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

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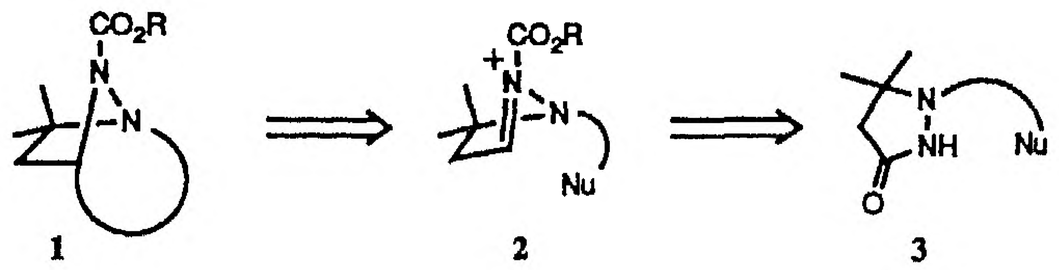
Summary: The efficient preparation of bridged diazabicyclics **1** from pyrazolidones **3** by cationic ring closure of endocyclic hydrazonium electrophiles **2** is described.

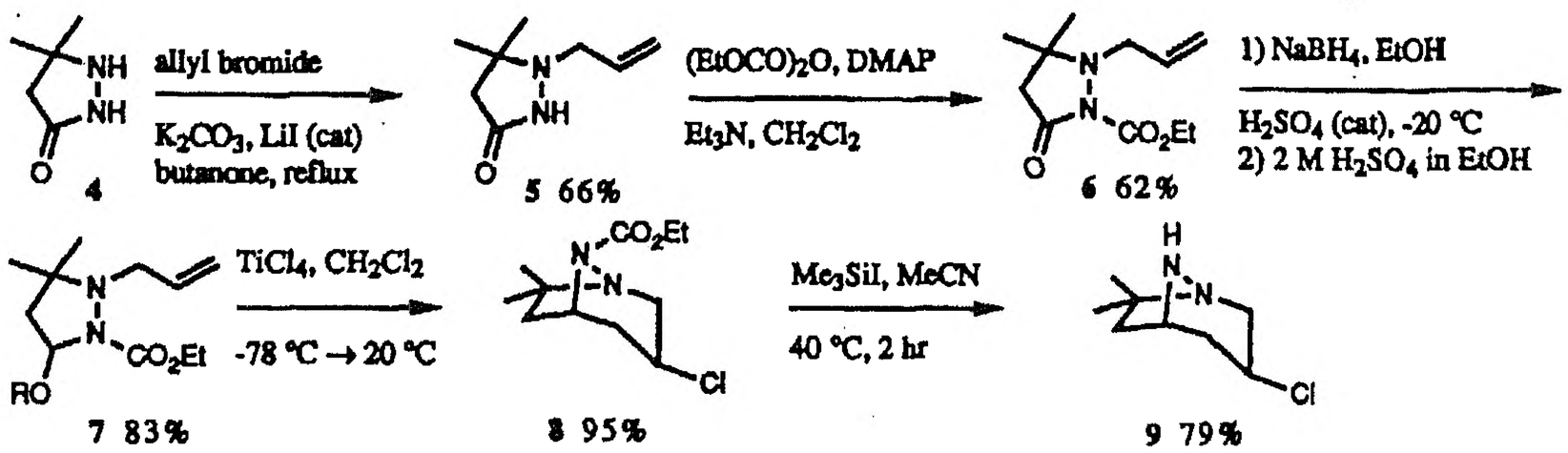
The recent interest in the biological[1] and physical[2] properties of cyclic hydrazine derivatives sharply contrasts with the relative paucity of methods for preparing this compound class. The major route for the construction of bridged hydrazines **1** is the 1,3-dipolar cycloaddition reaction[3] requiring 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 availability[4] 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.



1 **2** **3**

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 alkoxycarbonyl 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 reduction[6] 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 ion[7] 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 $TiCl_4$ (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 compound[9] (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 state[7] (see Scheme II, R = H).

