NMR ($CDCl_3$) δ 1.84 (m, 4 H), 2.19 (s, 3 H), 2.57 (m, 2 H), 3.84 (t, 2 H, J = 7 Hz), 5.66 (d, 1 H, J = 2 Hz), 6.48 (d, 1 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 137.5 (s), 126.9 (s), 107.8 (d), 97.1 (d), 45.3 (t), 23.7 (t), 21.2 (t), 20.9 (q); mass spectrum, m/e (relative intensity) 179 (36), 138 (10), 137 (100), 136 (47), 120 (30), 109 (14).

2-Acetoxy-3-acetyl-5,6,7,8-tetrahydroindolizine (10b): ^1H NMR ($CDCl_3$) δ 1.84 (m, 4 H), 2.27 (s, 3 H), 2.60 (m, 2 H), 4.25 (m, 2 H), 5.77 (s, 1 H).

2-Acetoxy-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine (9c): sublimation; mp 65 °C; 25% yield from **4c**; IR ($CHCl_3$) 3010, 2930, 1740, 1560, 1460, 1425, 1350, 1235, 1010; ^1H NMR ($CDCl_3$) δ 1.73 (m, 6 H), 2.19 (s, 3 H), 2.60 (m, 2 H), 3.77 (m, 2 H), 5.73 (d, 1 H, J = 2 Hz), 6.54 (d, 1 H, J = 2 Hz); mass spectrum, m/e (relative intensity) 193 (39), 152 (10), 151 (100), 150 (37), 134 (46), 123 (10). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.08; H, 7.91; N, 7.12.

2-Acetoxy-3-acetyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]-azepine (10c): ^1H NMR ($CDCl_3$) δ 1.73 (m, 6 H), 2.28 (s, 3 H), 2.36 (s, 3 H), 2.62 (m, 2 H), 4.55 (m, 2 H), 5.88 (s, 1 H).

6-Acetoxy-5-methyl-2,3-dihydro-1*H*-pyrrolizine (9d): flash chromatography using 70:30 ether–petroleum ether; mp 72 °C; 36% yield from **4d**; IR ($CHCl_3$) 3030, 1750, 1590, 1360, 1240; ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H), 2.25 (s, 3 H), 2.43 (m, 2 H), 2.86 (t, 2 H, J = 7 Hz), 3.83 (t, 2 H, J = 7 Hz), 5.66 (s, 1 H); mass spectrum, m/e (relative intensity) 179 (30), 138 (10), 137 (100), 136 (98), 120 (11). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.05; H, 7.44; N, 7.85.

6-Acetoxy-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (9e): flash chromatography using 55:45 petroleum ether–ethyl acetate; mp 93 °C; 51% yield from **4e**; IR ($CHCl_3$) 3000, 1760, 1600, 1580, 1565, 1510, 1360, 1300; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.17–2.65 (m, 2 H), 2.92 (t, 2 H, J = 7 Hz), 4.06 (t, 2 H, J = 7 Hz), 5.87 (s, 1 H), 7.36 (m, 5 H); mass spectrum, m/e (relative intensity) 241 (18), 200 (17), 199 (100), 198 (47), 182 (8). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.24; H, 6.16; N, 5.91. Found: C, 74.66; H, 6.26; N, 5.80.

2-Acetoxy-3-phenyl-5,6,7,8-tetrahydroindolizine (9f): flash chromatography using 75:25 petroleum ether–ethyl acetate; mp 105 °C; 53% yield from **4f**; IR ($CHCl_3$) 3010, 2960, 1755, 1610, 1585, 1510, 1415, 1370, 1350, 1230; ^1H NMR ($CDCl_3$) δ 1.86 (m, 4 H), 2.10 (s, 3 H), 2.82 (m, 2 H), 3.80 (m, 2 H), 5.84 (s, 1 H), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) 170.0 (s), 134.4 (s), 130.6 (s), 129.6 (d), 128.4 (d), 127.5 (s), 126.9 (d), 120.6 (s), 98.8 (d), 44.4 (t), 23.7 (t), 23.5 (t), 20.9 (t), 20.7 (q); mass spectrum, m/e (relative intensity) 255 (19), 214 (18), 213 (100), 212 (28), 196 (10). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48. Found: C, 75.15; H, 6.64; N, 5.41.

2-Acetoxy-3-phenyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine (9g): flash chromatography using 75:25 petroleum ether–ethyl acetate; mp 104 °C; 44% yield from **4g**; IR ($CHCl_3$) 3000, 2940, 1750, 1610, 1585, 1470, 1360, 1225; ^1H NMR ($CDCl_3$) δ 1.66 (m, 6 H), 2.01 (s, 3 H), 2.65 (m, 2 H), 3.73 (m, 2 H), 5.77 (s, 1 H), 7.20 (m, 5 H); mass spectrum, m/e (relative intensity) 269 (20), 228 (16), 227 (100), 226 (22), 210 (10), 196 (10). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.11; N, 5.20. Found: C, 75.91; H, 7.07; N, 5.37.

