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Tetrahedron Letters 45 (2004) 1407–1408
Tetrahedron Letters

Synthesis of benzo[4,5]imidazo[2,1-*a*]phthalazines

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Received 11 October 2003; revised 30 November 2003; accepted 11 December 2003

Abstract—5,9-Disubstituted benzo[4,5]imidazo[2,1-*a*]phthalazines are synthesized efficiently from acylbenzoic acids and 2-nitro-5-chlorophenylhydrazine. Nucleophilic substitution in phthalazinones gave a variety of the title compounds after reduction and cyclization.

An analysis of the reactivity of substituted 2-(2-aminobenzene)-phthalazine-1-ones has shown, that highly UV-luminescent products are formed, which have been identified as benzo[4,5]imidazo[2,1-*a*]phthalazines (Fig. 1).

This heterocyclic system has been investigated rather sporadically. [1–3] The first publication [1] on the synthesis of benzimidazophthalazines lacks analytical data not only on the title compounds, but also on intermediates. Moreover, only a few members of this class were described. In addition, the scope of the synthetic methodology to include other substituents was not discussed. Other research[2] mentions a single example of the title compound which, however, has a specific charge distribution, which distinguishes it from the uncharged structure. This property rendered it impossible to characterize by NMR or MS.

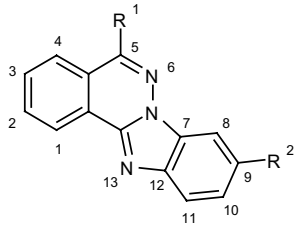

Figure 1. 5-R[1]-9-R[2]-Benzo[4,5]imidazo[2,1-*a*]phthalazine.

Razvi and Ramalingam [3] have synthesized several analogues of the title structure, but the most interesting point of their work is their more rational approach to the synthesis of substituted benzimidazophthalazines. Also they reported for the first time their biological activity, namely antihypertensive and antiinflammatory activity.

A synthesis of benzimidazophthalazines using aryl hydrazines substituted in the benzene ring to introduce the N–N group has been developed. Cyclization of such hydrazines with *o*-acylbenzoic acids (Scheme 1) leads to the generation of the phthalazine ring. This makes it easier to change substituents in position 4 of the phthalazinone. Thus, the employment of different *o*-acyl substituted benzoic acids gave a set of C-5 substituted benzimidazophthalazines. In the present work *o*-acetylbenzoic, *o*-benzoylbenzoic, and 2-(4-toluoyl)benzoic acids (**1a–c**) were used.

The reactions were carried out in a boiling ethanolic solution of concentrated sulfuric acid. Cyclization of 2-nitro-5-chlorophenylhydrazine **2** with acylbenzoic acids yielded 2-(2-nitro-5-chlorobenzene)-4-substituted phthalazin-1-ones **3a–c** (see Table 1 for yields). A chlorine atom in the *p*-position relative to the nitro group of the benzene ring is sufficiently activated for nucleophilic aromatic substitution, and was easily exchanged by aliphatic amines. Applying this reaction phthalazinones **4a–f** were prepared.

Nitrocompounds **3a–c** and **4a–f** were reduced to the corresponding anilines **5a–i** by hydrogenation with hydrogen at room temperature and at normal pressure. This process was carried out in a THF solution because of the solubility of the reagents and products. When a

