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SYNTHESIS OF 4-(1-ADAMANTYL)- AND 4-(1-ADAMANTYLMETHYL)- SUBSTITUTED HALOTHIAZOLES

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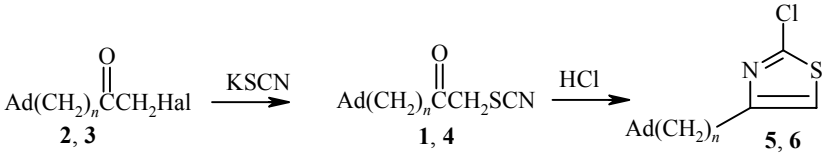
1-Adamantyl bromomethyl ketone and 1-adamantylmethyl chloromethyl ketone react with potassium thiocyanate in dimethylformamide to give the corresponding thiocyanatoketones which cyclize under the influence of HCl into 4-(1-adamantyl) and 4(-adamantylmethyl)chlorothiazole respectively. 4-(1-Adamantyl)-2-amino-5-bromothiazole and its N-derivative were synthesized by the reaction of 1-adamantyl dibromomethyl ketone with thioureas and N-substituted thiourea in acetonitrile.

Keywords: adamantyl- and adamantylmethyl-substituted halothiazoles, dibromo ketones, thioureas, thiocyanatoketones, cyclization.

Thiocyanatoketones, which are readily obtained from α-halo ketones [1], serve as starting materials for the synthesis of 2-aminothiazoles, thiazolin-2-ones [3], 2-iminothiazoles [4], and 2-halothiazoles [5].

In continuation of our work on the synthesis of heterocyclic compounds of the adamantane series based on halo ketones [6, 7] we have obtained for the first time new 2- and 5-halothiazoles with 1-adamantyl or 1-adamantylmethyl residues in position 4.

It was reported earlier [8] that 4-(1-adamantyl)thiazol-2-one was synthesized by the hydrolysis of (1-adamantoyl)methyl thiocyanate (**1**) which was obtained without isolation from 1-adamantyl chloromethyl ketone and potassium thiocyanate in acetone. We have extended this reaction to 1-adamantyl bromomethyl ketone (**2**) and 1-adamantylmethyl chloromethyl ketone (**3**). The corresponding thiocyanatoketones **1** and **4** were synthesized as dark red powders by boiling the halo ketones **2** and **3** with potassium thiocyanate in dimethylformamide. Methanol, ethanol, and dioxane were less satisfactory solvents for this reaction. Compounds **1** and **4** were converted into 4-(1-adamantyl)- (**5**) and 4-(1-adamantylmethyl)-2-chlorothiazoles (**6**) under the influence of dry HCl in ether.



2 Hal = Br; **3** Hal = Cl. **1**, **2**, **5** *n* = 0; **3**, **4**, **6** *n* = 1

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TABLE 1. Physicochemical Characteristics of the Compounds Synthesized

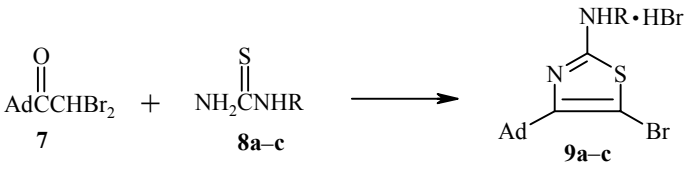
Compound	Empirical formula	Found, % / Calculated, %			R_f	mp, °C	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N				
1*	$C_{13}H_{17}NOS$				0.65 (a)	178-180	1700 (C=O), 2850 and 2900 (CH_2, Ad)	65
4*	$C_{14}H_{19}NOS$				0.77 (b)	143-145	1680 (C=O), 2850 and 2900 (CH_2, Ad)	92
5	$C_{13}H_{16}ClNS$	61.60 / 61.52	6.40 / 6.36	5.55 / 5.52	0.55 (c)	123-125	2850 and 2900 (CH_2, Ad)	78
6	$C_{14}H_{19}ClNS$	62.60 / 62.55	7.10 / 7.12	5.20 / 5.21	0.85 (b)	86-88	2860 and 2910 (CH_2, Ad)	56
9a	$C_{13}H_{18}Br_2N_2S$	39.60 / 39.61	4.60 / 4.60	7.15 / 7.11		145-148	2850 and 2900 (CH_2, Ad), 3290 (NH_2)	97
9b	$C_{19}H_{22}Br_2N_2S$	48.55 / 48.53	4.71 / 4.72	6.00 / 5.96		209-210	2850 and 2900 (CH_2, Ad), 3300 (NH)	91
9c	$C_{15}H_{20}Br_2N_2S$	42.88 / 42.90	4.80 / 4.80	6.69 / 6.67		203-205	1650 (C=O), 2850 and 2900 (CH_2, Ad), 3350 (NH)	96

