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Functionally Substituted Alkylbenzotriazoles: Reactivity of Alkylbenzotriazoles Toward Electrophilic and Nucleophilic Reagents

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ABSTRACT: *The reactivity of benzotriazolylacetone toward a variety of carbon and nitrogen electrophiles is reported. Several novel azolylbenzotriazoles as well as benzotriazolyl-cinnolines have been synthesized.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:141–145, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10009

INTRODUCTION

The observation that alkyl functions attached to a benzotriazole ring nitrogen activate the ring toward electrophiles has stimulated considerable interest in the chemistry of functionally substituted alkylbenzotriazoles in recent years [1–3]. In a previous paper, we have shown that the methylene function in benzotriazolylacetone is reactive toward aromatic diazonium salts [4], and that this reaction could be utilized for synthesis of, otherwise not readably obtainable, benzotriazolylpyridazines and benzotriazolylphthalazines.

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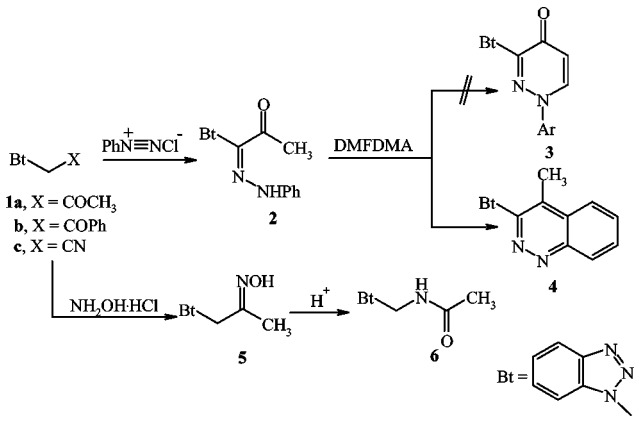
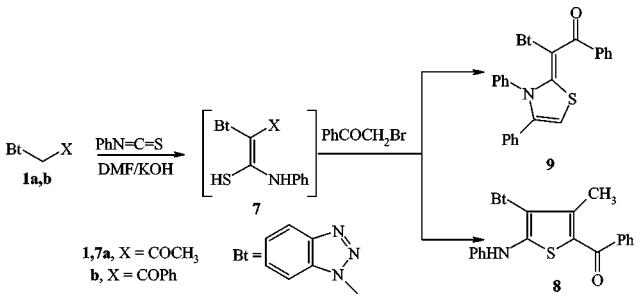
RESULTS AND DISCUSSION

In conjunction with this work, we here report further on the reactivity of alkylbenzotriazoles toward nitrogen and carbon electrophiles. Thus, as described earlier [4], benzotriazolylacetone **1a** coupled with benzenediazonium chloride in a Japp–Kilingemann type of reaction to yield the corresponding phenylhydrazone **2**. Attempted conversion of compound **2** into the pyridazine **3** by treatment with dimethylformamide dimethylacetal (DMFDMA) in refluxing xylene, as reported earlier for methyl 2-arylhydrazono-3-oxopentanoate [5], resulted in cyclization of compound **2** to the cinnoline **4**. Compound **4** could also be formed by refluxing **2** in xylene. Similar thermal cyclizations of 2-arylhydrazonopropanals into cinnolines have recently been reported from our laboratories [6]. Compound **1a** also reacted with hydroxylamine hydrochloride to yield a product that may be formulated as the oxime **5** or its Beckmann rearrangement product **6**. Structure **6** was established for the reaction product, based on its identity with an authentic specimen [7].

