Synthesis of novel 2-propenoyl amides, esters, heterocyclic compounds and their screening as antifungal and antibacterial agents

Ahmed El-Ziatya,*, Abdelaal Abdalha, Ashraf Hamedb, Sayed Shiba and Abdelhafed Abdullhaa

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1. Introduction

The recent wide importance of 2-propenoylamides [1,2], 2-propenoates [3-6], besides, the interesting biological and pharmacological activities of many heterocyclic systems, like, benzoaxazoles [7], pyrimidines [8], pyridopyrimidines [9], oxazoles [10], benzoazazines [11,12], oxadiazoles [13] and pyrazoles [14] encourage the authors to gather these moieties hoping to produce a valuable new compounds of expected antibacterial and antifungal activity. We report here the synthesis of 2-propenoyl amides, 2-propenoyl esters and some heterocyclic systems by developed, simple convenient and efficient procedure. Also this modified method is fast, cheap and unequivocal preparation with improved yields.

2. Experimental

2.1. Instrumentation

Melting points were taken on Griffin and Geory melting point apparatus and are uncorrected. FT-IR spectra were recorded on Pye Unicam SP 1200 spectrophotometer using the KBr wafer technique. 1H NMR spectra were determined on Varian Gemini 300 MHz using TMS as internal standard. All chemical shifts (δ) are expressed in ppm. All the NH or OH protons are exchangeable on addition of D2O. The elemental analyses were investigated by Elemental analyzer Vario EL III.

2.2. Syntheses

2.2.1. 2-cyano-3-(2',4'-dichloropheny1)acryloyl chloride (3)

A mixture of 2 (10 g) and thionyl chloride (15 mL) was heated on water bath for 3 hours. The excess thionyl chloride was distilled under reduced pressure; the solid separated was collected, triturated with petroleum ether 40-60 °C, dried and recrystallized from benzene to give 3 (Scheme 1). Yellow. Yield: 90%. M.p.: 88-90 °C. FT-IR (KBr, ν, cm⁻¹): 2205 (C≡N), 1738 (C=O). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 8.39 (s, 1H, =CH), 8.04 (d, 1H, J = 8.4 Hz, Ar-H), 7.77 (s, 1H, Ar-H) 7.60 (d, 1H, J = 8.4 Hz, Ar-H). Anal. calcd. for C10H4Cl3NO: C, 46.42; H, 1.55; N, 5.34%.

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1H, J (d, ppm): 10.35 (s, 1H, NH), 8.36 (s, 1H, =CH), 8.06 (d, 1H, J = 8.4 Hz, Ar-H), 7.88 (s, 1H, Ar-H), 7.69 (d, 1H, J = 8.4 Hz, Ar-H), 7.58 (d, 2H, J = 8.4 Hz, Ar-H), 6.9 (d, 2H, J = 8.4, Ar-H), 3.74 (s, 3H, OCH3). Anal. calcd. for C17H12Cl2N3O: C, 56.6; H, 2.65; N, 11.67. Found: C, 56.65; H, 2.99; N, 11.61.

2.2.4. (E)-3-(2,4-chlorophenyl)-2-(5-phenyl-1,3,4-oxadiazol-2-yl)acrylonitrile (11)

A mixture of 10 (1 g) and phosphorus oxychloride (10 mL) was heated on water bath for 6 hours. After cooling the reaction mixture was poured on crushed ice (20 g). The solid separated was filtered, washed with water (50 mL) and dried and recrystallized from ethanol to give 11 (Scheme 2). Green. Yield: 75%. M.p.: 176-178 °C. FT-IR (KBr, v, cm⁻¹): 2205 (C≡N). 1H NMR (300 MHz, CDCl3, δ, ppm): 8.56 (s, 1H, Ar-H) 8.27 (d, 1H, J = 8.4 Hz, Ar-H) 8.14 (d, 1H, J = 8.1 Hz, Ar-H) 7.54-7.43 (m, 6H, Ar-H, SPh+Iaryl). Anal. calcd. for C17H12ClN3O: C, 59.67; H, 2.65; N, 12.28. Found: C, 59.72; H, 2.61; N, 12.33.

