New Routes to 1-Functionally Substituted Arylbenzotriazoles: 3-Benzotriazol-1-yl-pyridazine-4-ones, 5-Benzotriazol-1-yl-pyridazine-6-ones and 5-Benzotriazol-1-yl-pyridazine-6-imines

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Condensation of 1-arylhydrazono-1-benzotriazol-1-yl 2-propanones (**5a-c**) with DMF DMA afforded 1-aryl-3-benzotriazol-1-yl-1,4-dihydropyridazine-4-ones (**8a-c**). While condensation of 1-functionally substituted methylbenzotriazoles **3b,c** with 2-arylhydrazono-3-oxoarylpropanal **13a,b** give 3-aroyl-5-(benzotriazolyl-1-yl)-1,6-dihydro-1-phenylpyridazine-6-ones and 6-imines **14a-d**.

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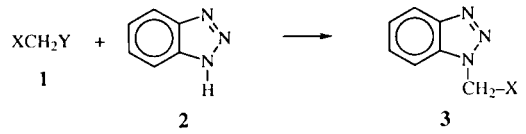
Pyridazinones comprise a very interesting class of heteroaromatic because of their significant biological and pharmaceutical properties [1-5]. As a part of our program directed towards developing new approaches to synthesising pyridazinones with substitution patterns required for a biological chemistry program [6-8], we report here a novel synthesis of several pyridazinones in which a benzotriazol ring is incorporated.

Thus the required **3a-c** were prepared from the reaction of the appropriate α-chloropropanone **1a** or haloacetic acid derivative **1b,c** with 1,2,3benzotriazol **2** in the presence of a phase transfer catalyst under conditions described earlier by Katritzky and coworkers [9,10] (Scheme 1).

Scheme 1



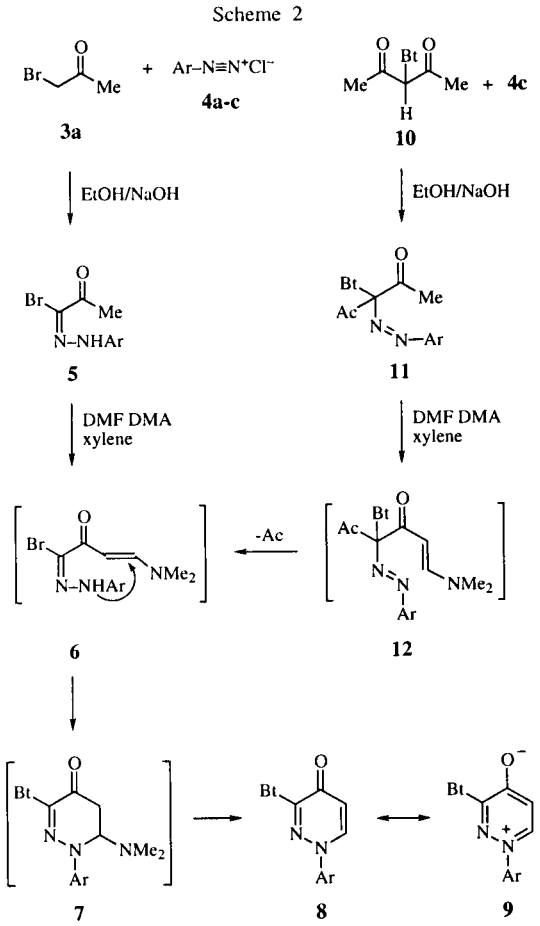
2-3: a, X = COMe, Y = Cl; b, X = CO_2Et, Y = Cl; c, X = CN, Y = Br

The compound **3a** coupled readily with aryl diazonium salts **4a-c** in ethanolic sodium hydroxide solution at room temperature to afford in each case, one isoluble product as evidenced by tlc analysis. The isolated products were identified as arylhydrazones **5a-c** (Scheme 2) in excellent yield. Both elemental analyses and spectral data were in complete agreement with assigned structures. The IR spectra of **5a-c** showed in each case, two strong absorption band near 3446 and 1670 cm^{-1} due to NH and carbonyl group. The ^1H nmr spectra revealed a hydrazone NH resonance at δ 11.00 ppm.

On the other hand, when arylhydrazones **5a-c** were treated with dimethylformamide dimethylacetal in refluxing xylene the pyridazinones **8a-c** were formed.

