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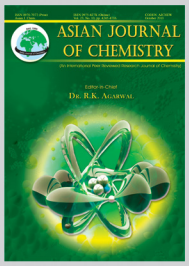

Ultrasound-Promoted Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-thiones *via* One-Pot, Three-Component Reaction Catalyzed by Formic Acid

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A simple method for the one-pot, three-component Biginelli condensation reaction of substituted aromatic aldehydes, β-ketoester and thiourea is described, employing anhydrous formic acid as an efficient catalyst using ultrasound irradiation method. Currently, ultrasound irradiation is applied in many fields of organic synthesis to shorten reaction times and easier workup matching with green chemistry protocols.

Key Words: Biginelli reaction, 3,4-Dihydropyrimidin-2-(1*H*)-thiones, Ultrasound, Formic acid.

INTRODUCTION

Pyrimidine derivatives are well known heterocyclic units realm of natural and synthetic organic chemistry due to their biological activities[1-12]. They show various interesting therapeutic and pharmacological properties including antiviral[2], antibacterial[1,5], antitumor[6,13,14] and antiflammatory[14-16] activities. These diverse properties prompted us to synthesize those derivatives and evaluate their inhibitory potential against tumor cells.

EXPERIMENTAL

Melting points were determined using an electrothermal IA9000 series digital capillary melting point apparatus. IR spectra were obtained as KBr discs on a 1000-Perkin Elmer FT-IR. ^{1}H and ^{13}C NMR spectra were recorded on Bruker-600 NMR in DMSO-d_6 as solvent and TMS as internal standard, chemical shifts are given in ppm. MS spectra were acquired with the aid of a Varian MAT 311-A 70 eV (Varian Fort Collins, USA), Microanalytical Center, Cairo University. Sonication was performed in a J.P. Selecta Ultrasonic cleaner with a frequency of 50/60 Hz and a nominal power of 770 W.

General procedure: Under atmosphere of nitrogen gas, a mixture of the aromatic aldehydes **1** (0.01 mol), ethyl acetoacetate **2** (1.30 g, 0.01 mol), thiourea **3** (0.76 g, 0.01 mol) and anhydrous formic acid (10 mL) were mixed and irradiated in the water bath of ultrasonic cleaner at 80 ºC. At the end of irradiation [(15-40 min), monitored by TLC], the solid products were filtered washed with ice water and ethanol (95 %), dried and recrystallized.

Ethyl-4-(4'-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a): White needles, m.p. 150 ºC (from benzene); yield 39 %; IR (KBr, ν_{max}, cm^{-1}): 3313 (NH), 1667 (C=O), 1196 (C=S); ^{1}H NMR (DMSO-d_6): 1.11 (3H, t, ^3J = 7.3, CH_3CH_2), 2.28 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 4.00 (2H, q, ^3J = 7.2, CH_3CH_2O), 5.10 (1H, d, J = 3.6, H-4), 6.90 (2H, d, ^3J = 9.0, H-3',5', AA' part of AA'XX' system), 7.12 (2H, d, ^3J = 9.0, H-2',6', XX' part of AA'XX' system), 9.63 (1H, br.s, NH), 10.31 (1H, br.s, NH); ^{13}C NMR: 14.0 (C-9), 17.1 (C-10), 53.4 (C-4), 55.1 (OCH_3), 59.5 (C-8), 100.9 (C-5), 144.8 (C-6), 165.1 (C-7), 173.9 (C-2), 113.8 (2C), 127.6 (2C), 135.6, 158.7 (sp^2 carbons); MS: m/z (%) 306 (97) [M$^+$] ($C_{15}H_{18}N_2O_3S$), 307 (13) [M + 1], 291 (12) [M-CH_3], 277 (100) [M-C_2H_5], 275 (9) [M-OCH_3], 261 (13), [M-OC_2H_5], 260 (30) [261-H.], 233 (73) [261-CO], 199 (19) [M-C_7H_7O], 77 (20) [$C_6H_5^+$].

