Studies with Functionally Substituted Methylbenzotriazoles: Novel Synthesis of Functionally Substituted Pyrazolo[5,1-c]-1,2,4-Triazines Benzotriazol-1-yl, 1-Pyrazol-4-yl Benzotriazoles and 1-Isoxazol-4-yl Benzotriazoles

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1-Benzotriazolylacetophenone **1** couples with aromatic diazonium salts to yield the corresponding coupling products **2**. Reaction of **1** with diazotized aminopyrazole afforded the benzotriazolylpyrazolo[5,1-c][1,2,4]triazine **6**. Compound **1** condensed with DMFDMA to yield the enaminone **7** which reacted with hydrazines to yield the pyrazoles **8a,b**. Isomeric pyrazoles **10** were synthesized via condensing **1** with phenylhydrazine and subsequent condensation of the formed phenylhydrazone **9** with DMFDMA. Reaction of **7** with hydroxylamine afforded the isoxazole **11** which was converted into the nitrile **13** on reflux in dioxane in the presence of sodium hydride. Compound **13** was also directly obtained from reaction of **1** with 1-cyanobenzotriazole. The reaction of **1** with hippuric acid and arylidenemalononitriles **18a-c** afforded the pyranone **17** and pyridine derivatives **23a-c**, respectively.

Keywords: Benzotriazol; Enaminone; Arylidinemalononitrile; Pyranone; Hippuric acid; Isoxazole.

INTRODUCTION

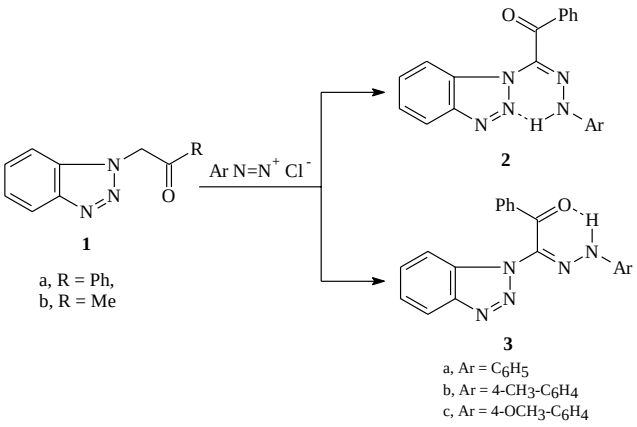
N-Functionally substituted methylbenzotriazoles can afford stabilized carbaniones under relatively mild basic conditions.[1-4] This phenomena has recently been extensively utilized by Katritzky et al. in synthetic heterocyclic chemistry.[5-7] Some time ago Katritzky et al. reported the synthesis of **1a** and described some of its reactions with electrophilic reagents.[8,9] In conjunction with our interest in developing synthesis of polyfunctionally substituted heteroaromatics as potential pharmaceuticals, agrochemicals, or dye intermediates, we have recently reported on the reactivity of **1b** towards aromatic diazonium salts.[10-12] In continuation of this work we report here on the reactivity of **1a** towards aromatic and heteroaromatic diazonium salts as well as reactivity of **1a** towards some carbon electrophiles.

RESULTS AND DISCUSSION

It has been found that **1a** couples readily with aromatic diazonium salts to yield the corresponding arylhydrazones. Although this product can exist as two forms, E form **3** or Z form **2**, only one form has been detected in ^{1}H NMR.

This is most likely form **2** as the hydrogen nitrogen bond is believed to be stronger than the oxygen hydrogen bond. Moreover, recent X-rays of similar systems have established preference for the H–N bond over the H–O bond.