The reactivity of benzotriazolylacetone **1a** toward a variety of carbon electrophiles has also been investigated with the aim of preparing novel

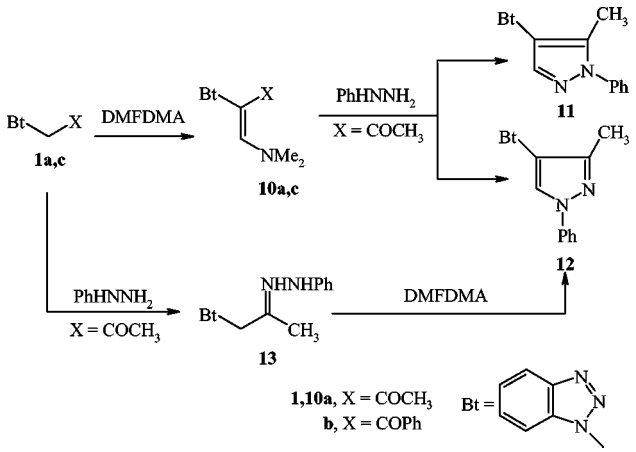


functionally substituted heteroaromatics. Thus treatment of **1a** with phenyl isothiocyanate in DMF solution in the presence of potassium hydroxide and subsequent treatment of the formed adduct **7** in situ with phenacyl bromide afforded the benzoylthiophene derivative **8**. Alternate reaction of benzotriazolylacetophenone **1b** with phenyl isothiocyanate, followed by treatment with phenacyl bromide afforded the thiazole derivative **9** as both ^{1}H-NMR and IR indicated the absence of an NH function, which should be present in the possibly formed thiophene derivative, as in the case of the reaction of benzotriazolylacetone **1a** with phenyl isothiocyanate and phenacyl bromide (Tables 1 and 2). This demonstrates the dependence of the course of this reaction on the nature of the substituent adjacent to the carbonyl moiety. Similar cyclizations of 2-mercapto 2-aminoketones into thiophenes and thiazoles have been reported earlier [8].



Compound **1a** condensed with dimethylformamide dimethylacetal in refluxing xylene to yield the enaminone **10a**. This reacted with phenylhydrazine to yield a pyrazole derivative that may be formulated as **11** or **12**. In order to establish the structure of this product, compound **1a** was condensed with phenylhydrazine, with subsequent treatment of the formed hydrazone **13** with dimethylformamide dimethylacetal. The product of this sequence of reactions proved to be different from that of the reaction of **10a** with phenylhydrazine. It can thus be stated that the reaction of **10a** with phenylhydrazine proceeded by initial addition of the unsubstituted hydrazine nitrogen to the activated double bond and subsequent cyclization of the formed adduct to afford the pyrazole **11**, whereas compound **12** arose by the alternate route, i.e condensation of **13** with dimethylformamide dimethylacetal.

Benzotriazolylacetonitrile has also been prepared and the reactivity of the methylene group toward nitrogen and carbon electrophiles has been investigated. Under a variety of conditions, compound **1c** failed to couple with aromatic diazonium salts; however, it condensed readily with dimethylformamide dimethylacetal to yield the enaminone **10c**.



Compound **1a** also reacted with hippuric acid in refluxing acetic anhydride to yield the pyranone **17** which is an extension of the Kepe-2H-pyranone synthesis [9], that enables the synthesis of pyranylbenzotriazoles. The formation of **17** is assumed to proceed by initial cyclization of hippuric acid into the oxazolone **14**, which then condenses with dimethylformamide dimethylacetal to yield **15**. Compound **15** then reacted with **1a** to yield **16** which rearranged into **17**.

Compound **10a** also reacted with an excess of hydroxylamine hydrochloride to yield the aminoisoxazolyl derivative **20**, which is assumed to proceed by reaction of the enaminone with two molecules of hydroxylamine hydrochloride, affording the dioxime **18**, that then loses a molecule of water to afford the α-cyano oxime **19**, followed by spontaneous cyclization to the aminoisoxazole. Alternatively, one may assume that hydroxylamine hydrochloride reacted with the enaminone, yielding the 3-unsubstituted 5-methylpyrazole derivative that, under basic reaction conditions, underwent ring cleavage to form the α-cyano ketone.

