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# Application of ZnO Nanorods for the Synthesis of Thiazole Derivatives *via* Multicomponent Reactions in Water

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**Abstract**

Simple three-component reactions between dialkyl acetylenedicarboxylate, primary amines and isothiocyanates in the presence of catalytic amount of ZnO nanorods are investigated in water at room temperature which produced thiazole derivatives in good yields.

***Key words****: One-pot reactions; ZnO nanorods, Isothiocyanates, Primary amines.*

## Introduction

Heterocycles are key compounds in the development of modern pharmaceutical chemistry, this being the reason why the design of amenable synthetic approaches for the synthesis of new heterocyclic systems is still an attractive challenge [1]. The thiazolium ring present in vitamin B1 serves as an electron sink and its coenzyme form is important for the decarboxylation of keto-acids [2]. Large numbers of thiazole derivatives have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory [3, 4], anti-tumour [5] anti-hyperlipidemic [6], anti-hypertensive [7], anti-HIV infections [8], and several other biological properties [9-11]. Multicomponent reactions (MCRs), with three or more reactants join in a one-pot procedure to afford a single product [12-14]. They are economically and environmentally useful because multi-step synthesis produce large amounts of trash frequently because of complex isolation actions frequently involving uncomfortable, toxic, and hazardous solvents after each step [15-18].

MCRs are absolutely suited for combinatorial library synthesis and increased utilize in the finding procedure for new drugs and agrochemicals [19]. They supply a dominant tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [20, 21]. Green chemistry

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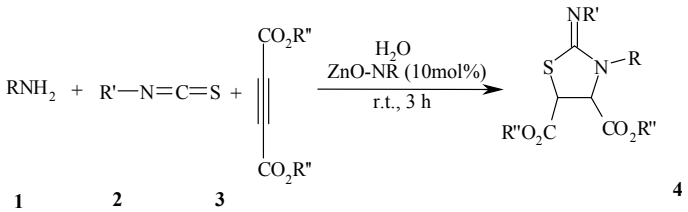
move towards hold out significant potential not only for reduction of byproducts, waste produced, and lowering of energy but also in the expansion of new methodologies toward before exclusive materials, using existing technologies [22]. Between existing part of chemistry, medicinal and pharmaceutical chemistry are possibly developed for greening [23].

Hence, we display a simple three-component reaction between activated acetylenic compounds, primary amines and isothiocyanates in the presence of catalytic amount of ZnO-NR in water at room temperature which produced thiazole derivatives **4** in excellent yields (Scheme 1).




| 1, 2, 3, 4 | R | R' | R" | Yield (%) of **4** |
|---|---|---|---|---|
| **a** | Ph | Me | Me | 85 |
| **b** | 4-MeO-$C_6H_4$ | Et | Me | 87 |
| **c** | 4-MeO-$C_6H_4$ | n-Bu | Et | 80 |
| **d** | 4-Me-$C_6H_4$ | $^t$Bu | Et | 80 |
| **e** | 4-Br-$C_6H_4$ | Me | Me | 85 |
| **f** | 4-$NO_2$-$C_6H_4$ | Me | Me | 87 |
| **g** | $^t$Bu | Me | Me | 83 |

**Scheme 1.** Synthesis of thiazole derivatives in the presence ZnO-NR.

## Experimental

ZnO nanorods are prepared according to literature procedure [24-26]. Other 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. IR spectra were measured on a Shimadzu IR-460 spectrometer. 1H NMR and $^{13}$C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively, and were obtained for solutions in $CDCl_3$ using TMS as the internal standard or 85% $H_3PO_4$ as the external standard.

*General Procedure for the Preparation of Nanorod ZnO (NR-ZnO)*

Sodium hydroxide (0.44 g) was dissolved in 75 mL of distilled water under vigorous stirring at room temprature. Afterwards, with the addition

of SDS (1.57 g) and $Zn(AcO)_2.2H_2O$ (0.6 g) to the mixture, the solution was refluxed for 1.5 h at 80 ◦C (pH=14). The product was collected by filtration and washed with distilled water and ethanol (96%) several times [24].

*General procedure for preparation of compounds* **4**

To a magnetically stirred mixture of primary amines 1 (2 mmol) and dialkyl acetylenedicarboxylate 2 (2 mmol) in water (5mL) was added mixture of isothiocyanates **3** and ZnO-ZR (10 mol%) at room temperature. The reaction mixture was then stirred. After completion of the reaction [TLC (AcOEt/ hexane 1:7) monitoring], the solid residue was filtered and washed by cold diethyl ether to afforded pure compounds **4**.

