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A New Method for the Synthesis of 1-(1-Isocyanoethyl)adamantane

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Abstract: A novel single-step method has been developed for the synthesis of 1-(1-isocyanoethyl)adamantane from 1-(1-adamantylethyl)amine, chloroform, and *t*-BuOK, in a dichloromethane/*tert*-butanol (1:1) medium, yielding 92%, which is 27% higher compared to the known method, without the use of highly toxic compounds. The product was characterized using ^{1}H and ^{13}C NMR spectroscopy, GC-MS, and elemental analysis.

Keywords: 1-(1-isocyanoethyl)adamantane; adamantane; isocyanide

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1. Introduction

Isocyanides are of interest as promising intermediate compounds for the synthesis of biologically active substances [1]. The presence of an isocyanide group allows them to participate in various chemical reactions such as nucleophiles, electrophiles, or radicals [2]. Isocyanides play a particular role in multicomponent reactions [3] such as Ugi [4] and Passerini reactions [5], making them versatile synthetic reagents.

Many natural isocyanides exhibit potent antibacterial, fungicidal, and anticancer properties [6]. For example, isocyanides isolated from marine sponges have shown high anti-malarial activity [7].

Introducing an adamantane fragment into a molecule increases its lipophilicity, which may lead to enhanced biological activity [8]. For instance, Singh and colleagues demonstrated that 1-isocyanoadamantane exhibits the highest inhibitory activity against the *Plasmodium yoelii* strain (IC_{50} = 0.04 μM) compared to other compounds synthesized by isocyanides [9].

Only five isocyanides of the adamantane series have been described in the literature: 1-isocyanoadamantane [9], 3-isocyanoadamantan-1-ol [10], 1-(3-isocyanopropyl)adamantane [11], 1-(1-isocyanoethyl)adamantane, and 2-isocyanoadamantane [12]. Therefore, the synthesis of new isocyanides of the adamantane series, as well as the development and optimization of known methods for their synthesis, is a relevant task (Figure 1).

Literature reports numerous studies on the synthesis of isocyanides [13]. One commonly used method is a two-step process based on the formation of formamide from the initial amine, followed by dehydration using phosphorus oxychloride ($POCl_3$) or triphosgene [6]. Using this method, 1-(1-isocyanoethyl)adamantane was obtained with a 65% yield over two steps [12]. However, $POCl_3$ and triphosgene are highly toxic substances that require careful handling.

In our previous work, we developed a method for obtaining 1-(3-isocyanopropyl)adamantane based on the known reaction of an amine with a mixture of chloroform and NaOH, promoting the formation of dichlorocarbene, in the presence of dichloromethane and *tert*-butyl alcohol [11]. It was found that the addition of *tert*-butanol contributed to an increase in the yield of the isocyanide to 88%.

