Russian Journal of Organic Chemistry, Vol. 37, No. 8, 2001, pp. 1153–1157. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 8, 2001, pp. 1212–1216.

Adamantylation of Imidazoles and Benzimidazole

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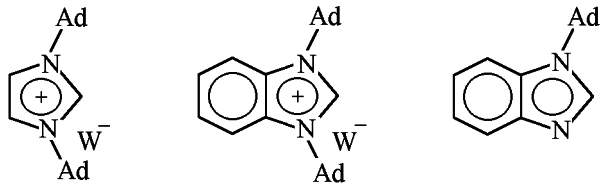
Received June 21, 2000

Abstract—For the first time is reported on substitution of a hydrogen atom in position 4 of the imidazole ring with an aliphatic substituent occurring in reaction between 1-bromoadamantane and imidazoles. The reaction proceeds alongside the substitution in position 1 at heating in excess imidazole. In *o*-dichlorobenzene solution adamantylation of benzimidazole afforded 1-(1-adamantyl)benzimidazole and 1,3-di(1-adamantyl)-benzimidazolium bromide. The specific features of the reactions course are described. The structure of compounds obtained is proved by ^{1}H NMR spectroscopy.

Adamantyl derivatives of azoles are used in preparation of sterically-protected stable carbenes [1]. However the adamantylation of nitrogen-containing heterocycles is poorly understood. The direct introduction of adamantyl groups into molecules of amines and heterocyclic compounds of azole and azine series with the use of adamantyl halides requires commonly high temperature and pressure [2, 3] due to relatively low reactivity of the reagent and its sublimation at elevated temperature (>100°C). The adamantylation of pyrazoles under pressure occurs both at nitrogen and carbon atoms of the ring and affords a mixture of 1-, 4-, and 5-substituted pyrazoles [2]. A direct introduction of 1-adamantyl substituent into imidazole or benzimidazole ring was not described. In [4] 1,3-di(1-adamantyl)imidazolium salts were prepared indirectly from 1-aminoadamantane, glyoxal, and formaldehyde in acid medium.

We report here on reaction of imidazoles **Ia, b** and benzimidazole **Ic** with 1-bromoadamantane (**II**) at 110–180°C and various reagents ratio.

We established that reaction of imidazoles **Ia, b** with 1-bromoadamantane (**II**) in excess of the corresponding imidazole (at molar ratio of compounds **I** and **II** equal to 8 : 1) at 110–180°C gave rise alongside the products of substitution in position 1, 1-(1-adamantyl)imidazoles **IIIa, b** (yield 46–53%), to products of replacement in position 4 of the imidazole ring, 4-(1-adamantyl)imidazoles **IVa, b** (yield 12–14%).



V **VIa, b** **VII**

R = H (**a**), CH_3 (**b**); Ad = 1-adamantyl.

Imidazoles **III** apparently form via intermediate salts A. We performed model experiments to clear up whether compounds **IV** arise from thermal rearrangement of initially formed isomers **III** or from a concurrent reaction of C-electrophilic substitution in the imidazole ring (through an intermediate B). They showed that both in the presence and in the absence of acids 1-substituted compound **IIIa** did not rearrange into 4-substituted compound **IV**. Neither occurred the reverse conversion of isomer **IVa** into isomer **IIa** at 110–180°C in the presence of excess imidazole. The model experiment with 2-methylimidazole (**Ib**) carried out under the same conditions but in the presence of potassium carbonate for scavenging the hydrogen bromide did not result in suppressing the substitution in 4-position (yield of compound **IVb** was 13–14%).

