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Aminal Exchange

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Reactions of *N*-(α-benzotriazolylalkyl)-*N*,*N*-dialkylamines with the dialkylamine corresponding to the dialkylamino substituent afford symmetrical aminals in good yields. Treatment with other dialkylamines gives mixtures of the unsymmetrical and the two symmetrical aminals. Cross-over experiments of symmetrical aminals demonstrates interconversions involving iminium ions and that equilibria exist in the systems.

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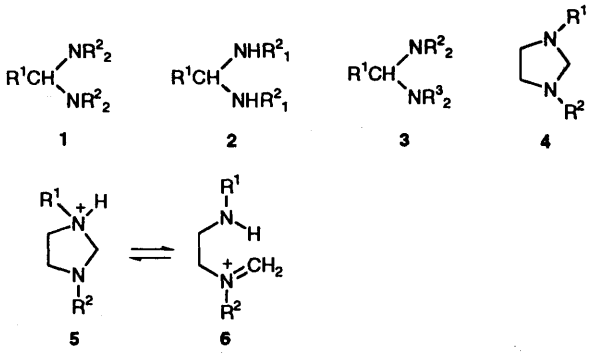
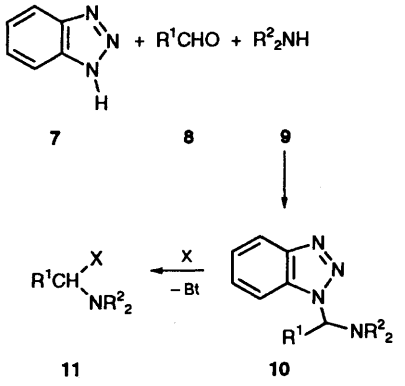
Aminals are usually formed by the condensation of carbonyl compounds with amines.[1] Aromatic aldehydes react with secondary amines at room temperature or in refluxing benzene under Dean–Stark conditions to form symmetrical aminals **1**.[1] Unhindered amines give yields as high as 90%, but increasing steric hindrance leads to progressively lower yields.[2-3] Symmetrical aminals **2** derived from primary amines are often formed easily, especially from aromatic primary amines, but **2** exist in solution in equilibrium with the derived imines and are fully converted into these imines upon attempted distillation.[4]

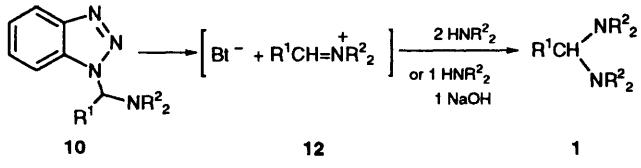
Unsymmetrical aminals are far less well known. Examples of type **3** in which R^2 is a bulky group were prepared from equimolar amounts of formaldehyde and two different amines in aqueous solution, but yields were only 6–15%.[5] The addition of hindered amines to methylene iminium salts provided a better route to some unsymmetrical aminals.[6] Reaction of pyrrolidinomethanol with amines also afforded low yields of unsymmetrical 1,1-methylenediamines.[6] Recently, some cyclic unsymmetrical aminals **4** have been prepared;[7] their cations **5** undergo ring-chain tautomerization with form **6**.[8] Non-cyclic unsymmetrical aminals from aldehydes other than formaldehyde have apparently not been described.



N-(α-Benzotriazolylalkyl)-*N*,*N*-dialkylamines **10** (readily available from the reaction of benzotriazole **7**, an aldehyde **8** and a secondary amine **9**) react easily with a range of different organometallic reagents including alkyllithium and Grignard reagents.[9-12] Replacement of benzotriazole by other nucleophiles gives rise to a variety of α-functionalized *N*,*N*-dialkylamines **11** (Scheme 1); *e.g.* sodium salts of alcohols and thiols to give *N*,*O*- and *N*,*S*-acetals.[13] Thus, reaction of adducts **10** with secondary amines should take place to afford aminals, and as an extension of our study of the synthetic potential of *N*-substituted benzotriazoles, we have now examined the displacement of the heterocycle from 1-aminomethylbenzotriazoles **11** with different amines and studied the disproportionation of the products.