Registry No. **1a**, 616-45-5; **1b**, 675-20-7; **1c**, 105-60-2; **2a**, 872-50-4; **2b**, 931-20-4; **2c**, 2556-73-2; **2d**, 2687-91-4; **2e**, 5291-77-0; **2f**, 4783-65-7; **2g**, 33241-96-2; **2h**, 61516-73-2; **4a**, 86208-87-9; **4b**, 86208-88-0; **4c**, 86208-89-1; **4d**, 115860-49-6; **4e**, 115860-50-9; **4f**, 115860-51-0; **4g**, 115860-52-1; **4h**, 115860-53-2; **6a**, 78167-68-7; **7a**, 97181-96-9; **7b**, 97202-63-6; **7c**, 97202-64-7; **7d**, 115860-54-3; **7e**, 115860-55-4; **7f**, 115860-56-5; **7g**, 115860-57-6; **8h**, 115860-58-7; **9a**, 115860-59-8; **9b**, 115860-61-2; **9c**, 115860-63-4; **9d**, 115860-65-6; **9e**, 115860-66-7; **9f**, 115860-67-8; **9g**, 115860-68-9; **10a**, 115860-60-1; **10b**, 115860-62-3; **10c**, 115860-64-5.

Synthesis of 2-Substituted Imidazoles and Benzimidazoles and of 3-Substituted Pyrazoles by Lithiation of *N*-(Dialkylamino)methyl Heterocycles[1]

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Received January 25, 1988

The lithiation of *N*-(dialkylamino)methyl (aminal) derivatives of imidazole, benzimidazole, and pyrazole (themselves readily available from the parent heterocycles, formaldehyde, and a secondary amine) occurs smoothly at the 2-, 2-, and 5-positions, respectively, upon treatment with *n*-butyllithium in ether or tetrahydrofuran. Reaction with electrophiles, and subsequent facile acid-catalyzed hydrolysis of the protecting group, provides 2-substituted imidazoles, 2-substituted benzimidazoles, and 3(5)-substituted pyrazoles in good overall yields.

Introduction

The lithiation of heterocyclic compounds containing an NH group normally leads only to the *N*-lithio derivative[3] but, when the nitrogen is substituted, C-lithiation can occur. If the N-substituent can be later removed, it serves as a protecting group for the NH. Thus the lithiation of, for example, imidazoles[4-5] occurs readily when the ring *N*-hydrogen atom is replaced. Many groups have been used for protection of imidazole in this way (cf. discussion in ref 5):

(a) The imidazole nitrogen is efficiently protected by an alkyl group,[3] but such compounds cannot be deprotected under normal conditions.

(b) Benzylic N-protection of imidazole[6] is unsatisfactory since competitive lithiation[5] at the benzylic methylene group is usually observed.

(c) *tert*-Butyl has also been used[5] for the protection of imidazole nitrogen, unfortunately, it was rather difficult to introduce and to remove.

(d) 1-(Triphenylmethyl)imidazole[7] has only a slight solubility in diethyl ether,[5] and thus the deprotonation step

(1) A paper in a series entitled "Heterocyclic Carbanions". For the previous paper, see: ref 18. Also see: ref 16 and 17.
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is retarded. Its solubility in THF is much better however.

(e) Alkoxymethyl N-protected imidazoles[8] are deprotonated at the 2-position by butyllithium in high yield, but a significant disadvantage of the alkoxymethyl protecting group is the severe deprotection conditions required and the comparatively low isolated yield of some of the products.[9]

(f) The use of dialkyloxymethyl[10] as the blocking group for the nitrogen of imidazole overcomes the hydrolysis problem of the monoalkoxymethyl group, but these dialkyloxymethyl protected imidazoles are quite moisture-sensitive.

(g) Trialkylsilyl N-protection[11] is unsuitable for imidazole because of the tendency for N to C silyl group rearrangements.

(h) Introduction of an arylsulfonyl group[12] onto an imidazole nitrogen appears to reduce the ease of metalation at the 2-position of the imidazole ring, and therefore requires more severe lithiation conditions.[5]

(i) Dimethylaminosulfonyl initially appeared to be one of the better protective groups available,[5,13] but it still requires several hours reflux in 2 M hydrochloric acid or 2% KOH for removal, and recent work has shown that the lithio derivative fails to react with electrophiles such as DMF.[14]

(j) Some of these problems have been overcome with the [2-(trimethylsilyl)ethoxy]methyl (SEM) group,[15] which is readily introduced, is stable under lithiation conditions and can be readily removed either by warming with dilute acid or with anhydrous tetrabutylammonium fluoride. However, the lithiated species did not give the expected products with alkyl halides other than methyl iodide, and acylation did not occur efficiently with acyl halides or anhydrides.[15b]

Thus many of these previously used protecting groups suffer from drawbacks; either they require strong reaction conditions for their introduction and/or removal or the lithiated derivatives fail to undergo reaction with certain electrophiles. Subsequent to the completion of the present work a report appeared on the use of the 1-ethoxyethyl protecting group,[14] which is hydrolyzed much more readily than the alkoxymethyl group while still having much greater stability than the dialkoxymethyl group. The lithiated species is also able to react efficiently with electrophiles such as DMF.

