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An efficient synthesis of thiazolane derivatives in the presence of *N*-formylmorpholine

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Abstract: N-formylmorpholine accelerated synthesis of thiazolane derivatives by employing of three-component reactions of primary amines, dialkyl acetylenedicarboxylates and isothiocyanates under solvent-free conditions at room temperature in a good yield. The above synthetic procedure offers rapid access to novel and diversely substituted thiazolane derivatives.

Keywords: *N*-formylmorpholine, Primary amines, Thiazolane, Three-component reaction, Green Chemistry.

Introduction

Multicomponent reactions (MCRs) are significant method for preparation of complex molecules from simple starting materials [1]. The molecules that were generated by this procedure is attracting for medicinal and synthetic chemists [2]. Also, producing many of substance by expand environmentally gentle paths is the important point in chemistry [3]. Green chemistry move towards procedure that decreases byproducts, waste and energy costs [4]. Of all the trends in chemistry, medicinal and pharmaceutical chemistry with their conventionally big volume of waste/product ratio, are ready for greening [5]. In addition, the removal of explosive organic solvents in organic synthesis is the most important purpose in green chemistry [6-8]. Heterocycles with nitrogen group are a main piece of natural and unnatural compounds with significant biological activity [9]. Also, several pesticides possessing a heterocycle with an S or an N atom are known in agriculture [10].

A large numbers of heterocycles with an S and N atoms have emerged as active pharmaceutical ingredients in several drugs for their potential of anti-inflammatory [11,12], anti-tumour [13] anti hyperlipidemic [14], anti-hypertensive [15], anti-HIV [16] and several other biological properties [17, 18]. In this research, we have investigated a simple three-component reaction between alkyl propiolates, primary amines and isothiocyanates in the presence of N-formylmorpholine under solvent-free conditions at room temperature. Herein by employing of 3-MCR in water, thiazolane derivatives **4** as product in good isolated yield was synthesized (Scheme **1**).

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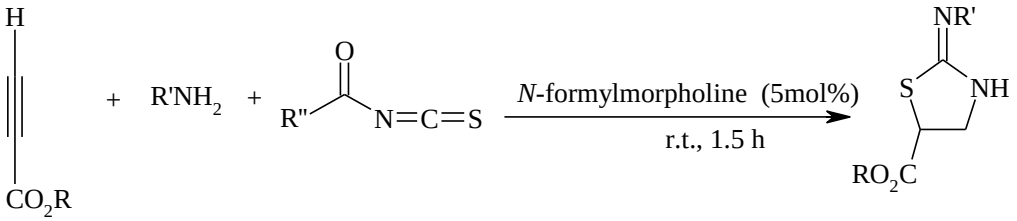


1 **2** **3** **4**

4	R	R'	R"	Yield (%) of **4**
a	Me	Me	Ph	75
b	Me	Et	4-MeO-C_6H_4	87
c	Et	n-Bu	4-MeO-C_6H_4	70
d	Et	^{t}Bu	4-Me-C_6H_4	75
e	Me	^{t}Bu	Ph	80

Scheme 1: Three-component reaction for synthesis of thiazolane derivatives.

