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ORIGINAL ARTICLE

Condensation of 5-aminobenzimidazoles with β-ketoester

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Abstract In the present work, we report the condensation of 5-aminobenzimidazoles with β-ketoesters leading to some new imidazo-[4,5-f]-quinoline derivatives. Based on the open chain intermediates obtention, the structure of the obtained imidazo-[4,5-f]-quinoline product has been discussed.

1. Introduction

It has been reported that some imidazoquinoline derivatives present pharmacological activities as immunomodulators (Kshirsagar et al., 2006; Smith et al., 2003; Hemmi et al., 2002). Some works based on the synthesis of these heterocycles, in which structural details are different (Spencer et al., 1977; Snyder et al., 1977; Alaimo et al., 1978; Spencer et al., 1975; Ichiwata and Shiokawa, 1969a,b; Mullok et al., 1970) lead us to report our contribution to these works by our research program on benzimidazole series (El Kihel et al., 1999a,b; Benchidmi et al., 1995).

The present work report the synthesis of imidazo-[4,5-f]-quinoline derivatives. The condensation of 5-aminobenzimidazoles with β-ketoesters leads to imidazoquinoline presenting one of the following two structures **A** or **B** (Fig. 1).

Thus, we have realized these condensations and studied the structure of the obtained compounds with spectroscopic data: NMR (^{1}H, ^{13}C) and mass.

Bobosiket al. (1992) have studied the condensation of 5-aminobenzimidazole with alkoxymethylene derivatives that give the products of nucleophilic substitution undergo thermal cyclizations to the corresponding imidazoquinolinones.

2. Results and discussion

2.1. Synthesis of open chain crotonic intermediates 3(a–f)

The open chain crotonic intermediates **3**(**a**–**f**) has been synthesized by condensation of 5-aminobenzimidazoles **1**(**a–c**) with β-ketoesters **2**(**a–b**) by heating of starting material at a temperature of 80 °C in order to avoid the formation of the other open chain amidic intermediate resulting of the attack of NH_2 on ester group (Scheme 1).

The structure of compounds **3**(**a**–**f**) has been established by spectroscopic data: NMR (^{1}H, ^{13}C) and mass.

The proton NMR spectra of these compounds present, in particular, one system ABX corresponding to protons in

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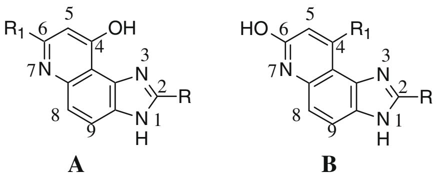


Figure 1 Different previous products A and B of cyclization of the open chain intermediates.

positions 4, 6 and 7 as well as one singlet corresponding to vinylic proton.

*2.2. Synthesis of imidazo-[4,5-f]-quinolines **4(a–f)***

The synthesis of imidazo-[4,5-f]-quinolines **4(a–f)** has been realized by cyclisation of the open chain crotonic intermediates **3(a–f)** in the ethyl acetylacetate by reflux heating of substrates during 6 hours (Scheme 2).The structure of imidazo-[4,5-f]-quinolines **4(a–f)** has been established by spectroscopic data: NMR (^{1}H, ^{13}C), mass and analytical data.

The proton NMR spectres show the presence of one system AB corresponding to protons H^8 and H^9, one singlet corresponding to quinolinic proton. The structure of the exclusive product was confirmed by the isolation of the crotonic open chain intermediate which was selectively cyclised in position 4 instead of position 6. This result differ significantly from those which have been described and shows that the site the more reactive is the position 5 or 6 (El Kihel et al., 1999b; Benchidmi et al., 1995).

3. Conclusion

The results reported in this work concerning the condensation of 5-aminobenzimidazoles with β-ketoesters leading to new 1H-imidazo-[4,5-f]-quinoline derivatives. The structures of the obtained compounds were established without problem by spectroscopic data of proton and carbon 13 NMR, mass. The open chain intermediates are useful in this reaction and the regioselectivity of the cyclization has been demonstrated by spectroscopic data.