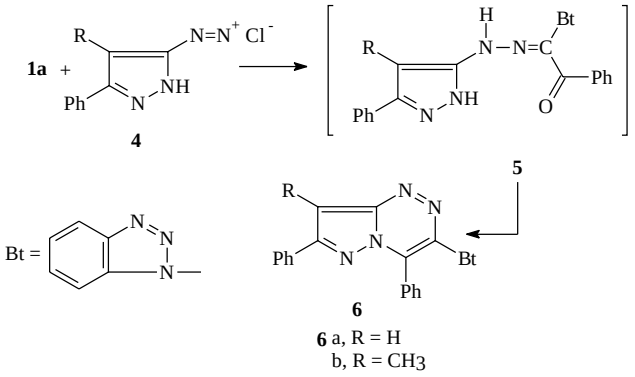
Scheme I



Compound **1a** also coupled with the diazotized aminopyrazole **4** to yield the pyrazolo[5,1-c][1,2,4]triazine derivative **6** which is believed to be formed via intermediates of the hydrazone **5** which cyclizes spontaneously under coupling reaction conditions.

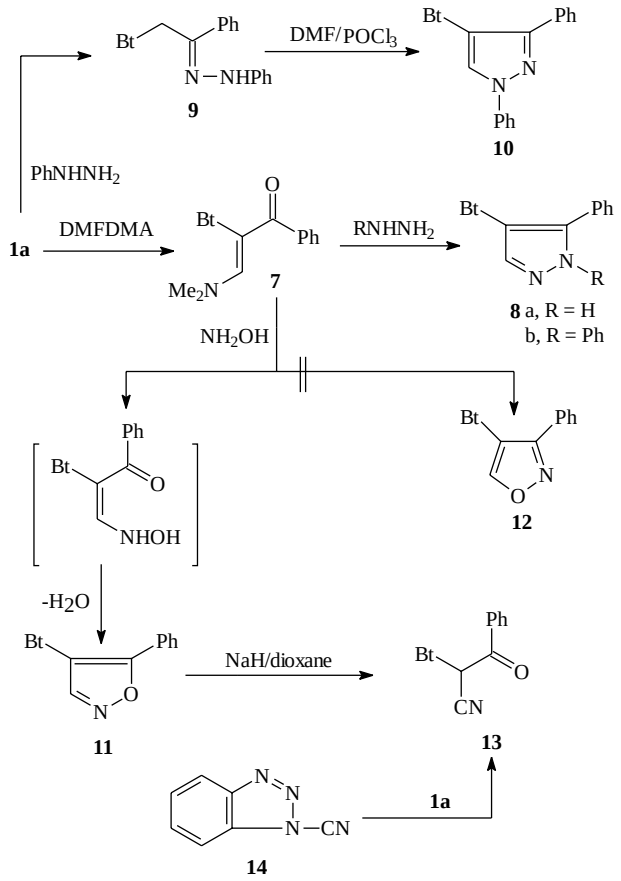
Condensation of **1a** with DMFDMA in refluxing xylene afforded the enaminone **7**. This reacted with hydra-

Scheme II



zine hydrate and phenylhydrazine to yield pyrazole derivatives which may be formulated as **8b** or isomeric **10**. Structure **8** could be established for this reaction product based on its non-identity with a sample of **10** prepared via condensing **1a** with phenylhydrazine to form phenylhydrazone **9** and subsequent reaction with DMFDMA.

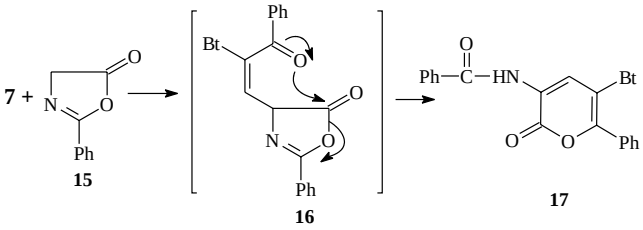
Scheme III



Compound **7** also reacted with hydroxylamine to yield an isoxazole derivative which may be formulated as **11** or isomeric **12**. Again, structure **11** could be established for the reaction product via its conversion into the nitrile derivative **13** on reflux in dioxane solution in the presence of sodium hydride. Compound **13** could be also obtained via direct cyanation of **1a** with N-cyanobenzotriazole **14**[13] (Scheme III).

