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Synthesis of methyl 2-[2-(alkylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate derivatives under solvent-free condition

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Abstract

An efficient synthesis of Methyl 2-[2-(alkylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate derivatives *via* simple three-component reaction and one-pot reactions between isoquinoline, dimethyl acetylenedicarboxylate and *N*-phenylthiourea is described under solvent-free conditions without using any additional catalyst.

Keywords: Isoquinoline; solvent-free; *N*-phenylthiourea; thiazolan; green chemistry.

Introduction

Multicomponent reactions (MCRs) are defined by three or more reactants joining in a one-pot procedure to afford a single product [1-4]. They are economically and environmentally useful because multi-step syntheses frequently produce a large amount of waste and also the complex isolation actions often involve uncomfortable, toxic, and hazardous solvents after each step [5-8]. MCRs are absolutely suited for combinatorial library synthesis and are increasingly utilized in discovery of new drugs and agrochemicals [9]. They represent a useful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [10 and 11]. Heterocycles are key compounds in the development of modern pharmaceutical chemistry, which is the reason why the design of amenable synthetic approaches for new heterocyclic systems is still significant challenge [12]. The thiazolium ring present in vitamin B1 serves as an electron sink and its coenzyme form is important for the decarboxylation of keto-acids [13]. Several pesticides possessing a heterocycle with an S or an N atom are known in agriculture. A large number of heterocycles has been emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory [14], anti-tumour [15] anti-hyperlipidemic [16], anti-hypertensive [17], anti-HIV infections [18], and several other biological properties [19 and 20]. Herein, we report the synthesis of methyl 2-[2-(alkylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden] acetate derivatives **4** *via* the reaction of isoquinoline **1**, dialkyl acetylenedicarboxylates **2** and phenylthiourea **3** which proceed smoothly under solvent-free conditions at room temperature (Figure 1).

Experimental

General

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and used without further purification.

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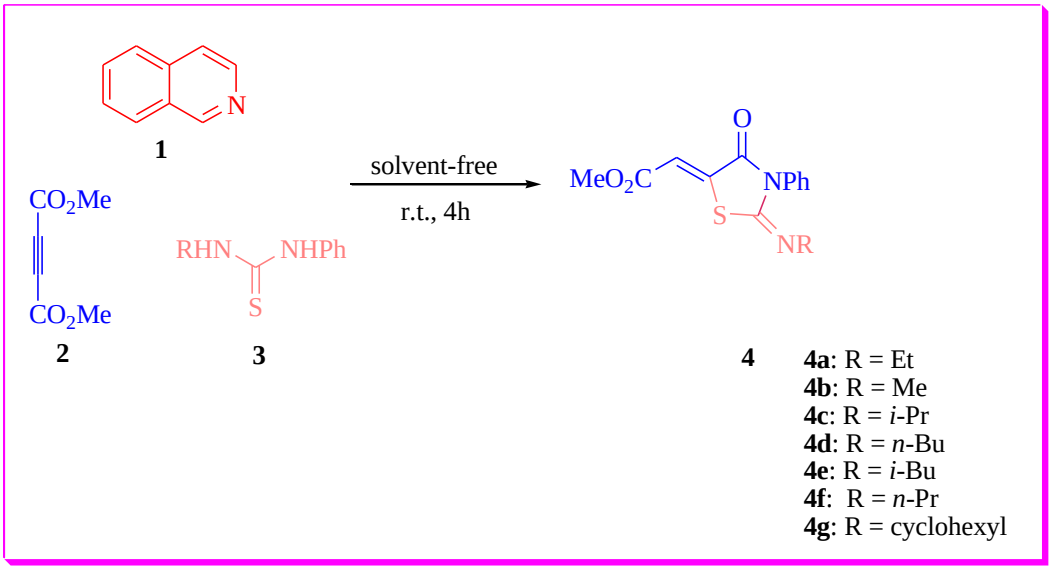

Figure 1. Synthesis of compounds **4a-g**

Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER DRX-400 AVANCE spectrometer at 400 and 100 MHz, respectively. ^{1}H and ^{13}C spectra were obtained for solutions in $CDCl_3$ using TMS as the internal standard.

