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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].

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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

Generel

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

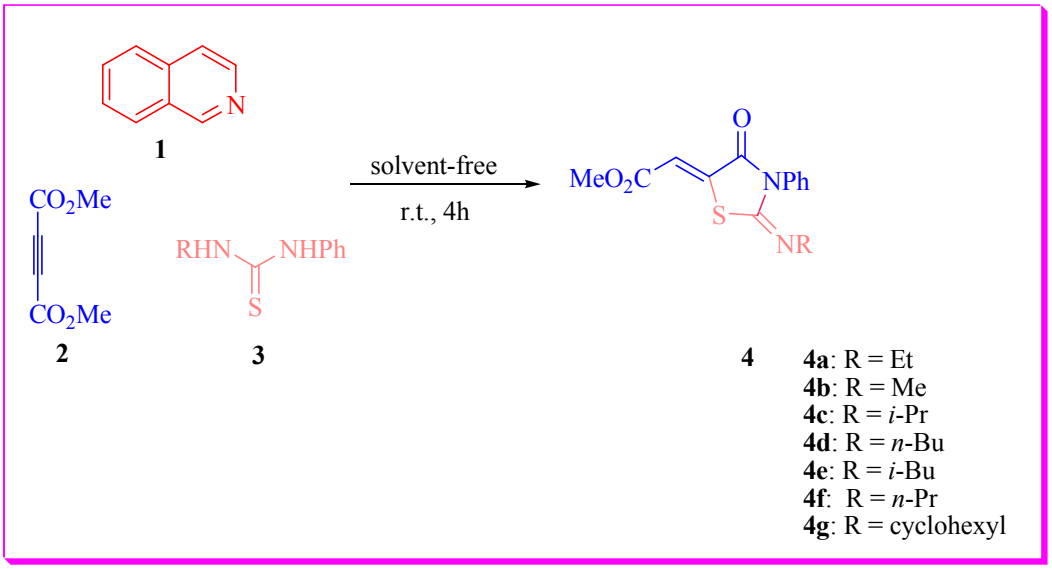

Figure 1. Synthesis of compounds **4a-g**.

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, ^3J = 7.0 Hz, CH_3), 3.64 (q, 2 H, ^3J = 7.0 Hz, CH_2), 3.73 (s, 3 H, OCH_3), 6.83 (s, 1 H, CH), 6.91 (dd, 2 H, ^3J = 8.6 Hz, ^3J = 1.2 Hz, 2 CH), 7.11 (t, 1 H, ^3J = 7.6 Hz, CH), 7.28 (dd, 2 H, ^3J = 9.0 Hz, ^3J = 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, ^3J = 8.8 Hz, ^3J = 1.3 Hz, 2 CH), 7.10 (t, 1 H, ^3J = 8.0 Hz, CH), 7.29 (dd, 2 H, ^3J = 8.6 Hz, ^3J = 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, ^3J = 6.9 Hz, CH), 3.73 (s, 3 H, OCH_3), 6.84 (s, 1 H, CH), 6.90 (dd, 2 H, ^3J = 8.5 Hz, ^3J = 1.2 Hz, 2 CH), 7.11 (t, 1 H, ^3J = 7.8 Hz, CH), 7.28 (dd, 2 H, ^3J = 8.6 Hz, ^3J = 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**.

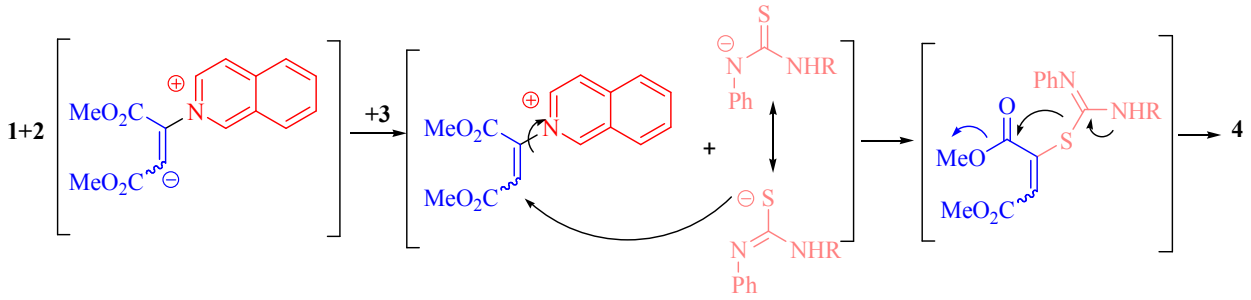

Figure 2. Possible mechanism for the formation of compounds **4**.

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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