Propionic acids in organic synthesis: Novel synthesis of benzimidazole, 3,1-benoxazine, 3-aminoquinazoline and 3-aminothieno[2,3-d]pyrimidine derivatives containing 2-naphthyl propionyl moiety

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Naproxenoyl chloride 2 is reacted with some nucleophilic reagents as ammonium thiocyanate and sodium azide to produce the novel isothiocyanate 3 and azide 4 derivatives, respectively. Interaction of isothiocyanate 3 with 1,2-phenylenediamine and anthranilic acid has produced the corresponding benzimidazole 5 and 3,1-benoxazine 7 derivatives, respectively. Treatment of acid azide 4 with p-toluidine afforded urea derivative 9. The novel quinazolinone 11 was synthesized by acylation of methyl anthranilate with acid chloride 2 followed by treatment with hydrazine hydrate.

Key words: Propionic acids, benzimidazole, benoxazine, aminoquinazoline, aminothienopyrimidine, naphthyl propionyl moiety, ammonium thiocyanate, sodium azide

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Derivatives of 2-arylpropionic acids are useful medicinal drugs having antiinflammatory activity. Also, many quinazolines and thieno[2,3-d]pyrimidines are known for their biological activities. In continuation of our research program on the synthesis of novel heterocyclic compounds exhibiting biological activity, we herein report the synthesis of urea, acid azide, quinazoline and thieno[2,3-d]pyrimidine derivatives containing 2-naphthyl propionyl moiety.

Reaction of naproxenoyl chloride 2 with ammonium thiocyanate in acetone under reflux gave naproxenoyl isothiocyanate 3 in good yield (Scheme I). The structure of the product 3 was deduced from IR spectrum which exhibited the presence of characteristic band for N=C=S functional at 2080 cm\(^{-1}\). Also, compound 2 was reacted with sodium azide in refluxing acetone to furnish the novel acid azide derivative 4. The IR spectrum showed a sharp band for N\(_3\) group at 2230 cm\(^{-1}\). In the present investigation the reactivity of isothiocyanate 3 towards some nucleophilic reagents was discussed. Thus, interaction of isothiocyanate derivative 3 with \(\alpha\)-phenylenediamine in toluene and triethylamine gave the novel benzimidazole derivative 5 (Scheme I). The structure of 5 was established on the basis of analytical and spectral data. The \(^1\)H NMR spectrum of 5 showed the presence of a doublet at \(\delta\) 1.54 for CH\(_3\) group, a singlet at 3.84 for OCH\(_3\) group, a quartet at 4.85 for CH, a multiplet at 7.07-7.85 for aromatic protons and two NH groups at 10.20 and 10.60 ppm. The formation of 5 was assumed to proceed via the addition of the nucleophilic group NH\(_2\) to isothiocyanate 3 followed by elimination of hydrogen sulphide. Also, treatment of isothiocyanate 3 with anthranilic acid and methyl anthranilate in acetone gave the thiourea derivatives 6a,b. On the other hand anthranilic acid underwent cyclocondensation reaction with isothiocyanate 3 in dioxane in presence of triethylamine to afford the novel 3,1-benoxazine derivative 7.

The novel urea derivative 9 was synthesized through reaction of 4 with p-toluidine under reflux in dry toluene. The formation of 9 is assumed to proceed via Curtius rearrangement of acid azide 4 into isocyanate 8 followed by interaction with p-toluidine to form urea derivative (Scheme I).

This part of the research was directed towards the synthesis of some quinazolinone derivatives containing asymmetric carbon atom in the 2- and 3- positions.
Thus, the anthranilic acid derivatives were subjected to acylation with naproxenoyl chloride 2 to yield the corresponding carboxamide derivatives 10a-c. The amide 10a was cyclized with hydrazine hydrate in n-butanol to the corresponding 3-氨基喹唑啉酮 derivative 11. Also, 3-氨基喹唑啉酮 derivative 13 was obtained upon refluxing 10b,c with acetic anhydride to form the benzoxazine derivatives 12a,b followed by treatment of 12b with hydrazine hydrate in n-butanol. In a similar manner, ethyl 4,5-disubstituted-2-氨基噻吩-3-羧酸酯 14a,b were reacted with naproxenoyl chloride 2 in benzene/TEA to furnish the corresponding amide derivatives 15a,b which on treatment with hydrazine hydrate yielded 3-氨基噻吩[2,3-d]嘧啶 16a,b (Scheme II).