Thus imidazole adamantylation in positions 1 and 4 proceeds simultaneously, and acids or bases do not considerably affect its direction. However the imidazole excess plays an important part in the process. Interestingly, in reaction of 1-bromoadamantane with sodium imidazolide prepared *in situ* by treating imidazole with sodium hydride the

1070-4280/01/3708-1153$25.00

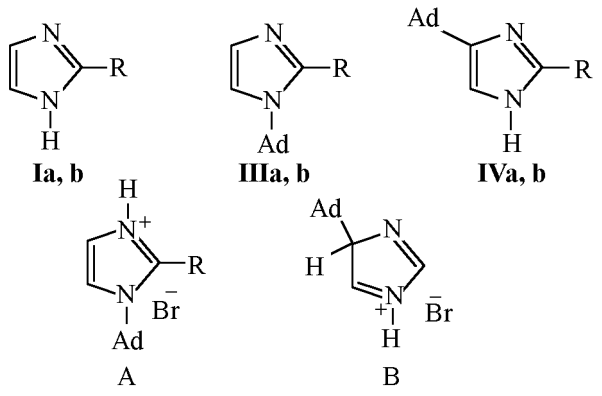
adamantylation into the imidazole ring nearly did not occur.

The synthesis of isomeric adamantylimidazoles **III, IV** by reaction of 1-bromoadamantane (**II**) with excess imidazole (**I**) can be used as preparative procedure for these compounds. This procedure has certain advantages as compared to the other modes of performing the process (at stoichiometric ratio of the reagents in solution in the presence of bases, by reaction of metal imidazolides) for it affords good yields of imidazoles **IIIa, b** and also furnishes their isomers **IVa, b**.

The reaction **I** → **IVa** also accompanies the preparation of 1,3-di(1-adamantyl)imidazolium salt (**V**) when the reaction of imidazole **I** is carried out at slight excess of 1-bromoadamantane (**II**) (at molar ratio of compounds **I** and **II** equal to 1 : 2–2.4) in various solvents (*o*-dichlorobenzene, nitrobenzene, acetic acid). This process hampers isolation of the pure salt **V**.

In the course of the above described reactions alongside compounds **IVa, b** arise also their hydrobromides evidencing partial dehydrobromination of bromoadamantane with basic imidazoles (regarding the bromoadamantane dehydrobromination see also [5]). The latter fact is also observed with the related benzimidazole despite its notably lower basicity (pK_a 5.5 [6]) as compared to imidazole (pK_a 7.0 [6]). For instance, we observed that quaternization of benzimidazole (**Ic**) with 1-bromoadamantane (**II**) in the presence of sodium acetate alongside 1,3-diadamantylbenzimidazolium bromide **VIa** formed also benzimidazole hydrobromide due to partial dehydrobromination of 1-bromoadamantane (**II**) although the hydrogen bromide was partially fixed by sodium acetate. Similarly proceeds the reaction of 1-(1-adamantyl)benzimidazole (**VII**) with 1-bromoadamantane (**II**) [yield of pure salt **VIa** here is 61%. but in the reaction mixture is present 1-(1-adamantyl)-benzimidazole hydrobromide]. Yet tributylamine (pK_b 11.04 [6]) does not effect the dehydrobromination of 1-bromoadamantane even in 5 h at 180–200°c apparently due to the sterical hindrance to approach of the reagents molecules.

Neither adamantylation of imidazole nor benzimidazole with 1-bromoadamantane provides products of 2-substitution: It is known [7, 8] that electrophilic reactions with imidazole systems do not affect this position, in contrast to acylation at C^2 [9] which we presume to occur by carbene mechanism.



W = Br (**V, VIa**), ClO_4 (**VIb**).

Note that tritylation, reaction related to adamantylation, occurs only to the position 1 of imidazole both in solution and in imidazole melt. The arising 1-tritylimidazoles also do not rearrange into 4-isomers under the described conditions.

