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Investigación

Reaction of 4(7)-Aminobenzimidazole with Ethyl 2-Alkylmalonates in 1,2,4-Trichlorobenzene

Lucía E. Valle-Aguilera,1* Marco M. González-Chávez,1 and Roberto Martínez2*

1 Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, Av. Dr. Manuel Nava 6, Zona Universitaria, San Luis Potosí, S. L. P., México
2 Instituto de Química [1], Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México, D. F. e-mail: robmar@servidor.unam.mx

Dedicado a la memoria de la Dra. Lydia Rodríguez-Hahn.

Resumen. La reacción del 4-(7)-aminobencimidazol (2) con malonato de etilo o 2-alilmalonato de etilo, utilizando el 1,2,4-triclorobenceno como disolvente, produce benzodiazepin-4,6-diones y acetamidobenzimidazoles. Sin embargo, la reacción de (2) con el 2-metilmalonato de etilo, o con derivados de 2-propilo o 2-butilo, produce, además de compuestos similares a los anteriores, un tercer compuesto identificado como una dihidroxyquinolina.

Abstract. The reaction of 4-(7)-aminobenzimidazole (2) with ethyl malonate or ethyl 2-allylmalonate, using 1,2,4-trichlorobenzene as the reaction solvent produces benzodiazepine-4,6-diones and acetamidobenzimidazoles. However, reaction of (2) with ethyl 2-methylmalonate as well as the 2-butyl and 2-propyl derivatives, produced unknown dihydroxyquinolines in addition to benzodiazepine-4,6-diones and acetamidobenzimidazoles.

Table 1. Product Distribution (%) of Reaction of 4(7)-aminobenzimidazole (2) with Ethyl 2-alkylmalonates (3).

<table>
<thead>
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<th>Compound</th>
<th>R</th>
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<tbody>
<tr>
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<td>35</td>
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<td>(13)</td>
<td>(51)</td>
<td>(0)</td>
</tr>
<tr>
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<td>C₃H₅</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(20)</td>
<td>(33)</td>
<td>(0)</td>
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</table>

* Yield obtained in previous work [4]
** This substituent was not used in previous work

Introduction

Since the discovery that 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-1-(1H)-one derivatives, designed with the acronym TIBO derivatives, display potent anti-HIV (human immunodeficiency virus, the causative agent of AIDS) activity [2], the synthesis of new 1,4-benzodiazepines has been the subject of intense study in many laboratories. Some of the most interesting novel developments include benzodiazepines (1) containing additional substituents in the tricyclic moiety [3]. Recently, as part of our research for new compounds with possible anti-HIV activity, we reported [4] that condensation of 4(7)-aminobenzimidazole (2) with ethyl 2-alkylmalonates (3) produces 4,5,6,7-tetrahydro-5-alkylimidazo[1,5,4-ef][1,5]benzodiazepine-4,6-diones (4), structurally similar to (1), and 2-alkyl-4(7)-(2'-ethoxycarbonyl)acetamidobenzimidazoles (5a-e). However, in order to improve the yields of compounds (4a-e) (see Table 1), the condensation was carried out using 1,2,4-trichlorobenzene (TCB)[5] as solvent (Fig. 1). We wish to report herein the results of this modification.

Results and Discussion

Refluxing a mixture of 4-(7)-aminobenzimidazole (2) and ethyl malonate (5a) in 1,2,4-trichlorobenzene gave the benzodiazepinone (4a) and the imidazole amide (5a) in yields significantly different than those obtained without TCB (54% vs 19% and 6% vs 54%, respectively). On the other hand, reaction of ethyl 2-methylmalonate as well as the 2-butyl and 2-propyl derivatives, produced unknown dihydroxyquinolines in addition to benzodiazepine-4,6-diones and acetamidobenzimidazoles.

Table 1. Product Distribution (%) of Reaction of 4(7)-aminobenzimidazole (2) with Ethyl 2-alkylmalonates (3).
quinoline (6b) in 30%, 23% and 22% yield, respectively. The formation of the dihydroxyquinoline 6b can be rationalized as a malonamide type synthesis [6] from (5b) as a possible intermediate, since the aforementioned method uses aniline and malonic ester derivatives as starting materials.

As an extension of these studies we examined the reactions of ethyl 2-propylmalonate (3c) and ethyl 2-butylmalonate (3d) with (2). The reaction of (2) with (3c) gave (4c), (5c) and (6c) in 8%, 21% and 53% yield, respectively, whereas reaction of (2) with 3d produced (4d), (5d) and (6d) in 14%, 17% and 35% yields. However, reaction of (2) with ethyl 2-allylmalonate (3e), resulted only in the obtention of benzodiazepin-4,6-dione (4e, 12%) and the acetamidobenzimidazole (5e, 41%). All structures were fully supported by their spectroscopic data. It is noteworthy that the 1H-NMR spectra of compounds (6b) and (6d) showed the characteristic signals for both the enol (6) and dienol (6’) form of these compounds [6] (Fig. 2).

In summary, the reaction of 7(4)-aminobenzimidazole (2) with ethyl 2-alkylmalonates, when the alkyl is a methyl, propyl or butyl group, using TCB as the reaction solvent, produces three compounds: benzodiazepin-4, 6-diones, acetamidobenzimidazoles and dihydroxyquinolines. On the other hand, when the 2-alkyl substituent is a hydrogen or an allyl group, the reaction gives benzodiazepin-4,6-diones and acetamidobenzimidazoles as the only products.

