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Catalyst-free synthesis of thiazole derivatives using propiolates

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Abstract: We reported a green, simple and efficient method for the synthesis of thiazole derivatives employing a multi-component and one-pot condensation reaction of activated acetylenic compounds, alkyl bromides and benzothiazole as nucleophile at ambient temperature in good yields. The structures of compounds were deduced from elemental analysis and their IR, ^{1}H NMR, ^{13}C NMR spectra. This new protocol offers advantages such as mild reaction conditions, short reaction time, easy work-up, and use of an inexpensive and non-toxic catalyst, high yields of biological active products and does not involve any hazardous solvent. Therefore, this procedure could be classified as green chemistry.

Keywords: Thiazole, Ethyl bromopyruvate, Ethylpyruvate, Propiolate.

Introduction

In general, multi-component reactions (MCRs) are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library syntheses, thus are finding increasing use in the discovery process for new drugs and agrochemicals [1-7]. In recent years, the research into novel active organic substances and into the design of molecular electronic devices has attracted considerable interest [8,9]. In this respect, several studies involved sulfur-containing compounds because they present good conduction in organic materials [10,11] or are relevant biologically. Also, sulfurcontaining anions have found extensive use as versatile reagents in organic synthesis.

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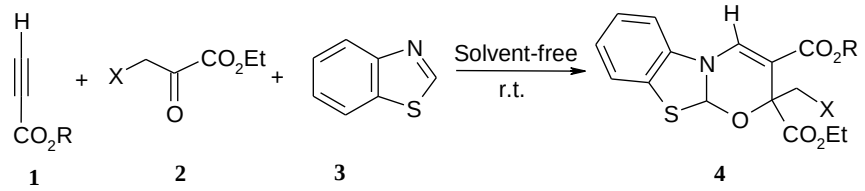
Some heterocyclic compounds containing a thiazole ring in their structures offer important applications in pharmaceutical as well as in agrochemical chemistry [12,13]. For example, ritonavir, an anti-HIV drug contains the thiazole moiety. These products, which have N and S atoms, are bridged easily with other molecules [14,15] or can coordinate several metal ions. For example, they could be used to entrap mercury in the environment [16] and as a new inhibitor for copper [17]. Herein, we describe an efficient procedure for direct synthesis of thiazole derivatives with Pyruvates in the Presence of Thiazol in dichloromethane at room temperature (Scheme **1**).

Result and Discussion

The reaction of **1** with **3** in the presence of pyruvates **2** led to 7-ethyl 5,6-dialkyl 7*H*-[1,3]thiazolo[2,3-*b*][1,3]oxazin-5,6,7-tricarboxylate **4** in 80-90% yields (Scheme **1**). Structures of compounds **4a–d** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited one triplet at 1.25 ($^{3}J_{HH}$ = 7.2) for methyl

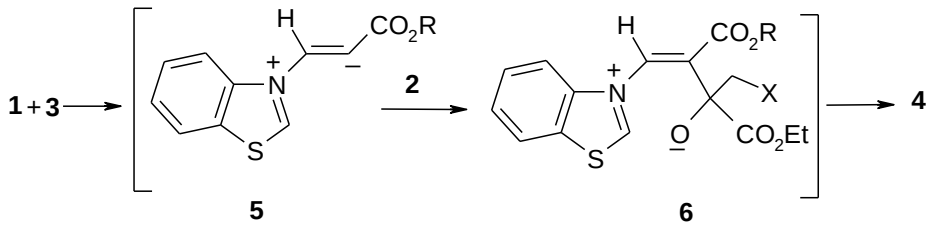
proton and two singlets at 3.68 and 3.89 for methoxy groups. Because of stereogenic center in these products, hydrogens of CH_2 and OCH_2 groups are diasterotopic, therefore, two doublets were observed at 4.09 ($^2J_{HH}$ = 10.9) and 4.17 ($^2J_{HH}$ = 10.9) for CH_2 group, one multiplet at 4.18-4.25 for OCH_2 moiety and one singlet at 6.60 ppm for CH groups. The carbonyl groups resonances in the ^{13}C NMR spectra of **4a** appear at 162.9, 164.1 and 167.5 ppm. The mass spectrum of **4a** displayed the molecular ion peak at *m/z* = 422.