Ethyl-4-(3'-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1b): White fine needles, m.p. 205 ºC (from acetic acid); yield 60 %; IR (KBr, ν_{max}, cm^{-1}): 3314 (NH), 1664 (C=O), 1197 (C=S); ^{1}H NMR (DMSO-d_6): 1.12 (3H, t, ^3J = 7.2, CH_3CH_2), 2.52 (3H, s, CH_3), 4.06 (2H, q, ^3J = 7.2, CH_3CH_2O), 5.20 (1H, d, J = 3.6, H-4), 7.9 (1H, dt, ^3J = 7.8, ^4J = 1.5, H-6'), 7.24 (1H, t, ^4J = 1.5, H-2'), 7.37 (1H, dt, ^3J = 7.8, ^4J = 1.8 and ^4J = 1.5, H-4'), 7.41 (1H, t, ^3J = 7.8, H-5'), 9.72 (1H, br.s, NH), 10.45 (1H, br.s, NH); ^{13}C NMR: 14.0 (C-9), 17.2 (C-10), 53.6 (C-4), 59.7 (C-8), 100.0 (C-5), 145.6 (C-6), 164.9 (C-7), 174.3 (C-2), 125.0, 126.3, 127.7, 130.7, 133.0, 145.8 (sp^2 carbons).

Ethyl-4-(3',4'-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1c): White fine needles, m.p. 123 ºC (from ethanol); yield 40 %; IR (KBr, ν_{max}, cm^{-1}): 3309 (NH), 1728 (C=O), 1139 (C=S); ^{1}H NMR (DMSO-d_6): 1.13 (3H, t, ^3J = 7.2, $\underline{CH_3}CH_2$), 2.51 (3H, s, CH_3), 3.71 (6H, s, $2OCH_3$), 4.03 (2H, q, ^3J = 7.2, $CH_3\underline{CH_2}O$), 5.12 (1H, d, J = 3.0, H-4), 6.70 (1H, dd, ^3J = 8.4, 4J = 1.8, H-6'), 6.82 (1H, d, ^4J = 1.8, H-2'), 6.91 (1H, d, ^3J = 8.4, H-5'), 9.63 (1H, br.s, NH), 10.31 (1H, br.s, NH); ^{13}C NMR: 14.1 (C-9), 17.1 (C-10), 53.5 (C-4), 55.3, 55.5 (2-OCH_3), 59.6 (C-8), 100.7 (C-5), 144.8 (C-6), 165.2 (C-7), 174.1 (C-2), 110.3, 111.7, 118.1, 135.9, 148.2, 148.4 (sp^2 carbons); MS: m/z (%) 307 (38) [M-C_2H_5], 275 (18) [M-$2OCH_3$ + H], 262 (26) [M-$COOC_2H_5$], 249 (43) [M-$COOC_2H_5$-CH_3 + H], 198 (30) [M-$C_8H_{10}O_2$], 189 (57), [249-NHCS-H], 101 (100) [189-2CO-$2CH_3$-2H].

Ethyl-4-(3'-methoxy-4'-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1d): White needles, m.p. 215 ºC (from ethanol); yield 41 %; IR (KBr, ν_{max}, cm^{-1}): 3415 (NH), 1689 (C=O), 1154 (C=S); ^{1}H NMR (DMSO-d_6): 1.13 (3H, t, ^3J = 7.2, $\underline{CH_3}CH_2$), 2.28 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 4.00 (2H, q, ^3J = 7.2, $CH_3\underline{CH_2}O$), 5.08 (1H, d, J = 3.0, H-4), 6.59 (1H, dd, ^3J = 7.8, ^4J = 1.2, H-6'), 6.73 (1H, d, ^3J = 7.8, H-5'), 6.79 (1H, d, ^4J = 1.2, H-2'), 9.05 (1H, s, OH), 9.59 (1H, br.s, NH), 10.29 (1H, br.s, NH); ^{13}C NMR: 14.1 (C-9), 17.1 (C-10), 53.6 (C-4), 55.5 (OCH_3), 59.5 (C-8), 100.9 (C-5), 144.6 (C-6), 165.2 (C-7), 173.9 (C-2), 110.8, 115.8, 118.5, 134.5, 146.1, 147.3 (sp^2 carbons); MS: m/z (%) 322 (100) [M$^+$] ($C_{15}H_{18}N_2O_4S$], 293 (93) [M-OCH_3 + 2H], 278 (31) [M-OC_2H_5 + H.], 249 (62) [278-CHO], 199 (70) [M-$C_7H_7O_2$], 77 (47) [$C_6H_5^+$].