Results and discussion

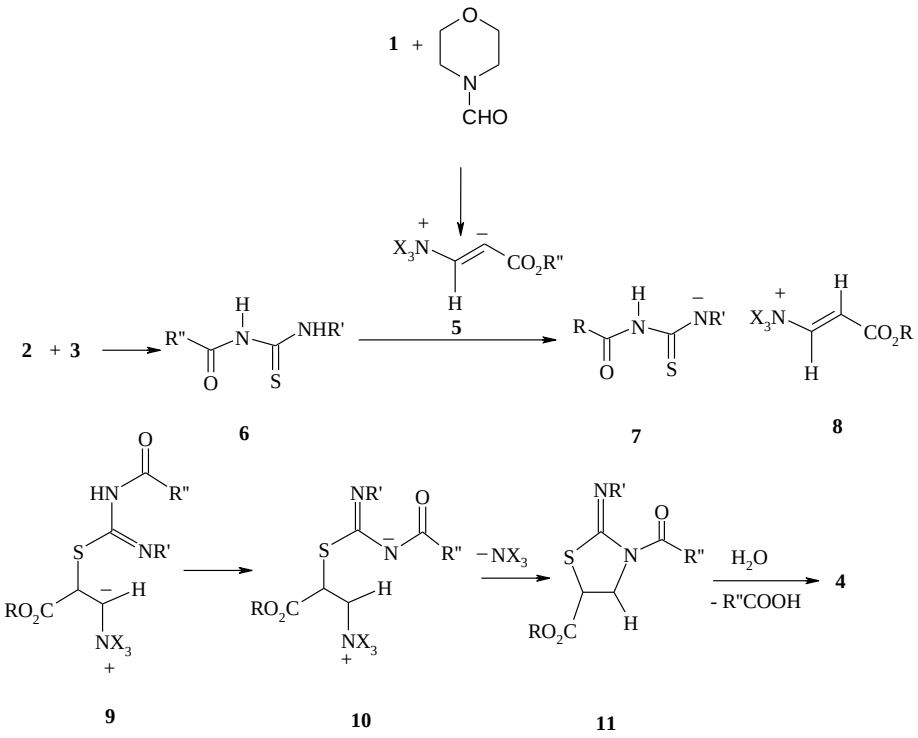
The structures of compounds **4a–e** were apparent from the ^{1}H NMR, ^{13}C NMR and IR spectra which are in agreement with the proposed structures. For example, the ^{1}H NMR spectrum of **4a** displayed two signals for vicinal methine protons at δ = 4.78 and 4.92, which appeared as two doublets with $^3J_{HH}$ values of 12.4 Hz. The methoxy groups were showed as two singlets at δ = 3.78 and 3.85. Observation of $^3J_{HH}$ = 12.4 Hz for the vicinal methine protons in **4a** indicates the dominance of anti arrangement. The carbonyl groups resonances in the ^{13}C NMR spectra of **4a** appeared at 172.5 (C=O), 173.7 (C=O) ppm. Also the mass spectra of **4a** displayed the molecular ion peak with the correct m/z values. A proposed mechanism for the formation of compound **4** is shown in Scheme **2**. Apparently, the zwitterionic intermediate of **6,** that formed from the reaction of *N*-formylmorpholine (X_3N) and the electron deficient acetylenic ester **1** is protonated by the intermediate **5** (That was generated in situ from the reaction of primary amine **2** and isothiocyanate **3**) to producing intermediates of **7** and **8**. Nucleophilic attack of the conjugate base of **7** on intermediate **8** leads to adduct **9**, which undergoes a proton transfer process to afford a new zwitterion **10**. Intramolecular cyclization reaction of **10** with the elimination of *N*-formylmorpholine group produces compound **11**. Finally, in the water media, with the elimination of the carboxylic acid from **11** leads to the product of **4** (Scheme **4**).

Conclusion

In summary, we report a reaction which involving alkyl propiolates and primary amines in the presence of catalytic amount of *N*-formylmorpholine at room temperature which affords a new route to the synthesis of functionalized pyrroles.

Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. 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.



Scheme 2: Proposed mechanism for the formation of **4**.

IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C, spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard.

General procedure for preparation of compounds 13:

To a magnetically stirred mixture of activated acetylenes **1** (2 mmol) and *N*-formylmorpholine (5 mol%) was added a mixture of isothiocyanates **3** and primary amines **2** (2 mmol) at room temperature. The reaction mixture was then stirred. After the completion of the reaction [6 h;TLC (AcOEt/hexane 1:7) monitoring], the solid residue was filtered and washed by cold diethyl ether to afforded pure compounds **4**.

Methyl 2-(methylimino)-1,3-thiazolane-5-dicarboxylate (4a):

Yellow powder, m.p. 164-166°C, yield: 0.26 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1567, 1456, 1385, 1257 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.24 (3 H, s, NMe), 3.75 (3 H, s, MeO), 3.87 (1 H, dd, $^{2}J_{HH}$ =16 Hz, $^{3}J_{HH}$ = 7 Hz, CH), 4.12 (1 H, dd, $^{2}J_{HH}$ =16 Hz, $^{3}J_{HH}$ = 3 Hz, CH), 4.78 (1 H, dd, $^{3}J_{HH}$ 7 Hz $^{3}J_{HH}$ 3 Hz, CH), 6.14 (1 H, broad, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 35.8 (NMe), 39.4 (CH), 47.5 (CH_2), 52.4 (MeO), 163.2 (C=N), 172.5 (C=O) ppm. MS, *m/z* (%): 174 (M^+, 15), 143 (84), 31 (100). Anal. Calcd for $C_6H_{10}N_2O_2S$ (174.22): C, 41.36; H, 5.79; N, 16.08. Found: C, 41.24; H, 5.62; N, 15.96%.

