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Alkylation of 1,2,3-Benzotriazole with Iodomethyl Ketones

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Abstract—Solvent-free reactions of 1,2,3-benzotriazole with 1-iodopropan-2-one and 1,3-diiodopropan-2-one in the absence of a catalyst involved alkylation of the heteroring at the N^1 atom and subsequent quaternization at the N^3 atom with formation of 1,3-bis(2-oxopropyl)-1*H*-1,2,3-benzotriazolium triiodide which is a new conducting ionic liquid. The reaction of 1,2,3-benzotriazole with 1,3-diiodopropan-2-one was accompanied by reductive deiodination of the iodomethyl groups in the initial ketone with hydrogen iodide liberated by N^1-alkylation. Triiodide ion readily exchanges for nitrate ion by the action of $AgNO_3$ to produce 1,3-bis(2-oxopropyl)-1*H*-1,2,3-benzotriazolium nitrate. The reaction of 1,2,3-benzotriazole with 2-iodo-1-phenylethan-1-one in melt resulted in the formation of 1,3-bis(2-oxo-2-phenylethyl)-1*H*-1,2,3-benzotriazolium triiodide.

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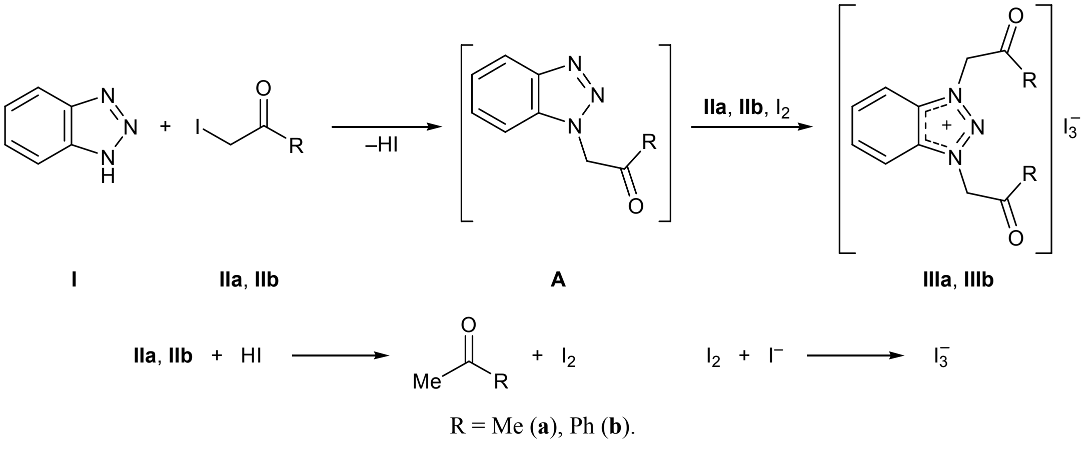
N-Alkyl-1,2,3-benzotriazoles and their derivatives exhibit analgesic, anti-inflammatory, diuretic, antiviral, antihypertensive, and antitumor activity [1, 2] and are used as herbicides [3], insecticides [4], and acaricides [5]. The main procedures for the synthesis of *N*-akylbenzotriazoles are based on alkylation of benzotriazole with various halogen derivatives in the presence of bases, crown ethers, or phase-transfer catalysts [1, 6]. The reaction in the absence of a catalyst is successful when the alkylating agent molecule contains a group that weakens the C–Hlg bond. A regioselective route to N^1-substituted benzotriazoles comprises alkylation of benzotriazole with α-chloro(bromo) ketones in the absence of a base on heating in benzene or toluene; as a result, α-(1,2,3-benzotriazol-1-yl) carbonyl compounds are formed as a single isomer in quantitative yield [7]. Alkylation of benzotriazole with α-iodo ketones was not studied.

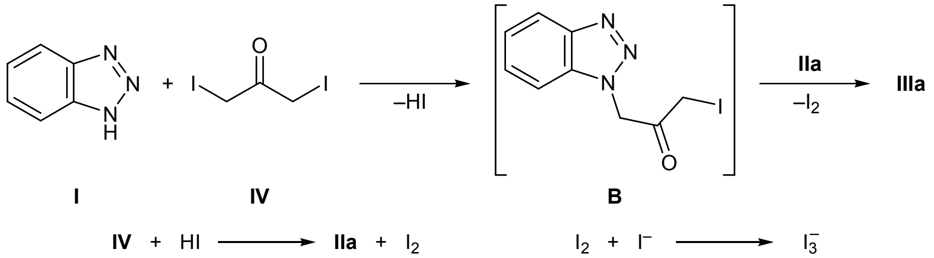
We examined alkylation of 1,2,3-benzotriazole (**I**) with 1-iodopropan-2-one (**IIa**) under solvent-free conditions in the absence of a catalyst. The reaction was carried out on heating to 90°C, and it afforded 67% of 1,3-bis(2-oxopropyl)-1*H*-1,2,3-benzotriazolium triiodide (**IIIa**) (Scheme 1). NMR monitoring of the reaction progress showed that the primary intermediate is N^1-substituted benzotriazole **A**. Hydrogen iodide

Scheme 1.