Formation of this product is assumed to proceed *via* initial condensation of dimethylformamide dimethylacetal with methylene function in **5** to form non-isoluble acylic intermediate **6** which readily undergoes intramolecular cyclization into **7** that subsequently aromatizes *via* the loss of dimethylamine (Scheme 2). IR spectra of this reaction product showed an absorption at 1629 cm^{-1} a low frequency value for carbonyl group. This may indicate the

Scheme 2



4-9: a, Ar = Ph; b, Ar = *p*-$MeOC_6H_4$; c, Ar = *p*-$O_2NC_6H_4$
10-12: Ar = 4-$O_2NC_6H_4$-; Bt = 1*H*-Benzotriazol-1-yl

importance in this compound of the resonance form **9**. The ^{1}H nmr revealed the pyridazinone protons as two doublets at δ 6.90 and δ 9.10 with J = 5Hz.

Condensation of the benzotriazole **2** with α-chloroacetylacetone in toluene and sodium hydride at reflux temperature to afford a yellow product, which was identified as 3-benzotriazol-1-yl-2,4-pentanedione **10**. This coupled readily with *p*-nitrophenyl diazonium chloride **4c** in ethanolic sodium hydroxide solution at room temperature to afford the corresponding 3-benzotriazol-1-yl-3-(4-nitrophenylhydrazone)-pentane-2,4-dione **11**. Both elemental analyses and spectral data are consistent with the assigned structure. Treatment of the arylhydrazone (**11**) with dimethylformamide dimethylacetal in refluxing xylene to afford a product identical in all respects (mp tlc and spectra) with that obtained previously from reaction of **5c** with dimethylformamide dimethylacetal. The formation of the compound **8c** from this reaction is believed to form *via* condensation of dimethylformamide dimethylacetal with **11** forming the non-isoluble intermediate **12**. The latter then eliminated an acyl group during the reaction yielding **6** which then underwent an intramolecular cyclization by loss of dimethylamine (Scheme 2).

Similarly, **3b** reacts with a 2-arylhydrazono-3-oxoarylpropanals **13a,b** in ethanolic potassium hydroxide solution at room temperature furnished in each case, one isoluble product as evidenced by tlc analysis. The isolated products were identified as 3-aroyl-5-(benzotriazol-1-yl)-1,6-dihyro-1-phenylpyridazine-6-one **14a,b** (Scheme 3). Both elemental analyses and spectra data were in complete agreement with the assigned structure. Similar reaction of **3c** with **13a,b** afforded 3-aroyl-5-(benzotriazol-1-yl)-1,6-dihydro-1-phenylpyridazine-6-imine (**14c,d**) in fair yield (60-75%). Much better yields for the desired products (87-88%) were obtained when the reaction was conducted in dioxane in presence of sodium hydride. Compounds **14a-d** were also obtained in almost the same yields as reported above when a mixture of benzotriazole and ethylchloroacetate or chloroacetonitrile with **13a,b** was heated in dioxan solution in presence of sodium hydride.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Shimadzu 2000 FTIR spectrometer. ^{1}H nmr and ^{13}C nmr spectra were recorded on a Bruker 80 MHz spectrometer with dimethyl-d_6 sulfoxide or deuteriochloroform as solvent and tetramethylsilane as an internal standard; chemical shifts are reported as δ units (ppm). Mass spectra were measured on GS/MS INCOL XL Finningan MAT. Microanalysis were performed on a LECO-CHNS 932 analyzer. Compounds **3a-c** and **13a,b** were prepared by the following published procedure [9-10] and [7], respectively.

General Procedure for the Synthesis of **5a-c**.

To a cold solution of **3a** (0.1 mol) in ethanol (100 ml) 20.0 g of sodium hydroxide was added. The mixture was then treated gradually with stirring at room temperature with a solution of the appropriate aryldiazonium salt (prepared from 0.1 mol of arylamine and the appropriate quantities of hydrochloric acid and sodium nitrile) as has been described earlier [11]. The product was separated on standing, collected by filtration and crystallized from ethanol.

1-Benzotriazol-1-yl-1-phenylhyrazono-2-propanone (**5a**).

This compound was obtained as brown powder in 76% yield, mp 185-186°; ir: ν 3446 (NH), 1683 cm^{-1} (CO); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.65 (s, 3H, Me), 7.12-8.25 (m, 9H, Ar-H), 11.00 ppm (br, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 189.9 (CO), 145.1 (C-3), 144.7, 142.7, 134.0, 129.3, 128.7, 125.2, 119.5, 118.5, 115.5, 110.7, (arom. Carbons), 24.8 ppm (Me).

Anal. Calcd. for $C_{15}H_{13}N_5O$: C, 64.50; H, 4.69; N, 25.07. Found: C, 64.35; H, 4.63; N, 25.06.

