Functionally substituted 1-alkylbenzotriazoles in Heterocyclic synthesis: Synthesis and Reactivity of Benzotriazol-1-yl amides.

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Abstract: The reactivity of benzotriazol-1-yl amides toward nucleophiles and electrophiles is reported. Several novel benzotriazolyl derivatives have been synthesized.

Keywords: benzotriazole, carbonion, bromination, Dimroth rearrangement

The considerable potential application of benzotriazole derivatives has stimulated considerable interest in benzotriazole chemistry.1-3 Recently Katritzky et al as well as Elnagdi et al., [4-9] have shown that benzotriazolylmethylketones have an active methylene moiety and in this way could utilize these compounds as precursors to functionally substituted aryl and heteroarylbenzotriazole derivatives.4-8 In this paper we report synthesis of benzotriazolyl amide and results of our trials to utilize these amides for synthesis of otherwise not readily accessible N-substituted benzotriazole derivatives for potential utility as agrochemicals and antioxidants.9,10 Thus, treatment of chloroacetylazolylamides 1-3 and the fused chloroacetamidothiophene 4 with benzotriazole in dry toluene and in the presence of sodium hydride has resulted in the formation of the corresponding benzotriazolyl derivatives 5-8. The required 1-4 were prepared from reaction of the respective heteroaromatic amines with chloroacetyl chloride in dioxane solution utilizing procedure recently reported from Elnagdi laboratories.11 These were assigned N-1 alkylated structures 5-8 rather than isomeric N-2 structure 9 based on 1H NMR that revealed the four benzotriazolyl protons at δ = 7.96, 7.76, 7.57 and 7.44 ppm are magnetically different. Isomeric N-2 structure should show only two signals for benzotriazolyl protons as it has a plain of symmetry (Scheme 1). Although Katritzky et al, have mentioned isolation of N-2 alkylated products on alkylating benzotriazoles. In our hands, no N-2 alkylation products could be traced in mother liquor or reaction. Elnagdi et al, have shown recently that in some cases the reaction give only regioselectively N-1 alkylation.4
Scheme 1

It contrast to reported ready coupling of benzotriazol-1-yl methylketones with aromatic diazonium salts compounds 5-8 failed to couple with the same reagents under a variety of conditions. This find thus parallel to reported inactivity of benzotriazolylacetonitrile and ethyl benzotriazolylacetate toward aromatic diazonium salts. Despite reports that the former reagents as will as benzotriazolylacetone condense readily with DMFDMA again 5-8 failed to react under a variety of conditions. First success was achieved with arylidenemalononitrile in pyridine where products of addition of reagents to malononitrile were isolated. These were formulated as 11 and 12 and are assumed to be formed via reaction of 5 and 6 with malononitrile, reported to exist in benzylidenemalononitrile solutions. Compounds 11 and 12 were also obtained from reaction of 5 and 6 with malononitrile in refluxing aqueous pyridine. This is a new route to 2,4-diaminopyridine. Alternate derivative of this type are known relatively rather rare. The presence of benzotriazole at C-5 help stabilize these system be by its electron attracting effect.
Scheme 2

Compound 5 and 8 could also be brominated yielding the bromo derivatives 13 and 14. The latter reacted with potassium thiocyanate to yield, through 15 and 16, thiazoles that can be formulated as 17 and 18 or 19 and 20; formed via a Dimroth rearrangement of intermediately formed 17 and 18. Structures 17 and 18 were excluded based on the fact that hydrolysis of reaction products in AcOH/HCl affords the thiazolidinone 19 and 20. It is believed that initially 17 and 18 are formed but rearranged into 19 and 20. The assumed rearrangement of 17 and 18 into 19 and 20 finds thus parallism to our recently observed rearrangement of N-alkylthiazolidine-2-imine into 2-aminothiazolidines. It is of value to report that rearrangement of 17 into 20 is a new example of the newly reported Dimroth type rearrangement of thiazollones of similar structure. Evidence of structure in this work by X-ray was presented.
Experimental

All melting points were measured on Stuart Scientific melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Pye Unicam SP 3-300 Spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded in deuterated dimethylsulfoxide ($DMSO$-$d_6$) on Bruker DPX 400 MHz spectrometer using tetramethylsilane ($TMS$) as an internal reference and results are expressed as $\delta$ (ppm) values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical center of Cairo University.