2.2.5. 6-(2,4-Dichlorophenyl)-4-hydroxy-1-methyl-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (12)

N-methylthiourea (0.45 g, 0.005 mol) was added to a solution of 3 (1.30 g, 0.005 mol) in dry benzene (50 mL) and triethylamine (0.05 g, 0.005 mol), the reaction mixture was refluxed for one hour. The solid formed was collected, washed with water (80 mL), dried and recrystallized from ethanol to give 12 (Scheme 2). Yellow. Yield: 80%. M.p.: 186-188 °C. FT-IR (KBr, v, cm⁻¹): 3449 (OH), 2211 (C≡N), 1633 (C=O). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 7.9 (d, 1H, J = 7.8 Hz, Ar-H) 7.8 (d, 1H, J = 7.8 Hz, Ar-H) 7.76 (s, 1H, Ar-H) 3.79 (s, 3H, NCH2). 1L (1H, OH). Anal. calcd. for C17H12ClN3OS: C, 46.17; H, 2.26; N, 13.46. Found: C, 45.81; H, 2.81; N, 13.43.

2.2.6. 1-(2-Cyano-3-(2,4-dichlorophenyl)acryloyl)-3-phenylurea (13)

A mixture of 3 (1.30 g, 0.005 mol), triethylamine (0.05 g, 0.005 mol) and phenylurea (0.681 g, 0.005 mol) in dry benzene (50 mL) was stirred for 2 hours. The separated solid was filtered, washed with water (80 mL), dried and recrystallized from benzene to give 13 (Scheme 2). Yellow. Yield: 60%. M.p.: 180-181 °C. FT-IR (KBr, v, cm⁻¹): 3231, 3129 (NH), 2229 (C≡N), 1704, 1660 (C=O). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 10.23 (s, 1H, NH), 8.5 (s, 1H, =CH), 8.06-8.53 (m, 8H, Ar-H), 5.8 (s, 1H, NH). Anal. calcd. for C17H12ClN3O: C, 56.69; H, 3.08; N, 11.67. Found: C, 56.62; H, 3.12; N, 11.59.

2.2.7. Synthesis of compounds 14 and 15

A mixture of 3 (1.30 g, 0.005 mol), triethylamine (0.05 g, 0.005 mol) and 2-aminoypyridine (0.47 g, 0.005 mol) in dry benzene (50 mL) was stirred for 2 hours. The separated solid was filtered, washed with water, dried and recrystallized from benzene to give 14 and then from ethanol to give 15 (Scheme 2).

2-Cyano-3-(2,4-dichlorophenyl)-N-(pyridin-2-yl)acrylamide (14): Yellow. Yield: 90%. M.p.: 210-211 °C. FT-IR (KBr, v, cm⁻¹): 3305 (NH), 2216 (C≡N), 1669 (C≡O). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 8.3 (s, 1H, =CH), 8.07 (d, 1H, J = 8.4 Hz, Ar-H) 6.03 (m, 3H, Ar-H), 7.6 (s, 1H, NH), 6.7-6.6 (m, 3H, Ar-H). Anal. calcd. for C17H12ClN3O: C, 56.63; H, 2.85; N, 13.21. Found: C, 56.59; H, 2.89; N, 13.28.
pyrimidine-3-carbonitrile (15). Yellow. Yield: 65%. M.p.: 152-153 °C. FT-IR (KBr, ν, cm⁻¹): 3444 (NH), 2186 (C≡N), 1681 (C=O). 1H NMR (300 MHz, DMSO-d₆): C, 46.90; H, 2.76; N, 16.41. Found: C, 46.85; H, 2.71; N, 16.38%.

2.2.8. Synthesis of compounds 16 and 17

Thiosemicarbazide (0.45 g, 0.005 mol) was added to a solution of 3 (1.30 g, 0.005 mol) in dioxane (20 mL) and triethylamine (0.505 g, 0.005 mol). The reaction mixture was refluxed for an hour. The solid formed was ammonium salt; the filtrate was concentrated, and the remaining semisol was recrystallized from benzene to give 16 and then from benzene/ethanol mixture to give 17 (Scheme 3).

1-(2,4-Dichlorobenzylidene)thiosemicarbazide (16) the structure was confirmed by m.p. with an authentic sample [15].

4-(2,4-Dichlorobenzylidene)-3-amino-1H-pyrazol-5-(4H)-one (17): Reddish brown. Yield: 84%. M.p.: 150-151 °C. FT-IR (KBr, ν, cm⁻¹): 3179, 3263, 3369 (NH, NH₂), 1645 (C=O), 1619 (C=N). 1H NMR (300 MHz, DMSO-d₆, δ ppm): 8.54 (s, 1H, NH), 8.35 (s, 1H, =CH), 7.4-7.2 (m, 3H, Ar-H), 4.4 (s, 2H, NH₂). Anal. calcd. for C₁₇H₁₀Cl₂N₂O: C, 56.63; H, 2.85; N, 13.21. Found: C, 56.56; H, 2.93; N, 13.21%.