1-Benzotriazol-1-yl-1-(*p*-methoxyphenylhydrazono)-2-propanone (**5b**).

This compound was obtained as yellow powder in 78% yield, mp 130-131°; ir: ν 3436 (NH), 1650 cm^{-1} (CO); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.70 (s, 3H, Me); 3.77 (s, 3H, OMe), 6.88 (d, 2H, J = 9Hz, Ar-H), 7.27-7.52 (m, 6H, Ar-H), 10.44 ppm (br, 1H, NH); ms: (Cl), *m/z* 309 (M$^+$).

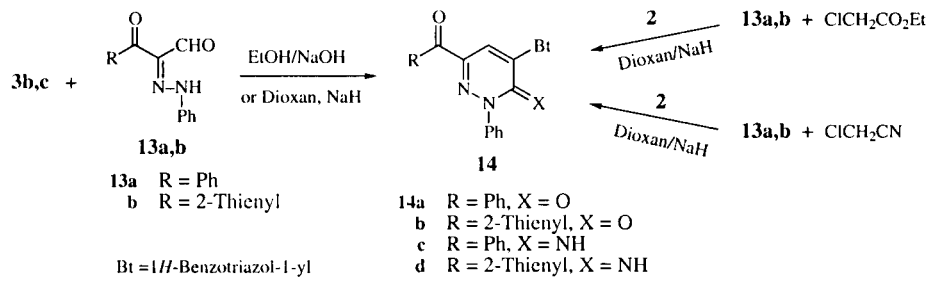
Anal. Calcd. $C_{16}H_{15}N_5O_2$: C, 62.21, H, 4.88; N, 22.64. Found: C, 62.36; H, 4.92; N, 22.35.

1-Benzotriazol-1-yl-1-(*p*-nitrophenylhydrazono)-2-propanone (**5c**).

This compound was obtained as yellow powder in 77% yield, mp 180-181°; ir: ν 3420 (NH), 1676 cm^{-1} (CO); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.72 (s, 3H, Me); 7.67 (d, 2H, J = 9Hz, Ar-H), 7.96-8.06 (m, 4H, Ar-H), 8.26 (d, 2H, J = 9Hz, Ar-H), 11.45 ppm (br, 1H, NH); ms: (CO, *m/z* 324 (M$^+$).

Anal. Calcd. for $C_{15}H_{12}N_6O_3$: C, 55.55, H, 3.73; N, 25.92. Found: C, 55.81; H, 3.90; N, 26.22.

Scheme 3



General Procedure for the Synthesis of **8a-c**.

A solution of each of **5a-c** (0.1 mol) in xylene (30 ml), was treated with dimethylformamide dimethylacetal (1.33 ml, 0.1 mol). The reaction mixture was refluxed for 7 hours, then poured into water. The solid product was collected by filtration and crystallized from a mixture of ethanol and acetic acid (1:1).

3-Benzotriazol-1-yl-1,4-dihydro-1-phenylpyridazine-4-one (**8a**).

This compound was obtained as pale yellow crystals in 83% yield, mp, 218-220°, ir: ν 1629 cm^{-1} (CO); ^1H nmr (dimethyl-d_6 sulfoxide): δ 6.98 (d, 1H, J = 5Hz, H-5), 7.52-7.78 (m, 9H, Ar-H), 9.08 (d, 1H, J = 5Hz, H-6); ms: (Cl, *m/z* 290 (M^+).

Anal. Calcd. For $C_{16}H_{11}N_5O$: C, 66.43; H, 3.83; N, 24.20. Found: C 66.70; H, 4.11; N, 24.17.

3-Benzotriazol-1-yl-1,4-dihydro-1-(*p*-methoxyphenyl)pyridazine-4-one (**8b**).

This compound was obtained as white crystals in 81% yield, mp, 290-291°, ir: ν 1629 cm^{-1} (CO); ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.82 (s, 3H, OMe); 6.96 (d, 1H, J = 5Hz, H-5), 7.07-8.15 (m, 8H, Ar-H), 8.99 (d, 1 H, J = 5Hz, H-6).

Anal. Calcd. for $C_{17}H_{13}N_5O_2$: C, 63.94; H, 4. 10; N, 21.93. Found: C, 63.97; H, 4.18; N, 21.61.

3-Benzotriazol-1-yl-1,4-dihydro-1-(*p*-nitrophenyl)pyridazine-4-one (**8c**).

This compound was obtained as brown crystals in 79% yield, mp, 328-330°, ir: ν 1648 cm-^{1} (CO); ^1H nmr (trifluoroacetic acid): δ 7.60-9.20 (m, 10H, Ar-H), ms: (Cl), *m/z* 334 (M^+).