*Dimethyl 2-(methylimino)-3-phenyl-1,3-thiazolane-4,5-dicarboxylate (***4a***)*

Yellow powder, m.p. 156-158°C, yield: 0.46 g (85%), IR (KBr) ($\nu_{max}$/$cm^{-1}$): 1745, 1738, 1698, 1657, 1574, 1467, 1382, 1215 $cm^{-1}$. Anal. Calcd. for $C_{14}H_{16}N_2O_4S$ (308.35): C, 54.53; H, 5.23; N, 9.08. Found: C, 54.62; H, 5.34; N, 9.23%. $^1$H NMR (500 MHz, $CDCl_3$): δ 2.83 (3 H, s, NMe), 3.75 (3 H, s, MeO), 3.82 (3 H, s, MeO), 4.76 (1 H, d, $^3J$ = 11.8, CH), 4.90 (1 H, d, $^3J$ = 11.8, CH), 7.23 (1 H, t, $^3J$ = 7.4, CH), 7.35 (2 H, d, $^3J$ = 7.6, 2 CH), 7.54 (2 H, t, $^3J$ = 7.6, 2 CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 34.6 (NMe), 42.7 (CH), 51.6 (MeO), 52.4 (MeO), 58.4 (CH), 122.8 (CH), 128.3 (2 CH), 129.6 (2 CH), 139.8 (C), 163.4 (C=N), 170.8 (C=O), 171.6 (C=O) ppm. MS, *m/z* (%): 308 ($M^+$, 15), 277 (86), 77 (64), 31 (100).

*Dimethyl2-(ethylimino)-3-(4-methoxyphenyl)-1,3-thiazolane-4,5-dicarboxylate (***4b***)*

Pale yellow powder, m.p. 168-170 °C, yield: 0.59 g (87%). IR (KBr) ($\nu_{max}$/$cm^{-1}$): 1742, 1736, 1686, 1632, 1525, 1487, 1325, 1219 $cm^{-1}$. Anal. Calcd. for $C_{16}H_{20}N_2O_5S$ (352.41): C, 54.53; H, 5.72; N, 7.95. Found: C, 54.64; H, 5.80; N, 8.10%. $^1$H NMR (500 MHz, $CDCl_3$): δ 1.24 (3H, t, $^3J$ = 7.3, $CH_3$), 3.27 (2 H, q, $^3J$ = 7.3, $CH_2$), 3.70 (3 H, s, MeO), 3.76 (3 H, s, MeO), 3.87 (3 H, s, MeO), 4.75 (1 H, d, $^3J$ = 12.2, CH), 4.87 (1 H, d, $^3J$ = 12.2, CH), 7.14 (2 H, d, $^3J$ = 7.8, 2 CH), 7.28 (2 H, d, $^3J$ = 7.6, 2 CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 14.2 ($CH_3$), 41.5 (CH2), 43.7 (CH), 51.5 (MeO), 52.6 (MeO), 55.4 (MeO), 59.3 (CH), 111.2 (2 CH), 130.3 (2 CH), 134.8 (C), 154.2 (C), 160.7 (C=N), 171.8 (C=O), 172.6 (C=O) ppm. MS, *m/z* (%): 352 ($M^+$, 10), 321 (64), 108 (96), 31 (100).

*Diethyl 2-(buthylimino)-3-(4-methoxyphenyl)-1,3-thiazolane-4,5-dicarboxylate (***4c***)*

White powder, m.p. 162-164 °C, yield: 0.70 g (80%), IR (KBr) ($\nu_{max}$/$cm^{-1}$): 1740, 1738, 1687, 1645, 1438, 1357, 1256 $cm^{-1}$. Anal. Calcd. for $C_{20}H_{28}N_2O_5S$ (408.51): C, 58.80; H, 6.91; N,

6.86. Found: C, 58.92; H, 6.98; N, 6.90%. 1H NMR (500 MHz, $CDCl_3$): δ 1.19 (3H, t, $^3J$ = 7.2, $CH_3$), 1.22 (3H, t, $^3J$ = 7.4, CH3), 1.28 (3H, t, $^3J$ = 7.3, $CH_3$), 1.68 (2 H, q, $^3J$ = 7.3, $CH_2$), 1.78 (2 H, m, $CH_2$), 2.83 (2 H, t, $^3J$ = 6.8, $NCH_2$), 3.75 (3 H, s, MeO), 4.12 (2 H, q, $^3J$ = 7.3, $CH_2O$), 4.23 (2 H, q, $^3J$ = 7.3, $CH_2O$), 4.62 (1 H, d, 3J = 11.7, CH), 5.02 (1 H, d, $^3J$ = 11.7, CH), 7.12 (2 H, d, $^3J$ = 7.6, 2 CH), 7.32 (2 H, d, $^3J$ = 7.6, 2 CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 13.3 ($CH_3$), 13.8 ($CH_3$), 14.3 ($CH_3$), 21.4 ($CH_2$), 32.5 ($CH_2$), 43.6 (CH), 54.8 (MeO), 59.5 (CH), 61.2 ($CH_2O$), 62.0 ($CH_2O$), 62.7 ($NCH_2$), 114.5 (2 CH), 130.8 (2 CH), 135.4 (C), 156.7 (C), 161.2 (C=N), 172.3 (C=O), 174.2 (C=O) ppm. MS, *m/z* (%): 408 ($M^+$, 8), 363 (84), 108 (68), 45 (100).

