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A New Approach to 1-Alkyl-1,3-dihydro-2*H*-benzimidazol-2-ones

Vicente Gómez-Parra, Félix Sánchez*, and Tomás Torres

Departamento de Química, Centro de Investigación Abelló, 28037 Madrid, Spain

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A new procedure for preparing 1-alkyl-1,3-dihydro-2*H*-benzimidazol-2-ones from *o*-nitroanilines by succesive ethoxycarbonylation, catalytic hydrogenation and thermal cyclization under neutral conditions is described.

(Keywords: Thermal cyclization)

Eine neue Synthese von 1-Alkyl-1,3-dihydro-2H-benzimidazol-2-onen

Eine neue Methode zur Darstellung von 1-Alkyl-1,3-dihydro-2*H*-benzimidazol-2-onen aus *o*-Nitroanilinen durch Ethoxycarbonylierung, katalytische Hydrierung und thermische Cyclisierung wird beschrieben.

Introduction

Several compounds incorporating the 1-alkyl-1,3-dihydro-2*H*-benzimidazol-2-one group show interesting biological activities. Oxatomide® is a clinically useful antiallergic[1], and domperidone® exhibits antiemetic properties[2], for example. On the other hand, compounds having this moiety are also valuable synthetic intermediates in the preparation of other effective therapeutic drugs[3,4].

The synthetic routes to 1-alkylated 1,3-dihydro-2*H*-benzimidazol-2-ones generally involve the condensation of 1,2-diaminobenzenes with carboxylic acid derivatives[5] or the direct monoalkylation of the benzimidazolone system[6,7].

Neither of these methods are useful in the regioselective preparation of N^1-alkylbenzimidazolones substituted on the aromatic ring. In addition, due to acidic or alkaline media employed in some cases, these procedures are unsuitable if sensitive substituents are present in the molecule.

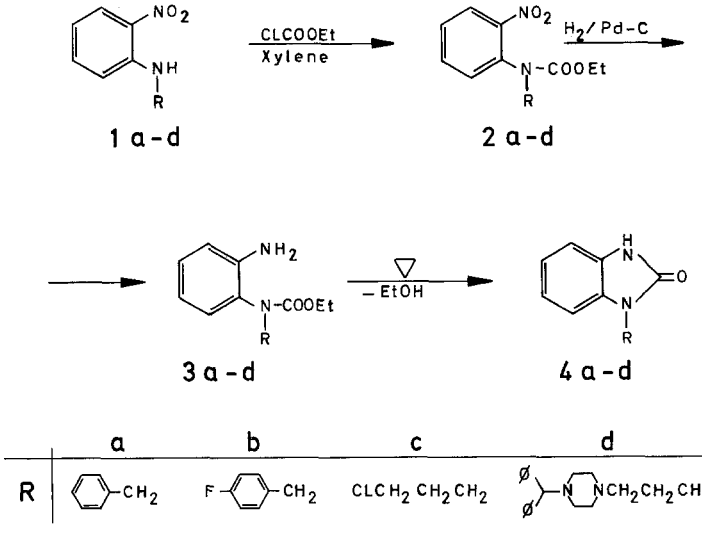
We report a new entry to these compounds, based on a three step sequence, starting from the easily available *o*-nitroanilines, which includes an uncommon N^3—CO ring closure[8].

Results and Discussion

The synthetic route leading to 1-alkylated 1,3-dihydro-2*H*-benzimidazol-2-ones is depicted in the formula scheme.

Firstly, we studied the ethoxycarbonylation of the nitroanilines **1**. Heating of **1a–c** and ethyl chloroformate in xylene led to the corresponding *N*-ethoxycarbonyl compounds **2a–c** in quantitative yields.

The preparation of **2d** required an indirect method, because the reaction of **1d** under the above mentioned conditions gave a mixture of products resulting from the cleavage of the bonds attached to piperazine[9]. Thus, **2c** underwent an easy nucleophilic displacement of the halogen with *N*-diphenylmethylpiperazine to afford **2d** in excellent yield.



In the second step, the nitrocompounds **2a–d** were catalytically reduced (Pd/C) to give the amines **3a–d** in nearly quantitative yields. **3d** can also be obtained from the chloro derivative **3c** by treatment with the corresponding amine.

Finally, the thermolysis of **3a–d** at 200–210 °C at atmospheric pressure afforded the benzimidazolones **4a–d** in high yields.