Recent work in this laboratory has shown that carbon dioxide can be used as an NH protecting group for the lithiation of indoles[16] and for a variety of other nitrogen heterocycles,[17] with the *N*-carboxyl group being readily introduced and removed under mild conditions in a simple one-pot procedure. However, the carbon dioxide method failed for a number of heterocyclic systems such as carbazole, tetrahydrocarbazole, imidazole, benzimidazole and pyrazole; although the lithium *N*-carbamates were readily formed in these cases, they failed to undergo C-lithiation.

We have recently described how lithiation can be achieved in the case of carbazole and tetrahydrocarbazole, by the use of *N*-(dialkylamino)methyl (aminal) protecting groups,[18] where lithiation occurs readily and cleanly at the adjacent aromatic position. 2,3-Dimethylindole also underwent lithiation using this method, but in this case metalation occurred on the C-2 methyl carbon.[18]

This lithiation of *N*-(dialkylamino)methyl heterocycles seemed to be worthy of further investigation, and the successful extension of this method to imidazole, benzimidazole, and pyrazole, and its comparison with existing methods, represents the subject of the present work.

Results and Discussion

The use of any protecting group in an organic reaction sequence normally involves the addition of two extra steps, namely the protection step and the deprotection step, but with an *N*-(dialkylamino)methyl group the latter step is virtually eliminated, since hydrolysis occurs very readily at room temperature on treatment with mild acid during the workup of the reaction. Thus the successful use of this type of group depends only upon how readily it can be introduced and whether the protected derivative undergoes the desired type of reaction.

(Dialkylamino)methyl derivatives of imidazole, benzimidazole, and pyrazole are all well-known,[19-22] and they are readily prepared from the parent heterocycles under Mannich reaction conditions,[23] so the utility of these groups with the above heterocyclic systems therefore depends solely upon the efficiency with which lithiation and subsequent reactions occur.

In the case of carbazole, the best solvent for the lithiation reaction was found to be hexane,[18] since this causes the dialkylamino group to coordinate to the butyllithium without any competition from the solvent. Lithiation did not occur without this complexation as was shown by the absence of any reaction with *N*-ethylcarbazole under the same conditions.[18] In the present case such a directed lithiation is probably less important since the *N*-alkyl derivatives of imidazole, benzimidazole, and pyrazole are all known to undergo metalation by using standard lithiation conditions.[3] This was confirmed when it was found that better yields of product were obtained after performing the lithiation reaction in ether or THF rather than in hexane.

Using published procedures, or minor modifications of

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Table I. Preparation of Substituted Heterocycles

entry	compd	electrophile	substituent	yield,[a] %	solvent	mp, °C	lit. mp or bp (mmHg), °C	ref
1	**3c**	$CH_3(CH_2)_3I$	$CH_3(CH_2)_3$	76		oil[b]	93/(0.02)	10
2	**3d**	$CH_3(CH_2)_3Br$	$CH_3(CH_2)_3CH(CH_2)_2CH_3$	27[c]	hexane	112–113		
3	**3e**	Ph_2CO	$Ph_2C(OH)$	72	$EtOH/CHCl_3$	187–189	189–190	24
4	**3f**	p-$CH_3C_6H_4CHO$	p-$CH_3C_6H_4CH(OH)$	60	$EtOH/CHCl_3$	178–179		
5	**3g**	p-$CH_3C_6H_4CO_2Et$	p-$CH_3C_6H_4CO$	65	EtOH	164–165		
6	**3h**	t-BuNCO	t-BuNHCO	62	EtOH	128–129		25
7	**6a**	D_2O	D	87	$EtOH/CHCl_3$	169–171	172–174	*d*
8	**6b**	CH_3I	CH_3	69	benzene	175–176	176	26
9	**6e**	Ph_2CO	$Ph_2C(OH)$	83	$EtOH/CHCl_3$	215–217	220–222	27
10	**6i**	$(CH_3)_2CHCHO$	$(CH_3)_2CHCHOH$	69	EtOH	225–227	227–228	28
11	**6j**	PhNCO	PhNHCO	79	EtOH	230–232	235–236	29
12	**6k**	cyclohexanone	cyclohexanol	72	EtOH/hexane	258–259	263	30
13	**9a**	D_2O	D	78	petroleum ether	64–66	69–70	*e*
14	**9b**	CH_3I	CH_3	55		oil[f]	72/(1.0)	31
15	**9e**	Ph_2CO	$Ph_2C(OH)$	48	EtOH	121–123		
16	**9l**	$PhCH_2Br$	$PhCH_2$	45		oil	140–150/(0.05)	32