Methyl 2-(ethylimino)-1,3-thiazolane-5-dicarboxylate (4b):

Yellow powder, m.p. 158-160°C, yield: 0.33 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1527, 1475, 1322, 1254 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (3 H, t, $^{3}J_{HH}$ = 7.5 Hz, Me), 3.32 (2 H, q, $^{3}J_{HH}$ = 7.5 Hz, NCH_2), 3.78 (3 H, s, MeO), 3.94 (1 H, dd, $^{2}J_{HH}$ =15.8 Hz, $^{3}J_{HH}$ = 8.2 Hz, CH), 4.23 (1 H, dd, $^{2}J_{HH}$ =15.8 Hz, $^{3}J_{HH}$ = 5.5 Hz, CH), 4.62 (1 H, dd, $^{3}J_{HH}$ 8.2 Hz $^{3}J_{HH}$ 5.5 Hz, CH), 6.22 (1 H, broad, NH) ppm.^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.2 (Me), 38.6 (CH), 43.5 (NCH_2), 45.2 (CH_2), 52.6 (MeO), 162.4 (C=N), 174.2 (C=O) ppm. MS, *m/z* (%): 188 (M^+, 20), 145 (78), 43 (100), 31 (100). Anal. Calcd for $C_7H_{12}N_2O_2S$ (188.25): C, 44.66; H, 6.43; N, 14.88. Found: C, 44.72; H, 6.53; N, 14.95%.

Ethyl 2-(butylimino)-1,3-thiazolane-5-dicarboxylate (4c):

White powder, m.p. 147-149°C, yield: 0.32 g (70%). IR (KBr) (ν_{max}/cm^{-1}): 1737, 1587, 1465, 1327, 1286 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, t, ^3J = 7.5, CH_3), 1.32 (3H, t, ^3J = 7.3, CH_3), 1.65 (2H, m, CH_2), 1.72 (2H, m, CH_2), 3.32 (2 H, t, ^3J = 6.8, NCH_2), 3.97 (1 H, dd, $^2J_{HH}$ =15.2 Hz, $^3J_{HH}$ = 7.8 Hz, CH), 4.28 (1 H, dd, $^2J_{HH}$ =15.2 Hz, $^3J_{HH}$ = 5.8 Hz, CH), 4.32 (2 H, q, ^3J = 7.3, CH_2O), 4.68 (1 H, dd, $^3J_{HH}$ = 7.8 Hz $^3J_{HH}$ = 5.8 Hz, CH), 6.10 (1 H, broad, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.5 (CH_3), 14.2 (CH_3), 21.8 (CH_2), 33.2 (CH_2), 42.4 (CH), 48.7 (CH_2), 61.8 (CH_2O), 63.4 (NCH_2), 165.7 (C=N), 173.5 (C=O) ppm. Anal. Calcd for $C_{10}H_{18}N_2O_2S$ (230.33): C, 52.15; H, 7.88; N, 12.16. Found: C, 52.23; H, 7.92; N, 12.27%. MS, *m/z* (%): 230 (M^+, 10), 185 (87), 45 (100).

Ethyl 2-(tert-butylimino)-1,3-thiazolane-5-dicarboxylate (4d):

Pale yellow powder, m.p. 167-169 °C, yield: 0.36 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1735, 1594, 1487, 1267 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (3H, t, ^3J = 7.5 Hz, CH_3), 1.32 (9H, s, Me_3C), 3.85 (1 H, dd, $^2J_{HH}$ =16.5 Hz, $^3J_{HH}$ = 8.9 Hz, CH), 4.18 (1 H, dd, $^2J_{HH}$ =16.5 Hz, $^3J_{HH}$ = 6.2 Hz, CH), 4.27 (2 H, q, ^3J = 7.5, CH_2O), 4.72 (1 H, dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 6.2 Hz, CH), 6.27 (1 H, broad, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.2 (CH_3), 28.7 (Me_3C), 39.4 (CH), 46.7 (CH_2), 48.9 (Me_3C), 62.0 (CH_2O), 161.8 (C=N), 174.2 (C=O) ppm. Anal. Calcd for $C_{10}H_{18}N_2O_2S$ (230.33): C, 52.15; H, 7.88; N, 12.16. Found: C, 52.24; H, 7.90; N, 12.26%. MS, *m/z* (%): 230 (M^+, 15), 173 (68), 57 (100).

Methyl 2-(tert-butylimino)-1,3-thiazolane-5-dicarboxylate (4e):

Yellow powder, m.p. 154-156 °C, yield: 0.35 g (80%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1584, 1432, 1295, 1127 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (9H, s, Me_3C), 3.78 (3 H, s, MeO), 3.90 (1 H, dd, $^2J_{HH}$ =16.8 Hz, $^3J_{HH}$ = 9.0 Hz, CH), 4.23 (1 H, dd, $^2J_{HH}$ =16.8 Hz, $^3J_{HH}$ = 6.5 Hz, CH), 4.75 (1 H, dd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 6.5 Hz, CH), 6.32 (1 H, broad, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 29.2 (Me_3C), 40.2 (CH), 47.8 (CH_2), 49.5 (Me_3C), 162.7 (C=N), 175.3 (C=O) ppm. Anal. Calcd for $C_9H_{16}N_2O_2S$ (216.30): C, 49.97; H, 7.46; N, 12.95. Found: C, 49.88; H, 7.37; N, 12.84%. MS, *m/z* (%): 216 (M^+, 20), 159 (88), 57 (100).

