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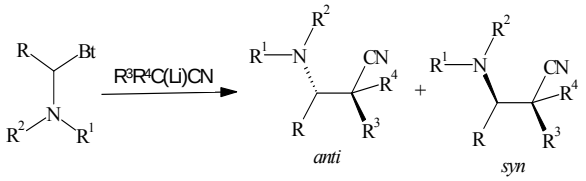

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Aminoalkylation of nitriles by iminium ions generated *in situ*

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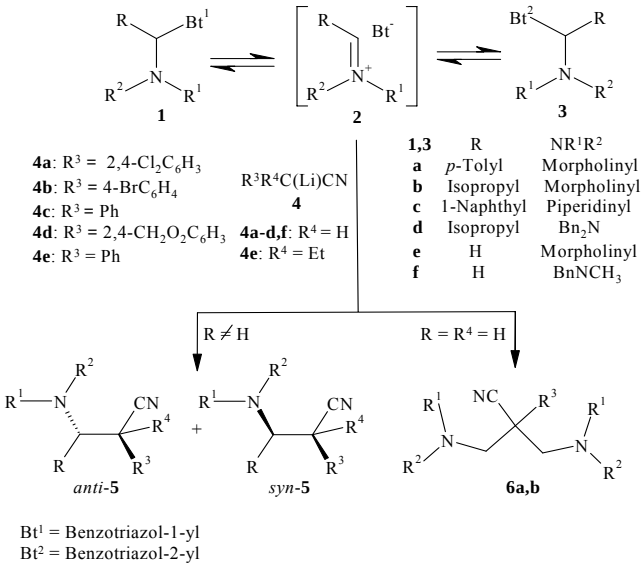
Abstract— Aminoalkylation of a series of primary and secondary nitriles with *N*-(*α*-aminoalkyl)benzotriazoles **1** (derived from a variety of secondary amines and aldehydes) proceeds smoothly providing the corresponding *β*-aminoalkyl nitriles **5a**–**j** in 66–97% yields.

N-(α-Aminoalkyl)benzotriazoles **1** are highly versatile synthetic intermediates used extensively in organic synthesis.[1] The methine carbon in these intermediates **1** possesses a high degree of electrophilicity, due to the existence of a mobile equilibrium with the benzotriazolide-iminium ion pair **2**.[2] Studies from our group have successfully applied this concept in their reactions with Grignard reagents and Reformatsky reagents to provide easy access to secondary and tertiary amines.[3] *N*-(α-Aminoalkyl)benzotriazoles are also valuable intermediates for the preparation of functionalized amines.[4] In the frame of our continuing efforts to develop benzotriazole methodology, we now report a new general and efficient synthesis of β-aminoalkyl nitriles based on the ability of **1** to react with metalated nitriles to produce the title compounds in good to excellent yields (Scheme 1 and Table 1).

The aminoalkylating reagents employed, *N*-(α-amino-alkyl)benzotriazoles **1a–f** are easily available by the well-established condensation of benzotriazole, an aldehyde, and a secondary amine.[5] Quenching metalated nitriles with various electrophilic substrates is a common procedure for introducing a cyano group into a molecular framework,[6] and we now report that the reaction of benzotriazole aminals **1** with metalated nitriles **4** provides a new access to β-aminoalkyl cyanides **5** and **6**.

We examined the reaction of adduct **1a** and the metalated nitrile **4a** under different conditions. When **1a** (1.0 equiv.) was reacted with **4a** (1.0 equiv.), prepared *in situ* by treatment of the corresponding nitrile with *n*-butyllithium (2 equiv.) in THF at –78 °C, β-amino cyanide **5a** was afforded in a yield of 89%. However, the yield of **5a** fell to 36% when the reaction was carried out in the presence of *t*-BuOK (2 equiv.) in DMSO at room temperature. Therefore, the lithiated nitriles **4a–e** were treated at –78 °C in THF with a series of **1** in THF at –78 °C.[7] In every case, the reaction proceeded smoothly giving the corresponding β-aminoalkyl cyanides, either as the mono-aminoalkylated products **5a–i** in 66–97% yields or doubly aminoalkylated products **6b** in 43% yield. Exceptionally, the reaction of **1e** with **4a** under the same reaction conditions provided **5j** in the yield of 72%, in addition to **6a** in 10% yield. The structures of **5** and **6** were assigned on the basis of their spectral data and elemental analyses.[8]