4. Experimental

All compounds were characterized by their ^{1}H-NMR and ^{13}C-NMR spectra as well as by microanalysis and HRMS spectra. NMR spectra were recorded on Bruker ARX 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C) spectrometer (δ-ppm/TMS, *J*-Hz); for ^{13}CNMR, the multiplicities were determined through DEPT. Microanalysis were performed by the "Laboratoire Central de Microanalyse du CNRS" (Lyon). Mass spectra were recorded on a Varian MAT 311 spectrometer. Melting points were measured using a Köfler apparatus and were uncorrected. Column chromatography was carried out by use of silica gel 60 Merck (230–400 Mesh).

*4.1. Reaction of 5-aminobenzimidazoles **1(a–c)** with 1,3-difunctional compounds*

A mixture of 5-aminobenzimidazoles **1(a–c)** (4.6 mmol) and 1,3-difunctional compounds (12.5 mmol) was heated with a steam bath at 80 °C until dissolution. The mixture was kept at this temperature for 2 hours. The crude product was filtered and recrystallised from ethanol.

*4.1.1. Ethyl 3-[6-(benzimidazolyl)amino]but-2-enoate **3a***

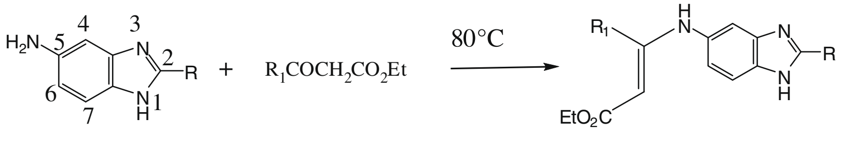
Yield = 75%; mp = 160–162 °C. ^{1}HNMR (DMSO-d$_6$): 1.22 (t, 3H, CH_3); 1.97 (s, 3H, CH_3); 4.09 (q, 2H, CH_2); 4.69 (s, 1H, =CH); 7.47 (d, 1H, H^4); 7.16 (dd, 1H, H^6); 7.64 (d, 1H, H^7); 8.29 (s, 1H, H^2); 10.39 (s, 1H, NH). ^{13}CNMR (DMSO-d$_6$): 14.5 (CH_3); 19.8 (CH_3); 58.1 (CH_2); 83.5 (=CH); 84.5, 119.9; 121.2 (ArCH); 159.0 (CH-2); 133.2, 142.9, 160.0; 165.2 (ArC); 169.6 (CO_2). HRMS, *m*/*z*: 245 (M), calcd for $C_{13}H_{15}N_3O_2$: 245.1165, found: 245.116.

*4.1.2. Ethyl 3-[6-(2-methylbenzimidazolyl)amino]but-2-enoate **3b***

Yield = 73%; mp = 142–144 °C. ^{1}HNMR (DMSO-d$_6$): 1.21 (t, 3H, CH_3); 1.93 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 4.10 (q, 2H, CH_2); 4.66 (s, 1H, =CH); 7.31 (d, 1H, H^4); 6.96 (dd, 1H, H^6); 7.47 (d, 1H, H^7); 10.34 (s, 1H, NH). ^{13}CNMR (DMSO-d$_6$): 14.4 (CH_3); 14.5 (CH_3); 19.7 (CH_3); 57.9 (CH_2); 84.1 (=CH); 118.8, 119.1; 122.2 (ArCH); 132.4, 133.7, 159.1; 160.0 (ArC); 152.3 (C-2); 169.4 (CO_2). HRMS, *m*/*z*: 259 (M), calcd for $C_{14}H_{17}N_3O_2$: 259.1321, found: 259.132.

*4.1.3. Ethyl 3-[6-(2-ethylbenzimidazolyl)amino]but-2-enoate **3c***

Yield = 69%; mp = 130–132 °C. ^{1}HNMR (DMSO-d$_6$): 1.21 (t, 3H, CH_3); 1.34 (t, 3H, CH_3); 1.94 (s, 3H, CH_3); 2.85 (q, 2H, CH_2); 4.08 (q, 2H, CH_2); 4.70 (s, 1H, =CH); 7.33 (d, 1H, H^4); 6.96 (dd, 1H, H^6); 7.49 (d, 1H, H^7); 10.35 (s, 1H, NH). ^{13}CNMR (DMSO-d$_6$): 12.1 (CH_3); 14.4 (CH_3); 19.7 (CH_3); 21.9 (CH_2); 57.9 (CH_2); 84.0 (=CH); 116.9, 118.1,