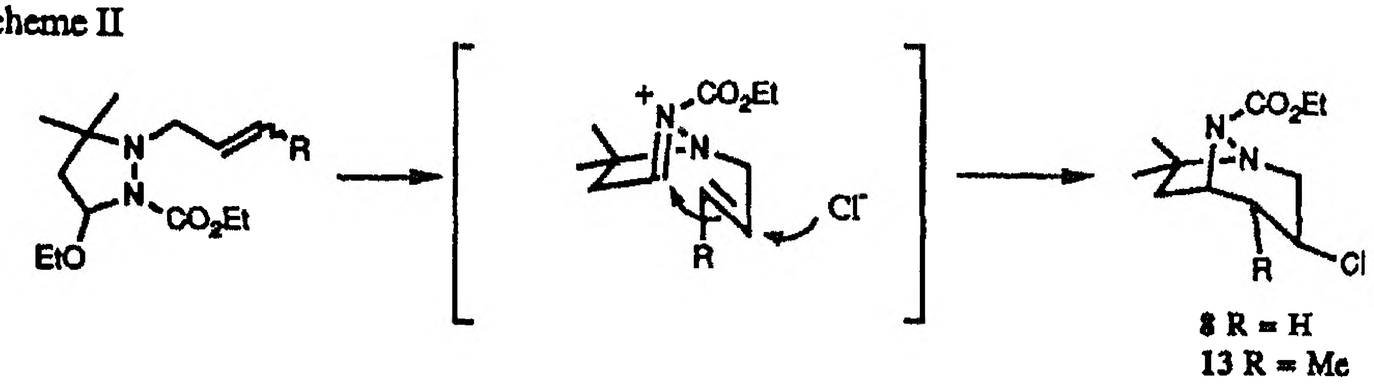
Scheme I



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 °C, followed by acylation with methyl cyanoformate.[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 $BF_3{\cdot}OEt_2$ 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.

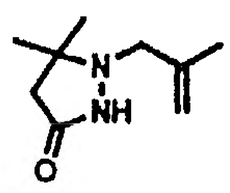
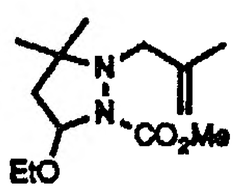
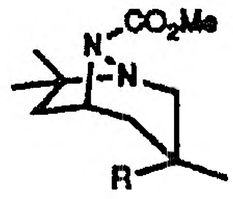
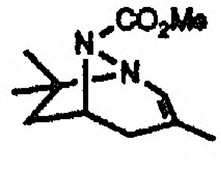
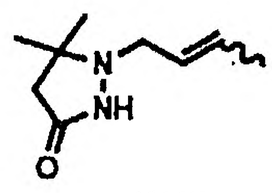
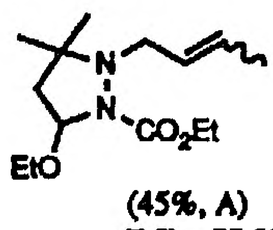
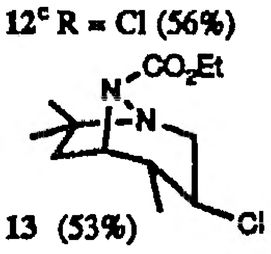
