Chemistry of Heterocyclic Compounds, Vol. 30, No. 5, 1994

SYNTHESIS OF 2-MERCAPTOIMIDAZOLES AND PYRROLES OF THE ADAMANTANE SERIES

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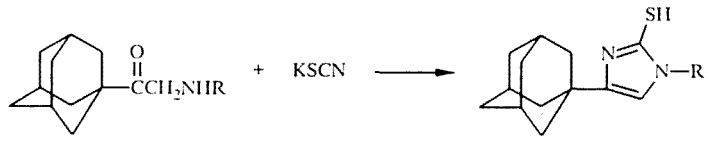
2-Mercaptoimidazole derivatives were prepared by the reaction of N-R-(adamantanoyl-1-methyl)amines with potassium thiocyanate. An attempt to synthesize pyrroles from the same amines with the Knorr reaction did not produce the anticipated results.

α-Aminoketones are the starting compounds for synthesis of 2-mercaptoimidazoles, which have an anti-inflammatory [1] action, and pyrroles, which have an anti-inflammatory [2] and antimicrobial [3] action. Synthesis of 2-mercaptoimidazoles of the aliphatic series from 1-(*tert*-butyl)-2-(isopropyl)methyl ketone is described in [4], and synthesis from primary α-aminoketone of the adamantane series is described in [5], but the yield of the compounds did not exceed 40%.

Pyrroles are prepared by the Knorr reaction in the reaction of acetoacetic ester with both haloketones in the presence of ammonia [6] and with primary [7] or secondary [1, 8] α-aminoketones, but in the last case, the yields of target products are a total of 2-16%.

In continuing our research on synthesis of adamantyl-substituted heterocycles with potential biological activity and studying the chemical properties of N-R-(adamantyl-1-methyl)amines (Ia-c) prepared from bromomethyl(1-adamantyl)ketone (II) and to determine the degree of the effect of radicals in keto and amino groups on the reactivity of compounds Ia-c, we investigated the reaction of Ia-c with potassium thiocyanate and acetoacetic ester.

The reaction of aminoketones Ia-c with potassium thiocyanate was conducted in heating in acetic acid for 6-13 h. 2-Mercaptoimidazoles (IIIa, b) were obtained from compounds Ia and Ib with yields of 16 and 36%, respectively.



Ia, b IIIa,b

I, III a R = CH_3, b R = *p*-$CH_3C_6H_4$

In similar conditions, compound Ic does not enter the cyclization reaction. Instead of the anticipated product (IIIc, R = 1-adamantyl), the starting α-aminoketone was separated, probably due to the steric hindrances caused by the large volume of the adamantyl radical in the amino group.

Absorption bands were found in the 2900-2910 and 2850-2860 (adamantane CH_2) and 2560-2600 cm^{-1} (SH) regions in the IR spectra of imidazoles IIIa, b.

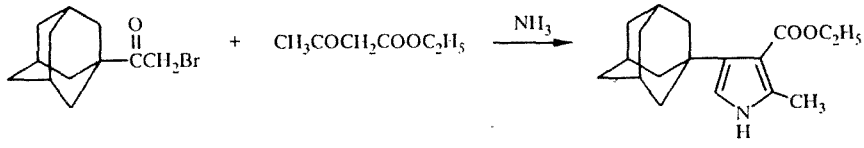
The reaction of aminoketones Ia-c with acetoacetic ester could not be conducted, and the starting compounds were separated even in boiling in absolute alcohol for many hours. However, the reaction of bromomethyl(1-adamantyl)ketone II with acetoacetic ester took place in the presence of ammonia at 20°C. 2-Methyl-4-(1-adamantyl)pyrrole-3-carboxylic acid ethyl ester (IV) was separated with a yield of 7%.

Samara State Technical University, Samara 443010. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 621-623, May, 1994. Original article submitted February 4, 1994.