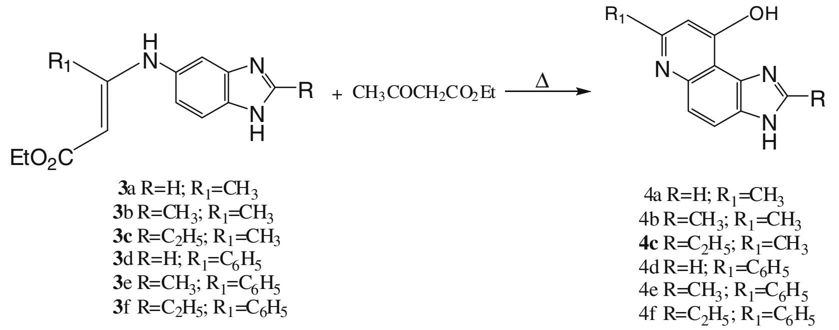


1a R=H
1b R=CH_3
1c R=C_2H_5

2a R_1=CH_3
2b R_1=C_6H_5

3a R=H; R_1=CH_3
3b R=CH_3; R_1=CH_3
3c R=C_2H_5; R_1=CH_3
3d R=H; R_1=C_6H_5
3e R=CH_3; R_1=C_6H_5
3f R=C_2H_5; R_1=C_6H_5

Scheme 1



Scheme 2

123.1 (ArCH); 132.4, 133.1, 157.2; 160.0 (ArC); 156.9 (C-2); 169.4 (CO_2). HRMS, *m/z*: 273 (M), calcd for $C_{15}H_{19}N_3O_2$: 273.1478, found: 273.147.

4.1.4. Ethyl 3-[6-(benzimidazolyl)amino]-3-phénylprop-2-enoate *3d*

Yield = 70%; mp = 202–204 °C. ^{1}HNMR (DMSO-d$_6$): 1.25 (t, 3H, CH_3); 4.15 (q, 2H, CH_2); 4.93 (s, 1H, =CH); 6.97 (d, 1H, H^4); 6.74 (dd, 1H, H^6); 7.22 (d, 1H, H^7); 7.35 (m, 5H, H$_{ar}$); 8.13 (s, 1H, H^2); 10.32 (s, 1H, NH). ^{13}CNMR (DMSO-d$_6$): 14.4 (CH_3); 58.8 (CH_2); 89.6 (=CH); 118.4, 120.3, 123.5, 128.1, 128.5; 129.5 (ArCH); 142.4(CH-2); 130.8, 134.8, 135.7, 159.5; 165.2 (ArC); 169.2 (CO_2). HRMS, *m/z*: 307 (M), calcd for $C_{18}H_{17}N_3O_2$: 307.1321, found: 307.132.

4.1.5. Ethyl 3-[6-(2-methylbenzimidazolyl)amino]-3-phenyl-prop-2-enoate *3e*

Yield = 68%; mp = 158–160 °C. ^{1}HNMR (DMSO-d$_6$): 1.24 (t, 3H, CH_3); 2.41 (s, 3H, CH_3); 4.15 (q, 2H, CH_2); 4.91 (s, 1H, =CH); 6.82 (d, 1H, H^4); 6.67 (dd, 1H, H^6); 7.18 (d, 1H, H^7); 7.24 (m, 5H, H$_{ar}$); 10.31 (s, 1H, NH). ^{13}CNMR (DMSO-d$_6$): 14.4 (CH_3); 14.5 (CH_3); 58.7 (CH_2); 89.2 (=CH); 117.6, 119.8, 123.2, 128.1, 128.4; 129.4 (ArCH); 131.1, 134.0, 135.7, 159.6; 161.2 (ArC); 151.8 (C-2); 169.2 (CO_2). HRMS, *m/z*: 321 (M), calcd for $C_{19}H_{19}N_3O_2$: 321.1478, found: 321.147.

