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Reactions with 1-Benzotriazolecarboxylic Acid Chloride. VIII. Synthesis of *N*-Hydroxyisocyanate Derivatives

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1,3,5-Trihydroxy-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (**5**), the trimer of hypothetical acid HO–N=C=O, was synthesized by hydrogenolysis of 1,3,5-tribenzyloxy-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (**4**). Similarly, the 1-(*N*-hydroxycarbamoyl)benzotriazole (**6**), as »solid HONCO donor«, was prepared by hydrogenolysis of its benzyl derivatives **2**. Compound **4** was obtained by trimerization of intermediary *N*-benzyloxyisocyanate (**3**), which liberates in the thermal dissociation of 1-(*N*-benzyloxycarbamoyl)benzotriazole (**2**). In the reaction with 2-phenylethylamine, compound **6** gave *N*-hydroxy-*N'*-(2-phenylethyl)urea (**7**).

Key words: 1-benzotriazolecarboxylic acid chloride, *N*-hydroxyisocyanate, 1,3,5-trihydroxy-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione, 1-(*N*-hydroxycarbamoyl)benzotriazole and 1-(*N*-benzyloxycarbamoyl)benzotriazole

INTRODUCTION

Earlier attempts to prepare esters or salts of the hypothetical acid HO–N=C=O have already been described in the literature,^{1–8} and numerous papers have reported theoretical studies and *ab initio* calculations of their possible structures.^{9–13} Hitherto, neither the monomer *N*-hydroxyisocyanate nor its oligomeric derivatives have been experimentally observed with certainty. On the other hand, some alkoxy isocyanates in the form of their corresponding trimers were reported,^{4,5,8} while Berndt⁷ in his work reported

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only formation of *N*-hydroxyisocyanate, in the form of a dimer, after thermal decomposition of 7,8-di-*t*-butyl-2,3,7,8-tetrahydroisoxazolo[5,4-*d*]isoxazole-3-one, but without complete characterization. However, in several Dow Chemical Co. patents, among numerous cited amines for the SO₂ removal from flue gases, the trimer form of *N*-hydroxyisocyanate, *i.e.* 1,3,5-trihydroxy-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (**5**), was also mentioned, but without data on its preparation procedure and its physicochemical properties.¹⁴

The synthetic utility and properties of *N*-substituted benzotriazoles,¹⁵ among others the application of 1-*N*-benzotriazolecarboxylic acid derivatives in the syntheses of carbamates,^{16,17} ureas, semicarbazides and carbazides,¹⁸ sulfonylureas,¹⁹ and hydroxyureidoalkane acid amides,²⁰ are well known.

Here, we describe a novel application of 1-*N*-benzotriazolecarboxylic acid chloride (**1**) in a simple procedure for the preparation of *N*-hydroxyisocyanate in the form of its trimer, *i.e.* 1,3,5-trihydroxy-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (**5**) and 1-(*N*-hydroxycarbamoyl)benzotriazole (**6**), the »solid HONCO donor« (Scheme).

RESULTS AND DISCUSSION

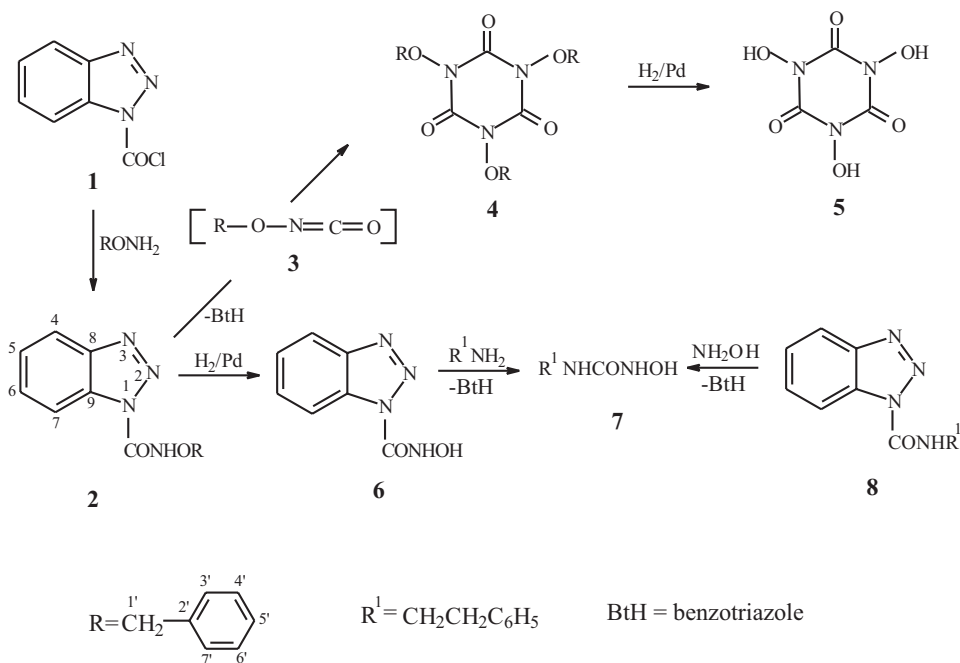
The 1-benzotriazolecarboxylic acid chloride (**1**) reacted with *N*-benzyl-oxamine to give 1-(*N*-benzyloxycarbamoyl)benzotriazole (**2**) in an analogous manner to that already described.¹⁶

