SYNTHESIS OF NEW 1,3-THIAZOLE DERIVATIVES; USING 1-(4-CARBAMOYLPHENYL)-3-METHYLTHIOUREA AND 1-METHYL-3-(QUINOLIN-8-YL)THIOUREA AS STARTING MATERIALS

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ABSTRACT

A series of novel 1,3-thiazoles have been synthesized in good yields, using dialkyl acetylenedicarboxylate, benzamide and quinoline derivatives of thiourea in ethanol.

Keywords: Thiourea, dimethyl acetylene dicarboxylate, diethyl acetylene dicarboxylate, thiazoline.

1. INTRODUCTION

Since the past few decades, heterocyclic chemistry has been one of the most important disciplines in organic synthesis and pharmaceutical chemistry¹. A large numbers of these compounds have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory^{2,3}, anti-tumor⁴, anti-hyperlipidemic⁵, anti-hypertensive⁶, anti-HIV infections⁷, and several other biological properties^{8,9}.

One of the most important groups of five-membered heterocycles including S and N atoms, are thiazole compounds. Thiazole heterocycle is a component of many natural products and synthetic compounds exhibiting a wide range of biological activity¹⁰⁻¹³. The pharmacological activities and their coordination properties are important features to prepare metal complexes with potential therapeutic activity or as model of metal-enzyme¹⁴. In addition, the thiazole ring present in vitamin B1 serves as an electron ink and its coenzyme form is important for keto-acids decarboxylation¹⁵.

Reaction of dimethyl acetylene dicarboxylate (DMAD) with esters and amides of dithiocarboxylic acids are well known methods for preparation of five membered S, and S, N-heterocycles^{16,17}. Thioureas possessing more than two N-H bonds react with (DMAD) to give 1:1 molar-methanol adducts¹⁷.

Because of the importance of thiazole compounds, studies on preparation of novel thiazole derivatives are of definite interest.

Hence, we investigated the reaction between activated acetylenic compounds, and thiourea derivatives which afforded 1,3-thiazolane derivatives 5 in good isolated yields (Scheme 1).

Scheme 1. Synthesis of 1,3-thiazole derivatives

2. EXPERIMENTAL

2.1. Materials and methods

Chemicals were either prepared in our laboratory or purchased from Merck or Fluka chemical companies, and were used without any further purification. All reactions were monitored by TLC, petroleum-ethyl acetate (3:1). Melting

points were determined with a hot-plate microscope apparatus. IR spectra were recorded in KBr, using a BRUKER FT-IR spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Bruker 400-MHz spectrometer using CDCl₃ and TMS as solvent and internal standard, respectively. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV.

2.2. General procedure for synthesis of 1-(4-carbamoylphenyl)-3-methylthiourea (3):

A round-bottomed flask (100mL) was charged with p-amino benzamid (0.13 g, 1 mmol) and methyl isothiocyanate (0.73 g, 1 mmol) in ethanol (30 mL). The reaction mixture was refluxed for 24 hours, stood for 5 min, and 20 mL water was added. The residue was filtered and dried to give 1-(4-carbamoylphenyl)-3-methylthiourea as a white powder in 93% yield, m.p.: 189-190, IR (KBr) ν_{max} (cm⁻¹): 1656 (C=O), 3068-3409 (NH, C-H), ¹H NMR (300 MHz, DMSO-d₆): δ (ppm): 3.35 (1H, s, CH₃), 7.28 (1H, s, NH, benzamide), 7.50 (2H, d, J = 8.4 Hz, arom), 7.82 (2H, d, J = 8.4 Hz, arom), 7.89 (1H, s, NH, benzamide), 7.92 (1H, s, NH, thiourea), ¹³C NMR (75 MHz, DMSO-d₆): δ (ppm): 31.1, 121.1, 128.0, 129.0, 129.1, 142.0, 142.1, 167.3, 180.8, MS, *m/z* (%): 209 (M, 28), 162 (82), 120 (100).

General procedure for synthesis of 1-methyl-3-(quinolin-8-yl)thiourea (3):