Compound **7** also reacted with hippuric acid to yield the pyranone **17** which is an extension of the Kepe-2H-pyranone synthesis,[14] that enables the synthesis of pyranylbenzotriazoles. This is believed to be formed via the condensing of **7** with **15** to yield **16** that isomerized into **17** under reaction conditions. Similar pyranone synthesis has been reported recently by us.[15]

Scheme IV

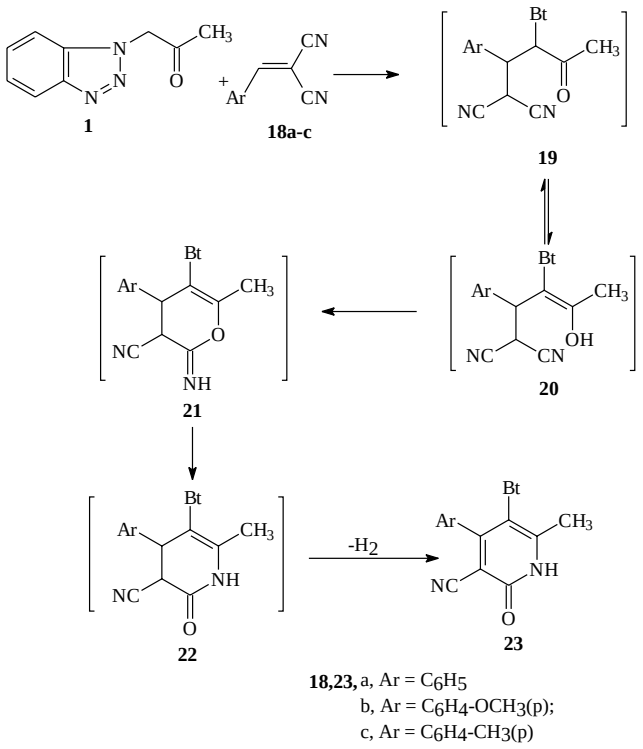


Compound **1b**[4] reacted with arylidenemalononitrile **18a-c** in refluxing ethanol in the presence of a catalytic amount of triethylamine to yield products that could be formulated as **23**. The formation of **23** is assumed to proceed via initial addition of the active methylene of **1b** to a double bond of **18** yielding the intermediate Michael adduct **19** or **20** which then cyclized into **21** and undergoes Dimorth type rearrangement to yield **22** which aromatizes via loss of hydrogen molecule to yield the final isolable product **23**.[17,18] (Scheme V).

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded with a FTIR-8201 PC spectrophotometer from Shimadzu. ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz spectrometer in DMSO-d_6 as solvent and TMS as an internal reference. Mass spectra were performed on a Shimadzu GCMS-QP-1000 EX using the direct inlet system and EI + QI MSLMRUPLR. Micro-analyses were performed by the Microanalytical Unit at Cairo University. Thin Layer chromatography was carried out on a 5 × 20 cm plate coated with

Scheme V



silica gel GF 254 type 60, mesh size 50-250. (Benzotriazol-1-yl)acetophenone **1a** was prepared according to the lit.,[9] and 1-cyanobenzotriazole **(14)** was prepared according to the lit.[13]

1-(Benzotriazol-1′-yl)-1-[arylhydrazono]acetophenone (3a-c)

General Procedure

A solution of the appropriate aryldiazonium chloride (0.005 mol) was added portionwise to a cold solution of **1** in ethanol (50 mL) in the presence of sodium acetate trihydrate (6 g) with stirring. After the addition was complete, the mixture was stirred at 0-5 °C for a further 4 h. The solid product that formed was collected, washed with water, dried, and recrystallized from ethanol.