Ethyl-4-(4'-chloroyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1e): White fine needles, m.p. 192 ºC (from benzene); yield 25 %; IR (KBr, ν_{max}, cm^{-1}): 3310 (NH), 1664 (C=O), 1197 (C=S), ^{1}H NMR (DMSO-d_6): 1.04 (3H, t, ^3J = 7.2, $\underline{CH_3}CH_2$), 2.44 (3H, s, CH_3), 4.06 (2H, q, ^3J = 7.2, $CH_3\underline{CH_2}O$), 5.11 (1H, s, H-4), 7.17 (2H, d, ^3J = 8.0, H-2',6', AA' part of AA'XX' system), 7.34 (2H, d, 3J = 8.0, H-3',5', XX' part of AA'XX' system), 9.61 (1H, br.s, NH), 10.33 (1H, br.s, NH); ^{13}C NMR: 14.2 (C-9), 17.1 (C-10), 53.6 (C-4), 59.7 (C-8), 100.0 (C-5), 145.0 (C-6), 164.7 (C-7), 174.1 (C-2), 127.8 (2C), 128.3 (2C), 132.4, 142.0 (sp^2 carbons); MS: m/z (%) 310 (83) [M$^+$] ($C_{14}H_{15}{}^{35}ClN_2O_2S$], 312 (27) [M + 2] ($C_{14}H_{15}{}^{37}ClN_2O_2S$], 281 (97) [M-$C_2H_5$], 237 (37) [M-$COOC_2H_5$], 199 (100) [M-$C_6H_4{}^{35}Cl$], 112 (51) [$C_6H_5{}^{35}Cl^+$].

Ethyl--(4'-bromoyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1f): White needles, m.p. 191 ºC (from ethanol); yield 49 %; IR (KBr, ν_{max}, cm^{-1}): 3326 (NH), 1670 (C=O), 1197 (C=S); ^{1}H NMR (DMSO-d_6): 1.09 (3H, t, ^3J = 7.2, $\underline{CH_3}CH_2$), 2.29 (3H, s, CH_3), 4.00 (2H, q, ^3J = 7.2, $CH_3\underline{CH_2}O$), 5.16 (1H, s, H-4), 7.17 (2H, d, ^3J = 6.6, H-2',6', AA' part of AA'XX' system), 7.55 (2H, d, ^3J = 6.6, H-3',5', XX' part of AA'XX' system), 9.70 (1H, br.s, NH), 10.42 (1H, br.s, NH); ^{13}C NMR: 14.0 (C-9), 17.2 (C-10), 53.5 (C-4), 59.6 (C-8), 100.2 (C-5), 145.4 (C-6), 164.9 (C-7), 174.2 (C-2), 120.8, 128.6 (2C), 131.5 (2C), 142.7 (sp^2 carbons); MS: m/z (%) 354 (66) [M$^+$] ($C_{14}H_{15}{}^{79}BrN_2O_2S$], 356 (58) [M + 2] ($C_{14}H_{15}{}^{81}BrN_2O_2S$), 325 (63) [M-$C_2H_5$], 199 (100) [M-$C_6H_4{}^{79}Br$].

Measurement of potential cytotoxicity by SRB assay: The growth suppressing potential compounds **1a-f** was investigated by determining their IC_{50} value by SRB assay against human tumor cell lines: HEPG2 (hepatocellular carcinoma), HELA (cervix adenocarcinoma) and MCF7 (human breast adenocarcinoma) using the method of Skehan *et al.*[18]. Cells were plated in 96-multiwell plate (10^4 cells/well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentrations of the compounds under test (0, 12.5, 25 and 50 µg/mL) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the latter for 48 h at 37 ºC and in atmosphere of 5 % CO_2. After 48 h, cells were fixed, washed and stained with sulforhodamine B stain. Excess stain was washed with acetic acid and attached stain was recovered with tris EDTA buffer. Colour intensity was measured in an ELISA reader. The relation between the surviving fraction and the concentration of the compound is plotted to get the survival curve of each tumor cell line after the specified compound. Doxorubicin was used as a reference drug.