The reactivity of 3-氨基喹唑啉酮 derivative 11 towards some carboxylic acid derivatives was studied. Thus, acylation of 11 with benzoyl chloride, chloroacetyl chloride and succinic anhydride afforded the carboxamide derivatives 17-19. The anticipated structures were verified on the basis of elemental and spectral data.

While, condensation of naproxenoyl chloride 2 with N- amino derivatives 20 and 21 in toluene/triethylamine afforded the novel amide derivatives 22 and 23, respectively (Scheme III). The elemental analysis and spectral data supported the proposed structure.

**Experimental Section**
Melting points are uncorrected. IR spectra were recorded (KBr pellet) on a Perkin-Elmer 1650 spectrometer. $^{1}$H NMR spectra were recorded on a Varian Gemini Spectrometer 200 (200 MHz), using
Compd | X | R
---|---|---
10 a | H | CH₃
b | H | H
c | Cl | H
12 a | H | -
b | Cl | -
14 | R | 
15 a,b | R | 
16 | R | 

Scheme II
DMSO-$d_6$ as a solvent and TMS as internal standard. Chemical shifts are expressed as $\delta$ in ppm. Microanalytical data were obtained from the microanalytical data unit at the Cairo University. Physical and analytical data for the synthesized compounds are given in Table I.

**Naproxenoyl chloride 2.** To a solution of naproxen 1 (0.01 mole) in $m$-xylene (30 mL), $PCl_3$ (5 mL) was added. The solution was refluxed for 3 hr, cooled and the solid was filtered off, washed with ether to give 2 as colourless crystals (Table I).

**2-(6-Methoxynaphthalene-2-yl) propionylisothiocyanate 3.** To a suspension of 2 (0.01 mole) in dry acetone (50 mL), ammonium thiocyanate (0.01 mole) was added. The solution was refluxed for 3 hr. The precipitated product was collected by filtration and recrystallized from benzene to give 3 (Table I).

**2-(6-Methoxynaphthalene-2-yl)propionylazide 4.** A mixture of 2 (0.01 mole) and sodium azide (0.01 mole) in dry acetone (40 mL) was refluxed for 3 hr. The precipitate that separated was filtered off, washed with ether and dried (Table I).

**N-(1H-Benzimidazole-2-yl)-2-(6-methoxynaphthalene-2-yl)propionamide 5.** A mixture of 3 (0.01 mole) and 1,2-phenylenediamine (0.01 mole) in dry toluene (40 mL) in presence of triethylamine (0.5 mL) was refluxed for 8 hr. The hot reaction mixture was filtered, cooled and the resulting solid was dried and recrystallized from ethanol to give 5 (Table I). $^1$H NMR (DMSO-$d_6$): $\delta$ 1.54 (d, 3H, CH$_3$), 3.84 (s, 3H,
2-{3-[2-(6-Methoxynaphthalene-2-yl)propionyl]-thioureido}-benzoic acid derivatives 6a,b. A mixture of 3 (0.01 mole) and anthranilic acid or methyl anthranilate (0.01 mole) in dry acetone (40 mL) was refluxed for 4 hr, allowed to cool, the solid product that obtained was collected by filtration and recrystallized from ethanol to give 6a,b (Table I). Mass spectrum of compound 6b exhibited a molecular ion peak at m/z 408 (35%) with base peak at m/z 94 and other peaks at m/z: 278 (25%), 265 (48%), 219 (90%), 148 (58%).