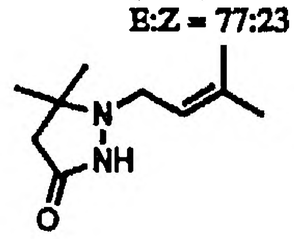
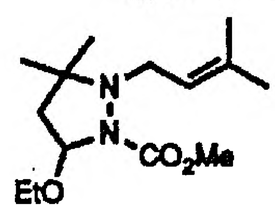
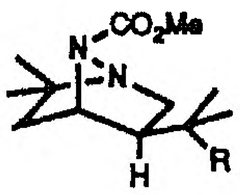
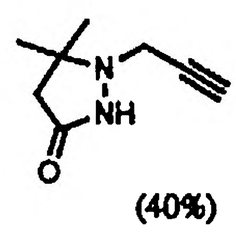
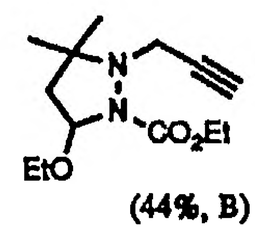
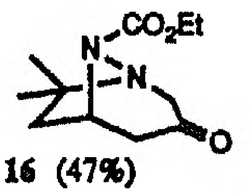
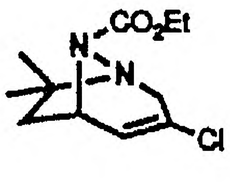
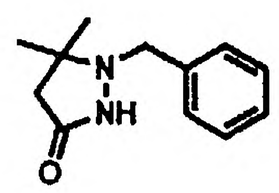
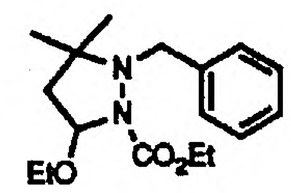
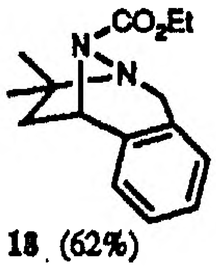
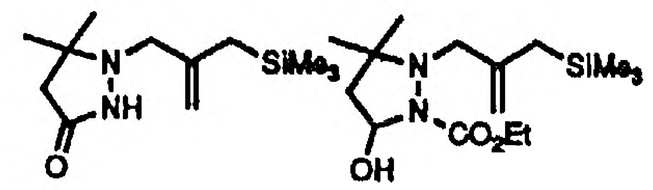
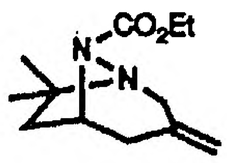
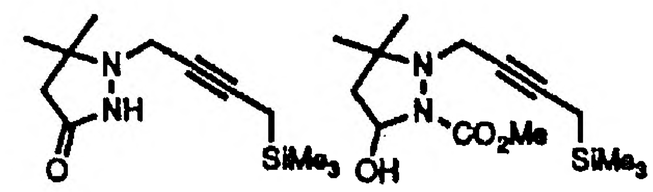
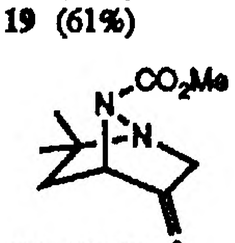
Scheme II