1-(Benzotriazol-1′-yl)-1-[phenylhydrazone]acetophenone (3a)

mp 208°; IR: 3222 (NH), 1706 (CO), 1625 (C=N); ^{1}H NMR (DMSO-d_6): δ = 7.1-8.22 (m, 14H, H-Ar); 11.9 (br, 1H, NH); MS: *m/z* = 341 (M^+, 2.9%), 313 ($M^+ - N_2$, 16.4%). Anal. Calcd. for $C_{20}H_{15}N_5O$: C, 70.38; H, 4.39; N, 20.52%. Found C, 70.40; H, 4.40; N, 20.60.

1-(Benzotriazol-1′-yl)-1-[4-methylphenylhydrazone]acetophenone (3b)

mp 184°; IR: 3228 (NH), 1696 (CO), 1628 (C=N); ^{1}H NMR (DMSO-d_6): δ = 1.35 (s, 3H, CH_3), 7.01-8.13 (m, 13H, H-Ar), 12.1 (s, 1H, NH); MS: *m/z* = 355 (M^+, 18%). Anal. Calcd. for $C_{21}H_{17}N_5O$: C, 70.98; H, 4.78; N, 19.70. Found C, 71.10; H, 4.60; N, 20.10.

1-(Benzotriazol-1′-yl)-1-[4-methoxyphenylhydrazone]-acetophenone (3c)

mp 179°; IR: 3220 (NH), 1685 (CO); ^{1}H NMR (DMSO-d_6): δ = 3.51 (s, 3H, CH_3), 7.03-8.21 (m, 13H, H-Ar), 11.1 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{17}N_5O_2$: C, 67.92; H, 4.58; N, 18.86. Found C, 67.90; H, 4.50; N, 19.0.

Pyrazolo[5,1-c][1,2,4]triazine derivatives (6a,b)

A solution of diazotized heterocyclic amines [prepared from (0.01 mol) of heterocyclic amine and the appropriate quantities of concentrated hydrochloric acid and sodium nitrite as has been previously described[16] was added with stirring to a cold solution of **1a** (0.01 mol) in ethanol (150 mL) and sodium acetate (5 g). The solid products so formed were collected by filtration and recrystallized from ethanol.

2-(Benzotriazol-1′-yl)-1,6-diphenylpyrazolo[5,1-*c*][1,2,4]-triazine (6a)

mp 216°; IR: 3050 (CH-Ar), 1615 (C=N); ^{1}H NMR (DMSO-d_6): δ = 6.5 (s, 1H, 4H pyrazole), 7.03 (m, 14H, H-Ar); MS: *m/z* = 389 (M^+, 23%). Anal. Calcd. for $C_{23}H_{15}N_7$: C, 70.95; H, 3.85; N, 25.19. Found C, 70.70; H, 4.00; N, 25.50.

2-(Benzotriazol-1′-yl)-5-methyl-1,6-diphenylpyrazolo[5,1-*c*][1,2,4]triazine (6b)

mp 226°; IR: 3047 (CH-Ar), 1606 (C=N); ^{1}H NMR (DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 7.36-8.14 (m, 14H, H-Ar); MS: *m/z* = 403 (M^+, 27%), 375 ($M^+ - N_2$, 10.4%). Anal. Calcd. for $C_{24}H_{17}N_7$: C, 71.34; H, 4.24; N, 24.42. Found C, 71.30; H, 4.30; N, 24.30.

2-(Benzotriazolo-1′-yl)-1-phenyl-3-dimethylaminoprop-2-en-1-one (7)

Equimolar amounts (0.01 mol) of **1** and N,N-dimethylformamide-dimethylacetal in dry toluene (30 mL) was heated under reflux for 5 h. The solvent was removed in vacuo and the formed solid product was collected by filtration and recrystallized from methanol to give a colorless product. mp 139-141°; IR: 2983 (CH-aliphatic), 1641 (CO); MS: *m/z* =

292 (M^+, 35%). Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.75; H, 5.51; N, 19.17. Found C, 69.80; H, 5.30; N, 19.80.

1-(Substituted pyrazol-4′-yl)benzotriazole 8a,b

A mixture of enamine **7** (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) in (30 mL) ethanol was refluxed for 4 h, then left to cool. The solid product so formed was collected by filtration and recrystallized from ethanol.

