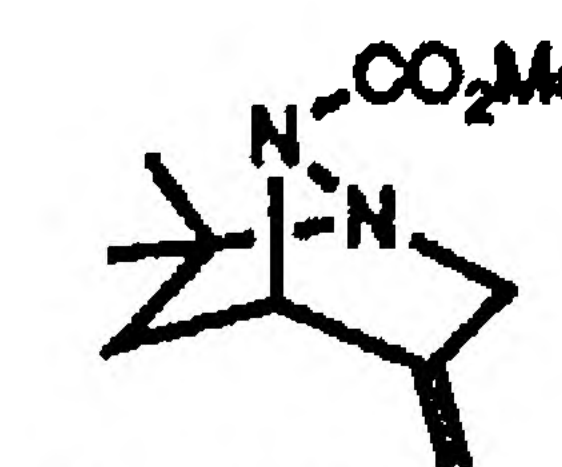
Scheme II



Compounds 10 and 12 were obtained as single isomers, but their stereochemistry could not yet be ascertained. We assume that the methyl substituent is equatorial in view of the severe steric interaction between the two endo-methyl groups in the alternative stereoisomer. The formation of a cyclization product with an equatorial methyl group requires a tertiary carbocation as intermediate, which is not unreasonable, especially so, because such an intermediate also explains the formation of olefin 11 as byproduct.

The sequence of entry 2 yielded a single cyclization product 13, of which the stereochemistry was easily inferred from the splitting pattern of the ^1H NMR signal of the hydrogen adjacent to the chlorine atom. This signal (dt, 3.76 ppm) showed two ax-ax couplings ($J = 10.8\text{ Hz}$) and one ax-eq coupling ($J = 6.3\text{ Hz}$, cf. compound 9). Apparently, only the E-isomer cyclized, if one assumes a mechanism as shown in Scheme II ($R = \text{Me}$). Entry 3 also produced single cyclization products 14 and 15, but now with the 1,7-diazabicyclo[2.2.1]-heptane skeleton. The bridgehead hydrogen of 14 showed a doublet at 4.43 ppm ($J = 4.9\text{ Hz}$) in the ^1H NMR

Table

entry	alkylation product (yield)	cyclization precursor (yield) ^a	acid	product(s) ^b (yield)
1	 (88%)	 (56%, B)	HCOOH TiCl ₄	 10 R = OCHO (37%)  11 (34%) 11 (16%)
2	 (61%) E:Z = 77:23	 (45%, A) E:Z = 77:23	TiCl ₄	 13 (53%)
3	 (82%)	 (41%, C)	HCOOH TiCl ₄	 14 R = OCHO (84%)  15 R = Cl (84%)
4	 (40%)	 (44%, B)	HCOOH TiCl ₄	 16 (47%)  17 (24%)
5	 (80%)	 (73%, A)	TiCl ₄	 18 (62%)
6	 (83%)	 (60%, A)	HCOOH BF ₃ ·OEt ₂	 19 (85%) 19 (61%)
7	 (68%)	 (37%, B)	HCOOH BF ₃ ·OEt ₂	 20 (42%) 20 (62%)

a) combined yields for alkoxy-carbonylation, reduction and (entries 1 to 5) ethanolysis; the capital letter refers to the method of alkoxy-carbonylation (see text). b) see ref. 9. c) chloride 12 was obtained as an inseparable mixture with 11.

spectrum, which proves the exo-orientation of the substituent.^{2a} Entries 4-7 gave single cyclizations products, of which the structures were readily inferred from the ¹H NMR spectra. The regiochemical influence of the trimethylsilyl substituent is fully reflected in the product structures of entries 6 and 7.

In summary, cyclic *N*-acylhydrazonium ions **2** are readily generated and are useful intermediates for the synthesis of a variety of elaborate hydrazines.

