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Oxidative Alkylation of Azoles: VII.* Adamantylation of Azoles via Oxidative Generation of 1-Adamantyl Cations

V. G. Tsypin, M. S. Pevzner, and E. L. Golod

St. Petersburg Technological Institute, Moskovskii pr. 26, St. Petersburg, 198013 Russia
fax: (812) 112 7791

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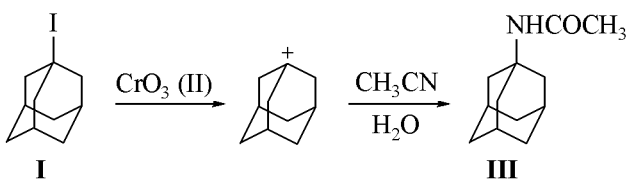
Abstract—A procedure has been developed for oxidative N-adamantylation of azoles with 1-iodoadamantane in the presence of chromium(IV) oxide or iodine(V) oxide. The procedure is applicable to azoles whose pK_{BH^+} value does not exceed 2.26.

We previously showed that 1-adamantyl cations generated in acid medium are capable of readily alkylating triazoles [2] and tetrazoles [3] to give the corresponding *N*-(1-adamantyl)azoles. Analogous reactions with pyrazoles [4] and imidazoles [5] are strongly limited by the basicity of substrates whose reaction centers can be protonated. For example, adamantylation of 4-nitropyrazole-3(5)-carboxylic acid (pK_{BH^+} –3.63) can be effected by 85% sulfuric acid (H_0 –8.29). Reduction of the sulfuric acid concentration to 72% (H_0 –6.2) makes it possible to perform the reaction with 4-nitropyrazole (pK_{BH^+} –2.00). The system phosphoric acid–acetic acid [weight ratio 4 : 1, H_0(calcd.) –1.8] was proposed for adamantylation of highly basic azoles, e.g., of pyrazole-3-carboxylic acid (pK_{BH^+} 0.78) [4]. Pyrazoles with pK_{BH^+} values larger than 0.8 cannot be involved in the above reaction. As concerns imidazole derivatives, in 85% sulfuric acid the corresponding adamantyl-substituted product can be obtained only from 4,5-dinitroimidazole (pK_{BH^+} –5.33). In the system phosphoric acid–acetic acid, the most basic imidazole substrate capable of being adamantylated is 4-nitroimidazole (pK_{BH^+} 0.05) [5]. Thus adamantylation of more basic azoles can be accomplished via reduction of the acidity function H_0 of the medium. However, in this case the concentration of reactive species, adamantyl cations, also decreases. Using 3-nitro-1,2,4-triazole as an example, we previously demonstrated [2] that the adamantylation process requires a sulfuric acid concentration no less than 70%. In order to obtain adamantyl derivatives of more basic azoles, we tried to take advantage of oxidative alkylation.

According to published data, alkyl halides, in particular alkyl iodides, are capable of reacting with nucleophilic species in the presence of inorganic oxidants [6–15]. A unimolecular scheme was proposed for reactions of alkyl iodides with nitric acid [7] and other oxidants [10]. This scheme includes formation of carbocation which is converted into alkyl chloride or alkyl bromide in the presence of HCl or HBr. Under these conditions, optically active 2-octyl iodide reacts with HBr to give the corresponding racemic product [7]. It is beleived that in the presence of nitric acid as oxidant the reaction involves generation of nitronium ion which attacks the substrate thus favoring formation of carbocation [8].

In the presence of NO_2BF_4 or $NOBF_4$, reactions of acetonitrile with alkanes and their derivatives R_3CX (X = Hlg, H, OAlk) at the tertiary carbon atom afford acetamides as a result of cleavage of the carbon–heteroelement bond. It is assumed that the initial interaction between nitronium cation and a lone electron pair of the heteroelement (Hlg or O) follows the Lewis acid–base interaction pattern [12–15]. The oxidation of *exo*-2-bromonorbornane gave a racemic mixture of the corresponding acetamides [14].

The adamantylation with 1-iodoadamantane (**I**) is likely to involve generation of carbocation. The reaction of **I** with acetonitrile in the presence of chromium(VI) oxide gave *N*-(1-adamantyl)acetamide



I **III**

* For communication VI, see [1].

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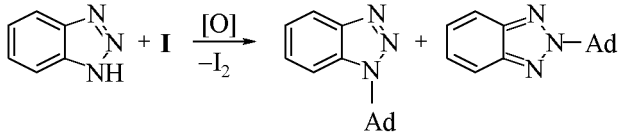
(**III**) in 69% yield. The yield of **III** was raised to 87% when the reaction was carried out with iodine(V) oxide (**IV**) as oxidant.