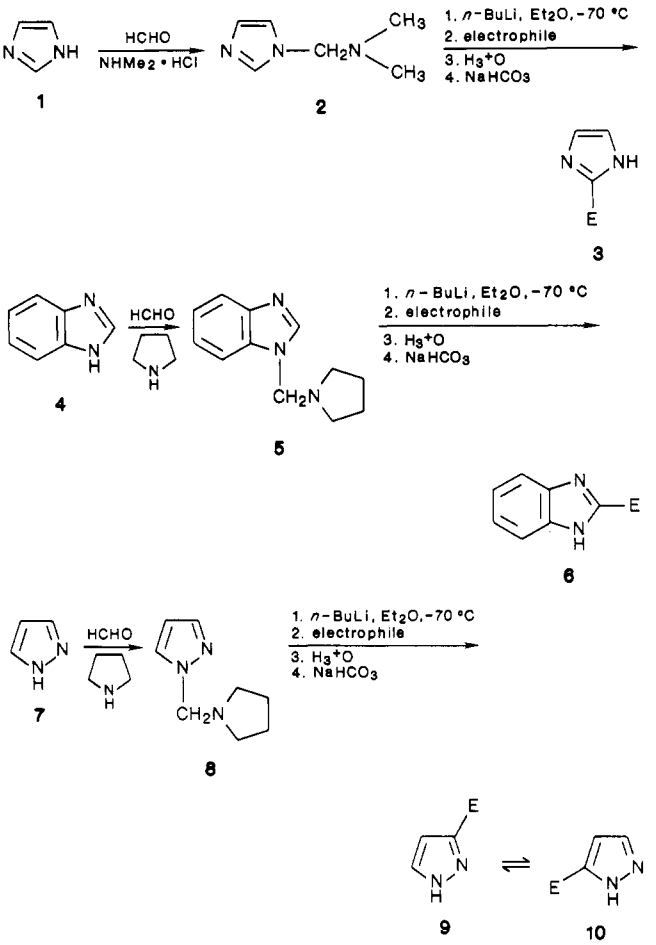
[a] Isolated yield. [b] Picrate: mp 96–97 °C (lit.[33] mp 96–97 °C). [c] Remainder **3c** (24%) and imidazole. [d] Melting point of benzimidazole. [e] Melting point of pyrazole. [f] Picrate: mp 141–143 °C (lit.[31] mp 143–144 °C).

them, we were able to prepare in quantity the (dimethylamino)methyl derivative of imidazole[19] and the pyrrolidinomethyl derivatives of benzimidazole[20] and of pyrazole.[22] All of these compounds (**2**, **5**, and **8**) underwent smooth lithiation, which occurred regiospecifically at the 2-position in imidazole and in benzimidazole and at the 5-position in pyrazole, upon treatment with *n*-butyllithium in diethyl ether. The resulting heterocyclic carbanions reacted with a variety of electrophiles, and subsequent workup under the normal conditions induced the expected facile acid-catalyzed hydrolysis of the protecting (dialkylamino)methyl group to provide directly the corresponding 2-substituted imidazoles (**3**), 2-substituted benzimidazoles (**6**), and 3-substituted (or 5-substituted in their tautomers **10**) pyrazoles (**9**), all unsubstituted at the 1-position, and all in good yields. No dilithiation products were observed.

The results summarized in Table I demonstrate that a wide range of electrophiles can be employed: primary (but not secondary) alkyl halides generally react readily (cf. the 2-substituted imidazole and benzimidazole of entries 1 and 8, and the 3(5)-substituted pyrazoles, entries 14 and 16). However a complication was noted with 1-bromobutane and imidazole (**2**), where further deprotonation (by unalkylated 2-lithioanion) at the α-position of the initial product led to formation of the 2-(4-octyl)derivative (**3d**). This result was not observed with 1-iodobutane (entry 1), presumably due to the faster rate of alkylation of the 2-lithio anion. Aldehydes and ketones (both aliphatic and aromatic) respectively afford the expected secondary (entries 4 and 10) and tertiary alcohols (entries 3, 9, 12, and 15), isocyanates as electrophiles give heterocyclic acid amides (Entries 6 and 11), esters give acyl-substituted heterocycles (entry 5), and deuteriation also takes place at the expected 2-position in benzimidazole (entry 7) and 3(5)-position in the case of pyrazole (entry 13). The yields of substituted heterocycles from *N*-(dialkylamino)methyl heterocycles range from 45% to 87%. Generally, the yields of 3(5)-substituted pyrazoles are not as high as those of 2-substituted imidazoles and 2-substituted benzimidazoles.

The 2-substituted imidazoles (**3**) and benzimidazoles (**6**) and 3(5)-substituted pyrazoles (**9** and **10**) were characterized analytically, by their ^1H and ^{13}C NMR spectra and by their IR spectra (see the Experimental Section). One point of interest regarding the spectra is that three imidazole ring carbon signals were observed in the ^{13}C NMR spectrum of 2-(*N*-*tert*-butylcarbamoyl)imidazole (**3h**) instead of two as expected for a 2-substituted imidazole derivative; presumably, intramolecular hydrogen bonding occurs in this compound, making C-4 and C-5 nonidentical.

Scheme I[a]



[a] D (**a**), CH_3 (**b**), $CH_3(CH_2)_3$ (**c**), $CH_3(CH_2)_3CH(CH_2)_2CH_3$ (**d**), $Ph_2C(OH)$ (**e**), p-$CH_3C_6H_4CH(OH)$ (**f**), p-$CH_3C_6H_4CO$ (**g**), t-BuNHCO (**h**), $(CH_3)_2CHCH(OH)$ (**i**), PhNHCO (**j**), 1-hydroxycyclohexyl (**k**), $PhCH_2$ (**l**).