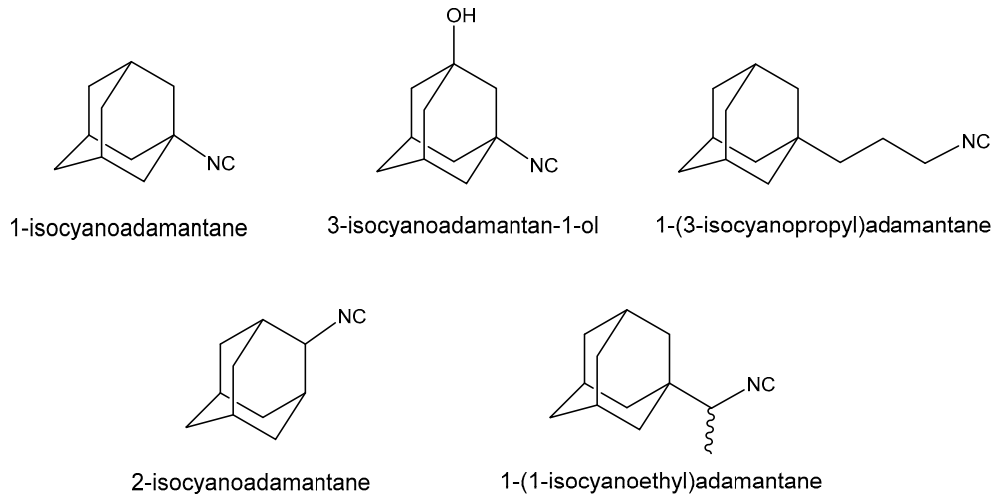


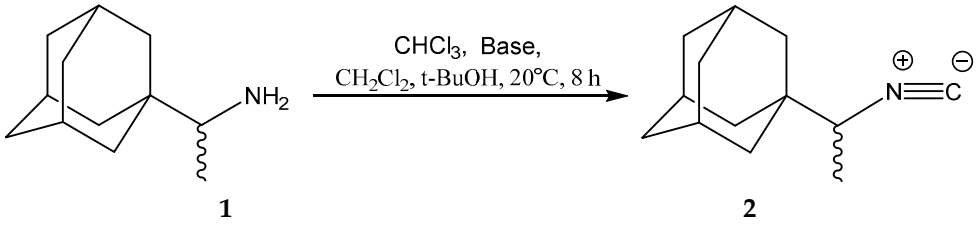
Figure 1. Adamantane series isocyanides.

However, investigations into the influence of the nature of the base on the yield of adamantyl-containing isocyanides have not been conducted previously.

Thus, this study is dedicated to the development of a new method for obtaining 1-(1-isocyanoethyl)adamantane.

2. Results and Discussion

Continuing these investigations, an attempt was made to improve the synthesis method of 1-(1-isocyanoethyl)adamantane **2** by selecting a base. Bases such as LiOH, NaOH, KOH, and potassium *tert*-butoxide (*t*-BuOK) were utilized. Comparative studies were conducted under analogous conditions involving NaOH (Scheme 1) for reference.



Scheme 1. Synthesis of 1-(1-isocyanoethyl)adamantane **2** from 1-(1-adamantylethyl)amine **1**, chloroform, and base in a mixture of dichloromethane: *tert*-butanol (1:1).

The yield of isocyanide **2** remains practically unchanged when the reaction is conducted in the temperature range from 20 °C to 40 °C; therefore, it is advisable to carry out the reaction at room temperature.

As evident from Table 1, in the presence of LiOH, the reaction does not proceed. This is likely due to the fact that LiOH is a weaker base (pK_b = 0.36) compared to NaOH (pK_b = −0.18) and KOH (pK_b = −0.46) [14], incapable of interacting with chloroform and generating dichlorocarbene in the reaction mixture. The higher yield of the isocyanide when using NaOH instead of KOH is likely attributed to better homogenization of the reaction mixture when using NaOH (Table 1).

The highest yields were achieved when using potassium *tert*-butoxide, possibly due to its higher solubility in the dichloromethane/*tert*-butanol solvent system compared to other bases.

Upon completion of the reaction (monitored by GC-MS), the reaction mixture was filtered to remove the precipitate, and the solvent was evaporated under reduced pressure. Subsequently, the reaction mixture was dissolved in hexane and the solution was decanted. Hexane was evaporated to obtain the isocyanide with a purity exceeding 97%

(GC-MS). The structure of the obtained isocyanide was confirmed by GC-MS and ^{1}H and ^{13}C NMR spectroscopy.

Table 1. Effect of temperature and the nature of the base on the yield of 1-(1-isocyanoethyl)adamantane.

Reaction Temperature, °C	Reaction Time, h	Base	Isocyanide Content in the Reaction Mass, %	pK_b [12]
40	8	LiOH	0	0.36
40	8	NaOH	86	−0.18
40	8	KOH	62	−0.46
40	8	*t*-BuOK	92	-
20	8	*t*-BuOK	91	-

The amount of isocyanide in the reaction mass was determined by GC-MS.

Thus, we optimized a single-step method for obtaining 1-(1-isocyanoethyl)adamantane **2** with a yield of 92% by reacting the amine with chloroform and *t*-BuOK in a dichloromethane and *tert*-butanol (1:1) mixture. The developed synthesis method has several advantages. Firstly, the reaction proceeds in a single step, significantly reducing labor costs. Secondly, there is no need to use anhydrous solvents, as the presence of water only slightly decreases the yield of the target isocyanide. Thirdly, the reaction employs readily available and low-toxicity reagents, such as *tert*-butanol and its potassium salt.