2-(6-Methoxynaphthalene-2-yl)-N-(4-oxo-4H-benzo[d][1,3]-oxazine-2-yl)propionamide 7. A mixture of 3 (0.01 mole) and anthranilic acid or methyl anthranilate (0.01 mole) in dioxane (40 mL) and a few drops of triethylamine was refluxed for 6 hr, then allowed to cool and poured into ice-water. The solid product was collected by filtration and recrystallized from benzene to give 7 (Table I). Mass spectrum of compound 7 revealed a molecular ion peak at m/z 374 (60%) and base peak at m/z 185.

1 - [1 - (6-Methoxynaphthalene-2-yl)-ethyl]3-(4-toly)urea 9. A mixture of 4 (0.01 mole) and p-toluidine (0.01 mole) in dry toluene (40 mL) was heated under reflux for 1 hr. On cooling, the precipitated solid was collected by filtration and recrystallized from benzene to give 9 (Table I). Mass spectrum of compound 9 showed a molecular ion peak at m/z 334 (25%) with base peak at m/z 107 and other peaks at m/z: 227 (14%), 185 (68%), 141 (18%).

2 - [2 - (6-Methoxynaphthalene-2-yl)-propionyl amino]benzoic acid derivatives 10a-c. A mixture of 2 (0.01 mole) and anilinic acid derivatives in benzene (40 mL) was heated under reflux for 4 hr. The solid product was collected and recrystallized from ethanol to give 10a-c (Table I).

3-Amino-2-[1-(6-methoxynaphthalene-2-yl)-3-(4H-quinazoline-4-one) 11. A mixture of compound 10a (0.01 mole) and hydrazine hydrate (0.12 mole) in n-butanol (20 mL) was heated under reflux for 10 hr. The solid product was collected and recrystallized from ethanol to give 11 (Table I). 1H NMR (DMSO-d6): 6 1.66 (d, 3H, CH3), 3.80 (s, 3H, OCH3), 5.12 (q, 1H, CH), 5.54 (s, 2H, NH2), 7.07-8.11 (m, 10H, Ar-H), 10.20, 10.60 (2s, 2H, 2NH).

2-[1-(6-Methoxynaphthalene-2-yl)ethyl]-benzo[d][3,1]-oxazine-4-ones 12a,b. Compound 10b or 10c (0.01 mole) was refluxed in acetic anhydride (10 mL) for 5 hr, then allowed to...
cool. The solid product was collected and recrystallized from benzene to afford 12a,b (Table 1).

3-Amino-6,8-dichloro-2-[1-(6-methoxy-naphthalene-2-yl)-ethyl]-3H-quinazoline-4-one 13. A mixture of 12b (0.01 mole) and hydrazine hydrate (0.12 mole) in ethanol (50 mL) was refluxed for 3 hr and allowed to cool. The solid product was collected and recrystallized from ethanol to give 13 (Table 1). Its mass spectrum 13 showed a molecular ion peak at m/z 413 (32%) and other peaks at m/z: 414 (M+1; 32%), 226 (25%), 172 (80%), 141 (100%), 74 (30%).

2-[2-(6-Methoxynaphthalene-2-yl)propionylamino]-thiophene-3-carboxylic acid ethyl ester 15a and 2-[2-(6-methoxynaphthalene-2-yl)propionylamino]-4, 5, 6, 7-tetrahydro-benzothiophene-3-carboxylic acid ethyl ester 15b. A mixture of 2 (0.01 mole) and aminothiophene 14a or 14b (0.01 mole) in dry benzene (40 mL) in the presence of triethylamine (0.5 mL) was heated under reflux for 24 hr. The solid product was collected and recrystallized from proper ethanol to give 15a,b (Table 1). 15a: 1H NMR: (DMSO-d6): δ 1.12 (t, 3H, CH3), 3.84 (s, 3H, OCH3), 4.04 (m, 3H, CH + CH2O), 7.10-7.80 (m, 6H, Ar-H), 10.65 (s, 1H, NH) and 10.85 (s, 1H, COOH).