We examined the possibility for oxidative adamantylation of azoles with 1,2,3-benzotriazole (**V**) as an example. The reaction was performed in dioxane in the presence of CrO_3 at 85–90°C (reaction time 4 h). As a result, a mixture of 1- and 2-(1-adamantyl)-1,2,3-benzotriazoles **VI** and **VII** [16] was obtained in an overall yield of 16%. The isomer ratio **VI**:**VII** was determined by GLC; it was equal to 72:28. The same reaction in dichloroethane occurred at a much lower rate, and the overall yield did not exceed 8%.



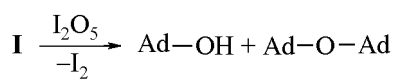
V **VI** **VII**

[O] = CrO_3, I_2O_5.

Iodine(V) oxide (**IV**) turned out to be a more efficient oxidant. In the presence of I_2O_5 the reaction was complete in 1 h, and the yield of isomeric mixture **VI**/**VII** was 67% (ratio 26:74). It should be noted that the adamantylation of **V** in sulfuric acid gave only isomer **VI** [16].

Next we studied a series of diazoles (pyrazoles and imidazoles) as substrates. They were selected in such a way that their basicity ranged pK_{BH^+} –2.00 to 6.99. The reactions were carried out in dioxane at 85–90°C using I_2O_5 as oxidant. The goal was to check the possibility for adamantylation to occur and to estimate the maximal pK_{BH^+} value at which the alkylation is still possible.

The oxidative alkylation process was complicated by the ability of 1-iodoadamantane (**I**) to react with compound **IV** in dioxane in the absence of a heteroaromatic substrate, yielding a mixture of 1-hydroxyadamantane (**VIII**, 53%) and 1,1′-diadamantyl ether (**IX**, 9%). Here, the complete conversion of 1-iodoadamantane (**I**) is attained in 3 h. No further change of the composition of the reaction mixture occurred with time.

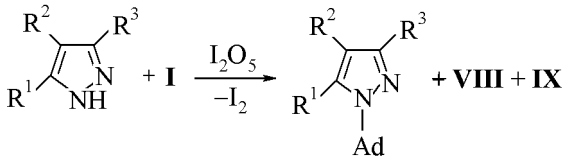


VIII **IX**

The formation of ether **IX** by reaction of 1-bromoadamantane with oxidants, specifically with copper(II) complex, was reported in [17, 18]. The reaction was not studied in detail, but it was assumed that the process follows a radical mechanism [18]. However, a ionic reaction pattern cannot be ruled out. Also, the stage of generation of adamantyl cation could involve formation of the $AdI^{+\cdot}$–$I_2O_5^{-\cdot}$ radical ion pair. Its subsequent decomposition can take either radical or ionic path. Assuming that the above radical ion pair decomposes to give adamantyl cation, the formation of 1-hydroxyadamantane (**VIII**) is likely to occur via direct abstraction of oxygen atom from the oxidant molecule. Another possible pathway is O-alkylation of 1-hydroxyadamantane (**VIII**), which leads to ether **IX** or (in the presence of a heteroaromatic substrate), to *N*-adamantylazole.

As substrates we chose 4,5-dichloroimidazole (**X**), 4-nitropyrazole (**XI**, pK_{BH^+} –2.00), 4-nitroimidazole (**XII**, pK_{BH^+} 0.05), 4-chloropyrazole (**XIII**, pK_{BH^+} 0.59), 4-bromo-3,5-dimethylpyrazole (**XIV**, pK_{BH^+} 2.26), pyrazole (**XV**, pK_{BH^+} 2.48), 3(5)-methylpyrazole (**XVI**, pK_{BH^+} 3.27), 4(5)-chloroimidazole (**XVII**), 4-bromoimidazole (**XVIII**, pK_{BH^+} 3.80), and imidazole (**XIX**, pK_{BH^+} 6.99). The pK_{BH^+} values were taken from [19].

The series of substrates can be divided arbitrarily into two groups. The first group includes azoles **XI**–**XIV**; their reactions with 1-iodoadamantane were characterized by complete conversion of the latter. Apart from compounds **VIII** and **IX**, the corresponding *N*-adamantylazoles were found among the products (see table).



XI, XIII, XIV **XX**–**XXII**

XI, **XX**, $R^1 = R^3 = H$, $R^2 = NO_2$; **XIII**, **XXI**, $R^1 = R^3 = H$, $R^2 = Cl$; **XIV**, **XXII**, $R^1 = R^3 = Me$, $R^2 = Br$.

