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Bis(dialkylamino)cyanoboranes: highly efficient reagents for the Strecker-type aminative cyanation of aldehydes and ketones†

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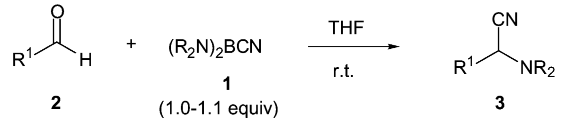
α-Dialkylamino nitriles are formed in excellent yields in the reactions of bis(dialkylamino)cyanoboranes with a wide array of carbonyl compounds.

The Strecker reaction has been one of the most important and useful C–C bond forming processes in organic synthesis,[1] since the α-amino nitrile products serve not only as the synthetic intermediates for α-amino acids, but also as versatile synthons in organic chemistry.[1a,2] Numerous modifications have been made to the original conditions, using aqueous media to improve the efficiency of this process. However, due to the reversible nature of the reaction, most modified ‘aqueous’ conditions still suffer from certain deficiencies, including the tedious isolation of pure α-amino nitriles from the reaction mixtures, which often contain unreacted starting materials and cyanohydrins as by-products. Important contributions in this area involve the development of some new cyano sources that are capable of an irreversible Strecker-type reaction in non-aqueous media.[3,4] It is likely that further improvement along this line will significantly expand the scope of the Strecker reaction for application to new synthetic technologies, including solid phase synthesis, automated synthesis, and high-throughput synthesis, in which simplification of all the reaction processes including work-up and isolation is decisively important.

In the course of our ongoing research program to explore new boron reagents in organic synthesis,[5] we became interested in the use of boron-bound cyanides as new cyanation reagents.[6,7] This interesting class of boron reagents has not been employed for cyanation reactions until very recently.[8] Fortuitously, we found that Strecker-type products were formed almost quantitatively, while attempting to react bis(diethylamino)cyanoborane with just an equimolar amount of aldehyde. In view of such an intriguingly efficient transfer of both the cyano group and the amino group from boron to a carbonyl carbon, we started to pursue the development of the new borane reagent for highly effective Strecker-type α-amino nitrile synthesis.

Reaction of bis(diethylamino)cyanoborane (**1a**, 1.0 equiv.) with benzaldehyde in THF at room temperature afforded α-diethylaminophenylacetonitrile (**3aa**) in 92% yield [eqn. (1), Table 1, entry 1].‡ When the reaction in THF-d_8 was monitored by ^{1}H NMR, clean conversion of the aldehyde to **3aa** ($t_{1/2}$ < 7 h) was observed with no detectable formation of intermediary species or the corresponding cyanohydrin, which would be derived from direct cyanation of benzaldehyde.§ Remarkably, the reaction was so clean that no purification of the crude material was needed after passing the reaction mixture through a short column of Florisil or silica gel. Alternatively, pure materials were obtained by pouring the reaction mixture into cold aqueous NH_4Cl followed by extraction with ether and removal of the solvent. This protocol was successfully applied to the α-amino nitrile synthesis from other aromatic and heteroaromatic aldehydes **2b–e** (entries 2–5). Cinnamaldehyde provided **3af** in 95% yield with no formation of an α-cyano enamine, which would be derived *via* double bond migration (entry 6).¶ Aliphatic aldehydes **2g–j** with varied steric hindrance also afforded the corresponding α-amino nitriles in almost quantitative yields under the same reaction conditions using **1a** (entries 7–10).



(1)

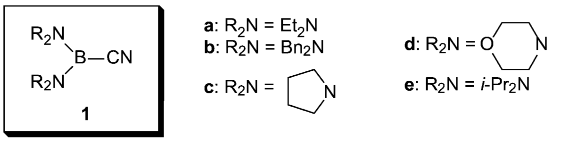
Cyanoboranes **1b–d** bearing dibenzylamino, pyrrolidino, and morpholino groups also worked effectively to give the corresponding α-amino nitriles in high yields at room temperature (Table 1, entries 11–13). For the ready preparation of those cyanoboranes, we established a convenient one-pot procedure in which boron trichloride was treated sequentially with a trimethylsilylated *sec*-amine (2 equiv.) and TMSCN (1 equiv.) at room temperature [eqn. (2)].‖ Cyanoboranes thus prepared could be used for aminative cyanation without further purification.

It should be noted that cyanoborane **1e** bearing bulky diisopropylamino groups exhibited considerably lower reactivity than the other cyanoboranes **1a–d** in the reactions with aldehydes. Thus, α-diisopropylamino nitriles were obtained in high yields at 50 °C, while almost no reaction took place at room temperature (entries 14 and 15).