Scheme 1



10 and **1** **a** R^1 = Ph, NR^2_2 = $N(CH_2)_4$
b R^1 = Ph, NR^2_2 = $N(CH_2)_5$
c R^1 = 4-MeO-C_6H_4, NR^2_2 = $N(CH_2)_4O$
d R^1 = 4-MeO-C_6H_4, NR^2_2 = $N(CH_2)_5$
e R^1 = Ph, NR^2_2 = $N(CH_2)_4O$

Scheme 2

Reaction of Benzotriazole Adducts **10** *with* N,N-*Dialkylamines to give Symmetrical Aminals*.—The adducts **10a,b,d** derived from pyrrolidine or piperidine and benzaldehyde or *p*-methoxybenzaldehyde reacted rapidly (3–5 min) with the corresponding amines in diethyl ether at 20 °C to afford symmetrical aminals **1a,b** and **1d**, respectively in good yield (Scheme 2). Use of two equivalents of the amine conveniently removed benzotriazole as its amine salt, which precipitated from the solution, rapidly driving the reaction to completion at room temperature. Alternatively, if one equivalent of the amine was used, benzotriazole could be removed as its sodium salt, by the action of solid or aqueous sodium hydroxide.

The morpholine adducts **10c** and **10e** were less reactive: no

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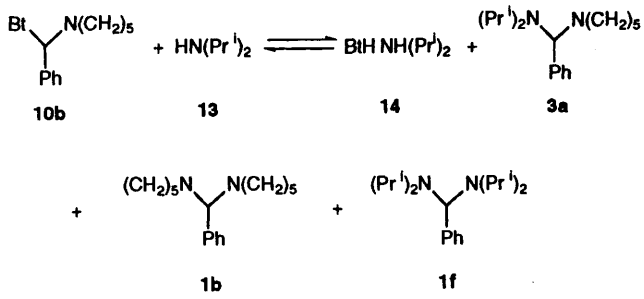
reaction took place between morpholine and the benzaldehyde adduct **10e** at room temperature and **1e** was not obtained. However, adduct **10c** bearing a methoxy group at the *para*-position of the araldehyde ring reacted smoothly over 20 min to give aminal **1c** in 89% yield. The lower reactivity is a consequence of a higher barrier to ionization and lower concentration of the intermediate iminium ions in the solution,[14] for the lower electron-donor character of the morpholine nitrogen, which is partially offset by the *p*-methoxy group in **10c**.

Confirmation of the structure and purity of the aminals **1a–d** was obtained from their ^{1}H NMR and ^{13}C NMR spectra and by comparing their melting points with literature values. However, this method is less convenient for the preparation of aminals than those in the literature.[2,3]

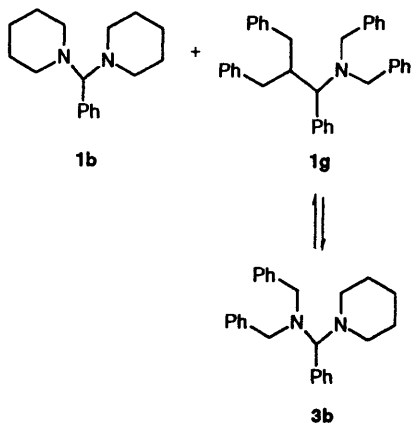
Reactions of the Adducts **10** *with* N,N-*Dialkylamines Directed toward Unsymmetrical Aminals.*—In an attempt to extend the above method to the preparation of unsymmetrical aminals, which are not prepared easily by conventional methods, we treated the benzotriazole adducts **10** with amines different from those corresponding to NR^2_2 in the adducts. When diisopropylamine was added to a solution of benzotriazole adduct **10b**, there was an immediate precipitation of diisopropylammonium benzotriazolate **14**, and the starting material was still present in the complex product mixture (Scheme 3). The existence of an equilibrium in which the produced benzotriazole amine salt reacted with the aminal to give a benzotriazole adduct was proved by recording the ^{13}C NMR spectrum of a mixture of the diisopropylamine-benzotriazole salt **14** (prepared from benzotriazole and diisopropylamine in benzene) and aminal **1b** in $CDCl_3$: the typical pattern of six peaks of a 1-substituted benzotriazole was observed, identical in all respects with that obtained by the forward reaction. The diagnostic N–CH(Ar)–N region suggested that in both forward and reverse reactions, the major components of the mixtures were the simple symmetrical aminals, with the desired unsymmetrical product in lesser amount as shown by ^{1}H and ^{13}C NMR spectroscopy. These reaction mixtures could not be separated by distillation or column chromatography, nor analysed by GC because of decomposition.