2.2.9. 3-(2,4-Dichlorophenyl)-2-(4,5-dihydrooxazol-2-yl) acrylonitrile (18)

A mixture of 3 (1.30 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol) and ethanolamine (0.305 g, 0.005 mol) in dry benzene (50 mL) was stirred for 2 hours. The separated solid was filtered, washed with water (50 mL), dried and recrystallized from ethanol to give 18 (Scheme 3). Yellow. Yield: 90%. M.p.: 220-222 °C. FT-IR (KBr, ν, cm⁻¹): 2209 (C≡N), 1642 (C=N). 1H NMR (300 MHz, DMSO-d₆, δ ppm): 7.77 (s, 1H, =CH), 7.69-7.40 (m, 3H, Ar-H), 3.61 (t, 2H, J = 6.90 Hz, CH₂-O), 1.84 (t, 2H, J = 6.90 Hz, N-CH₂). Anal. calcd. for C₁₃H₁₁ClN₂O: C, 53.96; H, 3.02; N, 10.49. Found: C, 53.89; H, 2.98; N, 10.51%.

2.2.10. 2-(Cyano-3-(2,4-dichlorophenyl)acrylamido) benzoic acid (19)

A mixture of 3 (2.60 g, 0.01 mol), triethylamine (1.01 g, 0.01 mol) and anthranilic acid (1.37 g, 0.01 mol) in dry benzene (100 mL) was refluxed for an hour. The solid separated was filtered, washed with water (100 mL), dried and recrystallized from benzene to give 19 (Scheme 3). Brown. Yield: 84%. M.p.: 172-173 °C. FT-IR (KBr, ν, cm⁻¹): 3359 (NH), 2220 (C≡N), 1689 (C=O). 1H NMR (300 MHz, DMSO-d₆, δ ppm): 10.75 (s, 1H, COOH), 8.39 (s, 1H, =CH), 8.07-7.94 (m, 4H, Ar-H), 7.89 (s, 1H, NH), 7.81-7.62 (m, 3H, Ar-H). Anal. calcd. for C₁₇H₁₀Cl₂N₂O: C, 56.53; H, 2.79; N, 7.76. Found: C, 56.68; H, 2.82; N, 7.68%.
2.2.11. 3-(2,4-Dichlorophenyl)-2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)acrylonitrile (20)

A mixture of 19 (2 g) and freshly distilled acetic anhydride (5 mL) was heated on a water bath for 6 hours. After cooling the solid separated was collected, washed with dry petroleum ether (40-60 °C), dried and recrystallized from ethanol to give 20 (Scheme 3): Green. Yield: 85%, M.p.: 172-173 °C. FT-IR (KBr, v, cm⁻¹): 2205 (C≡N), 1758 (C=O). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 8.52 (s, 1H, =CH), 7.43-7.40 (m, 4H, Ar-H). Anal. calcd. for C₁₇H₁₂Cl₂N₂O: C, 59.50; H, 2.56; N, 8.89. Found: C, 58.57; H, 2.49; N, 8.61%.

2.2.12. 2-Cyano-3-(2,4-dichlorophenyl)-N-(2-hydroxy phenyl) acrylamide (21)

A mixture of 3 (130 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol) and 2-aminophenol (0.54 g, 0.005 mol) in dry benzene (50 mL) was refluxed for an hour. The solid separated was filtered, washed with water (80 mL), dried and recrystallized from toluene to give 21 (Scheme 3): Yellow. Yield: 92%, M.p.: 108-110 °C. FT-IR (KBr, v, cm⁻¹): 3247, 3353 (NH). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 10.15 (s, 1H, NH), 9.4 (s, 1H, OH), 8.43 (s, 1H, =CH). Anal. calcd. for C₁₇H₁₄Cl₂N₂O: C, 57.68; H, 3.03; N, 8.41. Found: C, 57.56; H, 2.98; N, 8.32%.