The composition and structure of the compounds obtained were confirmed with elemental analyses, ^{1}H NMR spectra, molecular weight measurements, and their homogeneity was proved by TLC. Thus in the ^{1}H NMR spectra of substituted imidazoles **IIIa, b** appear the characteristic signals of protons from the imidazole ring C^2H (δ 7.64 ppm), $C^{4,5}$H (δ 7.01–7.06 ppm), and in the spectra of compounds **IVa, b** they are C^2H (δ 7.48 ppm), C^5H (δ 6.42–6.63 ppm), NH (δ 11.20–11.90 ppm). All the above signals are singlets. The resonances from adamantyl protons occur in the region δ 1.8–2.2 ppm. Alternative substitution in 2 position of the imidazole ring is excluded since in the spectrum appear only two signals from CH protons of equal intensity, and one thereof is located in the region characteristic of C^2H protons; besides, there is no splitting of imidazole protons signals originating from spin-spin coupling. In the spectrum of model 2,2'-diimidazolyl (**VIII**) that we have prepared as in [10] (see EXPERIMENTAL), and 2-methylimidazole [11] with substituted 2 position the signals from the protons $C^{4,5}$H are observed in the δ 6.9–7.1 ppm region. In the spectra both of 4-methylimidazole and imidazole appear the signals from C^2H protons (δ 7.6–7.7 ppm) and also from C^5H (δ 6.8–7.1 ppm). In the spectra of compounds **IVa, b** proton signals from C^5H, and in the spectrum of imidazole **IVa** also those from C^2H are slightly displaced upfield as compared to the signals in the spectra of model compound **VIII** and of 2-methylimidazole (C^5H δ 6.4–6.6, Δδ 0.2–0.7 ppm and C^2H δ 7.5, Δδ 0.1–0.2 ppm). The shift is induced

by the electron-donor effect of the adamantyl group, stronger in the near 5 position and weaker in the remote 2 position of the imidazole ring, The same effect is even stronger pronounced in the shift of signals from the more labile NH protons in the spectra of compounds **IVa, b** (δ 11.2–11.8, Δδ 0.5–1.5 ppm) as compared with the signals in the spectra of related 4-methylimidazole (δ 12.9 ppm) and imidazole (δ 12.4 ppm). For the sake of comparison should be noted that in the spectrum of 2-methylimidazole the signal of NH proton suffers still stronger shift: δ 10.9 ppm, Δδ 1.5–2 ppm apparently due to symmetrical electronic influence of the methyl group on both nitrogen atoms of the ring. Somewhat unusual is a stronger shift of the proton signals from CH_3 group (δ 2.19 ppm, Δδ 0.4 ppm) in the spectrum of compound **IVb** as compared with those in the spectrum of imidazole **IIIb** (δ 2.60 ppm) than should be expected from the longer distance of the methyl group from the adamantyl substituent in the imidazole ring of compound **IVb** than that of the C^2H in compound **IVa**. The latter fact may be rationalized by taking into account that in compound **IVb** as compared to **IIIb** is leaved the deshielding of the CH_3 protons by the neighboring C–H bonds of adamantyl (in the position 2 of the substituent).

The presence in the ^1H NMR spectra of the proton signals from NH groups and the molecular weight of compounds corresponding to a monomer also exclude for compounds **IVa, b** the possibility of a structure of a product of oxidative 4,4'-coupling.

EXPERIMENTAL

^1H NMR spectra were recorded on spectrometer Gemini 200 (200 MHz) at room temperature, internal reference TMS or HMDS. TLC was performed on Silufol plates (Czechia), eluent chloroform or a mixture chloroform–methanol, 10:1. Molecular weight of compounds **IIIa** and **IVa** was measured by cryoscopic method in benzene and camphor respectively. The model compound **VIII** was obtained as in [7] from glyoxasulfate, ammonia, and formaldehyde.