Anal. Calcd. for $C_{16}H_{10}N_6O_3$: C, 57.43; H, 3.01; N, 25.13. Found: C, 57.38; H, 3.04, N, 25.12.

3-Benzotriazol-1-yl-2,4-pentanedione (**10**).

A suspension of benzotriazole (1.2 g, 0.01 mmol) and sodium hydride (0.5 g, 60%) in toluene (30 ml), was refluxed for 1 hour, left to cool at room temperature, then α-chloroacetylacetone (1.34 g, 10 mmol) and 0.05 g of 81 crown-6 were added. The reaction mixture was refluxed for 6 hours. The solvent was evaporated under reduced pressure and the resulting solid product, so formed was collected by filtration, and crystallized from ethanol as yellow crystals (1.17 g, 79%), mp 82-84°, ir: ν 1726.4 cm^{-1} (2CO). ^1H nmr (dimethyl-d_6 sulfoxide): 1.80 (s, 6H, Me), 5.90 (s, 1H, CH), 7.54-8.12 (m, 4H, Ar-H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_c: 196.0 (2CO), 145.4, 134.7, 129.2, 124.9, 120.0, 110.7 (arom. carbons), 58.0 (CH), 22.2 (Me), ms: (Cl, *m/z* 217 (M^+).

Anal. Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.58; H, 5.19; N, 19.33.

3-Benzotriazol-1-yl-3-(*p*-nitrophenylhydrazone)pentane-2,4-dione (**11**).

To a cold solution of **10** (0.1 mol) in ethanol (50 ml) containing 20.0 g of sodium hydroxide, *p*-nitrophenyldiazonium chloride (0.1 mol) was added. The mixture was stirred at room temperature for 1 hour. The solid product, so formed was collected by filtration and crystallized from dimethylformamide/ethanol (1:1) as yellow crystals in 73% yield, mp 118-120°; ir: ν 1732 cm^{-1} (2CO); ^1H nmr (dimethyl-d_6 sulfoxide): 2.51 (s, 6H, 2Me), 7.57-8.20 (m, 8H, Ar-H); ^{13}C nmr (dimethyl-d_6 sulfoxide); 196.9 (2CO), 156.0, 145.1, 111.3, 134.2, 130.0, 129.1, 126.1, 124.9, 119.9, 115.5, 111.3 (aromatic carbons and C-3), 25.5 (2Me); ms (Cl, *m/z* 366 (M^+).

Anal. Calcd. For $C_{17}H_{14}N_6O_4$: C, 55.73; H, 3.85; N, 22.94. Found: C, 55.45; H, 3.91; N, 23.23.

General Procedure for the Synthesis of **8c** from **11**.

A suspension of **11** (3.66 g, 10 mmol) in xylene (30 ml), was treated with dimethylformamide dimethylacetal (1.33 ml, 10 mmol). The reaction mixture was refluxed for 10 minutes, then poured into water. The solid product, so. formed was collected by filtration and crystallized from ethanol as brown crystals of 3-benzotriazol-1-yl-1,4-dihydro-1-(4-nitrophenyl)pyridazin-4-one (**8c**) in 81% yield.

General Procedure for Synthesis of 3-Aroyl-5-(benzotriazol-1-yl)-1,6-dihydro-1-phenylpyridazine-6-ones and 6-imines (**14a-d**).

Method A.

A solution of **3b,c** (10 mmol), in ethanol (30 ml) was treated with each of **13a,b** (10 mmol) and potassium hydroxide (0.2 g). The reaction mixture was stirred overnight then heated for 30 minutes. The solvent was then evaporated under reduced pressure and the product obtained was triturated with water and neutralized with hydrochloric acid (10%). The solid product, that formed, was collected by filtration and crystallized from the proper solvent to give **14a-d** in 90, 89, 60 and 75% yield, respectively.

Method B.

A suspension of **3c** (10 mmol) in dioxane (20 ml) containing sodium hydride (0.6: 65%) was treated with each of **13a,b** (10 mmol). The reaction mixture was refluxed for six hours. The solvent was evaporated under reduced pressure. The remaining product was triturated with ethanol and water and then neutralized with hydrochloric acid (10%) then with water. The solid product, so formed, was collected by filtration and crystallized from dioxane to yield **14c-d** in 87 and 88% respectively.

Method C.

