# Synthesis of Mono- and Di-cyanoborane Adducts from Isonicotinoylhydrazones and Sodium Cyanoborohydride

*J. Chem. Research (S)*, 1998, 550–551
*J. Chem. Research (M)*, 1998, 2532–2544

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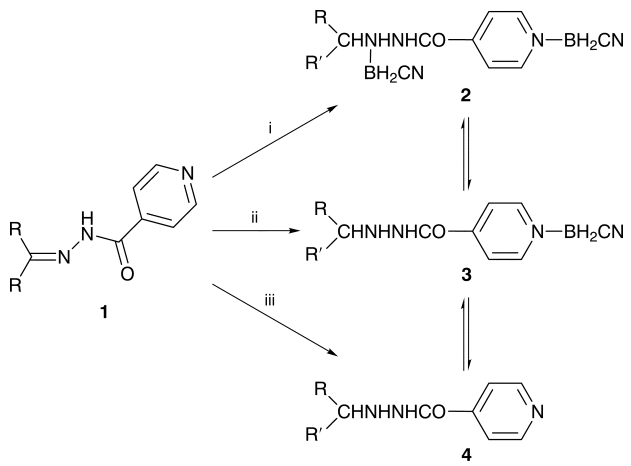
The synthesis of isonicotinohydrazide mono- and di-cyanoborane adducts **2** and **3** by reaction of isonicotinoylhydrazones **1** and sodium cyanoborohydride, their characterization (MS, IR, $^1$H, $^{13}$C and $^{11}$B NMR) and experimental conditions of the reaction course have been investigated and discussed.

In continuation of a research program on novel lipophilic Isoniazid (INH) analogues, designed in view of the re-emergence of tuberculosis and other mycobacterial infections so often AIDS-associated, a series of lipophilic isonicotinohydrazide-cyanoborane adducts have now been designed and synthesized, with the aim of extending the INH activity spectrum to AIDS-associated pathogens other than *Mycobacterium tuberculosis* and, hopefully, to neoplasias.

Cyanoborane adducts **2** and **3** have been obtained by the reaction of isonicotinoylhydrazones (ISNEs) **1** with sodium cyanoborohydride (1:2 molecular ratio, anhydrous THF solution, pH 3–5, room temperature), which acts both as reducing and $BH_2CN$-originating reagent[3–5] (Scheme 1).




R = H, Me
R′ = Ph, 4-$FC_6H_4$, 3-$CF_3C_6H_4$, 3,4-$(MeO)_2C_6H_3$

**Scheme 1** *Reagents and conditions*: i, $NaBH_3CN$/THF, pH 3–5, r.t.; ii, $NaBH_3CN$/MeOH, pH 3–5, heat

When R = H, both adducts **2** and **3** were obtained in comparable yields, whereas when R = Me compounds **3** were greatly predominant (> 95%). A simple alkaline work-up ($NaHCO_3$, KOH, sometimes only $H_2O$ required) of the crude reaction mixture allows us to obtain compounds **3** in high yields; compounds **2** are also partially transformed to **3** during separation of the crude mixture by flash chromatography on a silica gel column. The loss of $BH_2CN$ from **2** is favoured by the capability of the solvent to accept this molecule[3–5] and by the use of heat. Monocyanoboranes **3** proved to be more stable than **2** towards base-catalysed hydrolysis and heating; their complete conversion into hydrazides **4** can be obtained by vigorous heating (70 °C) in methanolic solution.

Some nicotinoylhydrazones, prepared for comparison, showed analogous behaviour. The structures of compounds **2**, **3** and **4** are in accordance with analytical and spectroscopic data (MS, IR, $^1$H, $^{13}$C and $^{11}$B NMR). Moreover the structure of **3** was identified by X-ray diffraction[6] (Fig. 1).

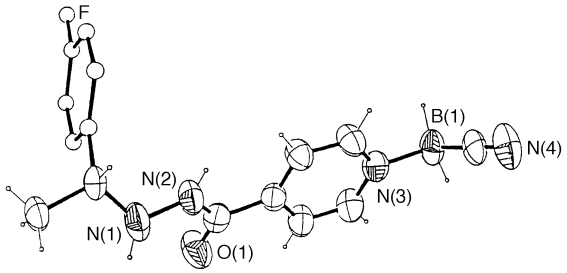



**Fig. 1**

In particular, IR spectra of cyanoboranes **2** and **3** are diagnostic because of strong absorptions between 2450 and 2405 $cm^{-1}$ and sharp, less intense bands at 2210–2200 $cm^{-1}$ ($BH_2$ and CN stretching, respectively), whereas FAB-MS spectra show a characteristic fragmentation pattern. In the $^1$H and $^{13}$C NMR spectra the isonicotinic moiety resonances of **1** and **4** are similar. In adducts **2** and **3** pyridine nitrogen coordination to the $BH_2CN$ moiety gives rise to downfield shifting of pyridine $\beta$- and $\gamma$-positions, which are particularly significant for $\beta$-protons, whereas, quite unexpectedly, $\alpha$-protons are moderately shielded by $BH_2CN$ coordination. As regards the arylalkyl moiety, in **3** and **4**, fast umbrella like motion centered on N-2′ leads to a time averaged symmetry plane between these protons which thus appear as a singlet (enantiotopic protons), whereas the coordination to the $BH_2CN$ moiety freezes N-2′ inversion, destroying this symmetry plane; thus methylene protons become diastereotopic and give rise, in consequence of NH-2′ coupling, to an ABX system, which simplifies to an AB pattern upon $D_2O$ exchange. $^{11}B\{^1H\}$ NMR spectra at 25 °C of both cyanoborane adducts **2** and **3** show a broad resonance in the range $\delta$ −16.5 to −19.0, which sharpens at higher temperature (70 °C) when two resolved boron resonances are observed for dicyanoborane adducts **2**, the higher field one attributable to $C_5H_4N{\cdot}BH_2CN$ and the lower field one to 2′NH·$BH_2CN$. At 70 °C the latter disappears more quickly than the former which gives rise to a much slower decrease ($t_{1/2} > 2$ h). At the end of such experiments (*ca.* 10 h at 70 °C), no more cyanoborane adducts are detected by $^{11}$B NMR spectra and the $^1$H NMR spectra only show the presence of hydrazides **4**.

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Dicyanoborane adducts **2** were never obtained in quantitative yields, even when using an excess of $NaBH_3CN$, suggesting that N-2′, because of the amidic group electron-drawing effect, behaves as a weak coordination site for $BH_2CN$, contrary to behavior reported by others for some alkyloxycarbonylhydrazones.[8] The same occurs with the benzaldehyde benzohylhydrazone which, under the usual experimental conditions, gives the 2′-NH·$BH_2CN$ adduct along with the corresponding hydrazide.

Techniques used: FAB-MS, IR, $^1H$, $^{13}C$ and $^{11}B$ NMR

References: 11

Tables: 6 (chemical-physical, microanalytical and $^1H$, $^{13}C$ and $^{11}B$ NMR data of compounds **2**, **3** and **4**)

*Received, 5th January 1998; Accepted, 15th June 1998*
*Paper E/8/00165K*

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