*General procedure for synthesis of **4a-4g***

Dimethyl acetylenedicarboxylate 2 (2 mmol) was slowly added to a magnetically stirred mixture of phenylthiourea **3** (2 mmol) and isoquinoline **1** (2 mmol), and the reaction mixture was stirred for 4 h at room temperature. After completion of the reaction, as indicated by TLC, the residue was purified by chromatography over silica gel (Merck 230-400 mesh) using an n-hexane-AcOEt mixture (12:1) as eluant to afford the pure compound **4**.

Methyl 2-[2-(ethylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate (4a).

Yellow powder; m.p. 150-152 °C, yield: 0.49 g (85 %). IR (KBr): 1718 (C=O), 1733 (C=O), 2976 (CH) cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, 3 H, ^{3}J = 7.0 Hz, CH_3), 3.64 (q, 2 H, ^{3}J = 7.0 Hz, CH_2), 3.73 (s, 3 H, OCH_3), 6.83 (s, 1 H, CH), 6.91 (dd, 2 H, ^{3}J = 8.6 Hz, ^{3}J = 1.2 Hz, 2 CH), 7.11 (t, 1 H, ^{3}J = 7.6 Hz, CH), 7.28 (dd, 2 H, ^{3}J = 9.0 Hz, ^{3}J = 8.6 Hz, 2 CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4 (Me), 52.5 (OMe), 58.4 (NCH_2), 116.0 (CH), 121.0 (2 CH), 125.3 (CH), 129.4 (2 CH), 141.7 (C), 147.2 (C), 151.5 (C=N), 165.0 (C=O), 166.4 (C=O). MS: *m/z* (%) = 290 (3) [M^{+}], 178 (12), 144 (40), 43 (100). Anal. Calcd for $C_{14}H_{14}N_2O_3S$ (290.34): C 57.92, H 4.86, N 9.65; found C 58.12, H 4.52, N 9.34 %.

Methyl 2-[2-(methylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate (4b).

Yellow powder, m.p. 147-149 °C; yield: 0.48 g (87 %). IR (KBr): 1715 (C=O), 1734 (C=O), 2966 (CH) cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, NCH_3), 3.72 (s, 3 H, OCH_3), 6.83 (s, 1 H, CH), 6.92 (dd, 2 H,^{3}J = 8.8 Hz, ^{3}J = 1.3 Hz, 2 CH), 7.10 (t, 1 H, ^{3}J = 8.0 Hz, CH), 7.29 (dd, 2 H, ^{3}J = 8.6 Hz, ^{3}J = 8.7 Hz, 2 CH). ^{13}C NMR (100 MHz, $CDCl_3$): 51.5 (OCH_3), 57.4 (NCH_3), 114.8 (CH), 120.0 (2 CH), 124.2 (CH), 128.4 (2 CH), 140.9 (C),

146.3 (C), 149.7 (C=N), 163.7 (C=O), 165.3 (C=O). MS: *m/z* (%) = 276 (3) [M^+], 247 (22), 217 (78), 199 (37), 59 (100). Anal. Calcd for $C_{13}H_{12}N_2O_3S$ (276.31): C 56.51, H 4.38, N 10.14; found C 56.21, H 4.47, N 9.93 %.

Methyl 2-[2-(isopropylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate (4c).

Yellow powder, m.p. 153-155 °C; yield: 0.54 g (90 %). IR (KBr): 1721 (C=O), 1738 (C=O), 2975 (CH) cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, 6 H, ^3J = 7.0 Hz, 2 CH_3), 3.68 (heptet, 1 H, CH, ^3J = 6.0 Hz), 3.89 (s, 3 H, OCH_3), 6.98 (s, 1 H, CH), 7.05 (dd, 2 H, ^3J = 8.0 Hz, ^3J = 1.2 Hz, 2 CH), 7.12 (t, 1 H, ^3J = 7.6 Hz, CH), 7.23 (dd, 2 H, ^3J = 8.8 Hz, ^3J = 8.6 Hz, 2 CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5 (2 Me), 51.8 (OMe), 58.1 (CH), 115.1 (CH), 120.8 (2 CH), 125.3 (CH), 128.7 (2 CH), 141.7 (C), 147.1 (C), 151.0 (C=N), 165.3 (C=O), 166.2 (C=O). MS: *m/z* (%) = 304 (3) [M^+], 289 (18), 245 (83), 227 (44), 59 (100). Anal. Calcd for $C_{15}H_{16}N_2O_3S$ (304.36): C 59.19, H 5.30, N 9.20; found C 59.31, H 5.08, N 9.30%.

Methyl 2-[2-(butylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate (4d).