* These compounds are unstable and are converted into an oily mass over 48 h.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Adamantyl		Other protons
	CH_2 (12H, d, J = 6.1 Hz)	CH (3H, s)	
5	1.70-1.75	1.85	6.55 (1H, s, 5-H_{Het})
6	1.65-1.70	1.95	2.50 (2H, s, Ad$\underline{CH_2}$); 6.62 (1H, s, 5-H_{Het})
9a	1.70-1.75	2.1	11.7 (2H, br. s, NH_2)
9b	1.66-1.72	2.05	6.6-7.6 (5H, m, Ph); 10.1 (1H, br. s, NH)
9c	1.65-1.75	1.98	1.12 (3H, s, CH_3C=O); 11.5 (1H, br. s, NH)

Unlike monohalo ketones of the adamantane series, the chemistry of which is well studied, the properties of adamantyl dibromomomethyl ketone (**7**) had not been studied. We have shown that dibromo ketone **7** reacts readily with N-R-thioureas **8a-c** to give the corresponding substituted 1-adamantylbromothiazoles **9a-c** in high yields (91-98%).



8, **9 a** R = H, **b** R = Ph, **c** R = Ac

The reactions were carried out in acetonitrile which facilitates complete solution of the reactants and separation of the end products as precipitates.

The examples cited provide a simple means for the synthesis of halogenated thiazoles containing adamantyl or methyladamantyl substituents.

EXPERIMENTAL

^{1}H NMR spectra of DMSO solutions with HMDS as internal standard were recorded with a Bruker AC-300 (300.13 MHz) instrument. IR spectra of KBr tablets were obtained on a Specord M-80 spectrometer. Purity of the compounds was monitored by TLC on Silufol UV-254 strips with acetone–CCl_4 (a), acetone (b), or ethanol (c). The physicochemical characteristics of the products are cited in Tables 1 and 2.

1-Adamantyl- (1) and 1-Adamantylmethylthiocyanatomethyl Ketone (4). Mixture of halo ketone **2** or **3** (1.9 mmol), potassium thiocyanate (2.1 mmol), and dimethylformamide (10 ml) was heated for 1-3 h until a clear solution was formed. The reaction mixture was poured into water, the precipitate was filtered off, washed with cold water, dried, and used without purification for further syntheses.

4-(1-Adamantyl)-2-chlorothiazole (5) and 4-(1-Adamantylmethyl)-2-chlorothiazole (6). Stream of dry HCl was passed into solution of thiocyanatoketone **1** or **4** (0.5 g) in absolute ether (10 ml) cooled in ice. The precipitate of product **5** or **6** was filtered off, washed with cold ether, and recrystallized from ethanol.

4-(-1-Adamantyl)-2-(R-amino)-5-bromothiazole Hydrobromides (9a-c). Solution of dibromo ketone **7** (1.5 mmol) in acetonitrile (5 ml) was added with stirring at room temperature to solution of thiourea **8** (2.2 mmol) in acetonitrile (15 ml). Stirring was continued (15 min to 1 h) until product **9** precipitated. The precipitate was filtered off and washed with acetonitrile.

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