1-(3′-Phenylpyrazole-4′-yl)benzotriazole (8a)

mp 169-70 °C; IR: 3280 (NH), 3035 (CH-Ar); ^{1}H NMR (DMSO-d_6): δ = 7.23-8.20 (m, 10H, H-Ar + H-3 pyrazole), 9.95 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{11}N_5$: C, 68.96; H, 4.21; N, 26.81. Found C, 68.90; H, 4.20; N, 26.90.

1-(2′,3′-Diphenylpyrazole-4′-yl)benzotriazole (8b)

mp 180-2 °C; IR: 3055 (CH-Ar); ^{1}H NMR (DMSO-d_6): δ = 7.36-8.20 (m, 15H, H-Ar + H-3 pyrazole). MS: *m/z* = 337 (M^+, 3.5%), 304 ($M^+ - N_2$, 46.4%). Anal. Calcd. for $C_{21}H_{15}N_5$: C, 74.70; H, 4.47; N, 20.82. Found C, 74.80; H, 4.50; N, 21.10.

2-(Benzotriazole-1′-yl)-1-phenyl-1-(phenylhydrazone)ethane (9)

A mixture of compound **1** (0.01 mol) and phenylhydrazine (0.01 mol) in (30 mL) ethanol and acetic acid (1 mL) was refluxed for 4 h, then left to cool and poured into cold water. The solid so formed was collected by filtration and recrystallized from ethanol to yield pale yellow crystals in 80% yield, mp. 139 °C; IR: 3301 (NH), 3050 (CH-Ar). MS: *m/z* = 327 (M^+, 23%). Anal. Calcd. for $C_{20}H_{17}N_5$: C, 73.39; H, 5.19; N, 21.40. Found C, 73.40; H, 5.20; N, 21.60.

1-(1,3-Diphenylpyrazole-4-yl)benzotriazole (10)

To a suspension of compound **9** (0.01 mol) in dry xylene (20 mL), dimethylformamidedimethylacetal (0.011 mol) was added. The reaction mixture was heated under reflux for 6 hr; the solvent was removed under reduced pressure. The resulting solid was filtered off and recrystallized from ethanol to give **10** as orange crystals, mp 123 °C; IR: 3035 (CH-Ar), 1625 (C=N); ^{1}H NMR (DMSO-d_6): δ = 7.24-8.31 (m, 15H, 14H, H-Ar + H-5 pyrazole); MS: *m/z* = 337 (M^+, 13%), 309 (M^+-N_2, 38%). Anal. Calcd. for $C_{21}H_{15}N_5$: C, 74.77; H, 4.45; N, 20.77. Found C, 74.90; H, 4.60; N, 20.70.

1-(5-Phenylisoxazole-4-yl)benzotriazole (11)

To a solution of **1a** (0.01 mol) in ethanol in the presence of sodium acetate (0.015 mol) was added (0.01 mol) of hydroxylamine hydrochloride. The reaction mixture was refluxed for 10 h and left to cool at room temperature; the solid product so formed was collected by filtration and recrystallized from ethanol as colorless crystals in 71% yield; mp 186-8 °C; IR: 3050 (CH-Ar), 1625 (C=N); ^{1}H NMR (DMSO-d_6): δ = 7.20-7.89 (m, 9H, H-Ar), 8.43 (s, 1H, H-3 isoxazine); MS: *m/z* = 262 (M^+, 18%), 234 ($M^+ - N_2$, 30%). Anal. Calcd. for $C_{15}H_{10}N_4O$: C, 68.63; H, 3.84; N, 21.42. Found C, 68.50; H, 3.90; N, 22.20.

1-(Benzotriazole-1′-yl)cyanoacetophenone (13)

Method A

A mixture of **11** (0.01 mol) and sodium hydride (0.01 mol) in dioxane was heated under reflux for 8 h; the reaction mixture was left to cool, then poured onto ice water and neutralized by HCl; the solid product so formed was collected by filtration and recrystallization from EtOH to yield a colorless crystals in (48% yield).