General Procedure for the preparation of benzotriazoly derivatives (5-8)

A solution of benzotriazole (0.1 mol) in dry toluene (100 ml) and sodium hydride was add (0.1 mol, 100%). The reaction mixture was refluxed for 1h, then left to at room temperature. After that the 18-crown-6 (0.05 g, 99%) and each of 1-4 (0.1 mol) were add and heated for 6 h. The solid product, so formed, was collected by filtration and crystallized from the proper solvent.

2-Benzotriazol-1-yl-N-(5-phenyl-1H-pyrazol-3-yl)-acetamide (5)

Compound 5 was obtained as white crystals from ethanol; mp 280°C; (47%) IR: $\text{Vmax}$/ (KBr) 3249-3300 (NH) 3091 (CH aromatic), 2965 (CH aliphatic) and 1692 cm$^{-1}$ (C=O). $^1$H NMR (400 MHz DMSO-$d_6$): 13.03(s, 1H, NH), 11.25(s, 1H, pyrazol NH), 7.34- 8.09 (m, 9-H, Ar-H), 6.91(s, 1H, pyrazol H-4) and 4.22 (s, 2H, CH$_2$). $^{13}$C NMR (400 MHz DMSO-$d_6$): 164.3 (C=O), 145.6 (C-3 pyrazol), 144.6 (C-5 pyrazol), 134.6, 128.7, 127.9, 124.5, 119.6, 118.5 (benzotriazol carbons), 129.9, 129.6, 128.7, 125.5 (phenyl carbons), 94.1 (C-4 pyrazol) and 50.6 (CH$_2$). MS [EI, 70eV]: m/z = [M$^+$] (318: 35.1%); Anal. Calcd for C$_{17}$H$_{14}$N$_6$O: C, 64.14; H, 4.43; N, 26.40 Found: C 64.05; H, 4.63; N, 26.26.

N-Benzothiazol-2-yl-2-benzotriazol-1-yl-acetamide (6)

Compound 6 was obtained as white crystals from ethanol; mp 287°C; (62%) IR: $\text{Vmax}$/ (KBr) 3200 (NH), 3065 (CH aromatic), 2970 (CH aliphatic) and 1688 cm$^{-1}$ (C=O). $^1$H NMR (400 MHz DMSO-$d_6$): 13.04 (s, 1H, NH), 7.03- 8.11 (m, 8H, Ar-H) and 4.34 (s, 2H, CH$_2$). $^{13}$C NMR (400 MHz DMSO-$d_6$): 164.6 (C=O), 158.2, 145.6, 132.0, 126.9, 124.6, 122.4, 121.3 (benzothiazol carbons), 134.6, 128.2, 127.4, 124.5.
119.7, 118.5 (benzotriazol carbons) and 50.5 (CH₂). MS [EI, 70eV]: m/z = [M⁺] (309: 22.2%); Anal. Calcd for C₁₅H₁₁N₅O: C, 58.24; H, 3.58; N, 22.64 Found: C 58.02; H, 3.72; N, 22.84.

