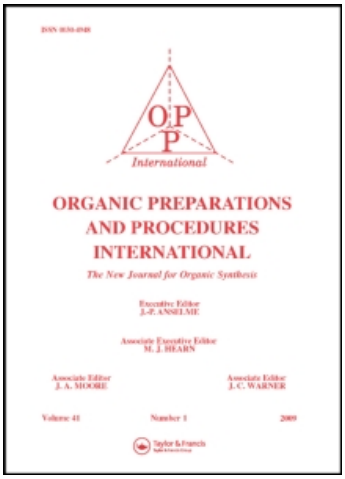

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A NOVEL ROUTE TO N-(BENZOTRIAZOL-1-YLMETHYL)AMIDES

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OPPI BRIEFS

A NOVEL ROUTE TO N-(BENZOTRIAZOL-1-YLMETHYL)AMIDES

Submitted by (01/29/92)

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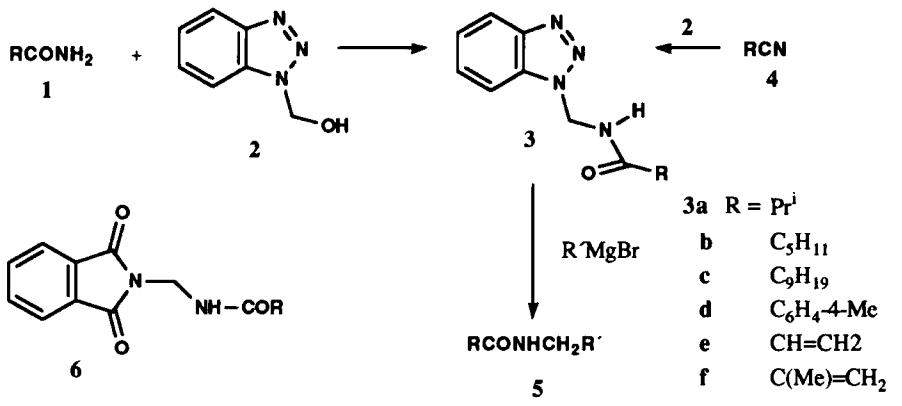
N-(Benzotriazol-1-ylmethyl)amides **3**, previously prepared from the unsubstituted amides **1** and 1-hydroxymethylbenzotriazole **2**,[1] have gained importance as amidoalkylating reagents. They react *inter alia* with Grignard reagents to yield N-substituted amides **5**[2] and with metal alkoxides to give N(α-alkoxyalkyl)amides.[3] We now report that these benzotriazole-derivatized amides can alternatively be prepared from nitriles **4** and alcohol **2** under boron trifluoride or acid catalysis. This can be considered an extension of the Ritter reaction;[4] a closer analogy is the reported reaction of N-hydroxymethylphthalimide with nitriles in the presence of H_2SO_4 to give compounds **6**.[5]



1-Hydroxymethylbenzotriazole (**2**), formed in situ from benzotriazole and paraformaldehyde, reacted with aliphatic nitriles at 120° in the presence of boron trifluoride etherate to give the corresponding N-(benzotriazol-1-ylmethyl)amides (**3**) in moderate to good yields. No reaction occurred at 20° as in the literature procedure for the boron trifluoride catalyzed Ritter reaction.[6] Use of 1-hydroxymethylbenzotriazole instead of benzotriazole and parafomaldehyde lowered the yield, probably because of decomposition of 1-hydroxymethylbenzotriazole under the reaction conditions into benzotriazole and formaldehyde; white insoluble material (paraformaldehyde) was observed in the condenser. Applying similar reaction conditions (120°) to 4-methylbenzonitrile produced a

complex mixture with only traces of the desired amide. However, a lower temperature (90°) and a prolonged reaction time (from 8 to 48 hrs), gave N-(benzotriazol-1-ylmethyl)-4- methylbenzamide (**3d**) in 32% yield.

Optimum conditions for the reactions of 1-hydroxymethylbenzotriazole (**2**) with acrylonitrile and methacrylonitrile utilized 15% oleum as the solvent and the catalyst at 20°. The crude products obtained after work-up were purified by recrystallization. Attempts to use the sulfuric acid conditions for the preparations of amides **3a-3c** gave low yields of the products, detected by NMR, in the complex reaction mixtures. On the other hand, the yields of amides **3e** and **3f** were not improved by boron trifluoride catalysis. We conclude that these three types of nitriles (aliphatic, aromatic and α,β-unsaturated) each require different conditions for the Ritter reaction with 1-hydroxymethylbenzotriazole (**2**).