Scheme 3

Cross-over Reaction of Symmetrical Aminals: an Equilibrium Process.—The production of a mixture of symmetrical and unsymmetrical aminals in the described reactions indicated that an additional equilibrium process was in operation, namely between the aminals themselves. This led us to search for the unsymmetrical products of cross-over processes in mixtures of different symmetrical aminals. The disproportionations were followed by the ^{1}H NMR and ^{13}C NMR spectra of equimolar mixtures of two different aminals.

The spectrum of an equimolar mixture of aminals **1b** and **1g** in $CDCl_3$ showed that after mixing for 5 min the disproportionation product **3b** had formed already. After several hours there was no change in the number and intensity



Scheme 4

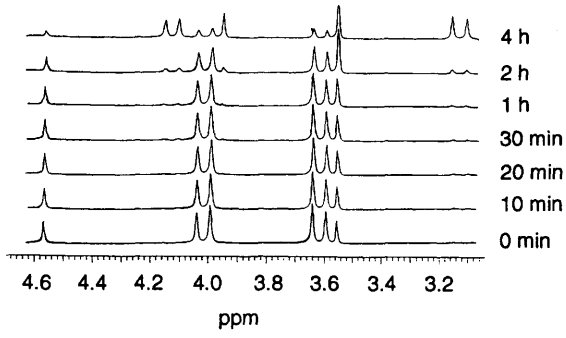


Fig. 1 Partial ^{1}H NMR spectra (δ 3–5) of a mixture of **1b** and **1e** as a function of time (in [$^2H_8$]toluene)

of the signals. This indicated that the equilibrium position between the starting materials and product was reached very quickly in $CDCl_3$. A much slower equilibrium process was observed in deuteriated dioxane and also in toluene.

Fig. 1 illustrates the slow equilibration between **1b**, **1g** and **3b** as reflected in their proton NMR spectrum. The region of benzylic and methinic protons (2.5–5.5 ppm) was monitored as a function of time. To a [$^2H_8$]toluene solution of **1b** (spectrum at 0 min), an equimolar amount of **1g** was added and spectra, acquired after two pulses, were recorded at times shown in Fig. 1. The singlet growing at δ 3.95 and the two doublets at δ 4.13 and 3.12 are due to the NC*H*(Ph)N hydrogen and the two benzylic proton groups, respectively, of the unsymmetrical aminal **3b**. The singlet at δ 4.57 is due to NC*H*(Ph)N of **1g**, whereas the corresponding peak of **1b** normally appearing at δ 3.55, is covered under the foreign peak at δ 3.55, which was also present in the spectrum of analytically pure **1g**.

A clearer picture can be obtained by monitoring the region δ 70–90 of ^{13}C NMR spectrum, where the resonances of NCH(Ar)N usually appear. Fig. 2 illustrates the changes in the ^{13}C NMR spectra of an equimolar mixture of compounds **1b** and **1g** as a function of time. The N*C*H(Ph)N ^{13}C resonance of **1g** in [$^2H_8$]-1,4-dioxane emerges at about δ 80 (Fig. 2, spectrum at 0 min). To the solution of **1g**, one equivalent of **1b** was added and the spectra were recorded at intervals indicated in Fig. 2. The peak at about δ 87.5 is due to **1b**. The new signal, emerging between the N*C*H(Ph)N peaks of the symmetrical starting aminals, presumably originates from the unsymmetrical compound **3b**. Similar observations were made for **1a** and **1b**, but in this case the new C atom [N*C*H(Ph)N] signal of the mixed aminal was extremely close to that of **1a**, so that detection of the equilibrium process was possible only in the 75 MHz ^{13}C NMR spectrum.