Table 1 Synthesis of α-amino nitriles by reaction of aldehydes with bis(dialkylamino)cyanoboranes[a]

Entry	Aldehyde (R^1)	**1** (NR_2)	Time/h	Product (% yield)[b]
1	**2a** (Ph)	**1a** (NEt_2)	20	**3aa** (92)
2	**2b** (p-$MeOC_6H_4$)	**1a**	8	**3ab** (93)
3	**2c** (p-$NO_2C_6H_4$)	**1a**	11	**3ac** (92)
4	**2d** (2-furyl)	**1a**	20	**3ad** (94)
5	**2e** (2-pyridyl)	**1a**	23	**3ae** (99)
6	**2f** ((*E*)-PhCH=CH)	**1a**	6	**3af** (95)
7	**2g** (*n*-Hex)	**1a**	1	**3ag** (96)
8	**2h** ($PhCH_2CH_2$)	**1a**	1	**3ah** (94)
9	**2i** (*c*-Hex)	**1a**	7	**3ai** (98)
10	**2j** (*t*-Bu)	**1a**	14	**3aj** (97)
11	**2i**	**1b** (NBn_2)[c]	4	**3bi** (92)
12	**2i**	**1c** (pyrrolidino)[c]	1	**3ci** (99)
13	**2i**	**1d** (morpholino)[c]	2	**3di** (99)
14[d]	**2i**	**1e** (N^iPr_2)	30	**3ei** (92)
15[d]	**2a**	**1e**	150	**3ea** (99)

[a] **1** (0.40 mmol) and aldehyde (0.40 mmol) were reacted in THF (0.7 mL) at room temperature unless otherwise noted. [b] Isolated yield. [c] Crude cyanoboranes **1b–d** (0.48 mmol) prepared by the one-pot procedure from BCl_3 were used. [d] Use of **1e** (0.44 mmol) at 50 °C.



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† Electronic supplementary information (ESI) available: detailed experimental procedures. See http://www.rsc.org/suppdata/cc/b2/b203645b/

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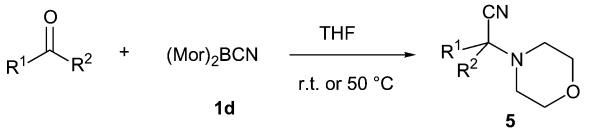
Furthermore, bis(dialkylamino)cyanoboranes were reacted even with ketones, giving the corresponding α-amino nitriles in high yields [eqn. (2), Table 2]. Cyclic ketones (entries 4 and 5) exhibited considerably higher reactivity than the acyclic ones, whose reactions, with the exception of acetone, required heating.



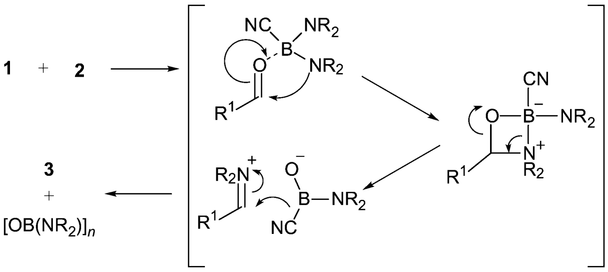
(2)

Table 2 Synthesis of α-amino nitriles by reaction of ketones with di(morpholino)cyanoborane **1d**[a]

	Ketone				
Entry	R^1	R^2	Temp./°C	Time/h	Product (% yield)[b]
1	Me	Me	20	20	**5a** (99)
2	$PhCH_2CH_2$	Me	50	24	**5b** (99)
3	Ph_2CH_2	Me	50	24	**5c** (92)
4	-$(CH_2)_5$-		20	5	**5d** (96)
5	-$(CH_2)_4$-		20	5	**5e** (92)

[a] **1d** (0.48 mmol) and ketone (0.40 mmol) were reacted in THF (0.40 mL), unless otherwise noted. [b] Isolated yield.

We propose the following mechanism for the formation of the Strecker-type products in the reaction of the cyanoboranes with carbonyl compounds (Scheme 1). After coordination of the carbonyl oxygen to the boron atom, nucleophilic attack of the boron-bound amino group to the carbonyl group may take place, leading to the formation of a four-membered cyclic intermediate. Cleavage of the C–O bond as well as the B–N bond in the four-membered ring may result in the formation of an iminium intermediate, to which the cyano group on the boron is transferred.



Scheme 1 Possible mechanism of the formation of α-amino nitriles in the reaction of bis(dialkylamino)cyanoboranes with aldehydes.

In summary, we found that bis(dialkylamino)cyanoboranes served as novel reagents for Strecker-type aminative cyanation. Emphasis may be placed on the high efficiency of these reagents, which feature: (1) mild reaction conditions, (2) requirement of just stoichiometric amounts of reagents, and (3) production of pure α-amino nitriles without tedious purification processes.

We thank Professor Masahiro Murakami for fruitful discussions.

Notes and references

‡ **Caution!** All operations, including work-up, should be carried out in a fume hood to avoid inhalation of hydrogen cyanide, which may be generated by hydrolysis of the cyanoboranes.

§ Also observed in the NMR analysis was a by-product that may be assignable to $[(Et_2N)BO]_n$.

¶ Longer reaction time resulted in the formation of the isomerization products (an *E*/*Z* mixture, 24% isomerization after 32 h).

‖ BCl_3 is treated with *N*-TMS *sec*-amines (2.0 equiv.) in CH_2Cl_2 at room temperature for 0.5 h and then with TMSCN (1.0 equiv) for 5 h (24 h for **1b**). After evaporation of the solvent with liberated TMSCl *in vacuo*, the cyanoborane is ready to use.

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