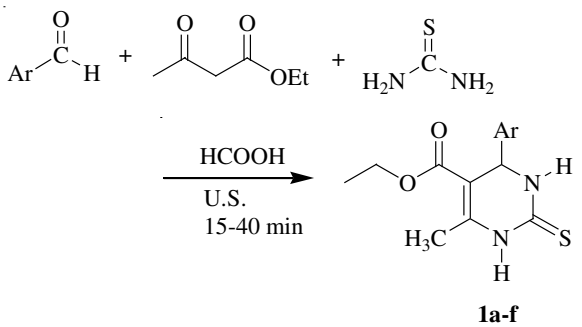
The cytotoxic activities of the prepared compounds **1a-f** including doxorubicin are summarized in Table-1. In general, all tested compounds **1a-f** are less active than doxorubicin on the three maintained cell lines.

TABLE-1
ANTITUMOR ACTIVITY OF COMPOUNDS **1a-f**

Compound	Cytotoxicity IC_{50} (m/mL)		
	HEPG2	HELA	MCF7
1a	16.50	20.70	17.20
1b	11.20	21.30	16.50
1c	12.40	19.00	19.20
1d	12.65	20.40	17.60
1e	7.24	16.80	12.70
1f	7.70	16.80	17.00
Doxorubicin	5.50	3.74	2.97

RESULTS AND DISCUSSION

Herein, we carried out the one-pot Biginelli synthesis of dihydropyrimidinethiones assisted by ultrasound irradiation using formic acid as catalyst in solvent-free conditions The condensation of ethylacetoacetate, substituted benzaldehyde and thiourea, catalyzed by formic acid gave poor to mild yields of compounds **1a-f** (**Scheme-I**).



1a-f

Ar
a: 4-$OCH_3C_6H_4$, **b**: 3-ClC_6H_4, **c**: 3,4-$OCH_3C_6H_3$,
d: 3-OCH_3, 4-OHC_6H_3, **e**: 4-ClC_6H_4, **f**: 4-BrC_6H_4

Scheme-I

In order to improve the yields, we did the experiment with different ratios of aldehydes, β-ketoester and thiourea but the yield would not further be improved. Further, we studied the influence of the amount of the catalyst on the yields as reported[17] but it would not affect too. The structures of the compounds have been elucidated based on their spectral data. In the IR spectra of **1a-f** displayed three characteristic bands at 3415-3310, 1728-1664 and 1197-1139 cm^{-1}, due to absorption of NH_2, C=O and C=S groups, respectively. The mass spectral data have been found to be inconformity with the assigned structure (see experimental part). The ^1H NMR spectrum of compound **1b** exhibited a triplet with J = 7.2 Hz at δ 1.12 ppm for ($\underline{CH_3}$-CH_2), quartet with J = 7.2 at δ 4.06 ppm for (CH_3-$\underline{CH_2}$-O-), in addition to a doublet at δ 5.20 ppm with J = 3.6 Hz due to coupling with NH. Aromatic protons in **1b** appeared a triplet of doublets at δ 7.9 ppm (J = 7.8, 1.5 Hz) for H-6', triplet at δ 7.24 ppm J = 1.5 Hz for H-2', triplet of doublets at δ 7.37 ppm (J = 7.8, 1.8, 1.5 Hz) for H-4' and triplet at δ 7.41 ppm with J = 7.8 Hz for H-5', the spectrum also showed two broad singlets at δ 10.45 and δ 9.72 ppm due to the resonances of the two NH protons. The ^{13}C NMR spectral data of **1b** (Fig. 1) revealed 14 signals and this is as expected for the proposed structure. The chemical shift assignment of ^{13}C NMR was based on DEPT and HETCOR experiments.

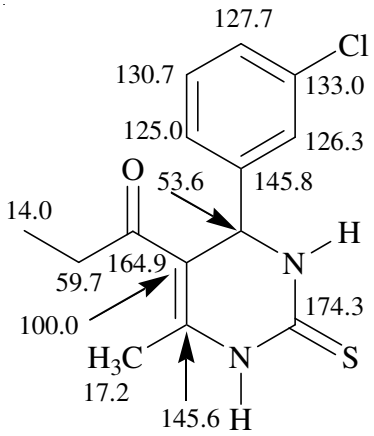


Fig. 1. ^{13}C NMR data of **1b**

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