In summary, our synthetic sequence for the functionalization of heterocycles offers advantages over a number of other existing methods in that the protecting group can be introduced and especially removed very easily; the protected derivatives are stable toward distillation, recrystallization,[18] and chromatography on alumina;[18] the

lithiation procedure is simple; a wide range of electrophiles can be used; and the yields are generally high. More hindered electrophiles (e.g. 2-iodopropane) failed to react, while the results obtained with 2-bromobutane show that the 2-lithio anion of imidazole **2** is still quite basic, despite the base-weakening effect of coordination with the (dimethylamino)methyl group. Thus, there are obvious limitations to the utility of the present method in that hindered and acidic substrates cannot be used, but apart from that the method appears to be quite general and should be applicable to a variety of other analogous heterocyclic systems.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope, and are uncorrected. IR spectra were recorded on a Perkin-Elmer 283B spectrophotometer. 60-MHz ^{1}H NMR spectra were obtained on a Varian EM 360 spectrometer and ^{13}C (25 MHz) NMR spectra were recorded on a JEOL FX100 spectrometer. Elemental analyses were performed under the supervision of Dr. R. W. King of this Department. Diethyl ether and tetrahydrofuran were dried by refluxing with sodium and benzophenone and used directly after distillation under dry argon.

Preparation of *N*-(Dialkylamino)methyl Heterocycles. 1-[(Dimethylamino)methyl]imidazole (2). According to the procedure of Stocker et al.,[19] imidazole (20.4 g, 0.3 mol) and 97% dimethylamine hydrochloride (26.0 g, 0.3 mol) were dissolved in water (50 mL) and concentrated hydrochloric acid was added until the pH was just less than 5. Aqueous formaldehyde solution (37%, 27 g, 0.33 mol) was added, and the mixture was allowed to stand at room temperature for 48 h. The solution was made strongly alkaline with 20% KOH solution, and the organic material was salted out with K_2CO_3 and extracted with chloroform. The combined organic layers were dried (K_2CO_3) and concentrated to give an oil, which was distilled under vacuum (29.3 g, 78%): bp 100–102 °C (2 mmHg) [lit.[19] bp 95 °C (1.5 mmHg)]; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 6 H, CH_3), 4.64 (s, 2 H, CH_2), 6.96 (s, 1 H, H-5), 7.03 (s, 1 H, H-4), and 7.49 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 40.8 (CH_3), 68.1 (CH_2), 118.9 (C-5), 127.8 (C-4), and 136.7 (C-2).

1-(1-Pyrrolidinomethyl)benzimidazole (5). This compound was prepared according to the literature procedure[20] and distilled: yield 60%; bp 155 °C (0.1 mmHg) [lit.[20] bp 195–200 °C (1 mmHg)]; ^{1}H NMR $CDCl_3$) δ 1.66 (m, 4 H, CH_2), 2.55 (m, 4 H, CH_2N), 4.88 (s, 2 H, NCH_2N), 7.26 (m, 2 H, H-5 and H-6), 7.45 (m, 1 H, H-7), 7.78 (m, 1 H, H-4), and 7.88 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 23.0 (CH_2), 50.1 (CH_2N), 62.3 (NCH_2N), 109.8 (C-7), 119.4 (C-4), 121.6 (C-5), 122.4 (C-6), 133.9 (C-7a), 140.8 (C-3a), and 142.9 (C-2).

1-(1-Pyrrolidinomethyl)pyrazole (8). A mixture of pyrazole (10.2 g, 0.15 mol), 37% formaldehyde solution (13.4 mL, 0.16 mol), and pyrrolidine (11.7 g, 0.16 mol) in ethanol (50 mL) was heated under reflux for 5 h, and the solvent was removed under vacuum. The residue was diluted with water and extracted with ethyl acetate. After drying with Na_2SO_4, the solution was concentrated and the resulting oil was distilled under vaccum to give 1-(1-pyrrolidinomethyl)pyrazole[22] (12.6 g, 56%): bp 73–77 °C (2.7 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 4 H, CH_2), 2.57 (m, 4 H, CH_2N), 4.91 (s, 2 H, NCH_2N), 6.15 (s, 1 H, 4-H), and 7.35 (m, 2 H, 3-H and 5-H); ^{13}C NMR ($CDCl_3$) δ 24.0 (CH_2), 50.4 (CH_2N), 69.1 (NCH_2), 105.7 (C-4), 130.2 (C-5), and 139.5 (C-3).

