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*Short Note*

# *N*-[(1*R*)-1-(4-Chlorophenyl)ethyl]-Cyanamide

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**Abstract:** The title compound was synthesized by electrophilic cyanation of commercially available (*R*)-4-chloro-α-methylbenzylamine with cyanogen bromide in diethyl ether, and isolated as a yellow oil in 84% yield. It was characterized by $^{1}$H and $^{13}$C{$^{1}$H] NMR, IR, HRMS, and specific rotation measurements.

**Keywords:** cyanamides; electrophilic cyanation; cyanogen bromide; amines; chiral molecules

## 1. Introduction

Cyanamides are attractive 1C-2N building blocks for the construction of nitrogen-rich molecules such as amidines, guanidines, or ureas [1–3]. Moreover, the cyanamide moiety is present in a number of biologically active molecules, such as the cathepsin K protease and the type 4 phosphodiesterase inhibitors **A** [4] and **B** [5], respectively, or the insecticides thiacloprid (**C**) [6] and sulfoxaflor (**D**) [7] (see Figure 1).

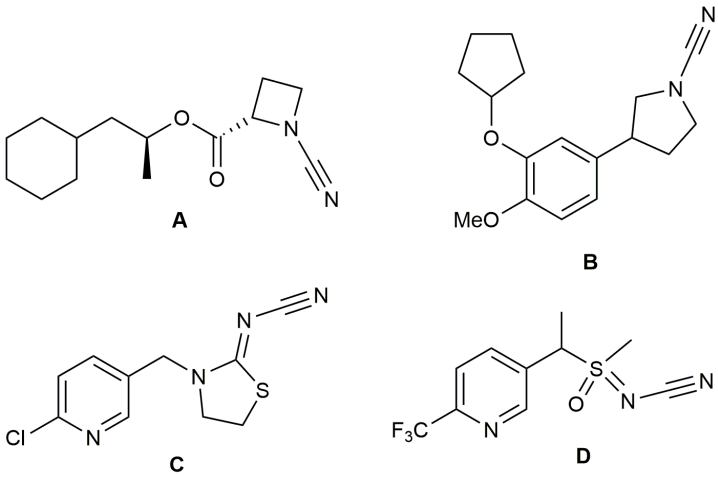


**Figure 1.** Structure of the biologically active cyanamides (**A**–**D**).

According to their significance in synthetic organic chemistry, a large variety of methods for the preparation of cyanamides have been developed [1–3,8]. Among them, the electrophilic cyanation of amines (primary or secondary) is nowadays the most prevalent and effective one, with cyanogen bromide (BrCN) being commonly employed as the electrophilic cyanide source [1–3,8]. Following this route, we report herein the synthesis and characterization of *N*-[(1*R*)-1-(4-chlorophenyl)ethyl]-cyanamide, a novel chiral cyanamide that could have potential application as an advanced intermediate in asymmetric synthesis.

## 2. Results and Discussion

Synthesis of *N*-[(1*R*)-1-(4-chlorophenyl)ethyl]-cyanamide **2** was successfully achieved by following the procedure described by Kaushik and co-workers for the preparation of

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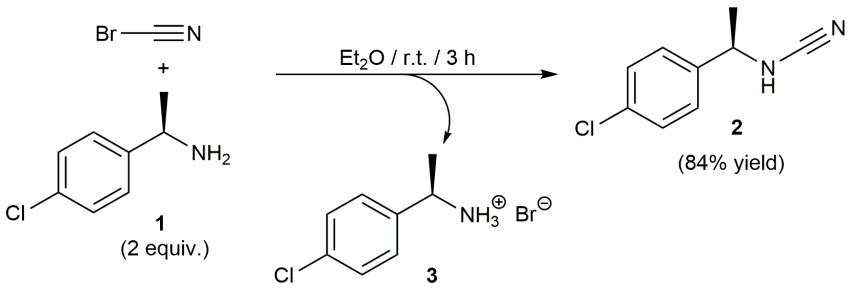
related *N*-monosubstituted cyanamides [9]. Thus, as shown in Scheme 1, the addition of 2 equivalents of (*R*)-4-chloro-α-methylbenzylamine **1** to a diethyl ether solution of BrCN led to the clean formation of cyanamide **2**, which was isolated as a yellow oil in 84% yield. The HBr released during the cyanation reaction is neutralized by the excess of the amine, generating the corresponding ammonium salt **3**, which precipitates from the ethereal solution, thus allowing its separation from **2** by simple filtration. Alternatively, compound **2** could be synthesized in 77% yield by reacting equimolar amounts of BrCN and amine **1** in diethyl ether containing anhydrous sodium carbonate (2 equivalents) at −20 °C for 4 h, as described by Harrison and co-workers for related systems [10].




