Fused heterocycles. Part I. Synthesis of some annelated 1,2,4-triazole systems from [4-(1*H*-benzimidazol-2-yl)-phthalazin-1-yl]hydrazine

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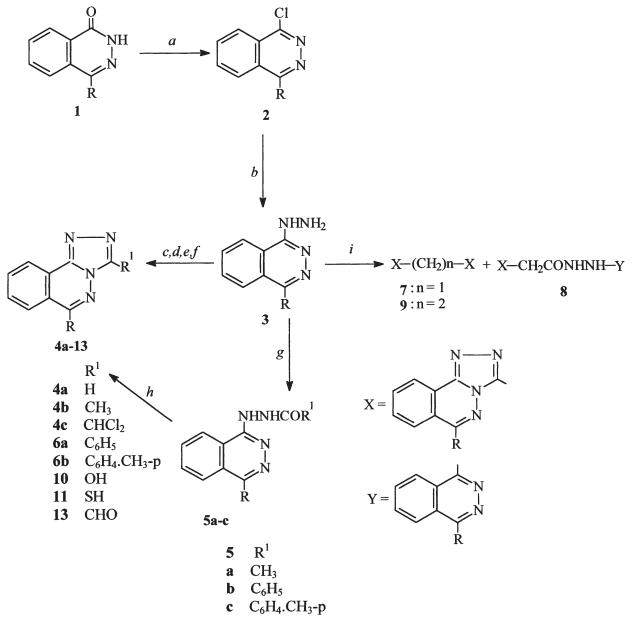
Substituted 6-(1*H*-benzimidazol-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazine derivatives containing alkyl, aryl, hydroxyl, mercapto, methylthio and formyl substituents at position 3 have been synthesised. Di-[6-(1*H*-benzimidazol-2-yl)-3-[1,2,4]triazolo[3,4-*a*]phthalazin-3-yl]alkanes have been obtained by the use of dicarboxylic acids or their esters in the above condensations. Methylation reactions of the triazolo-phthalazine system are reported.

Keywords: benzimidazoles, 1-hydrazinophthalazines, fused phthalazines, fused 1,2,4-triazoles, alkylation

As part of our interest in the chemistry of ring-fused [1,2,4]triazole systems,[9] we have studied the [1,2,4]triazolo[3,4-*a*]phthalazine system. This ring system was first reported[10] in 1951, interest being directed mainly towards the antihypertensive properties. Prompted by these observations, we thought it worthwhile to synthesise a new series of [1,2,4]triazolo[3,4-*a*]phthalazines having a benzimidazol-2-yl moiety at the 6-position, with the objective of obtaining new biologically active compounds.

In the present work, 4-(1*H*-benzimidazol-2-yl)phthalazin-1(2*H*)-one (**1**), required as a starting material, was conveniently prepared by the ring opening of benzimidazo[1,2-*b*]isoquinoline-5,12-dione with hydrazine hydrate.[11] This with $POCl_3/PCl_5$ on a steam bath gave 4-(1*H*-benzimidazol-2-yl)-1-chlorophthalazine (**2**) in good yield. On heating with ethanolic hydrazine hydrate, **2** gave the [4-(1*H*-benzimidazol-2-yl)phthalazin-1-yl]hydrazine (**3**) which was used as a key intermediate for the synthesis of the title compounds (Scheme 1).



Scheme 1

3-Alkyl-6-(1*H*-benzimidazol-2-yl)-[1,2,4]triazolo [3,4-*a*] phthalazines (**4a–c**) were prepared by treating [4-(1*H*-benzimidazol-2-yl)phthalazin-1-yl]hydrazine (**3**) with either an aliphatic acid, namely, formic acid, acetic acid or dichloroacetic acid, or the corresponding ortho esters. The use of ortho esters usually gave better yields and were the reagents of choice in the preparation of most of the fused 1,2,4-triazole systems.

The reaction of hydrazine (**3**) with an equimolar amount of acetyl chloride, benzoyl chloride or *p*-toluoyl chloride in dry pyridine at 0°C gave 2-acetyl-, 2-benzoyl- or 2-(4-toluoyl)-1-[4-(1*H*-benzimidazol-2-yl)phthalazin-1-yl]hydrazines (**5a–c**) which underwent cyclisation with phosphorus oxychloride to yield 3-methyl-, 3-phenyl- or 3-*p*-tolyl-6-(1*H*-benzimidazol-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazines **4b** and **6a,b**, respectively; low yields were obtained by this procedure. It was found that the most efficient method of formation of the 3-aryl derivatives was the fusion of aromatic acids with compound **3**. When the two reactants were heated together at 200°C for 5 hr, there was good conversion into the desired products, with little decomposition, and no intermediate hydrazide was isolated. The work-up procedure used in the phosphorus oxychloride reaction was virtually eliminated, and this greatly improved the yield in the over-all reaction sequence.

When equivalent amounts of [4-(1*H*-benzimidazol-2-yl)phthalazin-1-yl]hydrazine (**3**) and a dicarboxylic acid, its anhydride, or its ester were heated together at elevated temperatures, the bis-condensation products di[6-(1*H*-benzimidazol-2-yl)-3-[1,2,4]triazolo[3,4-*a*]phthalazin-3-yl]alkanes **7**, **9**, were formed readily.