3-Amino-2-[1-(6-methoxynaphthalene-2-yl)ethyl]-5,6-dimethyl-3H-thieno[2,3-d]-pyrimidine-4-one 16a and 3-amino-2-[1-(6-methoxynaphthalene-2-yl)ethyl]-5,6,7,8-tetrahydro-3H-benzo[4,5][thieno[2,3-d]pyrimidine-4-one 16b. A mixture of 15a or 15b (0.01 mole) and hydrazine hydrate (0.01 mole) in n-butanol (15 mL) was heated under reflux for 12 hr. The solid product was collected and recrystallized from DMF/H2O to give 16a,b (Table 1). 16a: 1H NMR (DMSO-d6): δ 1.63 (d, 3H, CH3), 2.35, 2.38 (2s, 6H, 2CH3), 3.80 (s, 3H, OCH3), 5.10 (q, 1H, CH), 5.56 (s, 2H, NH2), 7.10-7.80 (m, 6H, Ar-H); 16b: (KBr, cm−1): 3400, 3300 (NH2), 3050 (CH-arom), 2990 (CH-aliph), 1680 (C=O); 1H NMR DMSO-d6: δ 1.67, 2.48 (tetrahydrobenzo-H), 3.84 (s, 3H, OCH3), 4.05 (q, 1H, CH), 4.42 (s, 2H, NH2), 7.10-7.80 (m, 6H, Ar-H).

N-[2-[1-(6-Methoxynaphthalene-2-yl)ethyl]-4-oxo-4H-quinazoline-3-yl]benzamide 17 and 2-chloro-N-[2-[1-(6-methoxynaphthalene-2-yl)ethyl]-4-oxo-4H-quinazoline-3-yl]acetamide 18. A mixture of compound 11 (0.01 mole) and benzyol chloride or chloro acetyl chloride (0.01 mole) in pyridine (30 mL) was refluxed for 1 hr and allowed to cool and acidified with HCl. The solid product was collected and recrystallized from ethanol to give 17 and 18, respectively. Mass spectrum of 18 displayed a molecular ion peak m/z 421 (10%) with base peak at m/z 330.

N-[2-[1-(6-Methoxynaphthalene-2-yl)ethyl]-4-oxo-4H-quinazoline-3-yl] succinamic acid 19. A mixture of 11 (0.01 mole) and succinic anhydride (0.01 mole) in ethanol (30 mL) was refluxed for 3 hr and cool. The obtained product was recrystallized from benzene to afford 19 (Table 1); 1H NMR (DMSO-d6): δ 1.63 (d, 3H, CH3), 2.75-3.0 (2t, 4H, 2CH2), 3.83 (s, 3H, OCH3), 4.25 (q, 1H, CH), 7.1-8.1 (m, 10H, Ar-H), 10.65 (s, 1H, NH) and 10.85 (s, 1H, COOH).

N-(2-Benzyl-6,8-dichloro-4-oxo-4H-quinazoline-3-yl)-2-(6-methoxynaphthalene-2-yl)propionamide 22 and N-(2-benzoyl-5,6-dimethyl-4-oxo-4H-thieno[2,3-d]pyrimidine-3-yl)-2-(6-methoxynaphthalene-2-yl)propionamide 23. A solution of 2 (0.01 mole) and 20 or 21 (0.01 mole) in toluene (50 mL) in the presence of triethylamine (0.5 mL) was refluxed for 48 hr. The reaction mixture was filtered, then cooled and the resulting solid was dried and recrystallized from proper solvent to give 22 and 23, respectively (Table 1). Compd 22: 1H NMR (DMSO-d6): δ 1.52 (d, 3H, CH3), 2.17 (s, 2H, CH2), 3.87 (q, 1H, CH), 3.99 (s, 3H, OCH3), 7.20-8.10 (m, 13H, Ar-H), 12.85 (s, 1H, NH); 23: 1H NMR (DMSO-d6): δ 1.52 (d, 3H, CH3), 2.47 (s, 2H, CH2), 3.8 (q, 1H, CH), 3.88 (s, 3H, OCH3), 7.10-7.80 (m, 11H, Ar-H), 12.39 (s, 1H, NH).

References