References

[1] (a) Domling, A. *Chem. Rev.* **2006**, *106*, 17e89; (b) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *11*, 1967-1983; (c) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168-3210; (d) Kolb, J.; Beck, B.; Almstetter, M.; Heck, S.; Herdtweck, E.; Domling, A. *Mol. Divers.* **2003**, *6*, 297-313 (e) Domling, A.; Ugi, I.; Werner, B. *Molecules* **2003**, *8*, 53-66.

[2] (a) Bon, R. S.; Vliet, B. V.; Sprenkels, N. E.; Schmitz, R. F.; Kanter, F. J. J.; Stevens, C. V.; Swart, M.; Bickelhaupt, F. M.; Groen, M. B.; Orru, R. V. A. J. *Org. Chem.* **2005**, *70*, 3542-3553(b) Banfi, L.; Basso, A.; Guanti, G.; Kielland, N.; Repeto, C.; Riva, R. *J. Org. Chem.* **2007**, *72*, 2151-2160; (c) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811-1813.

[3] Anastas, P.; Williamson, T. *Green Chemistry, Frontiers in Benign Chemical Synthesis and Procedures*; Oxford Science Publications: New York, **1998**.

[4] Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun*. **2001**, 2159-2169.

[5] Sheldon, R. A. *Chem. Ind*. **1997**, 12.

[6] Sabbaghan, M.; Hossaini, Z. *Comb. Chem. High Throughput Screen.*, **2012**, *15*, 745-748.

[7] (a) Hosseini-Sarvari, M.; Sharghi, H.; Etemad, S. *Helv. Chim. Acta*, **2008**, *91*(4), 715-724. (b) Paul, S.; Bhattacharyya, P.; Das, A. R. *Tetrahedron Letters*, **2011**, *52*, 4636-4641.

[8] Shaterian, H. R.; Mohammadnia, M. *J. Mol. Liq.*, **2013**, *177*, 353-360.

[9] (a) Blair, L. M.; Sperry, J. *J. Nat. Prod.* **2013**, *76*, 794–812; (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev*. **2013**, *113*, 1–35; (c) Dhara, S.; Ahmed, A.; Nandi, S.; Baitalik, S.; Ray, J. K. *Tetrahedron Lett.* **2013**, *54*, 63–65; (d) Singha, R.; Dhara, S.; Ray, J. K. *Tetrahedron Lett*. **2013**, *54*, 4841–4843; (e) Ghosh, M.; Ahmed, A.; Dhara, S.; Ray, J. K. *Tetrahedron Lett.* **2013**, *54*, 4837–4840; (f) Dhara, S.; Ghosh, M.; Ray, J. K. *Synlett* **2013**, A–C.

[10] Breslow, R. *J. Am. Chem. Soc.*, **1958**, *80*, 3719-3726.

[11] Miwatashi, S.; Arikawa,Y.; Kotani, E.; Miyamoto, M.; Naruo, K. I.; Kimura, H.; Tanaka,T.; Asahi, S.; Ohkawa, S. *J. Med. Chem.* **2005**, *48*, 5966-5979.

[12] Papadopoulou, C.; Geronikaki, A.; Hadjipavlou-Litina, D. *Il Farmaco*, **2005**, *60*, 969-973

[13] Kumar, Y.; Green, R.; Borysko, K. Z.; Wise, D. S.; Wotring, L. L.; Townsend, L. B. *J. Med. Chem.*, **1993**, *36*, 3843-3848

[14] Pereira, R.; Gaudon, C.; Iglesias, B.; Germain, P.; Gronemeyer, H.; de Lera, A. R. *Bioorg. Med. Chem. Lett*., **2006**, *16*, 49-54.

[15] Tsurumi, Y.; Ueda, H.; Hayashi, K.; Takase, S.; Nishikawa, M.; Kiyoto, S.; Okuhara, M. *J. Antibiotic*, **1995**, *48*, 1066-1072.

[16] Bell, F. W.; Cantrell, A. S.; Hoberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M. *J. Med.Chem.*, **1995**, *38*, 4929-4936.
[17] Millan, D. S.; Prager, R. H.; Brand, C.; Hart, P. H. *Tetrahedron*, **2000**, *56*, 811-816.
[18] Wang, W. L.; Yao, D.Y.; Gu, M.; Fan, M. Z.; Li, J. Y.; Xing, Y. C.; Nan, F. J. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 5284.