2.2.13. 2-(Benzoxazol-2-yl)-3-(2,4-dichlorophenyl) acrylonitrile (22)

A mixture of 21 (1 g) and phosphorus oxychloride (10 mL) was heated on water bath for 6 hours. After cooling the reaction mixture was poured on crushed ice (20 g). The solid separated was filtered, washed with water (50 mL), dried and recrystallized from ethanol to give 22 (Scheme 3): Green. Yield: 82%. M.p.: 150-152 °C. FT-IR (KBr, v, cm⁻¹): 2205 (C≡N) and 1622 (C=O). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 8.6-7.8 (m, 3H, Ar-H), 7.43-7.40 (m, 4H, Ar-H). Anal. calcd. for C₁₇H₁₂Cl₂N₂O: C, 60.98; H, 2.55; N, 8.89. Found: C, 60.86; H, 2.51; N, 8.81%.

2.3. Antimicrobial and antifungal activities

A filter paper sterilized disc saturated with measured quantity of the sample with concentration of 20 mg/mL was placed on a plate containing solid bacterial medium (nutrient agar broth) or fungal medium (Dox’s medium) which was heavily seeded with the spore suspension of the tested organism. After incubation, the diameter of the clear zone of inhibition surrounding the sample was taken as a measure of the inhibitory power of the sample against the particular test organism [16-19].

The selected samples were screened against Gram-positive: *Staphylococcus aureus* and Gram-negative *Escherichia coli*. Antifungal activity was tested using *Aspergillus flavus* and *Candida albicans* (Table 1).

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* Solvent: Chloroform; 0: no activity (inhibition zone less than 7 mm); 7-10 weak activity; 11-15 moderate activity; more than 15 strong activity.
3. Results and discussion

In continuation of our efforts to study the reactivity of 2-propenoyl chlorides towards some nitrogen and oxygen nucleophilic reagents [20-23], we reported herein, the synthesis of a new compound, (E)-2-cyano-3-(2,4-dichlorophenyl)acryloyl chloride 3 via the common route condensation of 2,4-dichlorobenzaldehyde with ethyl cyanoacetate in the presence of piperidine, to give the corresponding (E)-ethyl 2-cyano-3-(2,4-dichlorophenyl)acrylate, 1, [24]. Hydrolysis of 1 in alcoholic solution of sodium hydroxide (1:1 mole) gave (E)-2-cyano-3-(2,4-dichlorophenyl)acrylic acid, 2, [25]. Refluxing the acid 2 with thionyl chloride yielded the new acryloyl chloride derivative 3 in good yield (Scheme 1).

The acryloyl chloride derivative 3 was reacted with phenol, 4-chlorothiophenol and primary amines such as, 4-methoxyaniline, 4-methylaniline-3-chloroaniline and 3-amino pyridine in dry benzene in the presence of triethylamine to give acrylate, thioacrylate and acrylamides, 4-9, respectively (Scheme 2).

On the other hand, reaction of the acryloyl chloride derivative 3 with benzoyl hydrazine as a bifunctional nucleophile under the same conditions gave the benzoyl hydrazide derivative 10 which underwent ring closure upon heating with POCI₃ to give the oxadiazole derivative 11 (Scheme 2). When the acryloyl chloride derivative 3 was allowed to react with methylthiourea, phenylurea and 2-aminopyridine as 1,3-binucleophilic reagents, it gave the tetrahydropyrimidine-2-thione derivative 12, 1-acryloyl-3-phenyl urea derivative 13 and a mixture of acrylamide derivative 14 and pyridopyrimidine derivative 15, respectively (Scheme 2).

The formation of compound 12 can be represented by the following pathway (Scheme 4). The formation of compounds 14 and 15 can be explained by the following pathway (Scheme 5).

When the acryloyl chloride derivative 3 was allowed to react with thiourea, thiourea and 2-amino pyridine, it gave a mixture of the thiosemicarbazone 16 and the pyrazolidone derivative 17 (Scheme 3). The acryloyl derivative 3 condensed with ethanolamine to give the dihydroxazole derivative 18 (Scheme 3). 2-Propenoyl amide 19 was prepared by condensation of 3 with anthranilic acid in the presence of triethylamine (TEA). The structure of 19 was confirmed chemically by ring closure using acetic anhydride whereby the benzoxazinone 20 was obtained (Scheme 3).
The acrylamide derivative 21, which was prepared by the reaction of 3 with 2-aminophenol, gave the benzoxazole derivative 22 upon heating with phosphorus oxychloride (Scheme 3).

The formation of compounds 16 and 17 can be represented by the following pathway Scheme 6.

4. Conclusion

2-Propanoyl derivatives and some heterocyclic compounds with antibacterial and antifungal activities were synthesized from readily obtainable starting materials such as 2-cyano-3-[2',4'-dichlorophenyl]acryloyl chloride, 3.

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References