Preparation of Substituted Heterocycles. General Procedure. A solution of the *N*-(dialkylamino)methyl heterocycle (10 mmol) in 40 mL of diethyl ether or tetrahydrofuran in a Schlenk type reactor under an argon atmosphere was cooled to −70 °C, and *n*-butyllithium (4.2 mL of 2.5 M *n*-hexane solution) was slowly added dropwise. The resulting suspension was kept at −70 °C for 1 h. The electrophile (10.5 mmol) in 5 mL of diethyl ether or THF was added at −70 °C. The reaction mixture was allowed to return to 25 °C and stirred at that temperature for a few hours. Aqueous hydrochloric acid (2 N) was added, the organic solvent was removed, and then the solution was neutralized with $NaHCO_3$. The resulting precipitate was collected and recrystallized from a suitable solvent to give the pure substituted heterocycle. In the case of water-soluble imidazoles and pyrazoles, the products were extracted with chloroform, and the organic layer was dried with $MgSO_4$, removal of the solvent gave crude product, which was purified by column chromatography (silica gel, ethyl acetate, or chloroform). For melting points and recrystallization solvents, see Table I.

2-Butylimidazole (3c): ^{1}H NMR ($CDCl_3$) δ 11.07 (s, 1 H, NH), 6.99 (s, 2 H, Im H), 2.84 (t, 2 H, CH_2), 0.70–2.00 (m, 7 H, CH_2 and CH_3); ^{13}C NMR ($CDCl_3$) δ 148.5 (C-2), 119.8, 30.3 (CH_2), 27.1, 21.8, 13.3 (CH_3).

2-(4-Octyl)imidazole (3d): ^{1}H NMR ($CDCl_3$) δ 12.67 (s, 1 H, NH), 6.97 (s, 2 H, Im H), 2.91 (pentet, 1 H, CH), 0.60–2.05 (m, 16 H, CH_2 and CH_3); ^{13}C NMR ($CDCl_3$) δ 152.4 (C-2), 120.9, 39.8 (CH), 37.4, 34.9, 29.8, 22.7, 20.8, 14.0 (CH_3). Anal. Calcd for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.31; H, 11.15; N, 15.49.

(Imidazol-2-yl)diphenylmethanol (3e): ^{1}H NMR (DMSO-d_6) δ 7.25–7.70 (m, 11 H, Ar H and NH), 7.12 (s, 2 H, Im H), 3.55 (br, 1 H, OH); ^{13}C NMR (DMSO-d_6) δ 151.2 (C-2), 146.2 (C-4), 126.9, 126.8, 126.3, 121.1, 77.3 (COH); IR ($CHBr_3$) ν 3400 (NH), 3200 (OH), 1580, 1440, 1020, 740 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.80; H, 5.60; N, 11.20. Found: C, 76.55; H, 5.50; N, 10.89.

α-(Imidazol-2-yl)-4-methylbenzyl alcohol (3f): ^{1}H NMR (DMSO-d_6) δ 7.42 (d, 2 H, Ar H), 7.20 (d, 2 H, Ar H), 6.98 (s, 2 H, Im H), 6.20 (br, 1 H, NH), 5.78 (s, 1 H, CH), 3.45 (br, 1 H, OH), 2.28 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6) δ 150.4 (C-2), 140.4 (C-4), 136.0, 128.5, 128.4, 126.3, 69.5 (CHOH), 20.7 (CH_3); IR ($CHBr_3$) ν 3400 (NH), 3200 (OH), 1610, 1450, 1030, 770 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89. Found: C, 69.91; H, 6.38; N, 14.64.

2-(4-Methylbenzoyl)imidazole (3g): ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 13.15 (br, 1 H, NH), 8.60 (d, 2 H, ArH), 7.43 (d, 2 H, Ar H), 7.40 (s, 2 H, Im H), 2.45 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6) δ 180.1 (CO), 151.0, 144.2, 142.2, 132.5, 129.7, 127.6, 20.4 (CH_3); IR ($CHBr_3$) ν 3400 (NH), 1640 (CO), 1600, 1405, 1380, 1300, 890, 760 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.97; H, 5.38; N, 15.05. Found: C, 70.71; H, 5.49; N, 14.89.

2-(*N*-*tert*-Butylcarbamoyl)imidazole (3h): ^{1}H NMR (CDCl_3) δ 13.42 (br, 1 H, CONH), 7.52 (br, 1 H, NH), 7.23 (s, 2 H, Im H), 1.55 (s, 9 H, CMe_3); ^{13}C NMR ($CDCl_3$) δ 158.5 (CONH), 141.6, 128.9, 119.2, 51.4, 28.6; IR ($CHBr_3$) ν 3400 (NH), 3150 (CONH), 1640, 1610, 1050 cm^{-1}. Anal. Calcd for $C_8H_{13}N_3O$: C, 57.49; H, 7.78; N, 25.15. Found: C, 57.25; H, 7.82; N, 25.02.

2-Methylbenzimidazole (6b): ^{1}H NMR (DMSO-d_6) δ 7.40–7.80 (m, 2 H, Ar H), 7.10–7.40 (m, 2 H, Ar H), 2.58 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6) δ 151.8, 138.8, 120.9, 113.9, 14.4.