**Scheme 1.** Synthesis of *N*-[(1*R*)-1-(4-chlorophenyl)ethyl]-cyanamide **2**.

The IR spectrum of compound **2** showed characteristic N-H and C≡N vibrations appearing as strong absorption bands at 3193 and 2218 $cm^{-1}$, respectively. The recorded $^{1}H$ and $^{13}C\{^{1}H\}$ NMR spectra were also fully consistent with the proposed formulation (copies of the NMR spectra are provided as Supplementary Materials). Thus, the $^{1}H$-NMR spectrum showed, in addition of the aromatic resonances for the 4-chlorophenyl unit, a broad signal at 4.14 ppm assigned to the NH proton, a doublet ($^{3}J_{HH}$ = 6.9 Hz) at 1.56 ppm associated with the methyl group, and a quartet of doublets at 4.41 ppm for the methinic proton, which couples both the $CH_3$ ($^{3}J_{HH}$ = 6.9 Hz) and NH ($^{3}J_{HH}$ = 4.2 Hz) groups. Regarding the $^{13}C\{^{1}H\}$ NMR spectrum, the appearance of a singlet signal at 114.7 ppm, not present in the starting amine **1**, is probably the most relevant feature, as it confirms that a C≡N unit has been incorporated in the product. Typical resonances for the methinic and methyl carbons at $\delta_C$ 55.0 and 22.0 ppm, respectively, are also present in the spectrum, along with those of the 4-chlorophenyl unit ($\delta_C$ 134.2 and 139.8 ppm for the quaternary carbons, and $\delta_C$ 127.6 and 129.1 ppm for the CH ones). The specific optical rotation of compound **2** was measured in $CHCl_3$ solution, giving a value of $[\alpha]_D^{20}$ = +288.4°, a dextrorotary behavior also observed for the starting amine **1** ($[\alpha]_D^{20}$ = +31.0° in $CHCl_3$) [11]. In order to complete its characterization, the HRMS of **2** was also recorded (see Figure 2). Contrary to our expectations, the molecular ion peak ($[M]^+$ = 180.0454) was not present in the mass spectrum. Instead, a mass corresponding to the protonated trimer **E** (*m/z* 541.1401) was observed, a fact not entirely surprising, since *N*-monosubstituted cyanamides are known to cyclotrimerize easily into isomelamines under thermal conditions [12]. The rest of the ion peaks found in the spectrum seem to result from the fragmentation of this trimer and were assigned to the species **F**–**I**, depicted in Figure 2. In view of the mass spectrum obtained, doubts could arise about the real nature of the compound obtained in the reaction of (*R*)-4-chloro-α-methylbenzylamine **1** with BrCN. However, the direct formation of trimer **E** can be ruled out based on the recorded NMR spectra, since for **E** characteristic signals for the C=NH units should appear at $\delta_H$ 6–7 ppm and $\delta_C$ 140–150 ppm [12]. Finally, it should also be noted that HPLC measurements on compounds **1** and **2** indicated no erosion of optical purity (97%) during the cyanation process (details are given in the Supplementary Materials).