The oxidative adamantylation of heteroaromatic substrates includes two concurrent processes: (1) adamantylation and (2) transformation of initial 1-iodoadamantane (**I**) into compounds **VIII** and **IX** under the action of oxidant. The first pathway prevailed in the adamantylation of relatively weakly basic azole **XI**, and 1-(1-adamantyl)-4-nitropyrazole (**XX**) was the major product. In the reactions with more basic azoles **XIII** and **XIV** the contribution of pathway (2) was greater.

Reactions of 1-iodoadamantane (**I**) with azoles **V** and **XI**–**XIV** in the presence of I_2O_5 (**IV**)

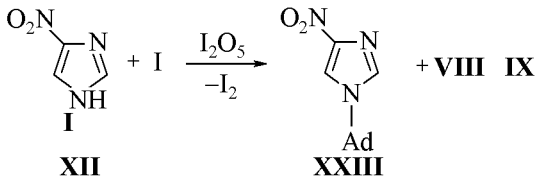
Azole no.	**I**-to-azole molar ratio	Reaction time, h	Yield, %			
			N-adamantylazole		**VIII**	**IX**
Va[a]	1 : 1.5	4	**VI**, 12	**VII**, 4	–	–
V	1 : 1.5	1	**VI**, 17	**VII**, 50	–	–
XI	1 : 1.5	3	**XX**, 58	–	Traces	Traces
XII	3 : 1	9	**XXIII**, traces	–	78	Traces
XIII	3 : 1	10	**XXI**, 18	–	61	14
XIII	1 : 1.5	10	**XXI**, 15	–	32	7
XIII	1 : 3	10	**XXI**, 11	–	71	Traces
XIV	3 : 1	10	**XXII**, traces	–	71	15
XIV	1 : 1.5	10	**XXII**, 13	–	3	18
XIV	1 : 3	10	**XXII**, 17	–	55	5
–[b]	–	3	–	–	53	9

[a] In the presence of CrO_3 (**II**) as oxidant.

[b] Reaction of 1-iodoadamantane (**I**) with I_2O_5 (**IV**) in the absence of heteroaromatic substrate.

Raising the amount of 1-iodoadamantane (**I**) in the reaction with azole **XIII** resulted in insignificant increase of the yield of 1-(1-adamantyl)-4-chloropyrazole (**XXI**). This may be due to increase of the concentration of adamantyl cations in the reaction mixture. On the other hand, the highest yield of 1-(1-adamantyl)-4-bromo-3,5-dimethylpyrazole (**XXII**) in the reaction of **I** with azole **XIV** was attained when the substrate was taken in excess. Presumably, this is the result of increase in the azole concentration and its relatively high basicity (pK_{BH^+} 2.26). It should be noted that azole **XV** whose basicity is greater only slightly (pK_{BH^+} 2.48) failed to react with 1-iodoadamantane under the same conditions. On the whole, raising the azole-to-**I** ratio leads to decrease in the yield of ether **IX**.

Only traces of 1-(1-adamantyl)-4-nitroimidazole (**XXIII**) were detected among products of the reaction of 1-iodoadamantane with azole **XII**. This fact may be explained by very poor solubility of the substrate in dioxane and hence low concentration of **XII** in the reaction mixture. Compound **XII** could give rise to two isomeric products; however, traces of only one of them, compound **XXIII**, were detected.



XII **XXIII**

Our attempt to obtain adamantyl derivative of azole **X** was unsuccessful: the substrate reacted with oxidant **IV** through elimination of the chlorine atom, and the resulting more basic azole **XVII** did not react with 1-iodoadamantane.

Azoles **XV**–**XIX** belonging to the second group failed to react with 1-iodoadamantane over a period of 10 h, and the substrates were recovered from the reaction mixture. No reaction occurred even when the amount of the initial azole, e.g., imidazole **XIX**, was reduced from 1.5 to 0.5 mol per mole of **I**. Probably, highly basic azoles having increased electron density on the nitrogen atom are capable of reacting with the oxidant. Taking into account that this process is heterogeneous [iodine(V) oxide is almost insoluble in dioxane], the oxidant is completely deactivated. Therefore, the process is likely to stop at the stage of formation of a complex with partial electron transfer from the heteroring to the vacant orbital of the active center in the oxidant. The presence of N-unsubstituted azoles among the products indicates that the electron transfer is just partial and, probably, reversible.

Thus the reaction under study can be regarded as a method of alkylation of azoles, where the active species, adamantyl cation, is generated via oxidation of 1-iodoadamantane.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Perkin–Elmer R-12 spectrometer (60 MHz) in $CDCl_3$ using HMDS as internal reference. GLC analysis was performed on an LKhM Model 3700 chromatograph;

stationary phase 5% SE-30 on Chromaton N-AW-DMCS (0.1–0.125 mm); oven temperature 100 to 300°C; injector and detector temperature 270°C.