2-Benzotriazol-1-yl-N-pyridin-2-yl-acetamide (7)
Compound 7 was obtained as white crystals from ethanol; mp 280°C; (30%) IR: Vmax/ (KBr) 3195 (NH), 3076 (CH aromatic), 2962 (CH aliphatic) and 1670 cm⁻¹ (C=O). ¹H NMR (400 MHz DMSO-d₆): 12.32 (s, 1H, NH), 8.81 (d, 1H, J = 4 Hz pyridine H-6), 8.76 (d, 1H, J = 8 Hz pyridine H-3), 8.69 (m, 1H, pyridin H-4), 7.96 (d, 1H, J = 8 Hz Ar-H), 7.76 (m, 1H, Ar-H), 7.75 (m, 1H, Ar-H), 7.44 (d, 1H, J = 8 Hz Ar-H), 7.33 (m, 1H, pyridine H-5) and 4.24 (s, 2H, CH₂). ¹³C NMR (400 MHz DMSO-d₆): 166.2 (C=O), 147.1, 144.1, 138.7, 118.8, 118.0 (pyridin carbons), 134.2, 130.2, 127.3, 122.5, 118.7, 118.5 (benzotriazol carbons) and 50.6 (CH₂). MS [EI, 70eV]: m/z = [M⁺-1] 252 (1.7%); [M⁺-2] 251 (15.5%); [M⁺-3] (250 : 100 %); Anal. Calcd for C₁₃H₁₁N₅O: C, 61.65; H, 4.38; N, 27.65 Found: C 61.43; H, 4.58; N, 27.84.

2-Benzotriazol-1-yl-N-((thieno[3,4:3',4']benzo[b]pyran-4-one)-3-yl)-acetamide (8)
Compound 8 was obtained as white crystals from DMF; mp 200°C; (62.5%) IR: Vmax/ (KBr) 3262 (NH), 3099 (CH aromatic), 2925 (CH aliphatic), 1710 (C=O) and 1687 cm⁻¹ (C=O ring). ¹H NMR (400 MHz DMSO-d₆): 11.50 (s, 1H, NH), 7.31 – 8.11 (m, 8H, Ar-H), 7.82 (s, 1H, thienyl) and 4.41 (s, 2H, CH₂). ¹³C NMR (400 MHz DMSO-d₆): 167.5 (C=O), 158.6, 150.5, 145.7, 130.7, 130.2, 124.7, 119.7, 111.4 (coumarin carbons), 149.1 (thineyl C-3), 134.3 128.2, 125, 4, 124.58, 117.6, 117.3, 107.3 (thineyl C-1) and 50.6 (CH₂). MS [EI, 70eV]: m/z = [M⁺] (376 : 31.4%); Anal. Calcd for C₁₉H₁₂N₅O₃S: C, 60.63; H, 3.21; N, 14.89 Found: C 60.55; H, 3.12; N, 14.76.

Reaction of 5 and 6 with benzylidenemalononitrile
A solution each of 5 or 6 (0.1 mol) in pyridine (15 ml) and benzylidenemalononitrile was add (0.1 mol). The reaction mixture was refluxed for 1h. The solid product was collected by filtration and crystallized from proper solvent.

4,6-Diamino-3-benzotriazol-1-yl-1-(5-phenyl-1H-pyrazol-3-yl)-1H-pyridin-2-one (11)
Compound 11 was obtained as white crystals from ethanol; mp 261-263°C; (62%) IR: Vmax/ (KBr) 3390, 3178 (2NH₂), 3250 (pyrazol NH), 3044 (CH aromatic) and 1686 cm⁻¹ (C=O). ¹H NMR DMSO-d₆: 11.64 (s, 1H, pyrazol NH), 7.22-7.98 (m, 9H, Ar-H),
6.93 (s, 1H, pyrazol H-4), 3.85 (s, 1H, pyridin H-5), 2.83 (s, 2H, NH₂) and 2.71 (s, 2H, NH₂). ¹³C NMR (400 MHz DMSO-d₆): 154.4 (C=O), 144.3, 141.6, 108.1, 86.2 (pyridinone carbon), 145.24 (C-3 pyrazol), 140.50 (C-5 pyrazol), 134.46, 128.74, 127.95, 124.47, 119.60, 118.45 (benzotriazol carbon), 129.90, 129.27, 128.44, 125.58 (phenyl carbon) and 94.14 (C-4 pyrazol). MS [EI, 70eV]: m/z = [M⁺ +1] (385 : 33.6%); Anal. Calcd for C₂₀H₁₆N₈O: C, 62.49; H, 4.20; N, 29.15 Found: C 62.24; H, 4.43; N, 29.34.