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- These products were characterized by IR, ¹H-NMR, ¹³C-NMR and accurate mass measurements. The spectral data corresponded to the given structures. Some selected data are: **9** ¹H-NMR (CDCl₃, 200 MHz) 1.13 (s, 3 H, CH₃(exo)), 1.42 (s, 3 H, CH₃(endo)), 1.67 (d, 1 H, *J* = 12.9 Hz, (CH₃)₂CCHH(endo)), 1.89 (dd, 1 H, *J* = 12.9, 7.6 Hz, (CH₃)₂CCHH(exo)), 2.12 (m, 2 H, NCHCH₂CHCl), 3.20 (dd, 1 H, *J* = 11.1, 14.0 Hz, NCHH(ax)), 3.35 (dd, 1 H, *J* = 6.2, 14.0 Hz, NCHH(eq)), 3.60 (m, 1 H, NCH), 3.79 (bs, 1 H, NH), 4.20 (tt, 1 H, *J* = 11.1, 6.3 Hz, CClH). ¹³C-NMR (CDCl₃, 50 MHz) 22.9 (q, CH₃), 31.9 (q, CH₃), 42.2 (t, NCHCH₂CHCl), 45.3 (t, (CH₃)₂CCH₂), 50.9 (d, CHCl), 57.7 (d, NCH), 58.1 (t, NCH₂), 65.6 (s, C(CH₃)₂). **11** ¹H-NMR (C₆D₆, 65 °C, 250 MHz) 1.09 (s, 3 H, CH₃), 1.14 (s, 3 H, CH₃), 1.20 (dd, 1 H, *J* = 12.3, 5.4 Hz, (CH₃)₂CCHH(endo)) 1.15-1.25 (m, 1 H, C=CCHH), 1.28 (s, 3 H, CH₃), 1.79 (dd, 1 H, *J* = 12.2, 7.9 Hz, (CH₃)₂CCHH(exo)), 2.56 (d, 1 H, *J* = 15.7 Hz, C=CCHH), 3.54 (s, 3 H, CO₂CH₃), 4.46 (bs, 1 H, NCH), 7.50 (s, 1 H, CHO). ¹³C-NMR (50 MHz, CDCl₃) 19.6 (q, CH₃), 24.2 (q, CH₃), 29.3 (q, CH₃), 37.4 (t, CH₂C=C), 45.8 (t, (CH₃)₂CCH₂), 52.6 (q, CO₂CH₃), 53.6 (d, NCH), 73.2 (s, NC(CH₃)₂), 124.7 (s, C=CCH₃), 134.8 (d, C=CH), 154.6 (s, CO). **13** ¹H-NMR (200 MHz, CDCl₃) 1.03 (d, 3 H, *J* = 6.7 Hz, CHCH₃), 1.18 (s, 3 H, NCCH₃(exo)), 1.30 (t, 3 H, *J* = 7.0 Hz, CH₂CH₃), 1.36 (s, 3 H, NCCH₃(endo)), 1.63 (d, 1 H, *J* = 12.7 Hz, (CH₃)₂CCHH(endo)), 1.88 (dd, 1 H, *J* = 12.7, 8.0 Hz, (CH₃)₂CCHH(exo)), 2.12 (m, 1 H, CH₃CH), 3.10 (dd, 1 H, *J* = 14.4, 11.2 Hz, NCHH(ax)), 3.42 (dd, 1 H, *J* = 5.9, 11.1 Hz, NCHH(eq)), 3.76 (dt, 1 H, *J* = 6.3, 10.8 Hz, CHCl), 4.26 (m, 2 H, CH₃CH₂), 4.35 (m, 1 H, NCH). ¹³C-NMR (50 MHz, CDCl₃) 14.7 (q, CH₂CH₃), 15.5 (q, CHCH₃), 22.6 (q, NCCH₃), 31.3 (q, NCCH₃), 40.1 (t, (CH₃)₂CCH₂), 43.5 (d, CHCH₃), 56.1 (t, NCH₂), 57.6 (d, NCH), 59.7 (d, CHCl), 61.5 (t, CH₂CH₃), 65.1 (s, C(CH₃)₂), 153.2 (s, CO). **14** ¹H-NMR (250 MHz, C₇D₈, 90 °C) 0.88 (d, 1 H, *J* = 11.3 Hz, (CH₃)₂CCHH(endo)), 0.93 (s, 3 H, NCCH₃(exo)), 1.05 (s, 3 H, NCCH₃(endo)), 1.25 (s, 3 H, CHCCH₃), 1.29 (s, 3 H, CHCCH₃), 1.52 (dd, 1 H, *J* = 5.0, 11.3 Hz, (CH₃)₂CCHH(exo)), 1.96 (t, 1 H, *J* = 7.3 Hz, (CH₃)₂CCH), 2.60 (dd, 1 H, *J* = 6.8, 12.6 Hz, NCHH), 2.98 (dd, 1 H, *J* = 7.9, 12.6 Hz, NCHH), 3.48 (s, 3 H, CO₂CH₃), 4.43 (d, 1 H, *J* = 4.9 Hz, NCH), 7.61 (s, 1 H, OCHO). ¹³C-NMR (50 MHz, CDCl₃) 23.3 (q, CH₃), 23.8 (q, CH₃), 25.1 (q, CH₃), 30.5 (q, CH₃), 47.0 (t, (CH₃)₂CCH₂), 52.0 (t, NCH₂), 52.4 (d, (CH₃)₂CCH), 54.1 (d, NCH), 61.0 (q, CO₂CH₃), 66.3 (s, C(CH₃)₂N), 83.5 (s, C(CH₃)₂O), 153.7 (s, CO₂CH₃), 159.9 (d, OCHO).
- Substitution with non-activated alkylhalides is also possible albeit with lower yields; e.g. 4-bromo-1-butene gave the *N*-butenyl derivative in 21% yield.
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