The sequence shown could be applied to a regioselective synthesis of 1-alkyl-1,3-dihydro-2*H*-benzimidazol-2-ones substituted on the aromatic ring from corresponding *o*-nitroanilines. The usefulness of this general method is not limited by the presence of acid or base sensitive groups.

Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer model 257 grating spectrophotometer, $\bar{\nu}$ values in cm^{-1}. ^{1}H-NMR spectra were obtained on a Varian-EM 360 spectromoter; signals are reported in δ units with *TMS* as internal standard. Silica gel Merck 60 (70–230 mesh), F_{254} (layers 2 mm) and DC-Alufolien 60 F_{254} (layers 0.2 mm) were normally used for column, preparative and analytical t.l.c.

N-Alkyl-*o*-nitroanilines (**1 a–d**) were prepared by described methods[1,2].

N-Ethoxycarbonyl-N-alkyl-o-nitroanilines (**2 a–c**)

General Procedure: A stirred mixture of the corresponding *o*-nitroaniline (20 mmol) and ethyl chloroformate (60 mmol) in xylene (30 ml) was heated at reflux temperature for 14–18 h. The solvent was evaporated in vacuo to give pure carbamates **2 a–c** in quantitative yields as oily residues, which were used without further purification. Analytical samples were obtained by preparative t.l.c. with petroleum ether-ethyl acetate as eluent (Table 1).

N-Ethoxycarbonyl-N-[3-(4-diphenylmethylpiperazin-1-yl)prop-1-yl]-o-nitroaniline (**2 d**)

A flask equipped with a water-separator system was charged with **2 c** (1.8 g, 6.3 mmol) *N*-diphenylmethylpiperazine (1.4 g, 5.55 mmol), finely powdered anhydrous potassium carbonate (9.6 g, 4.35 mmol), potassium iodide (50 mg) and methylisobutylacetone (12 ml) and the mixture was stirred at reflux temperature overnight. After cooling, the solid was filtered off and washed with acetone. The filtrates were evaporated at reduced pressure and the residue chromatographed on silica gel (short column), using petroleum ether-ethyl acetate as eluent, to give **2 d** (2.5 g, 90%) as a thick oil (Table 1).

N-Ethoxycarbonyl-N-alkyl-o-phenylenediamine (**3 a–d**)

General Procedure: A mixture of the corresponding nitro compound **2 a–d** (10 mmol) and 10% palladium on carbon (500 mg) in methanol (50 ml) was magnetically stirred under atmospheric pressure hydrogen for 2–4 h, the reaction was monitored by t.l.c. The catalyst then was removed by filtration and the filtrate concentrated under reduced pressure to give pure amino compounds **3 a–d** as oils, in nearly quantitative yields, which were used directly in the next step. Analytical samples were obtained by chromatography on silica gel (short column) using petroleum ether-ethyl acetate as eluent (Table 1).

N-Ethoxycarbonyl-N-[3-(4-diphenylmethylpiperazin-1-yl)prop-1-yl]-o-phenylenediamine (**3 d**)

In a manner similar to that described above for the preparation of **2 d**, starting from the chloro derivative **3 c** (1.35 g, 5.3 mmol), *N*-diphenylmethylpiperazine