(Benzimidazol-2-yl)diphenylmethanol (6e): ^{1}H NMR (DMSO-d_6) δ 7.10–7.90 (m); ^{13}C NMR (DMSO-d_6) δ 158.3, 145.5, 137.9, 127.7, 127.3, 127.1, 121.9, 115.1, 77.7 (COH); IR ($CHBr_3$) ν 3380 (NH), 3150 (OH), 1580, 1480, 1400, 1315, 1035, 990, 730 cm^{-1}. Anal. Calcd for $C_{20}H_{16}N_2O$: C, 80.00; H, 5.33; N, 9.33. Found: C, 80.25; H, 5.42; N, 9.04.

1-(Benzimidazol-2-yl)-2-methylpropan-1-ol (6i): ^{1}H NMR (DMSO-d_6) δ 8.42 (s, 1 H, NH), 7.45–7.80 (m, 2 H, Ar H), 7.10–7.40 (m, 2 H, Ar H), 4.55 (d, 1 H, CHOH), 3.50 (br, 1 H, OH), 2.17 (m, 1 H, CH), 0.93 (d, 6 H, CH_3); ^{13}C NMR (DMSO-d_6) δ 157.3, 137.0, 121.1, 114.5, 72.6 (CHOH), 33.6, 17.5; IR ($CHBr_3$) ν 3400 (br, NH), 3170 (OH), 1420, 1380, 1010, 730 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.47; H, 7.37; N, 14.74. Found: C, 69.23; H, 7.56; N, 14.49.

2-(Phenylcarbamoyl)benzimidazole (6j): ^{1}H NMR (DMSO-d_6) δ 7.75–8.25 (m, 4 H), 7.20–7.70 (m, 5 H), 6.35 (br, 2 H, NH); ^{13}C NMR (DMSO-d_6) δ 157.2, 145.5, 138.4, 138.1, 128.5, 123.9, 123.5, 120.4, 116.2; IR ($CHBr_3$) ν 3400 (NH), 3210 (CONH), 1650 (CO), 1580, 1540, 1420, 730 cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.89; H, 4.64; N, 17.72. Found: C, 70.72; H, 4.51; N, 17.81.

1-(Benzimidazol-2-yl)cyclohexan-1-ol (6k): ^{1}H NMR (DMSO-d_6) δ 8.30 (br, 2 H, NH and OH), 7.45–7.80 (m, 2 H), 7.10–7.40 (m, 2 H), 1.95 (m, 4 H, CH_2), 1.45–1.80 (m, 6 H); ^{13}C NMR (DMSO-d_6) δ 161.1, 138.5, 120.8, 114.7, 69.8 (COH), 36.8, 25.0, 21.3; IR ($CHBr_3$) ν 3120 (br, NH, OH), 2910, 1420, 965, 735 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.22; H, 7.41; N, 12.96. Found: C, 71.95; H, 7.67; N, 12.75.

3-Methylpyrazole (9b): ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 2 H), 2.65 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 141.0, 131.3, 114.8, 18.7.

(Pyrazol-3-yl)diphenylmethanol (9e): ^{1}H NMR ($CDCl_3$) δ 7.21 (s, 10 H), 7.21 (d, 1 H, J = 3 Hz, C_5H), 5.80 (d, 1 H, J = 3 Hz, C_4H) ^{13}C NMR ($CDCl_3$) δ 153.9, 146.2, 133.2, 127.8, 127.4,

127.3, 105.2, 78.1 (COH); IR ($CHBr_3$) ν 3350 (NH), 3200 (OH), 1610, 1500, 740 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H,5.64; N, 11.19. Found: C, 76.46; H, 5.64; N, 11.26.

3-Benzylpyrazole (9l): ^1H NMR ($CDCl_3$) δ 7.32 (d, 1 H, C5-H), 7.25 (s, 5 H, Ph H), 6.12 (d, 1 H, C4-H), 3.98 (s, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 141.8, 133.6, 129.1, 128.7, 127.5, 119.8, 116.5, 44.2; IR (neat) ν 3300 (NH), 1610, 950, 765, 720 cm^{-1}.

Acknowledgment. We thank the New Zealand Medical Research Council for a grant to G.W.R.

Registry No. 1, 288-32-4; 2, 23230-39-9; 3c, 50790-93-7; 3c·picrate, 107054-49-9; 3d, 116997-21-8; 3e, 5228-76-2; 3f, 117024-16-5; 3g, 116997-22-9; 3h, 79711-72-1; 5, 19213-18-4; 6a, 61233-51-0; 6b, 615-15-6; 6e, 1235-28-5; 6i, 13794-25-7; 6j, 13745-42-1; 6k, 5805-32-3; 7, 288-13-1; 8, 91272-98-9; 9a, 53848-78-5; 9b, 1453-58-3; 9b·picrate, 14710-76-0; 9e, 116997-23-0; 9l, 32251-82-4; $CH_3(CH_2)_3I$, 542-69-8; $CH_3(CH_2)_3Br$, 109-65-9; Ph_2CO, 119-61-9; p-$CH_3C_6H_4CHO$, 104-87-0; p-$CH_3C_6H_4CO_2Et$, 94-08-6; t-BuNCo, 1609-86-5; $(CH_3)_2CHCHO$, 78-84-2; PhNCO, 103-71-9; cyclohexanone, 108-94-1.