4.1.6. Ethyl 3-[6-(2-ethylbenzimidazolyl)amino]-3-phenylprop-2-enoate *3f*

Yield = 75%; mp = 144–146 °C. ^{1}HNMR (DMSO-d$_6$): 1.24 (t, 3H, CH_3); 1.27 (t, 3H, CH_3); 2.75 (q, 2H, CH_2); 4.15 (q, 2H, CH_2); 4.91 (s, 1H, =CH); 6.84 (d, 1H, H^4); 6.67 (dd, 1H, H^6); 7.20 (d, 1H, H^7); 7.34 (m, 5H, H$_{ar}$); 10.32 (s, 1H, NH). ^{13}CNMR (DMSO-d$_6$): 12.0 (CH_3); 14.3 (CH_3); 21.8 (CH_2); 58.6 (CH_2); 89.1 (=CH); 117.6, 118.8, 122.2, 128.1, 128.5; 129.7 (ArCH); 131.5, 134.1, 135.8, 155.8; 159.6(ArC); 151.6 (C-2); 169.2 (CO_2). HRMS, *m/z*: 335 (M), calcd for $C_{20}H_{21}N_3O_2$: 335.1634, found: 335.163.

4.2. Formation of the cyclised products

The open chain intermediates **3(a–f)** (2.4 mmol) and ethyl acetoacetate (3.6 mmol) were heated under reflux for 5 h. After cooling, the obtained solid product was filtered off. The solid was chromatographed on silica gel (eluent: CH_2Cl_2/MeOH 95/5), then recrystallised from DMF.

4.2.1. 4-Hydroxy-6-methyl-1H-imidazo-[4,5-f]-quinoline *4a*

Yield = 84%; mp = 344–346 °C. ^{1}HNMR (DMSO-d$_6$–TFA): 2.42 (s, 3H, CH_3); 6.11 (s, 1H, H^5); 7.39 (d, 1H, H^9, J_{AB} = 8.8 Hz); 7.96 (d, 1H, H^8, J_{AB} = 8.8 Hz); 8.16 (s, 1H, H^2). ^{13}CNMR (DMSO-d$_6$–TFA): 19.3 (CH_3); 108.3 (=CH); 121.2, 122.5 (ArCH); 129.7, 132.3, 144.2; 155.6 (ArC); 141.0 (CH-2); 148.5 (N=C); 176.5 (C–O). HRMS, *m/z*: 199 (M), calcd for $C_{11}H_9N_3O$: 199.0751, found: 199.075. Analysis: $C_{11}H_9N_3O$ (199.2); calcd. C, 66.32; H, 4.55; N, 21.09; found C, 66.46; H, 4.41; N, 21.18.

4.2.2. 4-Hydroxy-2,6-dimethyl-1H-imidazo-[4,5-f]-quinoline *4b*

Yield = 82%; mp > 400 °C. ^{1}HNMR (DMSO-d$_6$–TFA): 2.74 (s, 3H, CH_3); 2.94 (s, 3H, CH_3); 7.00 (s, 1H, H^5); 7.84 (d, 1H, H^9, J_{AB} = 9.0 Hz); 8.17 (d, 1H, H^8, J_{AB} = 9.0 Hz). ^{13}CNMR (DMSO-d$_6$–TFA): 11.8 (CH_3); 19.5 (CH_3); 108.5 (=CH); 116.5, 119.7 (ArCH); 124.6, 127.7, 137.4; 142.2 (ArC); 155.1 (N=C); 151.8 (C-2); 169.5 (C–O). HRMS, *m/z*: 213 (M), calcd for $C_{12}H_{11}N_3O$: 213.0907, found: 213.091. Analysis: $C_{12}H_{11}N_3O$ (213.2); calcd. C, 67.59; H, 5.20; N, 19.71; found C, 67.76; H, 5.11; N, 19.58.

4.2.3. 2-Ethyl-4-hydroxy-6-methyl-1H-imidazo-[4,5-f]-quinoline *4c*

Yield = 82%; mp = 308–310 °C. ^{1}HNMR (DMSO-d$_6$–TFA): 1.20 (t, 3H, CH_3); 2.51 (s, 3H, CH_3); 3.02 (q, 2H, CH_2); 7.02 (s, 1H, H^5); 7.74 (d, 1H, H^9, J_{AB} = 9.0 Hz); 7.94 (d, 1H, H^8, J_{AB} = 9.0 Hz). ^{13}CNMR (DMSO-d$_6$–TFA): 13.6 (CH_3); 23.4 (CH_3); 23.8 (CH_2); 110.7 (=CH); 111.8; 122.2 (ArCH); 125.2, 128.5, 132.5; 143.5 (ArC); 161.3 (N=C); 142.1 (C-2); 171.5 (C–O). HRMS, *m/z*: 227 (M), calcd for $C_{13}H_{13}N_3O$: 227.1064, found: 227.106. Analysis: $C_{13}H_{13}N_3O$ (227.3); calcd. C, 68.70; H, 5.77; N, 18.49; found C, 68.76; H, 6.81; N, 18.38.