A tentative mechanism for this transformation is proposed in Scheme **2**. It is conceivable that, the initial event is the formation of the 1:1 adducts **5** from the Reaction of propiolate **1** with benzothiazol **3** which is subsequently attacked by pyruvates to produce **6**. Intermediate **6** undergoes cyclization reaction to generate **4**.



1, 2, 4	R	X	Yield (%) of **4**
a	Me	Br	90
b	Et	Br	85
c	Me	H	85
d	Et	H	80

Scheme 1: Synthesis of thiazole derivatives



Scheme 2: proposed mechanism for synthesis of thiazole derivatives **4**

Conclusions

In conclusion, the reaction of deficient acetylenic compounds with pyruvates in the presence of thiazol or benzothiazol led to thiazole derivatives in excellent yields. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

Experimental

All compounds in these reactions were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus; uncorrected. IR Spectra: Shimadzu IR-460 spectrometer. ^1H and ^{13}C NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; □ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

*General Procedure for the Preparation of Compounds **4a-d:***

Thiazol (2 mmol) were added to a mixture of pyruvates (2 mmol) and activated acetylenic ester (2 mmol) at room temperature. The reaction mixture was then stirred for 12 h to afford the pure compounds **4a-d**.

7-ethyl 5,6-dimethyl 7-bromomethyl-7H-[1,3]thiazolo[2,3-b][1,3]oxazin-5,6,7-tricarboxylate (4a):

Yellow oil, yield: 0.76 g (90%). IR (KBr): 1725, 1591, 1549, 1473, 1368, and 1015. ^{1}H NMR: 1.25 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 3.68 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.09 (1 H, *d*, $^2J_{HH}$ = 10.9, CH), 4.17 (1 H, *d*, $^2J_{HH}$ = 10.9, CH), 4.18-4.25 (2 H, *m*, OCH_2), 5.69 (1 H, *d*, $^3J_{HH}$ = 4.5, CH), 6.19 (1H, *d*, $^3J_{HH}$ = 4.5, CH), 6.60 (1 H, *s*, CH). ^{13}C NMR: 13.9 (Me), 31.8 (CH_2Br), 51.9 (OMe), 52.1 (OMe), 62.9 (OCH_2), 79.6 (C), 91.0 (CH), 102.7 (CH), 109.3 (C), 128.8 (CH), 141.7 (C), 162.9 (C=O), 164.1 (C=O), 167.5 (C=O). EI-MS: 422 (M^+, 10); 350 (20), 348 (20), 167 (25), 149 (60), 84 (100), 57 (62). Anal. Calcd for $C_{14}H_{16}BrNO_7S$ (422.24): C, 39.82; H, 3.82; N, 3.32; found: C, 39.80; H, 3.80; N, 3.31%.

7-ethyl 5,6-diethyl 7-bromomethyl-7H-[1,3]thiazolo[2,3-b][1,3]oxazin-5,6,7-tricarboxylate (4b):