The reaction of 1 equivalent of diethyl malonate with 2 equivalents of [4-(1*H*-benzimidazol-2-yl)phthalazin-1-yl]hydrazine (**3**) yielded not only di[6-(1*H*-benzimidazol-2-yl)-3-[1,2,4]triazolo[3,4-*a*]phthalazin-3-yl]methane (**7**, n = 1), but also the monocyclised product, 6-(1*H*-benzimidazol-2-yl)[1,2,4]triazolo[3,4-*a*]phthalazin-3-acetic acid 2-[4-(1*H*-benzimidazol-2-yl)phthalazin-1-yl]hydrazide (**8**). However, succinic acid and succinic anhydride when heated with [4-(1*H*-benzimidazol-2-yl)phthalazin-1-yl]hydrazine (**3**) formed only the dicondensation product di[6-(1*H*-benzimidazol-2-yl)-3-[1,2,4]triazolo[3,4-*a*]phthalazin-3-yl]ethane (**9**, *n* = 2). When ethyl cyanoacetate was heated with **3**, the product actually isolated was identified as **7** (*n* = 1). A possible method of formation of this product involves initial hydrolysis of the cyanide to the carboxylic acid, and then further reaction as described above to yield the dicondensation product.

Fusion of compound **3** with urea afforded 6-(1*H*-benzimidazol-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazin-3(2*H*)-one (**10**). Ethyl chloroformate was unsatisfactory as the cyclization agent in this system, no well-defined product being obtained. Spectral data indicated that this compound (**10**) exists predominantly in the keto form (ν_{CO} 1665 cm^{-1}). Reaction of 1-hydrazinophthalazine **3** with carbon disulfide and aqueous potassium hydroxide gave 6-(1*H*-benzimidazol-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazin-3(2*H*)-thione (**11**) in

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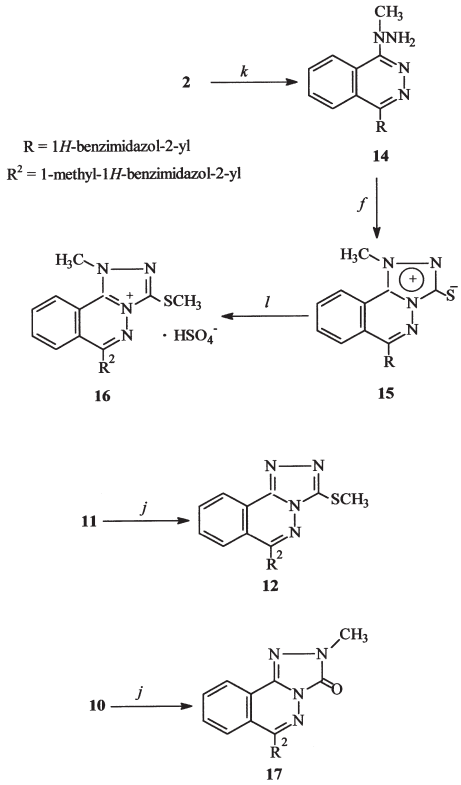

Scheme 2

excellent yield. Use of carbon disulfide in chloroform as the reaction medium gave the same thione **11**, except that under the former conditions the reaction was much faster, presumably because of the homogeneous reaction conditions. It was noticed that when carbon disulfide was added to a solution of the phthalazinylhydrazine derivative **3**, an initial precipitate of the intermediate dithiocarbamic acid soon separated and this slowly underwent cyclisation with elimination of hydrogen sulfide. The infrared spectrum indicated that this compound exists mainly in the thioamide form (ν_{CS} 1245 cm^{-1}) since no appreciable SH stretching absorption was detected (ν_{SH} 2600 cm^{-1}).

The thione **11**, on treatment with methyl iodide and aqueous base, was converted into methyl 6-(1-methyl-benzimidazol-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazin-3-yl sulfide (**12**) (Scheme 2).

Attempts to prepare 3-formyl substituted derivatives (**13**) of the fused-ring system utilising *n*-butyllithium and dimethylformamide failed. Acid hydrolysis of the bis-amine derived from 6-(1*H*-benzimidazol-2-yl)-3-dichloromethyl [1,2,4]triazolo[3,4-*a*]phthalazine (**4c**) and morpholine was, however, a successful synthetic route.

As there is more than one nitrogen atom at which alkylation can occur in this system, it was of interest to determine the most basic nitrogen atom. An unambiguous synthesis of a derivative with an N-alkyl group in a predetermined position was achieved in the following way. 1-[4-(1*H*-Benzimidazol-2-yl)phthalazin-1-yl]-1-methylhydrazine (**14**), prepared by treatment of 4-(1*H*-benzimidazol-2-yl)-1-chlorophthalazine (**2**) with methylhydrazine, on reaction with carbon disulfide gave anhydro-3-mercapto-1-methyl-6-(1*H*-benzimidazol-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazinium hydroxide (**15**) in good yield. Reaction of **15** with dimethyl sulfate in benzene afforded 1-methyl-3-methylthio-6-(1-methylbenzimidazol-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazinium hydrogen sulfate (**16**) whose NMR spectrum showed *N*-methyl signals at δ 3.54 and 4.07 and an *S*-methyl resonance at 2.90.

As expected, 2-methyl-6-(1-methylbenzimidazol-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazin-3-one (**18**) was readily obtained from 6-(1*H*-benzimidazol-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazin-3(2*H*)-one (**10**) by reaction with methyl iodide and potassium carbonate in acetone.

Techniques used: IR, ^{1}H and ^{13}C NMR

References: 11

Schemes: 2

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References cited in this synopsis

9 A.A.F. Wasfy, *Ind. J. Chem.,* **33B**, 1098 (1994).
10 J. Druey and B.H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).
11 A.L. Johnson, *J. Org. Chem.,* **41**, 836 (1976).