Similarly, 1-(4-carbamoylphenyl)-3-methylthiourea, compound -methyl-3-(quinolin-8-yl)thiourea was prepared as described above using 8-amino quinolin (0.14 g, 1 mmol) and methyl isothiocyanate (0.73 g, 1 mmol) in ethanol (30 mL). The reaction mixture was refluxed for 24 hours, stood for 5 min, and 20 mL water was added. The residue was filtered and dried to give 1-methyl-3-(quinolin-8-yl)thiourea as a white powder in 93% yield: m.p.: 129-130, IR (KBr) ν_{max} (cm⁻¹): 3022-3279 (N-H, C-H), ¹H NMR (300 MHz, DMSO-d₆): δ (ppm): 3.36 (3H, d, J = 4.4 Hz, CH₃), 7.54 (1H, t, J = 8.0 Hz, arom), 7.62-7.65 (2H, m, arom), 8.41 (1H, dd, J₁ = 8.0 Hz, J₂ = 1.6 Hz, arom), 8.92 (1H, dd, J₁ = 4.4 Hz, J₂ = 1.6 Hz, arom), 8.97 (1H, s, br, NH, thiourea), 9.09 (1H, d, J = 7.2 Hz, arom), 10.22 (1H, s, br, NH, thiourea), ¹³C NMR (75 MHz, DMSO-d₆): δ (ppm): 30.6, 117.5, 121.2, 122.0, 126.3, 127.8, 135.6, 136.6, 138.7, 148.5, 180.5, MS, *m/z* (%): 217 (M, 76), 184 (35), 144 (100).

2.3. General Procedure for the Preparation of thiazol derivatives using 1-(4-carbamoylphenyl)-3-methylthiourea and 1-methyl-3-(quinolin-8-yl) thiourea:

1-(4-carbamoylphenyl)-3-methylthiourea (1 mmol) or 1-methyl-3-(quinolin-8-yl)thiourea (1 mmol) was added to dialkyl acetylenedicarboxylate (1 mmol) in 5 mL ethanol. The mixture was refluxed for 30 minutes. The reactions were followed by thin layer chromatography (TLC) using hexane/ethyl acetate (3:1) as an eluent. After completion of the reaction, water (20 mL) was added and stirred magnetically for 5 min. Insoluble crude products were filtered, dried, and recrystallized from ethanol. All the products obtained were characterized by spectroscopic methods such as IR, ¹H NMR, ¹³C NMR and Mass.

The spectral data for products

Spectra Data of methyl -2-{2-[aminocarbonyl]phenyl}imino-3-methyl-4-oxo-1,3-thiazolan-5-ylidene} acetate (5a): Yield: 82 %; yellow solid, m.p. 130-132 °C; IR (KBr cm⁻¹): 1653, 1693, 1725 (C=O), 2985- 3365 (N-H, C-H), ¹H NMR (CDCl₃, 300 MHz): δ (ppm): 3.32 (3H, s, CH₃), 3.74 (3H,

s, OCH₃), 6.82 (1H, s, CH, vinyl), 7.06 (2H, d, J = 8.4 Hz, arom), 7.38 (1H, s, NH, benzamide), 7.92 (2H, d, J = 8.4 Hz, arom), 7.99 (1H, s, NH, benzamide); ¹³C NMR (CDCl₃, 75 MHz): δ (ppm): 29.3, 52.6, 115.3, 120.7, 122.1, 127.9, 128.9, 130.8, 141.0, 149.8, 152.1, 164.3, 165.7, 167.2, MS, *m/z* (%): 319 (M, 71), 159 (100),

Spectra Data of ethyl -2-[2-[aminocarbonyl]phenyl]imino-3-methyl-4-oxo-1,3-thiazolan-5-ylidene} acetate (5b): Yield: 84 %; yellow solid, m.p. 212-214°C; IR (KBr cm⁻¹): 1653, 1693, 1725 (C=O), 2985- 3364 (N-H, C-H), ¹H NMR (DMSO-d₆, 300 MHz): δ (ppm): 1.22 (3H, t, J = 7.2 Hz, CH₃), 3.35 (3H, s, CH₃), 4.19 (2H, q, J = 7.2 Hz, CH₂), 6.79 (1H, s, CH, vinyl), 7.06 (2H, d, J = 8.4 Hz, arom), 7.38 (1H, s, NH, benzamide) 7.92 (2H, d, J = 8.4 Hz, arom), 7.99 (1H, s, NH, benzamide); ¹³C NMR (DMSO-d₆, 75 MHz): δ (ppm): 13.9, 29.2, 61.5, 115.5, 120.7, 128.9, 130.8, 141.0, 149.9, 152.2, 164.3, 165.3, 167.2. MS, *m/z* (%): 333 (M, 100) 159 (90).