Keywords: Heterocycles; Cyclodehydration; Phthalazine; Benzoimidazole.
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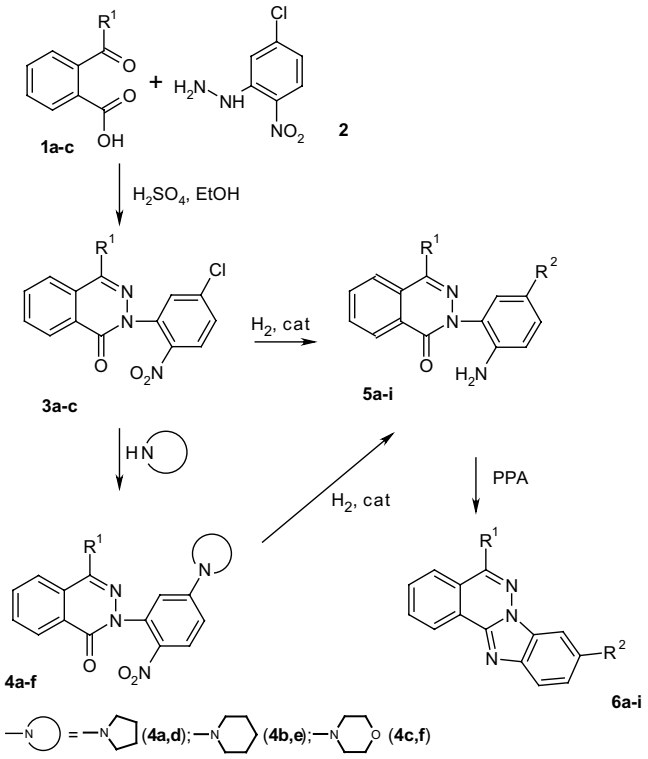
doi:10.1016/j.tetlet.2003.12.070



Scheme 1.

Table 1. Yields of benzoimidazophthalazines and intermediates

Product	R^1	R^2	Yield (%)
3a	CH_3	Cl	65
3b	Ph	Cl	54
3c	*p*-CH_3–C_6H_4	Cl	60
4a	CH_3	Pyrrolidyl	79
4b	CH_3	Piperidyl	74
4c	CH_3	Morpholyl	71
4d	Ph	Pyrrolidyl	78
4e	Ph	Piperidyl	81
4f	Ph	Morpholyl	68
5a	CH_3	Cl	65
5b	CH_3	Pyrrolidyl	40
5c	CH_3	Piperidyl	79
5d	CH_3	Morpholyl	71
5e	Ph	Cl	69
5f	Ph	Pyrrolidyl	49
5g	Ph	Piperidyl	66
5h	Ph	Morpholyl	69
5i	*p*-CH_3–C_6H_4	Cl	65
6a	CH_3	Cl	61
6b	CH_3	Pyrrolidyl	55
6c	CH_3	Piperidyl	45
6d	CH_3	Morpholyl	75
6e	Ph	Cl	42
6f	Ph	Pyrrolidyl	46
6g	Ph	Piperidyl	41
6h	Ph	Morpholyl	50
6i	*p*-CH_3–C_6H_4	Cl	55

Pd(0)-catalyst or fresh Raney nickel was used, only selective nitro group reduction occurred. Other fragments of the molecule remain unchanged (including R^2 = Cl). Anilines were obtained which were pure by TLC by crystallization from the reaction mixture (after filtration of the catalyst) by dilution with petrol ether (40–70 °C) in a 1:8 ratio.

Heating the aminophthalazinones **5a**–**i** in polyphosphoric acid (PPA) to 100–120 °C for a short time yielded benzimidazophthalazines **6a**–**i** by intramolecular cyclodehydration. The PPA was diluted with water in a 1:10 ratio, basified to pH = 8 and extracted with chloroform. Extracts were dried with anhydrous Na_2SO_4, evaporated under reduced pressure and the residue was recrystallized from ethanol.

The hydrogenation of the pyrrolidine-substituted nitrophthalazinone **4a** (R^1 = Me) was difficult, because the product of the reaction—2-(2-amino-5-pyrrolidine-benzene)-4-methyl-phthalazin-1-one is poorly soluble in THF and deactivates the catalyst. As an alternative we carried out the reduction of this compound in PPA with iron powder. In this way the reduction stage and the cyclodehydration stage were a 'one pot' synthesis. We added iron to the solution of the nitro compound in PPA at 100 °C in small batches. At the end of the process, the temperature was raised to 140 °C for a short period of time. The reaction mixture was worked up as in the case of the cyclodehydration of pure anilines **5a**–**i**. The yields of this process approximately equaled the overall yields in the two stage experiment.

A simple and efficient method is proposed for the synthesis of a practically unreported heterocyclic system—benzo[4,5]imidazo[2,1-*a*]phthalazine. A variety of the title compounds were synthesized employing different *o*-acylbenzoic acids and dialkylamines. The structures of all the compounds were established by NMR, MS, and elementary analysis.

References and notes

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