4.2.4. 4-Hydroxy-6-phenyl-1H-imidazo-[4,5-f]-quinoline *4d*

Yield = 79%; mp = 320–322 °C. ^{1}HNMR (DMSO-d$_6$–TFA): 6.59 (s, 1H, H^5); 7.60 (m, 3H, H^{ar}); 7.72 (d, 1H, H^9, J_{AB} = 8.8 Hz); 7.90 (m, 2H, H^{ar}); 8.07 (d, 1H, H8, J_{AB} = 8.8 Hz); 8.27 (s, 1H, H2). 13CNMR (DMSO-d$_6$–TFA): 107.7 (=CH); 112.4, 112.7, 124.1, 127.5; 128.8 (ArCH); 129.1, 130.2, 134.4, 137.6; 138.6 (ArC); 141.4(CH-2); 149.2 (N=C); 176.6 (C–O). HRMS, *m/z*: 261 (M), calcd for $C_{16}H_{11}N_3O$: 261.0907, found: 261.090. Analysis: C16H11N3O (261.3); calcd. C, 73.55; H, 4.24; N, 16.08; found C, 73.76; H, 4.15; N, 16.24.

4.2.5. 4-Hydroxy-2-methyl-6-phenyl-1H-imidazo-[4,5-f]-quinoline ***4e***

Yield = 80%; mp = 344–346 °C. ^{1}HNMR (DMSO-d_6–TFA): 2.89 (s, 3H, CH_3); 6.81 (s, 1H, H^5); 7.64 (m, 3H, H^{ar}); 7.91 (d, 1H, H^9, J_{AB} = 8.2 Hz); 7.91 (m, 2H, H^{ar}); 8.05 (d, 1H, H^8, J_{AB} = 8.2 Hz). ^{13}CNMR (DMSO-d_6–TFA): 12.0 (CH_3); 107.7 (=CH); 111.2, 117.1, 118.5, 125.8; 126.9 (ArCH); 127.6, 129.1, 130.8, 133.1; 138.4 (ArC); 150.9 (C-2); 153.2 (N=C); 174.3 (C–O). HRMS, *m/z*: 275 (M), calcd for $C_{17}H_{13}N_3O$: 275.1064, found: 275.106. Analysis: $C_{17}H_{13}N_3O$ (275.3); calcd. C, 74.17; H, 4.76; N, 15.26; found C, 74.05; H, 4.81; N 15.35.

4.2.6. 2-Ethyl-4-hydroxy-6-phenyl-1H-imidazo-[4,5-f]-quinoline ***4f***

Yield = 77%; mp = 280–282 °C. ^{1}HNMR (DMSO-d_6–TFA): 1.20 (t, 3H, CH_3); 3.04 (q, 2H, CH_2); 7.41 (s, 1H, H^5); 7.29 (m, 3H, H^{ar}); 7.92 (d, 1H, H^9, J_{AB} = 9.3 Hz); 7.49 (m, 2H, H^{ar}); 800 (d, 1H, H^8, J_{AB} = 9.3 Hz). ^{13}CNMR (DMSO-d_6–TFA): 13.7 (CH_3); 24.0 (CH_2); 110.3 (=CH); 112.3, 122.9, 125.8, 128.7; 131.6 (ArCH); 132.8, 133.9, 134.1, 137.8; 142.7 (ArC); 161.5 (C-2); 162.1 (N=C); 171.7 (C–O). HRMS, *m/z*: 289 (M), calcd for $C_{18}H_{15}N_3O$: 289.1220, found: 289.122. Analysis: $C_{18}H_{15}N_3O$ (289.3); calcd. C, 74.72; H, 5.23; N, 14.52; found C, 74.66; H, 5.11; N, 14.38.

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