Imidazole adamantylation. To 4.74 g (70 mmol) of imidazole **Ia** melt was added 3 g (14 mmol of 1-bromoadamantane (**II**) and 0.3 ml of *o*-dichlorobenzene, and the reaction mixture was heated at 110°C for 6 h. The excess imidazole was distilled off in a vacuum (1 mm Hg). Then the residue was dissolved in 20–25 ml of chloroform and washed first with water solution containing 2.3 g (28 mmol) of sodium acetate, and then with water (3 × 30 ml) till complete removal of imidazole. The organic phase was dried with anhydrous sodium sulfate, the solvent was removed. The residue obtained was treated with 30 ml of hexane. The precipitate of 4-(1-adamantyl)-imidazole (**IVa**) was filtered off and washed with hot hexane. Yield 0.7 g (12%), mp 227–228°C (from DMF). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.71 m (6H), 1.85 m (6H), 1.99 m (3H) (1-adamantyl); 6.63 s (1H, C^5H); 7.48 s (1H, C^2H); 11.80 s (1H, NH). Found, %: C 77.1; H 9.0; N 14.0. *M* 201. $C_{13}H_{18}N_2$. Calculated, %: C 77.2; H 9.0; N 13.9. *M* 202. The mother liquor was evaporated to dryness to obtain 1.5 g (53%) of 1-(1-adamantyl)imidazole (**IIIa**), mp 106–111°C (from hexane). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.77 m (6H), 2.09 m (6H), 2.23 m (3H) (1-adamantyl); 7.06 s (2H, $C^{4,5}H$), 7.64 s (1H, C^2H). Found, %: C 77.0; H 8.9; N 13.9. *M* 198. $C_{13}H_{18}N_2$. Calculated, %: C 77.2; H 9.0; N 13.9. *M* 202. Compounds **IIIb**, **IVb** were similarly prepared.

21-(1-Adamantyl)-2-methylimidazole (IIIb). Yield 30%, mp 123–125°C (from hexane). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.75 m (6H), 2.18 m (9H) (1-adamantyl); 2.60 s (3H, CH_3); 6.85 s, 7.01 s (2H, $C^{4,5}H$). Found, %: C 77.6; H 9.2; N 13.2. $C_{14}H_{20}N_2$. Calculated, %: C 77.7; H 9.3; N 13.0.

4-(1-Adamantyl)-2-methylimidazole (IVb). Yield 13%, mp 271–272°C (from DMF). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.70 m (6H), 1.80 m (6H), 1.97 m (3H) (1-adamantyl); 2.19 s (3H, CH_3); 6.42 s (1H, C^5H); 11.20 s (1H, NH). Found, %: C 77.8; H 9.4; N 13.0. $C_{14}H_{20}N_2$. Calculated, %: C 77.7; H 9.3; N 13.0.

Adamantylation of 2-methylimidazole in the presence of potassium carbonate. The boiling mixture of 4. 58 g (55.8 mmol) of 2-methylimidazole, 1.5 g (6.98 mmol) of 1-bromoadamantane, and 1.59 g (13.96 mmol) of potassium carbonate in 5 ml of *o*-dichlorobenzene was heated for 2.5 h. Then to the mixture was added 20 ml of benzene. The precipitate of inorganic salts was filtered off, the benzene solution was washed with water (3 × 20 ml), dried with anhydrous sodium sulfate, and the solution was left overnight. The formed precipitate of isomer **IVb** was filtered off. Yield of azole **IVb** 0.21 g (14%), mp 271–272°C (from DMF). The solution was treated with concn. HCl, stirred, 10 ml of water was added, the benzene layer was separated, a fresh portion of

benzene (20 ml) was added, the mixture was neutralized with 20% water solution of sodium hydroxide, the organic layer was washed with water and dried on anhydrous sodium sulfate. The benzene solution was evaporated in a vacuum, and the residue was ground with hexane (2–3 ml). The precipitate of isomer **IIIb** was filtered off. Yield 0.69 g (46%), mp 123–125°C (from hexane).