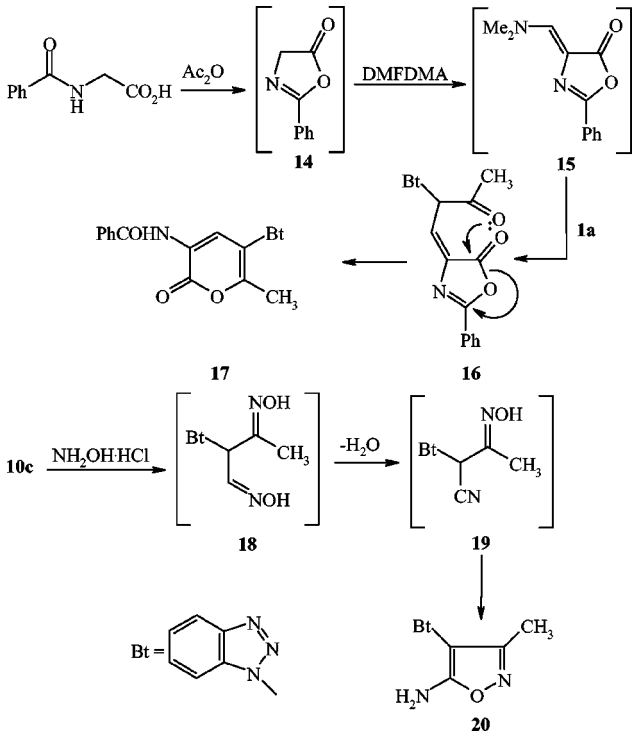
TABLE 1 Characterization Data of the Newly Synthesized Compounds

Compound No.	*mp (°C)*[a]	*Yield %*	*Mol. Formula*	*% Analysis*[b]			
				C	*H*	*N*	*S*
4	120	80	$C_{15}H_{11}N_5$	68.95 (68.71)	4.24 (4.27)	26.81 (26.65)	
6	200	68	$C_9H_{10}N_4O$	56.83 (56.64)	5.30 (5.36)	29.46 (29.67)	
8	252	82	$C_{24}H_{18}N_4OS$	70.23 (70.29)	4.42 (4.43)	13.65 (13.75)	7.33 (7.35)
9	215	85	$C_{29}H_{20}N_4OS$	73.72 (73.80)	4.27 (4.36)	11.86 (11.68)	6.77 (6.56)
10a	143	74	$C_{12}H_{14}N_4O$	62.59 (62.61)	6.13 (6.17)	24.33 (24.28)	
10c	135	85	$C_{11}H_{11}N_5$	61.95 (61.83)	5.20 (5.20)	32.85 (32.78)	
11	186	74	$C_{16}H_{13}N_5$	69.80 (69.87)	4.76 (4.78)	25.44 (25.23)	
12	180	70	$C_{16}H_{13}N_5$	69.80 (69.91)	4.76 (4.79)	25.44 (25.28)	
13	85	85	$C_{15}H_{15}N_5$	67.90 (67.86)	5.70 (5.71)	26.40 (26.47)	
17	196	90	$C_{19}H_{14}N_4O_3$	65.89 (65.68)	4.07 (4.9)	16.18 (16.29)	
20	102	68	$C_{10}H_9N_5O$	55.81 (55.72)	4.22 (4.26)	32.54 (32.63)	

[a]Solvent used: EtoH.
[b]Values indicate calculated and found (in parentheses) values, respectively.