A suspension of benzotriazole **2** (10 mmol) in dioxane (30 ml) containing sodium hydride (0.6 g, 60%) was treated with ethyl chloroacetate or chloroacetonitrile. The reaction mixture was then treated with each of **13a,b** (10 mmol) and refluxed for six hours then evaporated *in vacuo*. The solid product, so formed, was triturated with ethanol, neutralized with hydrochloric acid, then poured onto water. The solid product, that formed, was collected by filtration and crystallized from the proper solvent to give **14a-d** in 84, 86, 87 and 88%, yield, respectively.

5-Benzotriazol-1-yl-3-benzoyl-1,6-dihydro-1-phenylpyridazine-6-one (**14a**).

This compound was crystallized from ethanol and obtained as yellow crystals, mp 243-245° ir: ν 1678, 1647 cm^{-1} (CO). ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.43-8.44 (m, 15H, Ar-H and H-4).

Anal. Calcd. For $C_{23}H_{15}N_5O_2$: C, 70.16; H, 3.61; N, 17.75. Found: C, 69.90; H, 3.99; N, 17.30.

5-Benzotriazol-1-yl-3-(2-thienoyl)-1,6-dihydro-1-phenylpyridazine-6-one (**14b**).

This compound was crystallized from dioxane and obtained as yellow crystals, mp 287-289° ir: ν 1678, 1628 cm^{-1} (CO). ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.28-8.56 (m, 13H, Ar-H and H-4).

Anal. Calcd. for $C_{21}H_{13}N_5O_2S$: C, 63.16; H, 3.38; N, 17.53. Found: C, 63.19; H, 3.38; N, 17.50.

5-Benzotriazol-1-yl-3-benzoyl-1,6-dihydro-1-phenylpyridazine-6-imine (**14c**).

This compound was crystallized from dioxane and obtained as yellow crystals, mp 218-220° ir: ν 3447 (NH), 1641 cm^{-1} (CO). ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.10 (br, 1H, NH), 7.48-8.13 (m, 15H, Ar-H and H-4).

Anal. Calcd. for $C_{23}H_{16}ON_6$: C, 70.39; H, 4.11; N, 21.42. Found: C, 70.49; H, 4.15; N, 21.12.

5-Benzotriazol-1-yl-1,6-dihydro-3-(2-thienoyl)-1-phenylpyridazine-6-imine (**14d**).

This compound was crystallized from dioxane as yellow crystals, mp 262-263° ir: ν 3449 (NH), 1632 cm^{-1} (CO). ^1H nmr (dimethyl-d_6 sulfoxide): δ 10.33 (br, 1H, NH), 7.16-8.29 (m, 13H, Ar-H and H-4).

Anal. Calcd. For $C_{21}H_{14}OSN_6$: C, 63.31; H, 3.54; N, 21.10; S, 8.00. Found: C, 63.32; H, 3.79; N, 21.09; S, 8.14.

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REFERENCES AND NOTES

[1] T. Yamasaki, E. Kawaminami, F. Uchimura, Y. Okomota, T. Okawara, and M. Furukawa, *J. Heterocyclic Chem.* **29**, 825 (1992).

[2] K. Kaji, H. Nagashima, S. Nagao, K. Tabashi, and H. Oda, *Chem. Pharm.* Bull. **30**, 1030 (1982).

[3] S. Chem., and R. P. Panzica. *J. Org. Chem.* **46**, 2467 (1981).

[4] P. Shingh, and S. P. Gupta, *Indian J. Med. Res,* **69**, 804 (1979).

[5] T. Yamasaki, Y. Yoshihara, Y. Okomata, T. Okowara, and M. Furukawa, *J. Heterocyclic Chem,* **29**, 1313 (1992).

[6] H. Al-Awdhi, F. Al-Omran, M. H. Elnagdi, L. Infantes, C. Foces-Foces, N. Jagerovic, and J. Elguero, *Tetrahedron,* **51**, 12745 (1995).

[7] F. Al-Omran, M. M. Abdel Khalik, A. Abou-Elkhair, and M. H. Elnagdi, *Synthesis,* **91**, (1997).

[8] F. Al-Omran, M. M. Abdel Khalik, H. Al-Awadhi and M. H. Elnagdi, *Tetrahadron,* **52**, 11915, (1996).

[9] A. R. Katritzky and J. Wa, *Synthesis,* 597, (1994).

[10] A. R. Katritzky and I. V. Scherbkova, *J. Heterocyclic Chem.* **23**, 2031, (1996).

[11] S. M. Fahmy, N. M. Abed, M. R. Mohareb, M. H. Mohareb, and M. H. Elnagdi, *Synthesis,* 490 (1982)