1-(1-Adamantyl)benzimidazole (VII). To a suspension of 7.08 g (60 mmol) of benzimidazole (**Ic**) and 8.28 g (60 mmol) of anhydrous potassium carbonate in 30 ml of *o*-dichlorobenzene at bath temperature 190°C while stirring was added by portions within 1 h 14.2 g (66 mmol) of 1-bromoadamantane. The neck of the flask was left open for water evaporation. The precipitate was filtered off the hot reaction mixture, and the solution of 1-(1-adamantyl)benzimidazole (**VII**) was evaporated in a vacuum. The residue was treated with 5 ml of hexane, and the precipitate was filtered off. Yield 8.2 g (54%), mp 180–184°C (from acetonitrile). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.83 m (6H), 2.29 m (3H), 2.34 m (6H) (1-adamantyl); 7.25 m (2H), 7.70 m (1H), 7.85 m (1H) (H arom); 8.02 s (1H, C^{2}H). Found, %: C 80.8; H 8.2; N 11.3. $C_{17}H_{20}N_2$. Calculated, %: C C 80.9; H 8.0; N 11.1.

1,3-Di(1-adamantyl0benzimidazolium bromide (VIa) and perchlorate (VIb). (a) A mixture of 1.48 g (5.9 mmol) of 1-(1-adamantyl)benzimidazole (**VII**), 1.89 g (8.8 mmol) of 1-bromoadamantane (**II**), and 0.5 ml of *o*-dichlorobenzene was heated for 2 h at bath temperature 250°C. Then 0.48 g (2.2 mmol) of 1-bromoadamantane was added, and the mixture was heated for 1 h more. To the suspension of salt **VIa** obtained was added 6 ml of ether, the mixture was ground, and the precipitate was filtered off. Yield 2.48 g (90%), mp 297–298°C (from water). Yield of compound **VIa** after purification 1.69 g (61%). ^{1}ÆNMR spectrum ($CDCl_3$), δ, ppm: 1.89 m (12H), 2.39 m (6H), 2.66 m (12H) (1-adamantyl); 7.65 m (2H), 8.05 m (2H) (H arom); 9.20 s (1H, C^{2}H). Found, %: C 69.6; H 7.5; Br 17.0; N 6.0. $C_{27}H_{35}BrN_2$. Calculated, %: C 69.4; H 7.6; Br 17.1; N 6.0. After addition to the water solution of salt **VIa** 1.5-fold excess of sodium perchlorate we obtained a precipitate of perchlorate **VIb** in 95% yield, mp 258–261°C (from DMF). Found, %: C 66.7; H 7.3; Cl 7.3; N 5.7. $C_{27}H_{35}ClN_2O_4$. Calculated, %: C 66.6; H 7.2; Cl 7.3; N 5.8.

(b) A mixture of 2.36 g (20 mmol) of benzimidazole (**Ic**), 8.6 g (40 mmol) of 1-bromoadamantane (**II**), and 1.64 g (20 mmol) of sodium acetate in 4 ml of acetic acid was boiled for 12 h. Then 0.2 g (2.5 mmol) of sodium acetate and 1.07 g (5 mmol) of 1-bromoadamantane was added, and the heating continued for 4 h. To the cooled mixture 5 ml of acetone was added, and the precipitate was filtered off. The product obtained (10.5 g of salt **VIa** mixed with sodium bromide) was purified by extraction with 1 l of hot water. Yield of compound **VIa** 3.11 g (33%), mp 297–298°C. According to TLC and ^{1}H NMR data the compound obtained is identical to that prepared by procedure a. To the crystalline residue after extraction was added 5 ml of 2-propanol, the mixture was heated to boiling, cooled, the precipitate was filtered off and dried. Yield of 1-(1-adamantyl)benzimidazole (**VII**) 1 g (20%), mp 180–184°C (from acetonitrile).

The mother liquor (water solution after extraction and separation of salt **VIa**) was evaporated till 20 ml volume, then 20% solution of sodium hydroxide was added dropwise till neutral reaction. The separated precipitate was filtered off. Benzimidazole was separated in 0.8 g amount (34%), mp 172–174°C (from water), no depression of the melting point in the sample mixed with commercial benzimidazole. The IR spectrum of the compound obtained was also identical to that of the commercial substance.

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