Scheme 1. For designation of R, R^1R^2N, R^3 and R^4 in **5** and R^1R^2N and R^3 in **6** see Table 1.

* Keywords: Aminoalkylation; *N*-(*α*-aminoalkyl)benzotriazoles; *β*-aminoalkyl nitriles

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For β-aminoalkyl nitriles **5** containing two asymmetric carbon atoms, the reaction provided **5a,e,f** as single diastereoisomers and **5b–d,g** as diastereoisomeric mixtures. Assignment of the existing diastereoisomers of **5a,e,f** as *anti* has been accomplished on the basis of a partial X-ray dataset of highly twinned and unstable crystals of **5a** and X-ray crystallography of **5e** and **5f** (Figures 1 and 2). However, the aminoalkylated products **5b–d,g** were obtained as *anti* and *syn* diastereoisomeric mixtures. Their ^{1}H NMR spectra display two closely overlapping sets of signals and their ^{13}C NMR spectra generally show two sets of lines. Although the integrated intensities of the α-cyano proton in the ^{1}H NMR spectra of CDCl3 solutions indicated that the percentage of *anti*-isomers is slightly higher (53–62%) than *syn*-isomers in **5b–d**, for **5g** the major isomer is *syn* (69%). The structures of both the *anti* and *syn* diastereoisomers of **5d** and **5g**, as well as the *syn* diastereoisomer of **5c**, were definitively ascertained by their X-ray crystal structure analyses. The stereospecificity observed for **5a,e,f** suggests that aryl moieties containing an ortho substituent at the nucleophilic center (as in **5a**) or bulky groups at the electrophilic center (as in **5e,f)** control the stereoselectivity.

In summary, we have developed a new, efficient and general access to functionalized amines possessing a cyano group at the β-position via aminoalkylation of nitriles utilizing an easily accessible *N*-(α-aminoalkyl)benzotriazoles from inexpensive starting materials. The high yields of **5** (up to 97%) demonstrate the convenience of *N*-(α-aminoalkyl)benzotriazoles as *in situ*-generated iminium ion equivalents.

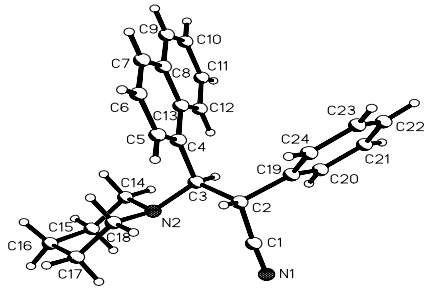

Figure 1. X-ray crystal structure of **5e**.

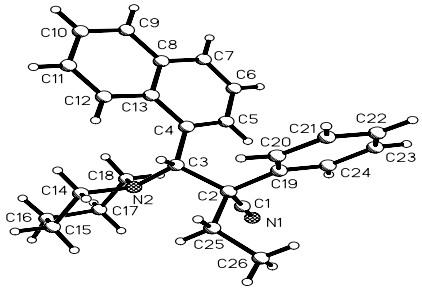

Figure 2. X-ray crystal structure of **5f**.