Yellow powder, m.p. 155-157 °C; yield: 0.54 g (85 %). IR (KBr): 1715 (C=O), 1741 (C=O), 2986 (CH) cm $^{-1}$. ^{1}H NMR(400 MHz, $CDCl_3$): δ 0.99 (t, 3 H, ^3J = 7.2 Hz, CH_3), 1.76 (sixtet, ^3J = 7.2 Hz, 2 H, CH_2), 1.43 (quntet, ^3J = 7.2 Hz, 2 H, CH_2), 3.82 (s, 3 H, OCH_3), 3.99 (t, 1 H, ^3J = 7.2 Hz, CH_2), 6.92 (s, 1 H, CH), 7.04 (dd, 2 H, ^3J = 8.3 Hz, ^3J = 1.3 Hz, 2 CH), 7.13 (t, 1 H, ^3J = 7.8 Hz, CH), 7.21 (dd, 2 H, ^3J = 8.6 Hz, ^3J = 8.9 Hz, 2 CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (Me), 21.3 (CH_2), 31.5 (CH_2), 52.3 (OMe), 57.9 (CH), 116.1 (CH), 121.2 (2 CH), 125.8 (CH), 129.5 (2 CH), 141.8 (C), 147.3 (C), 151.5 (C=N), 165.3 (C=O), 166.2 (C=O). MS: *m/z* (%) = 318 (5) [M^+], 267 (26), 259 (68), 241 (31), 59 (100). Anal. Calcd for $C_{16}H_{18}N_2O_3S$ (318.39): C 60.36, H 5.70, N 8.80; found C 60.20, H 5.45, N 9.08%.

Methyl 2-[2-(isobutylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate (4e).

Yellow powder, m.p. 154-156 °C; yield: 0.54 g (85 %). IR (KBr): 1718 (C=O), 1735 (C=O), 2981 (CH) cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, 3 H, ^3J = 7.0 Hz, 2 CH_3), 1.88–2.05 (m, 1 H, CH), 3.66 (d, 1 H, ^3J = 6.9 Hz, CH), 3.72 (s, 3 H, OCH_3), 6.84 (s, 1 H, CH), 6.91 (dd, 2 H, ^3J = 8.5 Hz, ^3J = 1.2 Hz, 2 CH), 7.12 (t, 1 H, ^3J = 7.8 Hz, CH), 7.26 (dd, 2 H, ^3J = 8.6 Hz, ^3J = 8.9 Hz, 2 CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (2 Me), 26.1 (CH_2), 52.4 (OMe), 58.3 (CH), 116.8 (CH), 121.0 (2 CH), 125.4 (CH), 129.4 (2 CH), 141.7 (C), 147.5 (C), 151.3 (C=N), 165.3 (C=O), 166.4 (C=O). MS: *m/z* (%) = 318 (5) [M^+], 267 (34), 259 (73), 241 (48), 59 (100). Anal. Calcd for $C_{16}H_{18}N_2O_3S$ (318.39): C 60.36, H 5.70, N 8.80; found C 60.19, H 5.83, N 8.93%.

Methyl 2-[2-(propylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate (4f).

Yellow powder, m.p. 151-153 °C; yield: 0.55 g (93 %). IR (KBr): 1725 (C=O), 1735 (C=O), 2985 (CH) cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91(t, 3 H, ^3J = 7.0 Hz, 2 CH_3), 1.75- 1.78 (m, 2 H, ^3J = 7.0 Hz, CH_2), 3.64 (t, 1 H, ^3J = 6.9 Hz, CH), 3.73 (s, 3 H, OCH_3), 6.83 (s, 1 H, CH), 6.90 (dd, 2 H, ^3J = 8.5 Hz, ^3J = 1.2 Hz, 2 CH), 7.10 (t, 1 H,^3J = 7.8 Hz, CH), 7.24 (dd, 2 H, ^3J = 8.6 Hz, ^3J = 8.9 Hz, 2 CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7 (Me), 23.8 (CH_2), 23.8 (CH_2), 52.5 (OMe), 58.2 (CH), 114.1 (CH), 121.2 (2 CH), 125.3 (CH), 129.1 (2 CH), 141.6 (C), 147.4 (C), 151.5 (C=N), 165.3 (C=O), 166.4 (C=O). EI-MS: *m/z* (%) = 304 (3) [$M]^+$, 289 (21), 245 (75), 227 (36), 59 (100). Anal. Calcd for $C_{15}H_{16}N_2O_3S$ (304.36): C 59.19, H 5.30, N 9.20; found C 58.90, H 5.41, N 9.03%.