EXPERIMENTAL SECTION

Melting points were determined with a hot-stage microscope and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer. Chemical shifts are in parts per million (δ) relative to TMS. Coupling constants (*J*) are in Hertz (Hz). Commercial nitriles, 2-methylpropionitrile (Matheson Coleman), hexanenitrile (Aldrich), decanenitrile (Fluka), *p*-toluonitrile (Aldrich), acrylonitrile (Eastman) and methacrylonitrile (Aldrich) were used for the reaction. 1-Hydroxymethylbenzotriazole (**2**) (colorless needles, mp- 146-147°, lit.[7] mp. 148-158°) was prepared by the reaction of benzotriazole with 37% formaldehyde in ether at room temperature.

N-(Benzotriazol-1-ylmethyl)amides (3a-3c). General Procedure.- Boron trifluoride etherate (1.85 mL, 15 mmol) was slowly added to a mixture of benzotriazole (1.19 g, 10 mmol), paraformaldehyde (0.6 g, 20 mmol) and the appropriate nitrile (20 mmol) stirred under nitrogen at 25°. The resulting brown, viscous mixture was heated at 120° for 8 hrs. After cooling, $CHCl_3$ (10 mL) was added, the mixture was diluted with water and neutralized with 10% NH_4OH. The chloroform layer was separated and the aqueous layer extracted with $CHCl_3$ (10 mL). The combined extracts were washed with brine (3 x 10 mL). After drying over Na_2SO_4 and removal of the solvent, amide **3** was separated by column chromatography (silica gel/$CHCl_3$) and recrystallized from diethyl ether.

N-(Benzotriazol-1-ylmethyl)-2-methylpropionamide (3a), colorless needles (0.70 g, 32% yield), mp. 113-114° (ethyl ether). ^1H NMR: δ 1.15 (d, 6H, *J* = 6.9), 2.55 (septet, 1 H, *J* = 6.9), 6.13 (d, 2H, *J* = 6.7, NCH_2N), 7.35 (ddd, 1H, *J* = 1.0, 6.9 and 8.2), 7.46 (ddd, 1H, *J* = 1.0, 6.9 and 8.1), 7.91 (dt, 1H, *J* = 8.3 and 1.0), 7.96 (dt, 1H, *J* = 8.3 and 1.0), 8.25 (t, 1H, *J* = 6.7, N-H). ^{13}C NMR: δ 19.1 (2C), 35.0, 51.0 (NCH_2N), 110.8, 118.9, 124.2, 127.6, 132.1, 145.6, 178.0 (C=O).

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.20; H, 6.40; N, 25.60

N-(Benzotriazol-1-ylmethyl)hexanamide (3b), colorless prisms (1.2 g, 50% yield), mp. 76- 78° (ethyl ether). ^1H NMR: δ 0.80 (m, 3H), 1.22 (m, 4H), 1.62 (quintet, 2H, *J* = 7.1), 2.29 (t, 2H, *J* = 6.9), 6.11 (d, 2H, *J* = 6.6, NCH_2N), 7.36 (m, 1H), 7.48 (m, 1H), 7.95 (m, 2H), 7.99 (bs, 1H, N-H). ^{13}C NMR: δ 13.7, 22.1, 24.8, 31.1, 36.0, 50.9 (NCH_2N), 111.0, 119.1, 124.3, 127.8, 132.3, 145.7, 174.1 (C=O).

Anal. Calcd. for $C_{13}H_{18}N_4O$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.16; H, 7.35; N, 22.73

N-(Benzotriazol-1-ylmethyl)decanamide (3c), colorless prisms (1.6 g, 64% yield), mp. 72-73° (ethyl ether). ^{1}H NMR: δ 0.85 (t, 3H, *J* = 6.6), 1.19 (m, 12H), 1.62 (m, 2H), 2.28 (t, 2H, *J* = 7.5), 6.11 (d, 2H, *J* = 6.8, NCH_2N), 7.37 (dd, 1H, *J* = 8.2 and 7.1),7.50 (dd, 1H, *J* = 8.2 and 7.1), 7.72 (t, IH, *J* = 6.6, N-H), 7.94 (d, 1H, *J* = 8.2), 7.97 (d, 1H, *J* = 8.2). ^{13}C NMR: δ 14.1, 22.5, 29.0, 29.1, 29.2, 29.3, 31.7, 36.2, 50.9 (NCH_2N), 111.1, 119.2, 124.3, 127.9, 132.3, 145.8, 174.1 (C=O).

Anal. Calcd. for $C_{17}H_{22}N_4O$: C, 67.52; H, 8.67; N, 18.53. Found: C, 67.35; H, 8.94; N, 18.40

N-(Benzotriazol-1-ylmethyl)-4-methylbenzamide (3d), colorless needles (0.88 g, 32% yield), mp. 181-182° (ethanol), was obtained in a procedure similar to the above with the following modifications: reaction time 48 hrs, temperature 90° and with 40 mmol of paraformaldehyde. ^{1}H NMR: δ 2.34 (s, 3H), 6.30 (d, 2H, *J* = 6.8, NCH_2N), 7.17 (d, 2H, *J* = 8.0), 7.34 (t, 1H, *J* = 7.7), 7.46 (dd, 1H, *J* = 8.0 and 7.3), 7.83 (d, 2H, *J* = 8.1), 8.51 (bt, 1H, *J* = 6.4, N-H). ^{13}C NMR: δ 21.4, 51.6 (NCH_2N), 111.2, 119.1, 124.3, 127.5 (2C), 127.9, 129.2 (2C), 129.9, 132.4, 142.8, 145.8, 167.8 (C=O).