TABLE 2 Spectral Data of the Newly Synthesized Compounds

Compound No.	ν_{max} *(cm^{-1})*	δ_H	*m/z*
4		2.65 (s, 3H, CH_3), 6.99–7.02 (m, 1H, arom. H), 7.48–7.83 (m, 5H, arom. H), 8.09–8.21 (m, 1H, arom. H), 9.10 (d, 1H, $J = 8$ Hz, arom. H)	261
6	3310 (NH), 1644 (CO)	1.73 (s, 3H, CH_3), 5.49 (s, 2H, CH_2), 7.39–7.43 (m, 1H, arom. H), 7.54–7.58 (m, 1H, arom. H), 7.78 (d, 1H, $J = 8$ Hz, arom. H). 8.05 (d, 1H, $J = 8$ Hz, arom. H), 11.02 (s, 1H, NH); ^{13}C NMR $\delta = 173.4$ (CO), 145.7, 134.1, 127.8, 123.9, 119.7, 109.2 (benzotriazolyl-C), 44.4 (CH_2), 21.6 (CH_3)	190
8	3053 (NH), 1586 (CO)	1.58 (s, 3H, CH_3), 6.29–6.42 (m, 2H, arom. H), 6.82–6.92 (m, 2H, arom. H), 7.05–7.15 (m, 4H, arom. H), 7.16–7.69 (m, 6H, arom. H), 10.35 (s, 1H, NH)	410
9	1603 (CO)	6.74–6.83 (m, 4H, arom. H), 7.01–7.45 (m, 15H, arom. H), 7.82 (s, 1H, thiazol-H)	472
10a	1682 (CO)	2.32 (s, 3H, CH_3), 3.30 (s, 3H.NCH_3), 3.32 (s, 3H, NCH_3), 7.31–7.54 (m, 2H, arom. H), 7.77–7.89 (m, 2H, arom. H), 8.30 (s, 1H, CH)	230
10c	2201 (CN)	3.28 (s, 3H, NCH_3), 3.30 (s, 3H,NCH_3), 7.24–7.47 (m, 2H, arom. H), 7.78–7.89 (m, 2H, arom. H), 8.27 (s, 1H,CH)	243
11		2.30 (s, 3H, CH_3), 7.52–7.78 (m, 9H, arom. H), 8.22 (s, 1H, 3-H)	275
12		2.30 (s, 3H, CH_3), 7.57–7.80 (m, 9H, arom. H), 8.27 (s, 1H, 5-H)	265
13	3359 (NH)	1.84 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 6.70–6.73 (m, 1H, arom. H), 6.94–7.16 (m, 4H, arom. H), 7.39–7.44 (m, 1H, arom. H), 7.53–7.58 (m, 1H, arom. H), 7.79–7.82 (m, 1H, arom. H), 8.07–8.10 (m, 1H, arom. H), 9.10 (s, 1H.NH). 9.18 (s, 1H.NH)	275
17	3346 (NH), 1731 (CO)	2.12 (s, 3H, CH_3), 7.51–7.88 (m, 9H, arom. H), 8.24 (s, 1H, H-4), 9.81 (s, 1H, NH)	346
20	3438, 3328 (NH_2)	2.27 (s, 3H, CH_3), 7.43 (t, 1H, $J = 8$ Hz, benzotriazolyl-H), 7.56 (t, 1H, $J = 8$ Hz, benzotriazolyl-H), 7.58–7.79 (m, 3H, NH_2, benzotriazolyl-H), 8.05 (d, 1H, $J = 8$ Hz, benzotriazolyl-H)	215



This, then reacted with another molecule of hydroxylamine hydrochloride to yield the final isolable aminoisoxazole. This latter reaction sequence seems to be the least likely one, as pyridine is a rather weak base and all reported isoxazole ring-cleavage reactions have been effected with alkali or alkali-metal salts. To our knowledge, this is the first reported formation of an aminoisoxazole from an enaminone.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr with a PyeUnicam SP 1100 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-3 90 spectrometer in [$^2H_6$] DMSO as solvent and TMS as an internal standard; chemical shifts are reported in δ units (ppm). Microanalyses were performed on a LECO CHNS-932 instrument. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University. Compounds **1a–c** and **2** were prepared by following the literature procedures [1,2] and [4], respectively.