To explain the foregoing observations a mechanistic scheme

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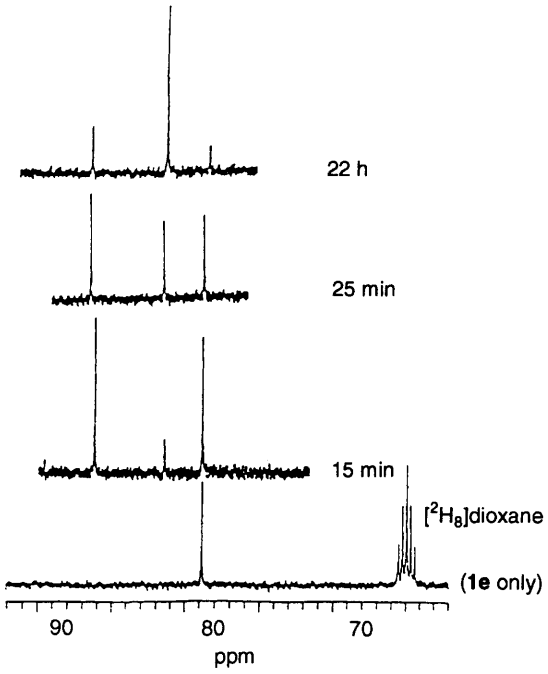
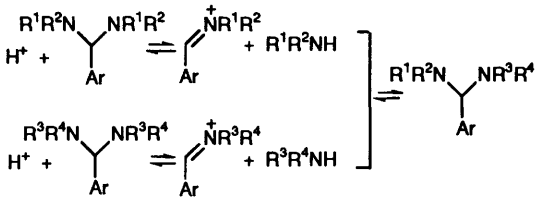


Fig. 2 Partial ^{13}C NMR spectra (δ 64–95) of a mixture of **1b** and **1e** as a function of time (in [$^2H_8$]-1,4-dioxane)



Scheme 5

is suggested (Scheme 5), which is also consistent with previous reports.[6,15] In solution, the aminal dissociates to give iminium cations probably under the influence of traces of acid which allow the equilibria of Scheme 5 to be set up, and recombines to form symmetrical and unsymmetrical aminals. We conclude that unsymmetrical aminals are intrinsically unstable species, incapable of isolation in the pure state.

Experimental

Melting points were determined with a Köfler hot-stage apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer; *J* values are given in Hz. High resolution mass measurements were recorded on an AEI MS-30 mass spectrometer.

Preparation of N-(α-*Benzotriazolylalkyl*)-N,N-*dialkylamine Adducts*.—Benzotriazole adducts **10b**,**c**,**e** were prepared according to the previously described methods (**10b**: oil; lit. oil. **10c**: m.p. 104–105 °C; lit. 104–105 °C. **10e**: oil; lit. oil).[14,16] Compounds **10a** and **10d**, not reported previously, were prepared according to a literature procedure.[14]

N-(α-*Benzotriazolylbenzyl*)*pyrrolidine* **10a**. The compound was obtained as a viscous oil (85%) (Found: M − 1, 277.1426. $C_{17}H_{18}N_4$ requires *M* − 1, 277.1453) δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.74 (4 H, br s), 2.67 (4 H, m), 6.68 (1 H, s), 7.2–7.4 (5 H, m), 7.50 (2 H, d, *J* 6.7) and 7.7–8.0 (2 H, m); δ_C(75 MHz; $CDCl_3$) 23.2, 49.8, 81.5, 112.0, 119.5, 124.0, 127.1, 127.3, 127.7, 128.0, 128.2, 128.8 and 136.7.