4,6-Diamino-1-benzothiazol-2-yl-3-benzotriazol-1-yl-1H-pyridin-2-one (12)

Compound 12 was obtained as pale brown crystals from methanol; mp 232-233°C; (54%) IR: V_max (KBr) 3200-3350 (2NH₂), 3099 (CH aromatic) and 1694 cm⁻¹ (C=O). ¹H NMR DMSO-d₆: 7.45-8.24 (m, 8H, Ar-H), 3.72 (s, 1H, pyridin H-5), 2.80 (s, 2H, NH₂) and 2.77 (s, 2H, NH₂). ¹³C NMR (400 MHz DMSO-d₆): 156.46 (C=O), 144.6, 142.4, 108.4, 86.2 (pyridinone carbons), 156.1, 144.6, 132.2, 126.7, 124.2, 122.4, 120.3 (benzothiazol carbons), 134.6, 128.2, 127.4, 124.5, 119.7 and 118.5 (benzotriazol carbons) MS [EI, 70eV]: m/z = [M⁺ +1] (375: 31%); Anal. Calcd for C₁₈H₁₃N₇O: C, 57.59; H, 3.49; N, 26.12 Found: C 57.34; H, 3.63; N, 26.34.

Bromination of benzotriazolyl derivatives

A suspension of 5 or 8 (0.1 mol) in glacial acetic acid (10 ml) was treated with bromine (0.1 mol). The reaction mixture was left to sun light for 5h. The crude product was collected by filtration and recrystalation from appropriate solvent.

2-Benzotriazol-1-yl-2-bromo-N-(5-phenyl-1H-pyrazol-3-yl)acetamide (13)

Compound 13 was obtained as pale brown crystals from ethanol and DMF (3:1); mp 250-252°C; (89%) IR: V_max (KBr) 3331 (NH), 3276 (NH pyrazol) 3016 (CH aromatic), 2942 (CH aliphatic) and 1685 cm⁻¹ (C=O). ¹H NMR (400 MHz DMSO-d₆): 13.50 (s, 1H, NH), 10.45 (s, 1H, NH pyrazol), 7.44-8.07 (m, 9H, Ar-H), 6.91 (s, 1H, pyrazol H-4) and 6.19 (s, 1H, CH-Br). ¹³C NMR (400 MHz DMSO-d₆): 166.3 (C=O), 145.2 (C-3 pyrazol), 145.5 (C-5 pyrazol), 136.5, 128.8, 127.9, 126.5, 119.86 118.6 (benzotriazol carbons), 130.2, 129.9, 128.4, 125.9 (phenyl carbons), 94.4 (C-4 pyrazol) and 72.5 (CH). MS [EI, 70eV]: m/z = [M⁺] (396: 34.2%); [M⁺ +2] (398: 26.1%); Anal. Calcd for C₁₇H₁₃BrN₆O: C, 51.40; H, 3.30; N, 21.16 Found: C 51.25; H, 3.59; N, 21.38.

2-Benzotriazol-1-yl-2-bromo-N-[(thieno[3,4:3',4']benzo[b]pyran-4-one)-3-yl]acetamide (14)
Compound 14 was obtained as white crystals from dioxan; mp 276°C; (73%) IR: \( V_{\text{max}} \) (KBr) 3362 (NH), 3059 (CH aromatic), 2925 (CH aliphatic), 1708 (C=O) and 1689 cm\(^{-1}\) (C=O). \(^1\)H NMR (400 MHz DMSO-d\(_6\)): 11.84 (s, 1H, NH), 7.42-8.11 (m, 8H, Ar-H), 7.80 (s, 1H, thienyl) and 6.21 (s, 1H, CH-Br). \(^1\)C NMR (400 MHz DMSO-d\(_6\)): 158.7 (C=O), 158.6, 150.5, 145.5, 130.7, 131.2, 124.7, 119.8, 111.4 (coumarin carbons), 150.1 (thienyl C-3), 134.4, 128.3, 125.3, 124.9, 117.5, 117.3, (benzotriazol carbons), 109.3 (thienyl C-1) and 71.9 (CH). MS [EI, 70eV]: m/z = [M\(^+\)] (454 : 42.8); [M\(^+\) +2] (456 : 41.2); Anal. Calcd for C\(_{19}\)H\(_{11}\)N\(_4\)BrO\(_3\)S: C, 50.12; H, 2.44; N, 12.31 Found: C 50.36; H, 2.25; N, 12.54.