 0009-3122/94/3005-0544$12.50

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Mp, °C	R_f (eluent)	IR spectrum ν, cm^{-1}	Yield, %
Ia	$C_{13}H_{21}NO$	68...70	0,648 (alcohol	2900, 2850, 1700, 3400	84
Ib	$C_{19}H_{25}NO$	117...118	0,71 (acetone CCl_4, 1 : 6)	2920, 2870, 1710, 3400	80
Ic	$C_{22}H_{33}NO$	252...254	0,371 (alcohol	2910, 2860, 1720, 3420	94
IIIa	$C_{14}H_{20}N_2S$	238...240	0,178 (acetone–CCl_4, 1 : 4)	2900, 2850, 2580	16
IIIb	$C_{19}H_{24}N_2S$	295...297	0,548 (acetone CCl_4, 1 : 4)	2910, 2860, 2600	36
IV	$C_{18}H_{25}NO_2$	192...193	0,064 (acetone CCl_4, 1 : 4)	2900, 2850, 3350, 1590, 1400	7



II IV

The IR spectrum of product IV exhibits absorption bands at 2900 and 2850 (adamantane CH_2), 3350 (NH), and 1590 and 1400 cm^{-1} ($COOC_2H_5$).

Obtaining pyrrole IV with a low yield indicates that the adamantyl radical in some way impedes cyclization of aminoketones Ia-c, and the presence of substituents at the amino group makes it impossible.

EXPERIMENTAL

The course of the reaction was monitored and the individuality of the substances was assessed by TLC on Silufol UV-254 plates. The IR spectra were made on a Specord M-80 in KBr pellets.

The properties of the synthesized compounds are reported in Table 1.

The data from elemental analysis are in agreement with the calculated values.

Methyl(adamantanoyl-1-methyl)amine (Ia, $C_{13}H_{21}NO$). A mixture of 1.5 g (6 mmole) of bromoketone II, 0.783 g (11.6 mmole) of methylamine hydrochloride, 0.5 g of Na_2CO_3, and 15 ml of ethyl alcohol was boiled for 3 h, cooled, poured in water, and the sediment was filtered off and recrystallized from aqueous alcohol.

(*p*-Tolyl)-(admantanoyl-1-methyl)amine (Ib, $C_{19}H_{25}NO$). A mixture of 1.5 g (6 mmole) of bromoketone II, 2.6 g (24 mmole) of *p*-toluidine, 0.5 g of Na_2CO_3, and 15 ml of alcohol was boiled for 10 h. The product was separated similar to amine Ia and recrystallized from alcohol.

(1-Adamantyl)-(adamantanoyl-1-methyl)amine (Ic, $C_{22}H_{33}NO$). A mixture of 1.5 g (6 mmole) of bromoketone II, 4.88 g (26 mmole) of aminoadamantane hydrochloride, 0.5 g of Na_2CO_3, and 15 ml of alcohol was boiled for 15 h. The product was separated similar to amine Ia and recrystallized from ether.

1-Methyl-2-mercapto-4-(1-adamantyl)imidazole (IIIa, $C_{14}H_{20}N_2S$). Here 0.5 g (2.4 mmole) of aminoketone Ia and 0.23 g (2.4 mmole) of potassium thiocyanate were boiled in 10 ml of glacial acetic acid for 13 h. The reaction mass was poured on ice and extracted with ether (3 × 10 ml). The combined extract was dried over anhydrous Na_2SO_4, the ether was distilled off, and the residue was recrystallized from chloroform.

1-(*p*-Tolyl)-2-mercapto-4-(1-adamantyl)imidazole (IIIb, $C_{19}H_{24}N_2S$). Here 0.5 g (1.8 mmole) of aminoketone Ib and 0.17 g (1.8 mmole) of potassium thiocyanate were heated for 6 h in 10 ml of glacial acetic acid. The product was separated similar to imidazole IIIa and recrystallized from chloroform.

2-Methyl-4-(1-adamantyl)pyrrole-3-carboxylic Acid Ethyl Ester (IV, $C_{18}H_{25}NO_2$). Here 2 g (7.8 mmole) of bromoketone II was added to a mixed solution of 15 ml of conc. NH_4OH in 15 ml of water. Then 0.72 ml (7.8 mmole) of acetoacetic ester was poured by drops into the suspension obtained at 20°C. The mixture was stirred for 2 days, diluted with water, and extracted with ether (3 × 10 ml). The combined extract was dried over anhydrous Na_2SO_4. The ether was distilled off and the product was recrystallized from acetone.

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