N-(α-*Benzotriazolyl*-4-*methoxybenyl*)*piperidine* **10d**. It was obtained as an oil (87%) (Found: M, 322.1730. $C_{19}H_{22}N_4O$ requires *M*, 322.1793) δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.33 (2 H, m), 1.58 (4 H, m), 2.4–2.7 (4 H, m), 3.72 (3 H, s), 6.73 (1 H, s), 6.80–6.90 (2 H, m), 7.2–7.4 (5 H, m) and 8.0–8.1 (1 H, m); δ_C(75 MHz; $CDCl_3$) 23.9, 25.7, 50.4, 54.9, 83.0, 111.8, 113.6, 119.5, 123.4, 123.5, 126.5, 126.6, 128.0, 128.5 and 159.3.

General Procedure for the Preparation of Aminals **1a–d**.—The benzotriazole adducts **10** were dissolved in diethyl ether and treated with 1 equiv. of a secondary amine and powdered NaOH, or (better) with 2 equiv. of the secondary amine. After stirring for 15 min at room temperature the resulting precipitate (water soluble) was either removed with an alkaline wash (2 mol dm^{-3} NaOH) or filtered and the solvent evaporated.

α,α-*Bis*(*pyrrolidinyl*)*toluene* **1a**. Obtained as a white solid (61%). M.p. 36.5–37.5 °C (from diethyl ether) (lit.,[17] 40–41 °C); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.6–1.7 (8 H, m), 2.4–2.6 (8 H, m), 3.90 (1 H, s) and 7.2–7.4 (5 H, m); δ_C(75 MHz; $CDCl_3$) 22.9, 49.3, 85.3, 127.1, 127.2, 128.9 and 136.3.

α,α-*Bis*(*piperidyl*)*toluene* **1b**. Obtained as a white solid (65%). M.p. 77–79 °C (from petroleum ether) (lit.,[17] 80–81 °C); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.37 (4 H, br s), 1.4–1.6 (8 H, m), 2.33 (8 H, br s), 3.56 (1 H, s) and 7.1–7.4 (5 H, m); δ_C(75 MHz; $CDCl_3$) 25.2, 26.2, 50.0, 89.7, 126.9, 127.1, 128.5 and 136.1.

α,α-*Bis*(*morpholino*)-4-*methoxytoluene* **1c**. Obtained as a white solid (89%). M.p. 116–118 °C (from benzene) (lit.,[17] 119–120 °C); δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.3–2.5 (8 H, m), 3.58 (1 H, s), 3.6–3.7 (8 H, m), 3.78 (3 H, s), 6.88 (2 H, d, *J* 8.7) and 7.11 (2 H, d, *J* 8.7); δ_C(75 MHz; $CDCl_3$) 49.5, 55.2, 67.2, 88.5, 113.1, 126.3, 129.8 and 159.1.

α,α-*Bis*(*piperidyl*)-4-*methoxytoluene* **1d**. Obtained as an oil (79%) (Found: M^+, 288.2124. $C_{18}H_{28}N_2O$ requires *M*, 288.2123); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.3–1.4 (4 H, m), 1.45–1.55 (8 H, m), 2.31 (8 H, br s), 3.51 (1 H, s), 3.77 (3 H, s), 6.85 (2 H, d, *J* 8.7) and 7.11 (2 H, d, *J* 8.7); δ_C(75 MHz; $CDCl_3$) 25.3, 26.2, 50.0, 54.9, 89.1, 112.5, 128.4, 129.4 and 158.4.

α,α-*Bis*(N,N-*dibenzylamino*)*toluene* **1g**. This compound was prepared, following a literature procedure:[2,3] by heating dibenzylamine and benzaldehyde in a 2:1 molar ratio in benzene under Dean–Stark conditions until the theoretical amount of water had been collected. The solvent was removed under vacuum and the residue was triturated with diethyl ether and petroleum to give a white solid. M.p. 138–140 °C (Found: C, 87.5; H, 7.2; N, 5.9. $C_{35}H_{34}N_2$ requires C, 87.1; H, 7.1; N, 5.8%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.53 (s, 2 H), 3.57 (s, 2 H), 3.95 (s, 2 H), 4.00 (s, 2 H), 4.57 (s, 1 H) and 7.1–7.4 (m, 25 H); δ_C(75 MHz; $CDCl_3$) 52.7, 79.7, 126.5, 126.9, 127.7, 128.0, 129.1, 129.6, 135.1 and 139.4.

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