Table 1, Synthesis of *β*-amino cyanides **5a–j** and **6a,b.**

Compd.	R	R^1R^2N	R^3	R^4	*anti:syn*	Yield[e] %
5a	*p*-Tolyl	Mor[a]	2,4-$Cl_2C_6H_3$	H	100:0[c]	89
5b	*p*-Tolyl	Mor[a]	4-BrC_6H_4	H	62:38[d]	94
5c	Isopropyl	Mor[a]	Ph	H	53:47[c,d]	97
5d	Isopropyl	Mor[a]	Ben[b]	H	55:45[c,d]	93
5e	1-Naphthyl	Piperidinyl	Ph	H	100:0[c]	79
5f	1-Naphthyl	Piperidinyl	Ph	Et	100:0[c]	66
5g	Isopropyl	Bn_2N	Ben[a]	H	31:69[c,d]	88
5h	H	$BnNCH_3$	Ph	Et	-	93
5i	H	Mor[a]	4-BrC_6H_4	H	-	70
5j	H	Mor[a]	2,4-$Cl_2C_6H_3$	H	-	72
6a	H	Mor[a]	2,4-$Cl_2C_6H_3$	-	-	10
6b	H	$BnNCH_3$	Ph	-	-	43

[a] Morpholinyl. [b] Benzo[1,3]dioxol-4-yl. [c] Structure determined by X-ray crystallography. [d] Diastereomeric ratio was evaluated by ^{1}H NMR analysis. [e] Yields of pure isolated products

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7. Typical experimental procedure for the synthesis of **5a–j** and **6a,b**: To a solution of **4** (2 mmol) in dry THF (10 mL) (prepared by treating the corresponding nitrile with 2 equiv. *n*-BuLi at -78 ^{o}C), at the same temperature, benzotriazole-adduct **1** (2 mmol) in THF (10 mL) was added. The mixture was stirred for 10 h while the temperature was allowed to rise to 20 ^{o}C, quenched with water and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (25 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. The resulted oil was chromatographed on a silica-gel column using hexanes/EtOAc 10:1 as eluent to give the pure product **5** and **6**; the yields are presented in Table 1.
8. Representative data: ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Gemini 300 MHz NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and $CDCl_3$ for ^{13}C as the internal reference).

(a) Compound **5a**: was obtained in 89% yield as colorless plates, mp 143−145 ^{o}C; ^{1}H NMR δ 7.39 (d, *J* = 2.2 Hz, 1H), 7.05-6.93 (m, 5H), 6.58 (d, *J* = 8.5 Hz, 1H), 5.02 (d, *J* = 5.4 Hz, 1H), 3.77−3.72 (m, 4H), 3.49 (d, *J* = 5.4 Hz, 1H), 2.58−2.55 (m, 4H), 2.31 (s, 3H); ^{13}C NMR δ 138.4, 134.7, 133.0, 132.4, 131.7, 130.0, 129.1, 128.9, 128.8, 127.2, 117.9, 70.5, 66.8, 51.7, 37.5, 21.1. Anal. Calcd. For $C_{20}H_{20}Cl_2O$: C, 64.01; H, 4.37; N, 7.46. Found: C, 64.22; H, 4.48; N, 7.44.

(b) Compound **6b**: was obtained in 43% yield as pale yellow plates, mp 53−55 ^{o}C; ^{1}H NMR δ 7.79−7.20 (m, 15H), 3.56 (AB system, *J* = 13.2 Hz, 2H), 3.49 (AB system, *J* = 13.2 Hz, 2H), 3.13 (AB system, *J* = 13 .6 Hz, 2H), 2.87 (AB system, *J* = 13.6 Hz, 2H) 2.15 (s, 6H); ^{13}C NMR δ 138.9, 137.3, 129.8, 129.0, 128.9, 128.5, 128.1, 128.0, 127.6, 127.0, 126.7, 125.7, 122.7, 64.2, 63.7, 50.8, 43.7. Anal. Calcd. For $C_{26}H_{29}N_3$: C, 81.42; H, 7.62; N, 10.96. Found: C, 81.45; H, 7.52; N, 10.71.

(c) Complete crystallographic data for all seven X-ray structures, as CIF files, have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos 281472 - 281478). Copies can be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (e-mail: deposit@ccdc.cam.ac.uk).