*3-(Benzotriazol-l-yl)-4-methylcinnolme (**4**)*

A solution of compound **2a** (2.79 g, 10 mmol) in xylene(30 ml) in the presence of a few drops of piperidine, was refluxed for 1 h. The solvent was removed and the residue, when cooled, deposited a solid, which was then crystallized from ethanol (cf. Tables 1 and 2).

*N-(Methylenbenzotriazol-l-yl)acetamide (**6**)*

To a stirred suspension of compound **1a** (1.75 g, 10 mmol) in acetic acid (10 ml), hydroxylamine hydrochloride (0.69 g, 10 mmol) was added. The reaction mixture was heated under reflux for 20 min. The solvent was removed and the residue when cooled, deposited a solid, which was crystallized from ethanol (cf. Tables 1 and 2).

*3-(Benzotriazol-l-yl)-5-benzoyl-4-methyl-2-(N-phenylamine) Thiophene (**8**)*

To a stirred suspension of compound **1a** (1.75 g, 10 mmol) and potassium hydroxide (0.06 g) in DMF (20 ml), phenyl isothiocyanate (1.35 g, 10 mmol) was added. 2-Bromoacetophenone (1.99 g, 10 mmol) was then added to the stirred solution after 15 h, and the reaction mixture was heated under reflux for 4 h. The solvent was removed and the residue, when cooled, deposited a solid, which was crystallized from ethanol (cf. Tables 1 and 2).

*2-[1′-(Benzotriazol-l-yl)-1′-benzoylmethylidene]-4-phenyl-N-phenylthiazole (**9**)*

Similar reaction conditions were employed as for compound **8** but using compound **1b** (2.37 g, 10 mmol). The target product **9** was crystallized from ethanol as yellow crystals.

General Procedure for the Preparation of Compounds **10a,c**

To a suspension of each of compounds **1a,c** (10 mmol) in xylene (20 ml), dimethylformamide dimethylacetal (1.19 g, 10 mmol) was added. The reaction mixture was heated under reflux for 6 h. The solvent was removed and the residue, when cooled, deposited a solid, which was crystallized from ethanol (cf. Tables 1 and 2).

*4-(Benzotriazol-l-yl)-5-methyl-1-phenylpyrazole (**11**)*

A mixture of compound **10a** (2.30 g, l0 mmol) and phenylhydrazine (1.08 g, 10 mmol) in ethanol (20 ml) was heated under reflux for 1 h. The solvent was removed and the residue, when cooled deposited a solid, which was crystallized from ethanol.

*1-(Benzotriazol-l-yl)-2-phenylhydrazonopropane (**13**)*

A mixture of compound **1a** (1.75 g, 10 mmol) and phenylhydrazine (1.08 g, 10 mmol) in ethanol (20 ml)

was heated under reflux for 1 h. The solvent was removed and the residue, when cooled, deposited a solid, which was crystallized from ethanol.

*4-(Benzotriazol-l-yl)-3-methyl-l-phenylpyrazole (**12**)*

Similar reaction conditions were employed as for compound **11** but using compound **13** (2.65 g, 10 mmol). The target product **12** was crystallized from ethanol to give yellow crystals.

*5-(Benzotriazol-l-yl)-3-benzoylamino-6-methyl-2H-pyrane-2-one (**17**)*

A solution of **1a** (1.75 g, 10 mmol) and hippuric acid (1.79 g, 10 mmol) in acetic anhydride was heated under reflux for 2 h. The reaction mixture was concentrated in vacuo. The solid product obtained upon cooling was filtered off and recrystallized from ethanol.

*5-Ammo-4-(benzotriazol-l-yl)-3-methyl-isoxazole (**20**)*

A mixture of compound **10a** (2.30 g, 10 mmol) and hydroxylamine hydrochloride (0.69 g, 10 mmol) in pyridine (20 ml) was heated under reflux for 2 h. The solvent was removed and the residue was diluted with ethanol, neutralized with dilute HC1, and when cooled, a solid was deposited. This solid was crystallized from dioxane (cf. Tables 1 and 2).

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