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SHORT COMMUNICATIONS

Synthesis of Adamantyl-Containing Isothiocyanates

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Adamantyl-containing isothiocyanates are promising precursors to thioureas that are efficient inhibitors of mammalian and human soluble epoxide hydrolase (sEH, EC 3.3.2.10) targeted by therapy of hypertonic, inflammatory, and pain disorders [1–4]. Thioureas are also promising as non-peptide inhibitors of plasminogen/urokinase activator (uPA) responsible for the development of cancer [5].

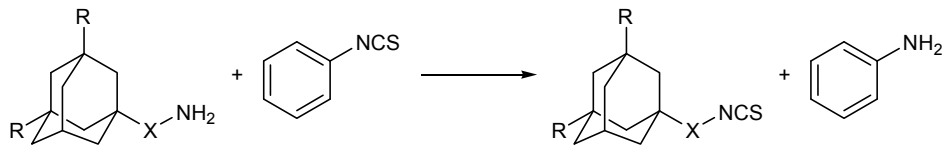
Traditional methods of synthesis of 1-adamantyl isothiocyanate are based on reactions of adamantan-1-amine with carbon disulfide in the presence of potassium hydroxide (20°C, 12 h) [6], of adamantan-1-amine with thiophosgene in the presence of potassium carbonate (25°C, 2 h) [7], of trimethylsilyl isothiocyanate with 1-chloroadamantane in the presence of titanium chloride in methylene chloride (0°C, 3 h) [8], and of 1-bromoadamantane with potassium thiocyanate in dimethylformamide (153°C, 5 h) [9]. However, these procedures require the use of corrosive and highly toxic reagents, and the syntheses are multistep.

Herein we report on the synthesis of adamantyl-containing isothiocyanates **1**–**3** (instead of expected thioureas) by heating a solution of adamantan-1-amine, 1,3-dimethyladamantan-1-amine, or 1-(1-adamantyl)-ethan-1-amine with phenyl isothiocyanate in boiling toluene for 3 h. The products were isolated in 65–80% yield after recrystallization from ethanol, and their structure was confirmed by ^{1}H NMR, IR, and mass spectra and elemental analyses.

The possibility for variation of the structure of the adamantane component, as well as easy isolation procedure, makes the proposed method quite general and applicable for the preparation of difficultly accessible isothiocyanates of the adamantane series.

1-Isothiocyanatoadamantane (1). Phenyl isothiocyanate, 7.84 g (0.058 mol), was added to a solution of 10.57 g (0.07 mol) of adamantan-1-amine in 150 mL of toluene, and the mixture was heated for 3 h at 110°C. When the reaction was complete, the solvent was distilled off, and the residue was recrystallized from ethanol. Yield 11.0 g (80%), mp 167–169°C [9]. ^{1}H NMR spectrum, δ, ppm: 1.41–2.18 m (15H). ^{13}C NMR spectrum, δ_C, ppm: 29.3 (C^3, C^5, C^7), 35.6 (C^4, C^6, C^{10}), 43.8 (C^2, C^8, C^9), 58.5 (C^1), 129.4 (NCS). Mass spectrum, *m*/*z* (I_{rel}, %): 193 (10) $[M]^+$, 135 (100) $[Ad]^+$.

1-Isothiocyanato-3,5-dimethyladamantane (2). Phenyl isothiocyanate, 7.84 g (0.058 mol), was added to a solution of 12.53 g (0.07 mol) of 3,5-dimethyladamantan-1-amine in 150 mL of toluene, and the mixture was heated for 3 h at 110°C. When the reaction was complete, the solvent was distilled off, and the product was isolated by vacuum distillation. Yield 10.05 g (65%), bp 141°C (400 Pa) [10]. IR spectrum,



1–3

1, X = bond, R = H; **2**, X = bond, R = Me; **3**, X = MeCH, R = H.

ν, cm^{-1}: 2065, 1190, 895, 675. ^1H NMR spectrum, δ, ppm: 0.82 s (6H), 1.35–2.15 m (13H). Mass spectrum, *m*/*z* (I_{rel}, %): 221 (10) $[M]^+$, 163 (100) $[(CH_3)_2Ad]^+$, 133 (13) $[Ad]^+$.

1-(1-Isothiocyanatoethyl)adamantane (3). Phenyl isothiocyanate, 7.84 g (0.058 mol), was added to a solution of 12.53 g (0.07 mol) of 1-(1-adamantyl)-ethan-1-amine in 150 mL of toluene, and the mixture was heated for 3 h at 110°C. When the reaction was complete, the solvent was distilled off, and the residue was recrystallized from ethanol. Yield 10.8 g (70%), mp 141°C. ^1H NMR spectrum, δ, ppm: 1.57 d (3H, CH_3, J = 7.2 Hz), 1.70–1.87 m (15H), 3.44 q (1H, CH, J = 7.2 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 221 (74) $[M]^+$, 163 (28) $[Ad - CH(CH_3)]^+$, 135 (100) $[Ad]^+$. Found, %: C 70.51; H 8.63; N 6.40; S 14.46. $C_{13}H_{19}NS$. Calculated, %: C 70.54; H 8.65; N 6.33; S 14.48.

The ^1H NMR spectra were recorded from solutions in DMSO-d_6 on a Bruker DRX 500 spectrometer (500 MHz); tetramethylsilane was used as internal standard. The mass spectra were obtained on an Agilent 5975 mass-selective detector coupled with an Agilent 7820 gas chromatograph (HP-5MS quartz capillary column, 30 m; carrier gas helium; oven temperature programming from 80 to 280°C; injector temperature 250°C). The elemental compositions were determined on a Perkin Elmer 2400 Series II analyzer.

Commercial adamantan-1-amine, 3,5-dimethyladamantan-1-amine, 1-(1-adamantyl)ethan-1-amine, and phenyl isothiocyanate (Aldrich) were used without additional purification. Toluene and ethanol were distilled before use.

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