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 Hz) and one ax-eq coupling (J = 6.3 Hz, cf. compound **9**). Apparently, only the E-isomer cyclized, if one assumes a mechanism as shown in Scheme II (R = 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 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%) 12[c] R = Cl (56%)	 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 alkoxycarbonylation, reduction and (entries 1 to 5) ethanolysis; the capital letter refers to the method of alkoxycarbonylation (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 ^{1}H 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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9. These products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and accurate mass measurements. The spectral data corresponded to the given structures. Some selected data are: **9** ^{1}H-NMR ($CDCl_3$, 200 MHz) 1.13 (s, 3 H, CH_3(exo)), 1.42 (s, 3 H, CH_3(endo)), 1.67 (d, 1 H, J = 12.9 Hz, $(CH_3)_2CCHH$(endo)), 1.89 (dd, 1 H, J = 12.9, 7.6 Hz, $(CH_3)_2CCHH$(exo)), 2.12 (m, 2 H, NCHCH_2CHCl), 3.20 (dd, 1 H, J = 11.1, 14.0 Hz, NC*H*H(ax)), 3.35 (dd, 1 H, J = 6.2, 14.0 Hz, NC*H*H(eq)), 3.60 (m, I H, NCH), 3.79 (bs, 1 H, NH), 4.20 (tt, 1 H, J = 11.1, 6.3 Hz, CCl*H*). ^{13}C-NMR ($CDCl_3$, 50 MHz) 22.9 (q, CH_3), 31.9 (q, CH_3), 42.2 (t, NCHCH_2CHCl), 45.3 (t, $(CH_3)_2CCH_2$), 50.9 (d, CHCl), 57.7 (d, NCH), 58.1 (t, NCH_2), 65.6 (s, $C(CH_3)_2$). **11** ^{1}H-NMR (C_6D_6, 65 °C, 250 MHz) 1.09 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.20 (dd, 1 H, J = 12.3, 5.4 Hz, $(CH_3)_2CCHH$(endo)) 1.15-1.25 (m, 1 H, C=CC*H*H), 1.28 (s, 3 H, CH_3), 1.79 (dd, 1 H, J = 12.2, 7.9 Hz, $(CH_3)_2CCHH$(exo)), 2.56 (d, 1 H, J = 15.7 Hz, C=CCH*H*), 3.54 (s, 3 H, CO_2CH_3), 4.46 (bs, 1 H, NCH), 7.50 (s, 1 H, CHO). ^{13}C-NMR (50 MHz, $CDCl_3$) 19.6 (q, CH_3), 24.2 (q, CH_3), 29.3 (q, CH_3), 37.4 (t, CH_2C=C), 45.8 (t, $(CH_3)_2CCH_2$), 52.6 (q, CO_2CH_3), 53.6 (d, NCH), 73.2 (s, $NC(CH_3)_2$), 124.7 (s, C=CCH_3), 134.8 (d, C=CH), 154.6 (s, CO). **13** ^{1}H-NMR (200 MHz, $CDCl_3$) 1.03 (d, 3 H, J = 6.7 Hz, CHCH_3), 1.18 (s, 3 H, $NCCH_3$(exo)), 1.30 (t, 3 H, J = 7.0 Hz, CH_2CH_3), 1.36 (s, 3 H, $NCCH_3$(endo)), 1.63 (d, 1 H, J = 12.7 Hz, $(CH_3)_2CCHH$(endo)), 1.88 (dd, 1 H, J = 12.7, 8.0 Hz, $(CH_3)_2CCHH$(exo)), 2.12 (m, 1 H, CH_3CH), 3.10 (dd, 1 H, J = 14.4, 11.2 Hz, NC*H*H(ax)), 3.42 (dd, 1 H, J = 5.9, 11.1 Hz, NC*H*H(eq)), 3.76 (dt, 1 H, J = 6.3, 10.8 Hz, CHCl), 4.26 (m, 2 H, CH_3CH_2), 4.35 (m, 1 H, NCH). ^{13}C-NMR (50 MHz, $CDCl_3$) 14.7 (q, CH_2CH_3), 15.5 (q, $CHCH_3$), 22.6 (q, $NCCH_3$), 31.3 (q, $NCCH_3$), 40.1 (t, $(CH_3)_2CCH_2$), 43.5 (d, $CHCH_3$), 56.1 (t, NCH_2), 57.6 (d, NCH), 59.7 (d, CHCl), 61.5 (t, CH_2CH_3), 65.1 (s, $C(CH_3)_2$), 153.2 (s, CO). **14** ^{1}H-NMR (250 MHz, C_7D_8, 90 °C) 0.88 (d, 1 H, J = 11.3 Hz, $(CH_3)_2CCHH$(endo)), 0.93 (s, 3 H, $NCCH_3$(exo)), 1.05 (s, 3 H, $NCCH_3$(endo)), 1.25 (s, 3 H, $CHCCH_3$), 1.29 (s, 3 H, $CHCCH_3$), 1.52 (dd, 1 H, J = 5.0, 11.3 Hz, $(CH_3)_2CCHH$(exo)), 1.96 (t, 1 H, J = 7.3 Hz, $(CH_3)_2CCH$), 2.60 (dd, 1 H, J = 6.8, 12.6 Hz, NC*H*H), 2.98 (dd, 1 H, J = 7.9, 12.6 Hz, NC*H*H), 3.48 (s, 3 H, CO_2CH_3), 4,43 (d, 1 H, J = 4.9 Hz, NCH), 7.61 (s, 1 H, OCHO). ^{13}C-NMR (50 MHz, $CDCl_3$) 23.3 (q, CH_3), 23.8 (q, CH_3), 25.1 (q, CH_3), 30.5 (q, CH_3), 47.0 (t, $(CH_3)_2CCH_2$), 52.0 (t, NCH_2), 52,4 (d, $(CH_3)_2CCH$), 54.1 (d, NCH), 61.0 (q, CO_2CH_3), 66.3 (s, $C(CH_3)_2N$), 83.5 (s, $C(CH_3)_2O$), 153.7 (s, CO_2CH_3), 159.9 (d, OCHO).

10. 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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