Spectra Data of methyl-2-[3-methyl-4-oxo-2-(8-kinolil-5-immino)-1,3-thiazolane-5-ylidene} acetate (5c): Yield: 95 %; yellow solid, m.p. 166-168 °C; IR (KBr cm⁻¹): 1647 (C=N), 1704, 1718 (C=O), ¹H NMR (DMSO-d₆, 300 MHz): δ (ppm): 3.45 (3H, s, CH₃), 3.67 (3H, s, CH₃), 6.79 (1H, s, CH), 7.32 (1H, d, J = 7.2 Hz, arom), 7.59 (1H, dd, J₁ = 8.4 Hz, J₂ = 4.4 Hz, arom), 7.63 (1H, t, J = 7.6 Hz, arom), 7.84 (1H, d, J = 8.0 Hz, arom), 8.43 (1H, d, J = 8.4 Hz, arom), 8.88 (1H, d, J = 3.6 Hz, arom); ¹³C NMR (DMSO-d₆, 75 MHz): δ (ppm): 29.3, 52.5, 114.9, 119.8, 122.0, 124.8, 126.6, 128.8, 136.3, 140.1, 141.2, 144.5, 150.0, 151.8, 164.3 165.7. MS, *m/z* (%): 327 (M, 42), 183 (42), 155 (100).

Spectra Data of ethyl-2-[3-methyl-4-oxo-2-(8-kinolil-5-immino)-1,3-thiazolane-5-ylidene} acetate (5d): Yield: 97 %; yellow solid, m.p. 100-102 °C; IR (KBr cm⁻¹): 1660 (C=N), 1696, 1726 (C=O), ¹H NMR (DMSO-d₆, 300 MHz): δ (ppm): 1.17 (3H, t, J = 7.2 Hz, CH₃), 3.45 (3H, s, CH₃), 4.12 (2H, q, J = 7.2 Hz, CH₂), 6.76 (1H, s, CH), 7.32 (1H, d, J = 7.2 Hz, arom), 7.60

(1H, q, J = 4.0 Hz, arom), 7.63 (1H, t, J = 7.6 Hz, arom), 7.84 (1H, d, J = 8.4 Hz, arom), 8.43 (1H, d, J = 7.6 Hz, arom), 8.88 (1H, d, J = 3.6 Hz, arom); ¹³C NMR (DMSO-d₆, 75 MHz): δ (ppm): 13.8, 29.3, 61.4, 115.1, 119.8, 122.0, 124.8, 126.6, 128.8, 136.3, 140.1, 144.5 150.0, 151.9, 164.3, 165.2, MS, *m/z* (%): 341 (M, 48), 183 (52), 155 (100).

3. RESULTS AND DISCUSSION

In this paper, we describe an investigation of the cyclo-addition of thiourea derivatives 3 with DMAD and DEAD to prepare new thiazole derivatives in a one-step procedure resulting in good to excellent yields (Scheme 1).

The cycloaddition of these isolable and stable thiourea derivatives, with dialkyl acetylene dicarboxylates proceeds, by a simple one step procedure. Compounds 5a-d were prepared in 82, 84, 95 and 97% yields, respectively. Thus the cycloaddition represented in Scheme 1 was accomplished by mixing the equimolar quantities of dialkyl acetylene dicarboxylates and thiazole derivatives in ethanol at reflux conditions. Thiourea derivatives have two active sites, nitrogen and sulfur, that are capable to react with the dialkyl acetylene dicarboxylates. Therefore, either the S or NH group of thiourea derivatives will attack the dialkyl acetylene dicarboxylates, followed by ring closure to produce the final products.

The structures of compounds 5a-d were assigned by consideration of their IR, ¹H NMR, ¹³C NMR spectroscopic and mass spectrometric data. For example, the ¹H NMR spectrum of 5a shows a singlet for methyl protons at 3.32 ppm. In the ¹³C NMR spectrum of 5a, signal corresponding to carbonyl group was observed at 165.7 ppm. The mass spectrum of 5a contained the molecular ion peak at *m/z* = 319.

To study the generalizability of this process, several examples were studied and are summarized in Table 1. In all cases studied, the reaction proceeded very well to give the corresponding thiazoles in good yields.

Table 1. Synthesis of thiazoles derivatives in ethanol.

NO	Ar	R	Product structure	Time (min)	Yield* (%)
1		Me		30	82
2		Et		30	84
3		Me		30	95
4		Et		30	97

* Isolated yields

The proposed mechanism for synthesis of thiazole compounds is shown in scheme 2. Our proposed mechanism includes, initial formation of the compound 3 by nucleophilic addition of sulfur atom to dialkyl acetylenedicarboxylate followed by H transfer. Subsequent, removing of alcohol followed by cyclization affords the corresponding product.

Scheme 2. The proposed mechanism for synthesis of 1,3-thiazole compounds.

4. CONCLUSIONS

In summary, we have synthesized a new series of thiazole compounds by condensation reaction of thiourea derivatives and dialkyl acetylene dicarboxylate in ethanol as green solvent. The attractive features of this protocol are simple procedure, cleaner reaction, satisfactory yields of products, simple reactions, isolation, and purification of the products, as well as its compliance with the green chemistry protocols which makes it a useful protocol for the synthesis of these classes of compounds.

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