Experimental

All melting points are uncorrected. The IR spectra were recorded on a Nicolet FT-55X spectrophotometer. 1H-NMR spectra were determined on a Varian FT-200 and Varian FT-300 instrument, obtained with the pulse sequence included as part of the spectrometer’s software; samples were dissolved in hexadeuterio-methyl sulfoxide or deuterio trifluoroacetic acid solutions tetramethylsilane as the internal standard. Column chromatography was carried out using silica gel 230-400 mesh (Merck

Fig. 1. Products of Reaction of 4(7)-aminobenzimidazole (2) with Ethyl 2-alkylmalonates (3).

Fig. 2. Enol (6) and dienol (6’) form of dihydroxyquinolines.
Kieselgel 60 F254). Thin layer chromatography was carried out using silica gel 60, 0.25 mm (Merck Kieselgel 60 PF254). All the solvents used were dried over appropriate drying agent.

The starting 4-(7)-aminobenzimidazole (2) was prepared following a reported procedure [7]. The ethyl 2-alkylmalonates (3a-e) were purchased from Aldrich. The 4,5,6,7-tetrahydro-5-alkylimidazo[1,5,4-ef][1,5]benzodiazepine-4,6-diones (4a-c,d,e) and 4(7)-(2'-ethoxycarbonyl-2'-alkyl)acetamido benzimidazoles (5a,c,d,e) have been previously prepared [4] and their structures were confirmed by their physical and spectral data.

Reaction of 4-(7)-Aminobenzimidazole 2 with Ethyl malonate 3a.

A solution of ethyl malonate (3a, 288 mg, 1.8 mmols) in TCB (3.0 ml) was added to 200 mg (1.5 mmoles) of 2 dissolved in hot ethanol. The mixture was stirred at 175°C for 3 h and after this time the solvent was removed in vacuo. The resulting oil was separated by flash chromatography (silica gel, chloroform: ethanol, 70:30) to yield 4a (162 mg, 54%; mp 280-282°C; lit. 278-279°C [4]) and 5a (22 mg, 6%; mp 169-171°C; lit. 170-171°C [4]) in pure form.

Reaction of 4-(7)-Aminobenzimidazole 2 with Ethyl 2-methylmalonate 3b.

Compound 2 (200 mg, 1.5 mmoles) was allowed to react with 3b (313 mg, 1.8 mmoles) according to the procedure described above to give compounds 4b (97 mg, 30%), 5b (90 mg, 23%) and 6b (78 mg, 22%) in pure form.

4,5,6,7-Tetrahydro-5-methylimidazo[1,5,4-ef][1,5]benzodiazepine-4,6-dione, 4b.

Mp 249-251°C; IR (KBr) 3291, 1703, 1638 cm⁻¹; ¹H NMR (DMSO-d₆, 200 MHz) δ 10.41 (1H, bs, NH), 8.25 (1H, s, H-2), 7.90 (1H, d, J = 7.8 Hz, H-8), 7.30 (1H, d, J = 7.9 Hz, H-10), 7.15 (1H, dd, J = 7.9, 7.9 Hz, H-9), 4.20 (1H, q, J = 6.9 Hz, H-5), 1.45 (3H, d, J = 6.9 Hz, CH₃-C5). Anal. C, 61.41; H, 4.21; calculated for C₁₁H₁₄N₂O₂, C, 61.39; H, 4.22.

4(7)-(2'-ethoxycarbonyl-2'-methyl)acetamidobenzimidazole, 5b.

Mp 292-293°C; IR (KBr) 3283, 1766, 1600 cm⁻¹; ¹H NMR (DMSO-d₆, 200 MHz) δ 9.12 (1H, bs, NH), 10.15 (1H, bs, NH-CO), 8.20 (1H, s, H-2), 7.90 (1H, d, J = 7.9 Hz, H-5), 7.27 (1H, d, J = 7.8 Hz, H-7), 7.16 (1H, dd, J = 7.8, 7.9 Hz, H-6), 4.15 (2H, q, J = 7.2 Hz, OCH₂-CH₃), 4.10 (1H, q, J = 7.0 Hz, H-3'), 1.3 (3H, t, J = 6.9 Hz, CH₃-C3'), 1.15 (3H, t, J = 7.2 Hz, CH₃-CH₂O). Anal. C, 59.89; H, 5.41; calculated for C₁₃H₁₄N₂O₃, C, 59.99; H, 5.42.

6,8-Dihydroxy-7-methyl-1H-imidazo[4,5-b]quinoline, 6b.

Mp 239-241°C; IR (KBr) 3246, 1708, 1628 cm⁻¹; ¹H NMR (DMSO-d₆, 200 MHz) δ 10.80 (1H, bs, OH), 8.29 (s, H-2), 7.62 (d, J = 8.5 Hz, H-5), 7.29 (d, J = 8.5 Hz, H-4), 5.30 (bs, NH-CO), 1.44 (s, CH₂-C₇), 6: 8.110.80 (1H, bs, OH), 8.40 (s, H-2), 7.78 (d, J = 8.7 Hz, H-5), 7.34 (d, J = 8.7 Hz, H-4), 2.03 (3H, s, CH₃-C7). Anal. C, 61.34; H, 4.20; calculated for C₁₃H₁₄N₂O₂, C, 61.39; H, 4.22.

Reaction of 4-(7)-Aminobenzimidazole 2 with Ethyl 2-propylmalonate 3c.

Compound 2 (200 mg, 1.5 mmoles) was allowed to react with 3c (364 mg, 1.8 mmoles) according to the procedure described above, to give compounds 4c (28 mg; 8% mp 184-186°C; lit. [4].

185-186°C), 5c (89 mg; 21%; oil; lit. [4] oil) and 6c in (194 mg, 53%).

References

1. Contribution No.1695 from Instituto de Química, UNAM
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