R = Me (**a**), Ph (**b**).

Scheme 2.



I IV B

$$\textbf{IV} + HI \longrightarrow \textbf{IIa} + I_2 \qquad I_2 + I^- \longrightarrow I_3^-$$

liberated in the first alkylation step partly reduces the initial iodomethyl ketone to molecular iodine, and the latter not only initiates generation of carbocation from ketone **IIa** but also favors formation of triiodide ion.

The physicochemical parameters of triiodide **IIIa** (a dark red thick oily substance), specifically the electric conductivity of its 0.1 N solution in THF equal to $1.5 \times 10^{-3}\ \Omega^{-1}\ cm^{-1}$, give grounds to recognize it as a new conducting ionic liquid.

Likewise, the reaction of benzotriazole **I** with 2-iodo-1-phenylethan-1-one (**Ib**) in melt (reaction time 3 h) led to the formation of 1,3-bis(2-oxo-2-phenylethyl)-1*H*-1,2,3-benzotriazolium triiodide (**IIIb**) in 71% yield.

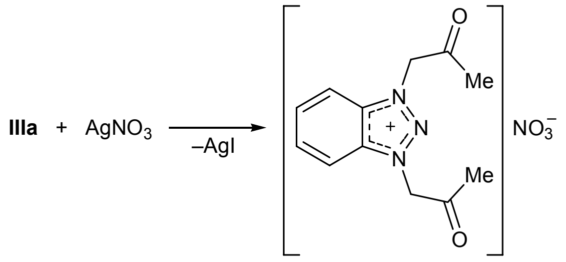
According to [7], N^1-alkylation of benzotriazole with 1,3-dichloropropan-2-one requires two equivalents of a base and yields bis(benzotriazol-1-yl)acetone. However, in the reaction of 1,3-diiodopropan-2-one (**IV**) with compound **I** we unexpectedly isolated 1,3-bis(2-oxopropyl)-3*H*-1,2,3-benzotriazolium triiodide (**IIIa**) (Scheme 2).

The IR, UV, and ^1H, ^{13}C, and ^{15}N NMR spectra of compound **IIIa** suggest that hydrogen iodide liberated in the first alkylation step reduces the iodomethyl group in adduct **B** thus preventing formation of 1,3-bis(benzotriazol-1-yl)acetone. It is also possible that HI reduces one iodomethyl group in initial diiodo ketone **IV** to monoiodo derivative **IIa** with liberation of molecular iodine which catalyzes quaternization of adduct **B** at the N^3 atom.

The structure of triiodides **IIIa** and **IIIb** was confirmed by their elemental composition and IR, UV, and ^1H, ^{13}C, and ^{15}N NMR spectra. The IR spectra of **IIIa** and **IIIb** contained absorption bands at 1739 and 1685 cm^{-1} typical of carbonyl stretching vibrations. Methylene groups on the nitrogen atoms in **IIIa** and **IIIb** gave signals at δ 6.41 and 6.63 ppm in the ^1H NMR spectra and at δ_C 61.35 and 54.99 ppm in the ^{13}C NMR spectra, respectively. Carbonyl carbon atoms resonated in the ^{13}C NMR spectra at δ_C 197.39 (**IIIa**) and 191.73 ppm (**IIIb**). Compounds **IIIa** and **IIIb** displayed in the two-dimensional ^{15}N HMBC spectra ^1H–^{15}N cross peaks between protons in the methylene groups and N^1/N^3 (δ_N –154.8 ppm) and N^2 (δ_N –23.9 ppm). In the UV spectra of quaternary salts **IIIa** and **IIIb** absorption bands typical of triiodide ion were observed at λ 293 and 358 nm [8].

Using compound **IIIa** as an example, we demonstrated the possibility for exchange of triiodide ion for nitrate by the action $AgNO_3$ (Scheme 3). As a result, we synthesized for the first time 1,3-bis(2-oxopropyl)-1*H*-1,2,3-benzotriazolium nitrate (**V**) as a colorless powder (mp 159–160°C) with a conductivity of $4.7 \times 10^{-12}\ \Omega^{-1}\ cm^{-1}$. Compound **V** showed in the IR spectrum a strong absorption band at 1384 cm^{-1} and a weak band at 825 cm^{-1} due to inorganic nitrate ion [9].

Scheme 3.



V

We can conclude that, unlike α-chloro(bromo) ketones studied previously [6, 7], high lability of the iodine atom in iodomethyl ketones not only promotes N^1-alkylation and N^3-quaternization of 1,2,3-benzotriazole but also gives rise to I_3^- ion.