Transannular Addition of α-Thia Carbanions to Unactivated Double Bonds. 5. Synthesis of (9*R*,10*S*)-*trans*-1-Thiadecalin[1]

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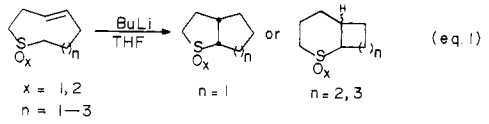
Received April 29, 1988

A synthesis of *trans*-1-thiadecalin in enantiomerically pure form is described that uses as the key step the recently discovered addition of α-thia carbanions (α-lithio sulfoxides or sulfones) to a transannular *E* double bond.[2] The required (*E*)-thiacyclodec-4-ene precursor was prepared by 2,3-sigmatropic rearrangement of a 7-membered cyclic sulfonium ylide[4] obtained in turn by elaboration of (*R*,*R*)-1,6-dibromo-3,4-hexanediol, a chiral synthon derived from D-mannitol. The product of the addition step was freed of the stereogenic diol unit, yielding the target compound. Its absolute configuration follows from straightforward NMR analysis of its diastereomeric precursors. The stereochemical aspects of the transannular cyclization (stereospecific in the sulfoxide case, 9:1 stereoselective in the sulfone) are briefly commented on.

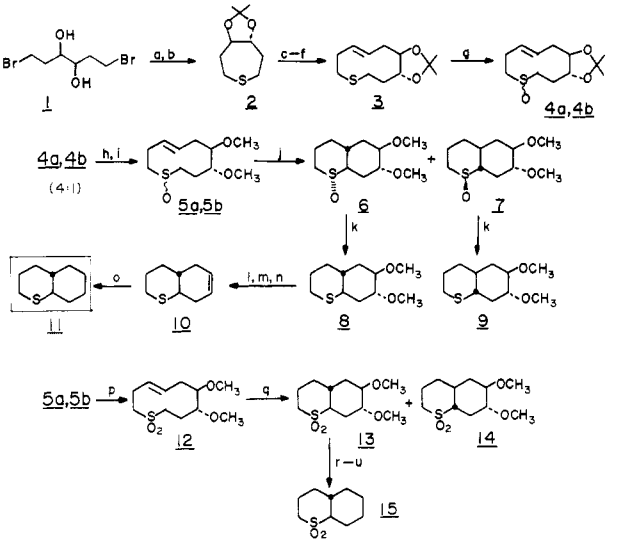
We have recently described a reaction of medium-ring homoallylic sulfoxides or sulfones whereupon, on treatment with a catalytic amount of butyllithium, transannular cyclization occurs leading to saturated bicyclics (eq 1).[2] The reaction occurs readily provided the double bond has the *E* configuration.



Since metalation induces carbanionic reactivity at the α carbons, the reaction may be described as a nucleophilic addition to an isolated double bond, a very rare process,[3] and, for what concerns C-nucleophiles, an unprecedented one.

Although the experimental evidence largely fits this description,[2c,d] several mechanistic facets remain to be elucidated, which are currently under investigation in our laboratory. The mechanistic ambiguities, however, do not hinder the exploitation of the reaction toward synthetic goals, and the present paper describes a synthesis that uses the transannular cyclization of a thiacyclodec-4-ene as the key step toward the preparation of *trans*-1-thiadecalin in enantiomerically pure form.

Scheme I[a]



[a] (a) $Me_2C(OMe)_2$, TsOH, benzene, 95.5%; (b) $Na_2S·9H_2O$, EtOH, 80%; (c) NCS, benzene; (d) CH_2=$CHMgBr$, THF; (e) CF_3SO_3Me, CH_2Cl_2; (f) t-BuOK, THF, −40 °C, 34.5% from 2; (g) MCPBA, CH_2Cl_2, −80 °C, 95%; (h) 0.1 N H_2SO_4, 83%; (i) MeI, NaH, DMF, 83%; (j) n-BuLi, THF, 0–20 °C, 77.8%, overall yield; (k) PCl_3, CH_2Cl_2, 75%; (l) Me_3SiCl, NaI, thiolane, ~3 equiv, 73%; (m) $MeSO_2Cl$, pyridine, 85.6%; (n) NaI, Zn, DMF, 150 °C, 75%; (o) RuO_2, MeOH/H_2O, 40 °C, H_2, 12 atm, 90%; (p) MCPBA, 0–20 °C, 96%; (q) n-BuLi, THF, 0–20 °C, 71%; (r) Me_3SiCl, NaI, CH_3CN, 77%; (s) $MeSO_2Cl$, pyridine, 90%; (t) NaI, Zn, DMF, 80%; (u) H_2, PtO_2, MeOH, 95%.

Results

Medium-size homoallylic thiacycloalkenes of *E* configuration can be conveniently obtained by 2,3-sigmatropic

(1) (a) Dedicated to the memory of Professor Gabriello Illuminati. (b) Financial support from CNR-Rome and Ministero Pubblica Istruzione is gratefully acknowledged.

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0022-3263/88/1953-5689$01.50/0 © 1988 American Chemical Society