*Diethyl 2-(tert-butylimino)-3-(4-methylphenyl) -1,3-thiazolane-4,5-dicarboxylate (***4d***)*

Yellow powder, m.p. 164-166 °C, yield: 0.59 g (80%), IR (KBr) ($\nu_{max}$/$cm^{-1}$): 1736, 1732, 1694, 1587, 1467, 1346, 1238 $cm^{-1}$. Anal. Calcd. for $C_{20}H_{28}N_2O_4S$ (392.51): C, 61.20; H, 7.19; N, 7.14. Found: C, 61.32; H, 7.25; N, 7.22%. 1H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, t, $^3J$ = 7.4, $CH_3$), 1.32 (3H, t, $^3J$ = 7.4, $CH_3$), 1.35 (9H, s, $Me_3C$), 2.28 (3 H, s, $CH_3$), 4.15 (2 H, q, $^3J$ = 7.4, $CH_2O$), 4.28 (2 H, q, $^3J$ = 7.4, $CH_2O$), 4.73 (1 H, d, $^3J$ = 11.5, CH), 4.96 (1 H, d, $^3J$ = 11.5, CH), 7.24 (2 H, d, $^3J$ = 7.5, 2 CH), 7.36 (2 H, d, $^3J$ = 7.6, 2 CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 13.8 (CH3), 14.2 ($CH_3$), 22.4 (CH3), 28.7 ($Me_3C$), 44.3 (CH), 48.7 ($Me_3C$), 58.7 (CH), 61.4 ($CH_2O$), 62.3 ($CH_2O$), 129.4 (2 CH), 130.2 (C), 131.4 (2 CH), 140.7 (C), 160.4 (C=N), 172.5 (C=O), 175.3 (C=O) ppm. MS, *m/z* (%): 392 ($M^+$, 20), 377 (84), 91 (84), 45 (100).

*Dimethyl2-(methylimino)-3-(4-bromophenyl)-1,3-thiazolane-4,5-dicarboxylate (***4e***)*

Yellow crystals, m.p. 183-185 °C, yield: 0.62 g (85%), IR (KBr) ($\nu_{max}$/$cm^{-1}$): 1737, 1732, 1695, 1587, 1485, 1436, 1342, 1225 $cm^{-1}$. Anal. Calcd. for $C_{14}H_{15}BrN_2O_4S$ (387.25): C, 43.42; H, 3.90; N, 7.23. Found: C, 43.53; H, 3.95; N, 7.32%. $^1$H NMR (500 MHz, $CDCl_3$): δ 3.12 (3H, s, NMe), 3.75 (3 H, s, MeO), 3.82 (3 H, s, MeO), 4.83 (1 H, d, $^3J$ = 11.8, CH), 4.92 (1 H, d, $^3J$ = 11.8, CH), 7.10 (2 H, d, $^3J$ = 7.8, 2 CH), 7.54 (2 H, d, $^3J$ = 7.8, 2 CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 34.5 ($NCH_3$), 44.2 (CH), 51.2 (MeO), 51.8 (MeO), 60.3 (CH), 116.7 (C), 129.7 (2 CH), 132.6 (2 CH), 139.4 (C), 162.3 (C=N), 172.4 (C=O), 173.8 (C=O) ppm. MS, *m/z* (%): 387 ($M^+$, 15), 356 (78), 156 (64), 31 (100).

*Dimethyl 2-(methylimino)-3-(4-nitrophenyl)-1,3-thiazolane-4,5-dicarboxylate (***4f***)*

Yellow powder, m.p. 174-176 °C, yield: 0.62 g (87%), IR (KBr) ($\nu_{max}$/$cm^{-1}$): 1738, 1733, 1687, 1592, 1474, 1445, 1348, 1274 $cm^{-1}$. Anal. Calcd. for $C_{14}H_{15}N_3O_6S$ (353.35): C, 47.56; H, 4.28; N, 11.89. Found: C, 47.64; H, 4.37; N, 7.40%. $^1$H NMR (500 MHz, $CDCl_3$):

δ 3.15 (3H, s, NMe), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.94 (1 H, d, $^3J$ = 12.0, CH), 4.98 (1 H, d, $^3J$ = 12.0, CH), 7.38 (2 H, d, $^3J$ = 7.6, 2 CH), 8.12 (2 H, d, $^3J$ = 7.6, 2 CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 34.8 ($NCH_3$), 44.5 (CH), 51.6 (MeO), 52.0 (MeO), 59.4 (CH), 129.4 (2 CH), 130.7 (2 CH), 138.6 (C), 143.2 (C), 161.8 (C=N), 172.6 (C=O), 174.2 (C=O) ppm. MS, *m/z* (%): 353 ($M^+$, 10), 322 (88), 122 (54), 31 (100).