Methyl 2-[2-(cyclohexylimino-)4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate (4g).

Yellow powder, m.p. 163-165 °C; yield: 0.62 g (90 %). IR (KBr): 1720 (C=O), 1733 (C=O), 2983 (CH) cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54–1.58 (m, 2 H, CH_2), 1.68–1.73 (m, 4 H, 2 CH_2), 1.87–1.93 (m, 4 H, 2 CH_2), 3.65 (t, 1 H, ^{3}J = 6.9 Hz, CH), 3.73 (s, 3 H, OCH_3), 6.84 (s, 1 H, CH), 6.90 (dd, 2 H, ^{3}J = 8.5 Hz, ^{3}J = 1.2 Hz, 2 CH), 7.11 (t, 1 H, ^{3}J = 7.8 Hz, CH), 7.28 (dd, 2 H, ^{3}J = 8.6 Hz, ^{3}J = 8.9 Hz, 2 CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2 (2 CH_2), 25.1 (CH_2), 31.0 (2 CH_2), 52.4 (OMe), 58.4 (CH), 116.2 (CH), 121.0 (2 CH), 125.6 (CH), 129.0 (2 CH), 141.6 (C), 147.4 (C), 151.5 (C=N), 165.4 (C=O), 166.5 (C=O). MS: *m/z* (%) = 344 (5) [M^{+}], 285(69), 261 (18), 227 (34), 59 (100). Anal. Calcd for $C_{18}H_{20}N_2O_3S$ (344.43): C 62.77, H 5.85, N 8.13; found C 62.86, H 5.71, N 8.24 %.

Results and discussion

The structures of **4a-g** compounds were apparent from the ^{1}H NMR, ^{13}C NMR and IR spectra. The ^{1}H NMR spectrum of **4a** exhibited all expected signals at δ 1.17 and 3.64 ppm for the ethyl moiety, broad singlet peek at δ 1.52, two singlet peeks at δ 3.37 and 3.72 ppm for two methoxy groups and a singlet at δ 6.85 ppm for an olefinic proton along with signals for the phenyl units at 6.90–7.31 ppm. The proton-decoupled ^{13}C NMR spectrum of **4a** showed 13 distinct resonances in agreement with the proposed structure.

A possible mechanism for this reaction is proposed in Figure 2. The zwitterionic intermediate **6** produced from the reaction of isoquinoline and dialkyl acetylenedicarboxylate is subsequently protonated by a phenylthiourea **3**, then attacked by the conjugate base of the phenylthiourea and cyclizated to produce **4**.

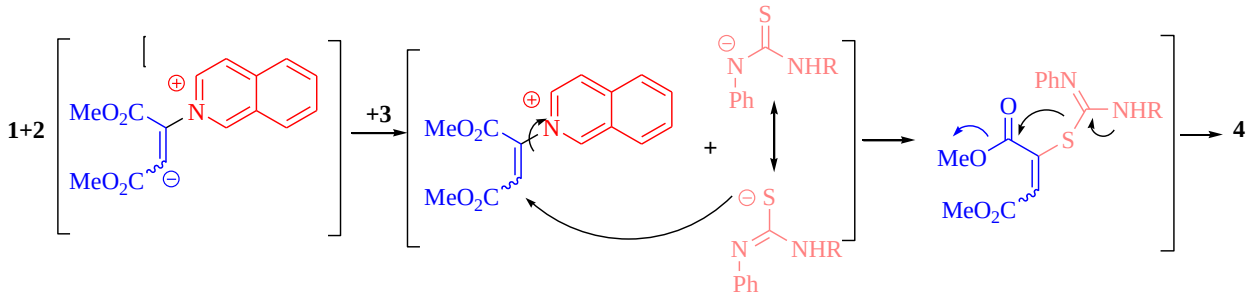

Figure 2. Possible mechanism for the formation of compounds **4**

Conclusion

In conclusion, we have reported a convenient one-pot route for the synthesis of methyl 2-[2-(alkylimino)-4-oxo-3-phenyl-1,3-thiazolan-5-yliden]acetate by reaction of isoquinoline, dimethyl acetylenedicarboxylate and phenylthiourea, at solvent-free conditions and r.t.

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