Method B

Compound **13** was obtained from reaction of **14** (0.01 mol) with **1a** (0.01 mol) according to Hughes et al.[13] The obtained product (60% yield) was confirmed by mp, mixed mp and spectral data in comparison with an authentic sample from method A. mp 158-160 °C; IR: 2218 (CN), 1678 (C=O); Anal. Calcd. for $C_{15}H_{10}N_4O$: C, 68.70; H, 3.81; N, 21.37. Found C, 68.90; H, 3.91; N, 21.40.

5-(Benzotriazole-1-yl)-3-benzoylamino-6-phenyl-2*H*-pyran-2-one (17)

A solution of **7** (0.01 mol) and hippuric acid (0.01 mol) in acetic anhydride was heated under reflux for 2 h. The reaction mixture was concentrated under reduced pressure. The formed solid product was filtered off and crystallized from EtOH to yield colorless crystals, mp 212-3 °C; IR: 3300 (NH), 1710 (C=O); ^{1}H NMR (DMSO-d_6): δ = 7.31-7.89 (m, 14H, H-Ar), 8.41 (s, 1H, H4-pyrane), 9.98 (s, 1H, NH); MS: *m/z* = 408 (M^+, 18%); Anal. Calcd. for $C_{24}H_{16}N_4O_3$: C, 70.54; H, 3.94; N, 13.76. Found C, 70.40; H, 3.90; N, 14.00.

3-(Benzotriazole-1-yl)-1H-6-oxo-2-methyl-4-arylpyridine-5-carbonitrile (23a-c)

General Procedure

A mixture of **1b** (0.01 mol) and arylidenemalononitriles **18a-c** in absolute ethanol (30 mL) containing triethylemine (5 drops) was boiled under reflux for 4 h. The reaction mixture was left to cool, poured onto cold water and neutralized by dilute hydrochloric acid. The formed solid product was filtered off and recrystallized from EtOH:DMF mixture.

3-(Benzotriazole-1-yl)-1*H*-2-methyl-6-oxo-4-phenylpyridine-5-carbonitrile (23a)

mp 304-306 °C; IR: 3259 (NH), 2222 (CN), 1739 (C=O); ^{1}H NMR (DMSO-d_6): δ = 1.98 (s, 3H, CH_3), 7.12-8.31 (m, 9H, H-Ar), 11.3 (s, 1H, NH); MS: *m/z* = 389 (M^+, 9.5%). Anal. Calcd. for $C_{19}H_{13}N_5O$: C, 69.72; H, 3.97; N, 21.40. Found C, 70.00; H, 3.90; N, 21.60.

3-(Benzotriazole-1-yl)-1*H*-2-methyl-4-(p-methoxyphenyl)-6-oxo-pyridine-5-carbonitrile (23b)

mp 290 °C; IR: 3213 (NH), 2221 (CN), 1739 (C=O); ^{1}H NMR (DMSO-d_6): δ = 1.93 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 7.13-8.19 (m, 8H, H-Ar), 13.98 (s, 1H, NH); MS: *m/z* = 357 (M^+, 6.6%), 391 (M^+-N_2, 44.9%). Anal. Calcd. for $C_{20}H_{15}N_5O_2$: C, 67.22; H, 4.20; N, 19.60. Found C, 67.10; H, 4.20; N, 19.80.

3-(Benzotriazole-1-yl)-1*H*-2-methyl-6-oxo-4-(p-tolyl)pyridine-5-carbonitrile (23c)

mp 320-2 °C; IR: 3260 (NH), 2219 (CN), 1725 (C=O); ^{1}H NMR (DMSO-d_6): δ = 1.23 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 7.01-8.12 (m, 8H, H-Ar), 13.01 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{15}N_5O$: C, 70.38; H, 4.39; N, 20.52. Found C, 70.10; H, 4.40; N, 20.30.

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