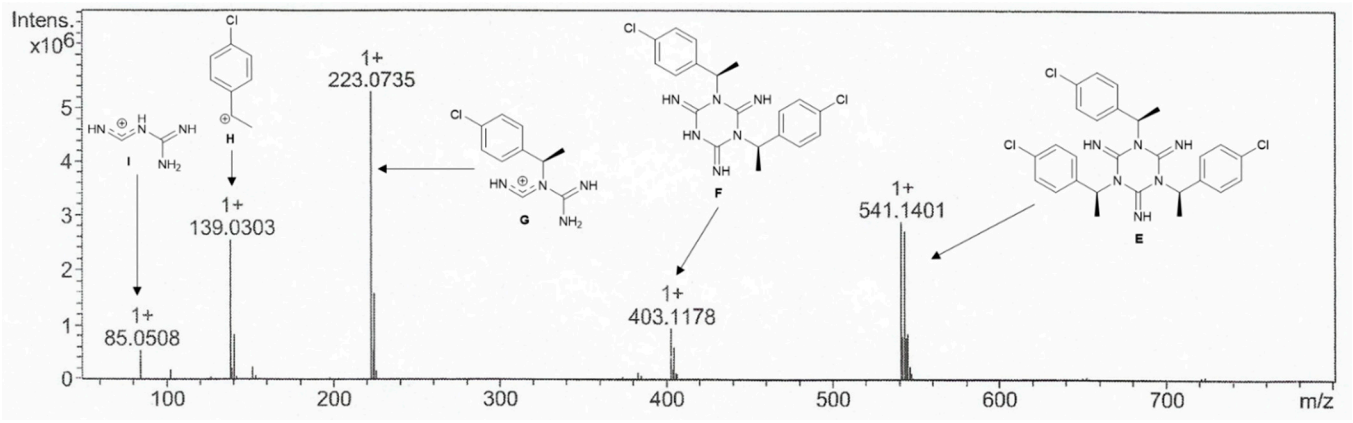



**Figure 2.** HRMS (ESI) obtained for *N*-[(1*R*)-1-(4-chlorophenyl)ethyl]-cyanamide **2**.

## 3. Materials and Methods

Cyanogen bromide and (*R*)-4-chloro-*α*-methylbenzylamine were obtained from Merck KGaA (Darmstadt, Germany) and used as received. Organic solvents were dried by standard methods and distilled under argon before use [13]. NMR spectra were recorded at room temperature on a Bruker DPX-300 instrument (Billerica, MA, USA), with the residual signal of the deuterated solvent employed ($CDCl_3$) as reference for the chemical shifts. The IR spectrum of compound **2** was recorded on a PerkinElmer 1720-XFT spectrometer (Waltham, MA, USA). HRMS data were provided by the General Services of the University of Oviedo employing a QTOF Bruker Impact II mass spectrometer. The optical rotation of **2** was measured using a Perkin-Elmer 241 polarimeter.

*N-[(1R)-1-(4-Chlorophenyl)ethyl]-Cyanamide (**2**)*

A solution of (*R*)-4-chloro-*α*-methylbenzylamine **1** (1.40 mL, 10 mmol) in 20 mL of diethyl ether was added dropwise to a solution of cyanogen bromide (0.530 g, 5 mmol) in 30 mL of diethyl ether at 0 °C (CAUTION: Cyanogen bromide is extremely toxic and should only be used in a fume hood with the appropriate personal protective gear [14]). The reaction mixture was then stirred at room temperature for 3 h. A white precipitate of the ammonium salt **3** appeared and was removed by filtration. The filtrate was washed with water (2 × 10 mL), dried with anhydrous $MgSO_4$, and filtered and concentrated under reduced pressure to give cyanamide **2** as a yellow oil, which was washed twice with hexane (2 × 5 mL). Yield: 0.759 g (84%). The characterization data for **2** are as follows: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.38–7.35 (m, 2H, $CH_{arom}$), 7.30–7.28 (m, 2H, $CH_{arom}$), 4.41 (qd, 1H, $^3J_{HH}$ = 6.9 and 4.2 Hz, C*H*Me), 4.14 (br s, 1H, NH), 1.56 (d, 3H, $^3J_{HH}$ = 6.9 Hz, Me) ppm. $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): $\delta$ = 139.8 (s, $C_{arom}$), 134.2 (s, $C_{arom}$),129.1 (s, $CH_{arom}$), 127.6 (s, $CH_{arom}$), 114.7 (s, C≡N), 55.0 (s, CHMe), 22.0 (s, Me) ppm. IR (neat): $\nu$ = 3193 (s), 2978 (m), 2902 (m), 2218 (s), 1902 (w), 1653 (w), 1597 (w), 1578 (w), 1494 (s), 1451 (m), 1412 (m), 1379 (m), 1337 (w), 1318 (w), 1295 (w), 1271 (w), 1209 (m), 1162 (m), 1123 (w), 1099 (s), 1014 (s), 885 (w), 829 (s), 778 (w), 722 (w) cm$-1$. HRMS (ESI): *m*/*z* 541.1401 [$C_{27}H_{27}N_6Cl_3$ + $H^+$] (calcd. for $C_{27}H_{28}N_6Cl_3$: 541.1441), 403.1178 [$C_{19}H_{20}N_6Cl_2$ + $H^+$] (calcd. for $C_{19}H_{21}N_6Cl_2$: 403.1204), 223.0735 [$C_{10}H_{12}N_4Cl$]$^+$ (calcd. for $C_{10}H_{12}N_4Cl$: 223.0745), 139.0303 [$C_8H_8Cl$]$^+$ (calcd. for $C_8H_8Cl$: 139.0309), 85.0508 [$C_2H_5N_4$]$^+$ (calcd. for $C_2H_5N_4$: 85.0509). $[\alpha]_D^{20}$ = +288.4° (*c* 1.0, $CHCl_3$).

## 4. Conclusions

In summary, *N*-[(1*R*)-1-(4-chlorophenyl)ethyl]-cyanamide has been synthesized in high yield by electrophilic cyanation of (*R*)-4-chloro-*α*-methylbenzylamine and spectroscopically characterized.

**Supplementary Materials:** The following are available online, Figures S1–S4: $^{1}$H-NMR, $^{13}$C{$^{1}$H} NMR, IR, and HRMS spectrum of compound **2**. Details on the determination of the optical purity of compounds **1** and **2**.

**Author Contributions:** Conceptualization, V.C.; synthesis and characterization of compound **2**, R.G.-F.; original draft preparation, P.C.; review and editing, V.C. All authors have read and agreed to the published version of the manuscript.

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