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.49; H, 5.23; N, 20.78

Unsaturated Amides 3e and 3f. General Procedure.- The appropriate nitrile (18 mmol) was added dropwise at 0° to a stirred solution of 1-hydroxymethylbenzotriazole (3.80 g, 18 mmol) in fuming H_2SO_4 (30 mL) containing 15% SO_3. After 5 days stirring at 20° the reaction mixture was poured into ice-water (300 g) and extracted with $CHCl_3$ (6 x 40 mL). The combined extracts were washed with saturated $NaHCO_3$ (2 x 100 mL) followed by water (200 mL) and dried over $MgSO_4$. After evaporation of the solvent, the solid product was recrystallized from 70% EtOH.

N-(Benzotriazol-1-ylmethyl)acrylamide (3e), colorless needles (1.00 g, 27%), mp. 135-136° (ethanol). ^{1}H NMR: δ 5.75 (d, 1H, *J* = 10.3), 6.19 (d, 2H, *J* = 6.6, NCH_2N), 6.21 (dd, 1H, *J* = 10.3 and 17.0), 6.42 (d, 1H, *J* = 17.0), 7.38 (dd, 1H, *J* = 7.9 and 7.4), 7.51 (dd, 1H, *J* = 7.3 and 8.0), 7.79 (bt, 1H, N-H), 7.98 (m, 2H). ^{13}C NMR: δ 50.97 (NCH_2N), 119.3, 124.4, 128.0, 128.6, 129.9, 132.4, 146.1, 165.9 (C=O).

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.21; H, 4.97; N, 27.83

N-(Benzotriazol-1-ylmethyl)methacrylamide (3f), colorless needles (10.9 g, 28%), mp. 169-171° (70% ethanol). ^{1}H NMR: δ 1.94 (s, 3H), 5.41 (s, 1H), 5.82 (s, 1H), 6.13 (d, 2H, *J* = 6.6, NCH_2N), 7.38 (m, 1H), 7.48 (m, 1H), 8.00 (m, 2H), 9.12 (bt, 1H, N-H). ^{13}C NMR: δ 18.1, 51.1 (NCH_2N), 110.8, 118.6, 120.7, 123.4, 127.0, 132.0, 138.4, 145.3, 168.3 (C=O).

Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25-91. Found: C, 60.85; H, 5.53; N, 26.34

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SYNTHESIS OF POTENTIAL PRECURSORS OF HEPTABOWTIENE, A NOVEL NON-BENZENOID HYDROCARBON

Submitted by (02/21/92) Arthur G. Anderson, Jr.* and Barry T. Murphy

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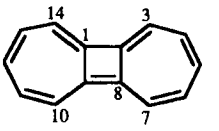
Tricyclo [7.5.0.0^{2,8}] tetradeca-1,3,5,7,9,11,13 heptaene (heptabowtiene), **1**, is a 4n + 2π electron, non-benzenoid , conjugate-unsaturated hydrocarbon for which some calculations of structural parameters have been performed;[1] however, no attempted synthesis was found in the literature. Additional calculations and the synthesis of two potential precursors (**12** and **13**) to **1** are now reported.[2] It was envisioned that **12** and/or **13** could be convened to **1** by (i) removal of the halides by radical hydrogenolysis (*e. g.*, with Ph_3SnH), (ii) reduction of the carbonyl groups to hydroxyls, (iii) bis-elimination to generate two additional ring double bonds, and (iv) vapor phase dehydrogenation over a Pd.C catalyst[3] or, alternatively, allylic bromination followed by dehydrohalogenation.



1

HMO, SCF[4] and SE (strain energy)[5] calculations[6] for planar **1** gave values of 66.3 kcal/mole for the SE and DE (delocalization energy) values of 74.8 kcal/mole (HMO) and 59.2 kcal/mole (SCF) for net RE (resonance energy) estimates of +8.5 and -7.1 kcal/mole, respectively. The HMO method showed two electrons in a nonbonding orbital, and the SCF calculations showed four antibonding electrons but a large HOMO-LUMO energy difference. SCF-MO calculations for fulvalene and heptafulvalene show filled antibonding MOs and large HOMO-LUMO gaps, yet these compounds have been synthesized and isolated.[7] The calculated bond orders of 0.536-0.646 (HMO) and 0.545-0.646 (SCF) and bond lengths of 1.401-1.419 Å (SCF) for **1** showed values close to those of benzene for the peripheral bonds and without bond alternation, and of 1.473 Å (SCF) indicative of more single