The initial azoles should dissolve in dioxane completely. The solvent should be purified from peroxide compounds and thoroughly dried. Otherwise, the reaction is strongly accelerated, and the major product is 1-hydroxyadamantane (**VIII**).

Reactions of azoles with 1-iodoadamantane in the presence of oxidant (general procedure**)**. To a solution of 0.5 g (1.91 mmol) of 1-iodoadamantane (**I**) in 5 ml of anhydrous dioxane we added in succession a required amount of N-unsubstituted azole and 0.96 g (2.87 mmol) of iodine(V) oxide (**IV**), and the mixture was stirred at 85–90°C until the initial 1-iodoadamantane disappeared (TLC). Liberation of iodine was observed within the first hour. The mixture was cooled and filtered, and the precipitate of I_2O_5 was washed with 3 ml of dioxane. The filtrate was combined with the washings and evaporated. The residue was dissolved in 20 ml of $CHCl_3$, and the solution was treated with 50 ml of 10% aqueous Na_2SO_3. The organic phase was separated, and the solvent was removed. The residue was washed with 50 ml of 5% aqueuos NaOH at 40–45°C and dried. Compounds **XX**, **XXI**, and **XXIII** were identified by TLC and GLC, by comparing with authentic samples which were specially synthesized according to the procedures reported in [4] (**XX**, **XXI**) and [5] (**XXIII**). In the reaction with azole **XI** 35 ml of dioxane was used to dissolve the substrate completely.

1-(1-Adamantyl)-4-bromo-3,5-dimethylpyrazole (XXII). After treatment with aqueous NaOH, the residue was treated with concentrated hydrochloric acid at 20–30°C. The filtrate was neutralized with 10% aqueous NaOH and extracted with 20 ml of $CHCl_3$. The extract was evaporated, and the residue was recrystallized from 70% aqueous 2-propanol. mp 131–132°C. ^{1}H NMR spectrum, δ, ppm: 1.7 m, 2.1 m, and 2.2 m (15H, adamantane), 2.4 s (6H, CH_3). Found, %: C 58.25; H 6.80; N 9.06. $C_{15}H_{21}BrN_2$. Calculated, %: C 58.51; H 5.84; N 8.68.

In the reactions with N-unsubstituted azoles **XV**–**XIX** the mixture was heated for 10 h. After cooling, the mixture was filtered, and the precipitate of I_2O_5 was washed with 3 ml of dioxane. The filtrate was combined with the washings and evaporated. The residue was washed with 10% aqueous NaOH at 50–60°C, dried, and recrystallized from 2-propanol. The product was 1-iodoadamantane (**I**) [20]. The filtrate was neutralized with hydrobromic acid to pH 7, and water was distilled off. The initial azoles were identified by the ^{1}H NMR spectra.

Reaction of 1-iodoadamantane (I) with benzotriazole (V). To a solution of 0.5 g (1.91 mmol) of 1-iodoadamantane (**I**) in 5 ml of anhydrous dioxane we added in succession 0.45 g (3.82 mmol) of benzotriazole (**V**) and 0.05 g (1.25 mmol) of chromium(VI) oxide (**II**). The mixture was stirred for 4 h at 85–90°C and was then treated according to the general procedure described above.

***N*-(1-Adamantyl)acetamide (III) (a) 1-Iodoadamantane (I)**, 0.5 g (1.91 mmol), and iodine(V) oxide (**IV**), 0.96 g (2.87 mmol), were added in succession to 10 ml of acetonitrile, and the mixture was stirred for 0.5 h at 40–50°C and was then treated according to the general procedure. Yield 0.32 g (87%), mp 148–150°C [12].

(b) 1-Iodoadamantane (**I**), 0.5 g (1.91 mmol), and chromium(VI) oxide (**II**), 0.05 g (1.25 mmol), were added in succession to 10 ml of acetonitrile, and the mixture was stirred for 2 h at 80°C and was then treated according to the general procedure. Yield 0.26 g (69%).

Reaction of 1-iodoadamantane (I) with iodine(V) oxide (IV). Iodine(V) oxide (**IV**, 0.96 g (2.87 mmol), was added to a solution of 0.5 g (1.91 mmol) of 1-iodoadamantane (**I**) in 5 ml of anhydrous dioxane. The mixture was stirred for 3 h at 85–90°C and was then treated according to the general procedure. A mixture of compounds **VIII** and **IX** was obtained. Yield 0.18 g. The products were separated by fractional crystallization from 2-propanol. The **VIII**:**IX** ratio was 85:15. Iodine(V) oxide, 0.4 g (1.2 mmol), was added to the resulting mixture, and the mixture was stirred for 3 h at 85–90°C. After appropriate treatment, the composition of the mixture did not change.

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