Table 1. *Spectral data of compounds* **2** *and* **3**

No.	Formula[a] (molecular weight)	IR[b]	^{1}H-NMR[c]
2a	$C_{16}H_{16}N_2O_4$ (300.3)	1710	8.1–7.8 (m, 1H arom), 7.6–6.9 (m, 3H arom), 7.28 (s, 5H, C_6H_5), 5.3–4.5 (m, 2H, CH_2), 4.17 (m, 2H, OCH_2CH_3), 1.15 (m, 3H, OCH_2CH_3)
2b	$C_{16}H_{15}FN_2O_4$ (318.3)	1710	8.1–7.8 (m, 1H arom), 7.7–6.7 (m, 7H arom), 5.4–4.4 (m, 2H, CH_2), 4.09 (m, 2H, OCH_2CH_3), 1.10 (m, 3H, OCH_2CH_3)
2c	$C_{12}H_{15}ClN_2O_4$ (286.7)	1710	8.1–7.2 (m, 4H arom), 4.10 (m, 2H, CH_2CH_3), 3.87 and 3.60 (2t, 4H, CH_2Cl, CH_2N), 2.5–1.8 (m, 2H, CH_2), 1.12 (m, 3H, OCH_2CH_3)
2d	$C_{29}H_{34}N_4O_4$ (502.6)	2805 1710	8.1–7.7 (m, 1H arom), 7.6–7.0 (m, 13H arom), 4.18 (s, 1H, CH), 4.4–3.5 (m, 4H, OCH_2CH_3, CH_2NCO), 2.7–2.1 (m, 10H, CH_2N), 2.1–1.5 (m, 2H, CH_2), 1.10 (m, 3H, OCH_2CH_3)
3a	$C_{16}H_{18}N_2O_2$ (270.3)	3460 3330 1685	7.6–6.5 (m, 4H arom), 7.25 (s, 5H, C_6H_5), 5.1–4.5 (m, 2H, CH_2), 4.18 (q, 2H, OCH_2CH_3), 3.5 (br, 2H, NH_2, removed by D_2O), 1.18 (t, 3H, OCH_2CH_3)
3b	$C_{16}H_{17}FN_2O_2$ (288.3)	3460 3330 1685	7.5–6.6 (m, 8H arom), 5.1–4.4 (m, 2H, CH_2), 4.18 (q, 2H, OCH_2CH_3), 4.1 (br, 2H, NH_2 removed by D_2O), 1.20 (t, 3H, OCH_2CH_3)
3c	$C_{12}H_{17}ClN_2O_2$ (256.7)	3450 3360 1690	7.5–6.5 (m, 4H arom), 5.5–3.0 (br, 2H, NH_2, removed by D_2O), 4.10 (q, 2H, OCH_2CH_3), 3.9–3.3 (m, 4H, CH_2Cl, CH_2N), 2.3–1.6 (m, 2H, CH_2), 1.17 (t, 3H, OCH_2CH_3)
3d	$C_{29}H_{36}N_4O_2$ (472.6)	3450[d] 3350 2805 1690	7.6–6.4 (m, 14H arom), 6.0–3.0 (br, 2H, NH_2 removed by D_2O), 4.37 (s, 1H, CH), 4.10 (q, 2H, OCH_2CH_3), 3.67 (m, 2H, CH_2NCO), 3.4–2.4 (m, 10H, CH_2N), 2.4–1.6 (m, 2H, CH_2), 1.17 (t, 3H, OCH_2CH_3)

[a] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.22, N ± 0.30, Cl ± 0.35.
[b] Neat, unless otherwise stated.
[c] In $CDCl_3$ solution.
[d] In KBr disc.

Table 2. *Physical and spectral data of compounds* **4**

No.	M.p. (°C) (recryst. solvent)	Formula[a] (molecular weight)	IR[b]	^{1}H-NMR[c]
4a	200–201 (ethanol)	$C_{14}H_{12}N_2O$ (224.3)	1690	7.30 (s, 5H, C_6H_5), 6.95 (m, 4H arom), 5.00 (s, 2H, CH_2)
4b	178–179 (isopropanol)	$C_{14}H_{11}FN_2O$ (242.2)	1685	7.7–6.8 (m, 8H arom), 5.00 (s, 2H, CH_2)
4c	118–120 (ethyl acetate/ *n*-hexane)	$C_{10}H_{11}ClN_2O$ (210.8)	1680	7.3–6.9 (m, 4H arom), 3.92, 3.65 (2t, 4H, CH_2Cl, CH_2N), 2.5–1.7 (m, 2H, CH_2)
4d	153–155 (isopropyl ether/ isopropanol)	$C_{27}H_{30}N_4O$ (426.6)	3190 2800 1695	7.6–6.8 (m, 14H arom), 4.20 (s, 1H, CH), 3.8 (m, 2H, CH_2NCO), 2.5–2.1 (m, 10H, CH_2N), 1.8 (m, 2H, CH_2)

[a] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.15, N ± 0.28, Cl ± 0.20.
[b] In KBr disc.
[c] In *DMSO-d_6* solution.

(1.26 g, 5 mmol), potassium carbonate (552 mg, 4 mmol), potassium iodide (50 mg) and methylisobutylacetone (10 ml), **3d** was obtained in 62% yield, after chromatography on silica gel (short column), as a thick oil, which solidified by treatment with ether; m.p.: 100–105 °C (Table 1).

1-Alkyl-1,3-dihydro-2H-benzimidazol-2-ones (**4a–d**)

General Procedure: Compounds **3a–d** (10 mmol) were heated at 210 °C under atmospheric pressure in the presence of calcium chloride for 60–90 min (Kugelrohr apparatus). The oily residue was solidified on cooling and recrystallised from the appropriate solvent to give **4a–d** in 80–85% yields. Physical and spectral data are given in Table 2.

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