EXPERIMENTAL

The IR spectra were recorded on a Bruker Vertex 70 spectrometer from samples prepared as KBr pellets or films. The ^1H, ^{13}C, and ^{15}N NMR spectra were measured on a Bruker DPX-400 instrument at 400.13, 100.61, and 40.56 MHz, respectively, using acetone-d_6 as solvent and reference (for ^1H and ^{13}C). The UV spectra were recorded on a Perkin Elmer Lambda 35 UV-Vis spectrophotometer. The electric conductivities were measured using a Radelkis OK-102/1 conductivity meter. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using chloroform–acetone (10 : 1) as eluent.

1,3-Bis(2-oxopropyl)-1*H*-1,2,3-benzotriazolium triiodide (IIIa). *a*. A mixture of 2 g (1 mmol) of ketone **IIa** and 0.5 g (0.5 mmol) of 1,2,3-benzotriazole (**I**) was heated under stirring at 80°C in an argon atmosphere until the initial ketone disappeared (9 h). The resulting thick material was dissolved in 10 ml of acetone and precipitated with 30 ml of hexane. This procedure was repeated in triplicate. The oily material was repeatedly washed with diethyl ether and dried under reduced pressure. Yield 1.72 g (67% on the reacted 1,2,3-benzotriazole), red thick oily substance. ^{1}H NMR spectrum, δ, ppm: 2.54 s (6H, CH_3), 6.41 s (4H, CH_2), 8.04–8.30 m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 27.47 (CH_3), 61.35 (CH_2), 110.94–135.87 (C_{arom}), 197.39 (C=O). ^{15}N NMR spectrum, δ_N, ppm: –154.8 (N^1, N^3), –23.9 (N^2). Found, %: C 23.72; H 2.31; I 58.75; N 7.76. $C_{12}H_{14}I_3N_3O_2$. Calculated, %: C 23.49; H 2.28; I 62.15; N 6.85.

b. A mixture of 2 g (0.6 mmol) of diiodo ketone **IV** and 0.36 g (0.3 mmol) of 1,2,3-benzotriazole (**I**) in 5 ml of anhydrous acetone was heated under reflux in an argon atmosphere until the initial ketone disappeared (7 h). After cooling, 10 ml of hexane was added, and the product was isolated as described above in *a*. Yield 0.8 g (43% on the reacted **I**), red thick oily substance. Its properties were identical to those of a sample prepared as described in *a*.

1,3-Bis(2-oxo-2-phenylethyl)-1*H*-1,2,3-benzotriazolium triiodide (IIIb). A solution 2.3 g (9 mmol) of 2-iodo-1-phenylethan-1-one (**IIb**) and 0.55 g (5 mmol) of 1,2,3-benzotriazole (**I**) in 5 ml of anhydrous acetone was kept for 6 days at room temperature under argon until the initial ketone disappeared (TLC). The mixture was diluted with 15 ml of hexane. An oily material separated and was reprecipitated twice with hexane from acetone, repeatedly washed with diethyl ether, and dried under reduced pressure. Yield 2.4 g (71%), red thick oily substance. ^{1}H NMR spectrum, δ, ppm: 6.63 s (4H, CH_2), 7.45–8.54 m (14H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 54.99 (CH_2), 111.41–145.02 (C_{arom}), 191.73 (C=O). ^{15}N NMR spectrum, δ_N, ppm: –154.8 (N^1, N^3), –23.9 (N^2). Found, %: C 35.44; H 2.70; I 50.63; N 6.10. $C_{22}H_{18}I_3N_3O_2$. Calculated, %: C 35.82; H 2.44; I 51.69; N 5.69.

1,3-Bis(2-oxopropyl)-1*H*-1,2,3-benzotriazolium nitrate (V). A solution of 0.24 g (9 mmol) of $AgNO_3$ in a mixture of alcohol with acetone was slowly added to a solution of 0.6 g (6 mmol) of triiodide **IIIa** in 5 ml of acetone until the originally dark red solution turned blue–violet. The mixture was heated for 1 h under reflux and was then kept for 1 h at room temperature until it turned light blue. The precipitate of AgI was filtered off, the filtrate was evaporated under reduced pressure, and the residue was dissolved in acetonitrile (5 ml) and precipitated with hexane (10 ml). The product was dried under reduced pressure. Yield 0.13 g (45%), light brown powder, mp 159–160°C. IR spectrum, ν, cm^{-1}: 1736 (C=O); 1384, 825 (NO_3). ^{1}H NMR spectrum, δ, ppm: 5.81 s (4H, CH_2), 7.36–8.26 m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 56.65 (CH_2), 110.61–145.91 (C_{arom}), 200.32 (C=O). Found, %: C 48.44; H 4.63; N 18.89. $C_{12}H_{14}N_4O_5$. Calculated, %: C 48.97; H 4.76; N 19.04.

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