In accordance with the well known properties of reactive carbamoylbenzotriazole,^{15, 16} and other carbamoylazoles,²¹ as well as the similarity to the reaction of *N*-benzyloxycarbamoylimidazole,⁵ compound **2** dissociated into benzotriazole and intermediary *N*-benzyloxyisocyanate (**3**), which trimerized to the already described 1,3,5-tribenzyloxy-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (**4**) (Scheme).

Whilst Staab and Benz⁵ isolated the cyanuric acid by the reduction of **4** with sodium in ethanol, we isolated the 1,3,5-trihydroxy-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (**5**) in quantitative yield by the hydrogenolysis of **4** using Pd/C as catalyst. Trimer **5** has acidic properties, and our preliminary results showed that it forms salts with different amines (triethylamine, imidazole, cyclohexylamine and 2-phenylethylamine) in the ratio 1:1, contrary to the cited application¹⁴ where it was inserted into a series of basic compounds.

The 1-(*N*-hydroxycarbamoyl)benzotriazole (**6**) was obtained from **2** under the same conditions of hydrogenolysis (Scheme).

Due to its ability of dissociation, compound **6** might be useful for the physicochemical property determination of monomeric *N*-hydroxyisocyanate, or as a convenient synthon in the preparative organic chemistry, *e.g.* for the synthesis of *N*-hydroxyurea derivatives (**7**). Analogously to the previously



Scheme

described reactions of carbamoylbenzotriazoles¹⁸ and hydroxylamine,²⁰ compound **7** was also obtained by aminolysis of 1-(*N*-2-phenylethyl-carbamoyl)benzotriazole (**8**) with *N*-hydroxylamine.

EXPERIMENTAL

Melting points of the synthesized compounds are uncorrected. The IR spectra were recorded on a FT-IR Perkin Elmer Paragon 500 spectrometer from samples dispersed in KBr pellets. ¹H and ¹³C NMR spectra were recorded with a Varian Gemini 300 spectrometer, operating at 300 and 75 MHz for the ¹H and ¹³C nucleus, respectively. All samples were measured from DMSO-*d*₆ or CDCl₃ solutions at 20 °C in 5 mm NMR tubes. Chemical shifts, in ppm, are referred to TMS. Mass spectra were scanned using an AutoSpecE instrument operating at 70 eV. TLC was performed using Merck Kieselgel 60 F₂₅₄ silica plates and the components were visualized using UV light (UV 254) and FeCl₃ reagent. Compounds were purified either by crystallization or column chromatography using Merck Kieselgel 60 (0.063–0.200 mm, 70–230 mesh), and were homogenous for TLC.

1-(*N*-Benzyloxycarbamoyl)benzotriazole (**2**)

A mixture of benzotriazole (1.19 g, 0.01 mol) in 20 mL of toluene and 10 mL of phosgene in toluene (20%) was heated for 1 hour at 90 °C. The solvent was removed

under reduced pressure, and the thus prepared 1-benzotriazolecarboxylic acid chloride¹⁶ (**1**) was used in the next reaction step without purification. A solution of **1** (1.81 g, 0.01 mol) in 15 mL of dioxane was added dropwise to a suspension of *O*-benzoyloxyamine hydrochloride (1.50 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in 30 mL of dioxane at 0–5 °C. After mixing for 3 hours at room temperature, the white precipitate (TEA × HCl) was removed by filtration, and the filtrate was evaporated under reduced pressure to give **2**, which was crystallized from ethyl acetate/ether solution.