Yellow Oil, yield: 0.76 g (85%). IR (KBr): 1732, 1685, 1583, 1504, 1453 and 1384. ^{1}H NMR: 1.22 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.28 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.35 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 4.12 (1 H, *d*, $^2J_{HH}$ = 10.5, CH), 4.18 (1 H, *d*, $^2J_{HH}$ = 10.5, CH), 4.19-4.23 (4 H, *m*, 2 OCH_2), 4.29-4.37 (2 H, *m*, OCH_2), 5.71 (1H, *d*, $^3J_{HH}$ = 4.6, CH), 6.20 (1H, *d*, $^3J_{HH}$ = 4.6, CH), 6.62 (1 H, *s*, CH). ^{13}C NMR: 13.8 (Me), 13.9 (Me), 14.0 (Me), 35.7 (CH_2Br), 61.0 (OCH_2), 62.4 (OCH_2), 62.7 (OCH_2), 78.4 (C), 90.9 (CH), 102.5 (CH), 113.4 (C), 121.4 (CH), 142.0 (C), 162.4 (C=O), 163.6 (C=O), 167.6 (C=O). EI-MS: 450 (M^+, 5); 377 (24), 375 (24), 370 (68), 231 (45), 229 (45), 84 (100), 73 (60). Anal. Calcd for $C_{16}H_{20}BrNO_7S$ (450.30): C, 42.68; H, 4.48; N, 3.11; found: C, 42.70; H, 4.50; N, 3.10%.

7-ethyl 5,6-dimethyl 7-methyl-7H-[1,3]thiazolo[2,3-b][1,3]oxazin-5,6,7-tricarboxylate (4c):

Yellow Oil, yield: 0.58 g (85%). IR (KBr): 1716, 1687, 1429, 1364, 1199 and 1103. ^{1}H NMR: 1.17 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.75 (3 H, s, Me), 3.65 (3 H, *s*, OCH_3), 3.82 (3 H, *s*, OCH_3), 4.12-4.17 (2 H, *m*, OCH_2), 5.61 (1 H, *d*, $^3J_{HH}$ = 4.6, CH), 6.11 (1 H, *d*, $^3J_{HH}$ = 4.6, CH), 6.52 (1 H, *s*, CH). ^{13}C NMR: 13.6 (Me), 23.6 (Me), 51.7 (OCH_3), 53.0 (OCH_3), 61.9 (OCH_2), 89.9 (C), 90.7 (CH), 101.3 (CH), 112.7 (C), 121.4 (CH), 138.4 (C), 163.1 (C=O), 164.5 (C=O), 169.8 (C=O). EI-MS: 343 (M^+, 10); 270 (85); 306 (66); 292(64), 284 (60);275 (85), 84 (100); 59 (67). Anal. Calcd for $C_{14}H_{17}NO_7S$ (343.35): C, 48.97; H, 4.99; N, 4.08; found: C, 48.95; H, 4.92; N, 4.02%.

7-ethyl 5,6-diethyl 7-methyl-7H-[1,3]thiazolo[2,3-b][1,3]oxazin-5,6,7-tricarboxylate (4d):

Yellow Oil, yield: 0.59 g (80%). IR (KBr): 1716, 1686, 1461, 1360, 1312 and 1025. ^{1}H NMR: 1.16 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.19 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.27 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.71 (3 H, s, Me), 4.00-4.18 (4 H, *m*, 2 OCH_2), 4.20-4.32 (2 H, *m*, OCH_2), 5.58 (1 H, *d*, $^3J_{HH}$ = 4.6, CH), 6.07 (1 H, *d*, $^3J_{HH}$ = 4.6, CH), 6.52 (1 H, *s*, CH). ^{13}C NMR: 13.8 (Me), 13.9 (Me), 14.0 (Me), 23.8 (Me), 60.8 (OCH_2), 61.7 (OCH_2), 62.5 (OCH_2), 78.2 (C), 90.7 (CH), 101.3 (CH), 112.5 (C), 121.6 (CH), 138.8 (C), 162.8 (C=O), 163.9 (C=O), 170.0 (C=O). EI-MS: 371 (M^+, 15); 298 (85); 225 (66); 292(64), 275 (85), 84 (100); 45 (84). Anal. Calcd for $C_{16}H_{21}NO_7S$ (371.41): C, 51.74; H, 5.70; N, 3.77; found: C, 51.70; H, 5.68; N, 3.71%.

Acknowledgements

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