**General Procedure for the preparation of thiazol-4-one derivatives (19 and 20)**

A suspension of 13 and 14 (0.1 mol) and potassium thiocyanate (0.3 mol) in MeCN (50 ml) was heated to reflux for 3 h. The reaction mixture was cooled and poured into water (150 ml) and after 1h; the crude product was collected by filtration and recrystalization from ethanol.

5-Benzotriazol-1-y1-2-(5-phenyl-1H-pyrazol-3-yl amino)-thiazol-4-one (19)

Compound 19 was obtained as brown crystals from ethanol and dioxan (3:1); mp 277°C; (70%) IR: \( V_{\text{max}} \) (KBr) 3280 (NH), 3220 (NH pyrazol), 3070 (CH aromatic), 2940 (CH aliphatic) and 1690 cm\(^{-1}\) (C=O). \(^1\)H NMR DMSO-d\(_6\): 13.21 (s, 1H, NH), 10.80 (s, 1H, NH pyrazol), 7.31-8.03 (m, 9H, Ar-H), 6.84 (s, 1H, pyrazol H-4) and 5.63 (s, 1H, CH). \(^1\)C NMR (400 MHz DMSO-d\(_6\)): 174.9 (C=O), 166.7 (thiazolone C-2), 145.2 (C-3 pyrazol), 145.5 (C-5 pyrazol), 136.7, 128.8, 127.7, 126.8, 119.9 118.7 (benzotriazol carbons), 132.2, 129.9, 128.4, 126.9 (phenyl carbons) and 94.5 (C-4 pyrazol) and 74.4 (CH). MS [EI, 70eV]: m/z = [M\(^+\)] (375 : 33.2%); Anal. Calcd for C\(_{19}\)H\(_{13}\)N\(_7\)O\(_3\): C, 57.59; H, 3.49; N, 26.12 Found: C 57.36; H, 3.35; N, 26.39.

5-Benzotriazol-1-y1-2-[(thieno[3,4;3',4']benzo[b]pyran-4-one)-3-ylamino]-thiazoline-4-one (20):

Compound 19 was obtained as pale orange crystals from ethanol; mp 286°C; (85%) IR: \( V_{\text{max}} \) (KBr) 3260(NH), 3090(CH aromatic), 2950(CH aliphatic) 1701(C=O) and 1674 cm\(^{-1}\) (C=O ring). \(^1\)H NMR DMSO-d\(_6\): 11.45(s, 1H, NH), 7.80 (s, 1H, thiienyl), 7.32-8.08 (m, 8H, Ar-H) and 5.97 (s, 1H, CH). \(^1\)C NMR (400 MHz DMSO-d\(_6\)): 174.9 (C=O), 166.7 (thiazolone C-2), 158.2 (C=O ring), 156.6, 148.5, 145.5, 132.7,
131.1, 124.5, 119.8, 111.4 (coumarin carbons), 150.1 (thineyl C-3), 134.4 128.3, 125.3, 124.7, 117.5, 117.4, (benzotriazol carbons), 108.28 (thineyl C-1) and 71,88 (CH). Anal. Calcd for C_{20}H_{11}N_{5}O_{3}S_{2}: C, 55.42; H, 2.56; N, 16.16 Found: C 55.36; H, 2.35; N, 16.32.

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**References**