2: Yield: 2.25 g (84%); m.p. 113–114 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3246s, 3113m, 3030m, 2947m, 2884w, 1728vs, 1603vw, 1484vs, 1367s, 1289m, 1231m, 1132w, 1093w, 1003vs, 924m, 869m, 751s, 699m, 563w; ¹H NMR (CDCl₃) δ/ppm : 9.95 (s, 1H, NH), 8.27 (d, 1H, $J = 8.2$ Hz, H7), 8.09 (d, 1H, $J = 8.5$ Hz, H4), 7.67 (t, 2H, $J = 7.7$ Hz, H5 and H6), 7.48 (t, 3H, $J = 7.1$ Hz, H4' H5' and H6'), 7.34 (d, 2H, $J = 4.4$ Hz, H3' and H7'), 5.14 (s, 2H, H1', -CH₂-); ¹³C NMR (CDCl₃) δ/ppm : 148.68 (C=O), 145.72 (C2'), 134.46 (C9), 131.54 (C8), 130.23 (C5), 129.28 (C3' and C7'), 128.97 (C5'), 128.63 (C4' and C6'), 125.66 (C6), 120.07 (C4), 113.49 (C7), 79.24 (C1'); MS m/z (%): 268 (1.5) M⁺, 146 (14.0), 119 (30.0), 105 (4.5), 91 (100.0), 77 (22.0), 64 (22.5).

Anal. Calcd. for C₂₄H₂₁N₃O₆ ($M_r = 268.27$): C 62.68, H 4.51, N 20.89%; found: C 63.01, H 4.48, N 20.78%.

1,3,5-Tribenzoyloxy-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (**4**)

A mixture of **2** (2.70 g, 0.01 mol) and imidazole (0.34 g) was stirred at 120–130 °C for 5 minutes. The clear melted mixture started to solidify, and an exothermic reaction occurred (the reaction mixture temperature rose to 150 °C). After 10 minutes, the mixture was cooled and suspended in 4 mL of acetone. The yielded product **4** was filtered off, washed with acetone and dried.

4: Yield: 1.12 g (83%); m.p. 249–250 °C (Lit.⁴ 239–241 °C; Lit.⁵ 241.5–242 °C); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3034w, 2956vw, 2924vw, 1740vs, 1457w, 1402vs, 1197m, 1001s, 905w, 750s, 696s, 476m; ¹H NMR (DMSO-*d*₆) δ/ppm : 7.56 (d, 2H, $J = 4.7$ Hz, H3' and H7'), 7.46 (t, 3H, $J = 4.9$ Hz, H4', H5' and H6'), 5.13 (s, 2H, H1', -CH₂-); ¹³C NMR (DMSO-*d*₆) δ/ppm : 145.37 (C=O), 133.94 (C1'), 130.01 (C4' and C6'), 129.51 (C5'), 128.82 (C3' and C7'); MS m/z (%): 181 (4.7), 91 (100.0), 77 (15.5).

Anal. Calcd. for C₂₄H₂₁N₃O₆ ($M_r = 447.43$): C 64.42, H 4.73, N 9.39%; found: C 64.15, H 4.83, N 9.74%.

1,3,5-Trihydroxy-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (**5**)

Compound **4** (0.95 g, 0.002 mol) was hydrogenated on Pd/C (10% Pd, 0.25 g) at room temperature under normal pressure, in 50 mL of dioxane, for 3 hours. The catalyst was filtered off from the reaction mixture and washed with dried dioxane (10 mL). The filtrate was evaporated under reduced pressure to afford product **5**, which was crystallized from acetone.

5: Yield: 0.37 g (100%); m.p. 255–256 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3535s, 3427s, 2916w, 2849w, 2706m, 1720vs, 1568s, 1434s, 1212m, 1164w, 1010s, 702s, 478s; ¹H NMR (DMSO-*d*₆) δ/ppm : 11.11 (s, H); ¹³C NMR (DMSO-*d*₆) δ/ppm : 147.19 (C=O); MS m/z (%): 177 (39.5) [M-H₂O]⁺, 161 (15.5), 129 (100.0), 118 (13.7), 102 (37.4), 97 (20.5), 86 (31.5), 74 (19.0), 70 (72.0), 60 (67.5).

Anal. Calcd. for C₃H₃N₃O₆ × 2H₂O ($M_r = 213.09$): C 16.91, H 3.31, N 19.72%; found: C 17.24, H 3.30, N 20.12%.

1-(N-Hydroxycarbamoyl)benzotriazole (6)

Compound **2** (1.34 g, 0.005 mol) was hydrogenated on 0.5 g of Pd/C in 40 mL of ethyl acetate for 1 hour. Product **6** was isolated analogously to **5** and crystallized from acetone/benzene mixture.