3. Materials and Methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 instrument (Bruker AXS Handheld Inc., Kennewick, WA, USA) (frequencies of 400 and 75 MHz) in DMSO-d_6 solution, with TMS as the internal standard. *J* values are given in Hz. GC-MS spectra were measured on an Agilent GC5975/MSD 7820 instrument (Agilent Technologies, Santa Clara, CA, USA) using electron impact (EI) ionization. Chromatographic separation was performed in split mode on a quartz capillary column HP-5MS (film thickness 30 m × 0.25 mm × 0.5 μm) with a programmed temperature regime (from 80 to 280 °C, 10 °C/min), using helium as the carrier gas at a flow rate of 1 mL/min, and with an injector temperature of 250 °C. Elemental analysis was conducted on a Perkin-Elmer Series II 2400 elemental analyzer (Perkin Elmer Inc., Waltham, MA, USA). TLC analysis was performed on Merck chromatographic plates with silica gel F254 fluorescent indicator (1.05554); sorbent: silica gel 60, layer thickness: 200 μm; pore size: 60 Å, particle size: 10–12 μm; binder: organic polymer (Merck KGaA, Darmstadt, Germany). Solvents and reagents were obtained from commercial sources.

Atom labeling for compound **2** is provided in Figure 2. Detailed spectral data are available in the Supplementary Materials.

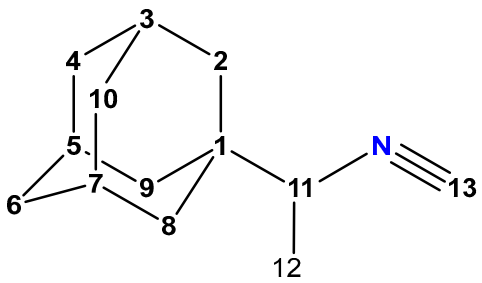


Figure 2. Carbon atom labeling for compound **2**.

The synthesis of 1-(1-isocyanoethyl)adamantane **2** was carried out according to the following procedure.

Into a flat-bottomed flask equipped with a magnetic stirrer, 0.8 g (4.5 mmol) of 1-(1-adamantylethyl)amine **1**, dissolved in 15 mL of dichloromethane, was added, along with 2.32 g (20.67 mmol) of potassium *tert*-butoxide and 15 mL of *tert*-butyl alcohol. Then, 0.54 mL (6.75 mmol) of chloroform was slowly added dropwise. The reaction mixture was stirred for 8 h at 20 °C. Upon completion of the reaction (monitored by GC-MS), the reaction mixture was filtered to remove the precipitate, and the precipitate was washed with 15 mL of dichloromethane. The filtrate and the washing dichloromethane were combined, washed with a 1N HCl solution, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the isocyanide with a purity >97%. The liquid was a light yellow color. The yield was 0.77 g (91%). ^{1}H NMR spectrum (DMSO-d_6), δ ppm: 3.43 (q, 1H, H11, J = 6.9 Hz); 2.00 (s, 3H, (H3, H5, H7)); 1.72–1.59 (m, 6H, (H4, H6, H10)); 1.57–1.46 (m, 6H, (H4, H6, H10)); 1.20 (dt, 3H, H12, $J1$ = 6.9 Hz, $J2$ = 2.3 Hz,). ^{13}C NMR spectrum (DMSO-d_6), δ ppm: 155.5 (C13), 60.06 (C11), 39.02 (C2, C8, C9), 37.57(C1), 36.72 (C4, C6, C10), 27.99 (C3, C5, C7), 15.26 (C12). Mass spectrum, m/z (I_{rel}.%): 189 (89% $[M]^+$), 174 (3% $[M\text{-}CH_3]^+$), 163 (2% $[M\text{-}NC]^+$), 135 (100% $[Ad]^+$), retention time = 11.648 min. Found, %: C 82.44; H 10.18; N 7.45. $C_{13}H_{19}N$. Calculated, %: C 82.48; H 10.12; N 7.40.

4. Conclusions

A new single-step method for obtaining 1-(1-isocyanoethyl)adamantane from 1-(1-adamantylethyl)amine, chloroform, and *t*-BuOK in a dichloromethane/*tert*-butanol (1:1) mixture with a yield of up to 92% has been developed, which is a 27% higher yield compared to the known method [12], without the use of highly toxic compounds. The developed method can be applied for the synthesis of other adamantane isocyanides, as well as isocyanides of aromatic and aliphatic structures. Compound **2** was identified by ^{1}H and ^{13}C NMR, GC-MS, and elemental analysis methods.

Supplementary Materials: The following supporting information can be downloaded online: ^{1}H NMR, ^{13}C NMR, and mass spectra; Figure S1: Chromatogram of compound **2**; Figure S2: Mass spectrum of compound **2**; Figure S3: NMR ^{1}H of compound **2**; Figure S4: NMR ^{13}C of compound **2**.

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Data Availability Statement: Data are contained within the article and Supplementary Materials.

Conflicts of Interest: The authors declare no conflicts of interest.

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