6: Yield: 0.82 g (92%); m.p. 132–134 °C; IR (KBr): $\nu_{\max}/\text{cm}^{-1}$: 3297s, 3132vs, 2939m, 2876s, 1750vs, 1711s, 1610vw, 1536s, 1489s, 1451s, 1368s, 1290s, 1240m, 1135m, 1104m, 1017vs, 936m, 870s, 785m, 744s, 644m; ^1H NMR (DMSO- d_6) δ/ppm : 8.86 (s, 1H, OH), 8.37 (s, 1H, NH), 7.92 (s, 2H, H4 and H7), 7.46 (d, 2H, $J = 3.43$ Hz); ^{13}C NMR (DMSO- d_6) δ/ppm : 162.68 (C=O), 138.68 (C9), 130.22 (C8), 125.65 (C5 and C6), 120.04 (C4), 113.48 (C7); MS m/z (%): 179 (20.0) [M+H] $^+$, 120 (20.0), 107 (20.3).

Anal. Calcd. for $\text{C}_7\text{H}_6\text{N}_4\text{O}_2$ (M_r 178.15): C 47.19, H 3.39, N 31.45%; found: C 47.52, H 3.75, N 31.12%.

N-Hydroxy-N'-(2-phenylethyl)urea (7)

A) A mixture of **6** (0.55 g, 0.003 mol) and 2-phenylethylamine (0.39 g, 0.0032 mol) in 30 mL of ethylacetate was stirred overnight at room temperature. The white precipitate of unknown structure (0.30 g) was filtered off, the filtrate was evaporated under reduced pressure and the residue was purified by column chromatography using a chloroform/methanol mixture (9.5:0.5). Fractions that were eluated after those with benzotriazole and showing one spot in TLC were collected, and the solvent mixture was evaporated under reduced pressure to afford compound **7**.

7: Yield: 0.184 g (34%); m.p. 118–119 °C; IR (KBr): $\nu_{\max}/\text{cm}^{-1}$: 3338vs, 3160m, 3027w, 2882s, 1613vs, 1556vs, 1499m, 1456w, 1422w, 1373w, 1218w, 1139m, 1082w, 815w, 770w, 704m.

Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2$ (M_r 180.21): C 59.99, H 6.71, N 15.55%; found: C 59.79, H 6.63, N 15.38%.

B) A mixture of 1-(*N*-2-phenylethylcarbamoyl)benzotriazole (**8**) (1.33 g, 0.005 mol), hydroxylamine hydrochloride (0.695 g, 0.01 mol) and triethylamine (1.52 g, 0.015 mol) in 20 mL of dioxane was heated at 90 °C for 2 hours. After overnight standing at room temperature, the yielded triethylamine hydrochloride was filtered off, the filtrate was evaporated under reduced pressure and the residue was purified analogously to that described under A. The melting point and IR spectrum of the obtained product were identical to an authentic sample from A.

CONCLUSION

Derivatives of *N*-hydroxyisocyanate, *i.e.* 1,3,5-trihydroxy-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (**5**) and 1-(*N*-hydroxycarbamoyl)benzotriazole (**6**) have been synthesized by hydrogenolysis of their corresponding benzyloxy derivatives using Pd/C as catalyist. Compounds **5** and **6** could be useful for the physicochemical property determination of monomeric *N*-hydroxyisocyanate or as convenient synthons in the preparative organic chemistry, for example **6** can be convenient for the synthesis of substituted *N*-hydroxyurea **7**. Structures of synthesized compounds were characterized by FT-IR, ^1H NMR, ^{13}C NMR and MS spectroscopy.

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SAŽETAK

**Reakcije klorida 1-benzotriazolkarboksilne kiseline.
VIII. Sinteza derivata N-hidroksiizocijanata**

Ivan Butula i Milena Jadrijević-Mladar Takač

1,3,5-trihidroksi-1,3,5-triazin-2,4,6(1*H*,3*H*,5*H*)-trion (**5**), trimerni oblik hipotetske HO–N=C=O kiseline, sintetiziran je hidrogenolizom 1,3,5-tribenziloksi-1,3,5-triazin-2,4,6(1*H*,3*H*,5*H*)-triona (**4**). Na sličan je način hidrogenolizom njegova benziloksi-derivata **2** pripremljen i 1-(*N*-hidroksikarbamoil)benzotriazol (**6**), »kruti HONCO donor«. Spoj **4** pripremljen je trimerizacijom intermedijarnog *N*-benziloksiizocijanata (**3**) koji se oslobađa pri termalnoj disocijaciji 1-(*N*-benziloksikarbamoil)benzotriazola (**2**). Spoj **6** u reakciji s 2-feniletilaminom daje *N*-hidroksi-*N'*-(2-feniletil)ureu (**7**).