*Dimethyl 2-(methylimino)-3-(tert-butyl)-1,3-thiazolane-4,5-dicarboxylate (***4g***)*

Yellow powder, m.p. 170-172 °C, yield: 0.45 g (83%), IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1742, 1740, 1578, 1458, 1362, 1327 cm$^{-1}$. Anal. Calcd. for $C_{12}H_{20}N_2O_4S$ (288.36): C, 49.98; H, 6.99; N, 9.71. Found: C, 49.84; H, 6.86; N, 9.65%. $^1$H NMR (500 MHz, $CDCl_3$): δ 1.56 (9 H, s, $Me_3C$), 3.07 (3H, s, NMe), 3.75 (3 H, s, MeO), 3.82 (3 H, s, MeO), 5.02 (1 H, d, $^3J$ = 11.8, CH), 5.12 (1 H, d, $^3J$ = 11.8, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 28.6 ($Me_3C$), 36.5 ($NCH_3$), 44.6 (CH), 52.0 (MeO), 52.4 (MeO), 55.8 (Me3C), 59.2 (CH), 168.2 (C=N), 173.4 (C=O), 174.8 (C=O) ppm. MS, *m/z* (%): 288 ($M^+$, 15), 285 (78), 231 (48), 31 (98), 57 (100).

## Results and discussion

The method that is used for the synthesis of NR-ZnO was reported in literature [23]. The average crystal sizes for NR-ZnO are about 30 nm. Nanorod morphology was obtained using SDS. The morphologies of the products were confirmed by SEM (Figure 1). It seems that the NR-ZnO morphology outcome of cylindrical contrary micelles in aqueous solutions of SDS.

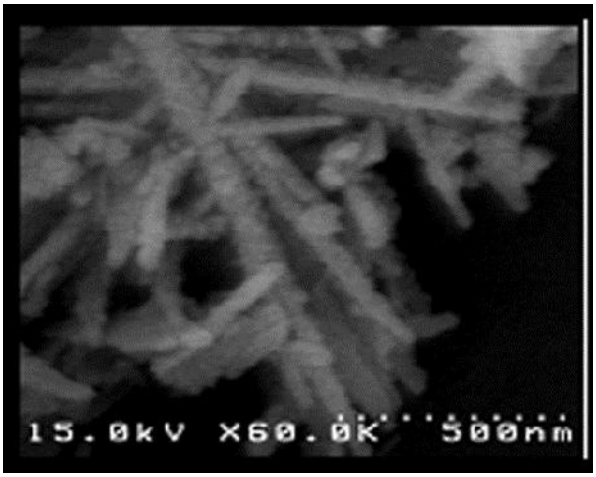



**Figure 1.** SEM image of ZnO nanorods.

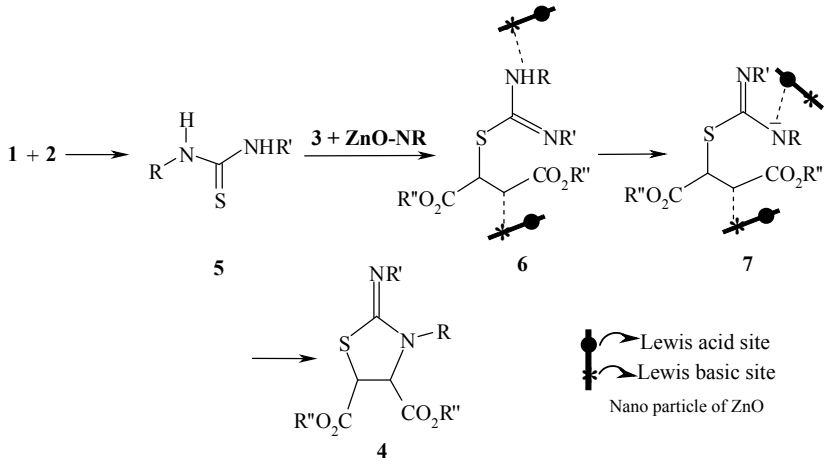
The three-component reaction between primary amines **1**, isothiocyanates **2** and dialkyl acetylenedicarboxylate **3** in the presence of catalytic amount of ZnO-NR at room temperature produced thiazole derivatives **4** in excellent yields (Scheme 1).

The structures of compounds **4a–g** were deduced from the $^{1}H$ NMR, $^{13}C$ NMR, Mass and IR spectra which are in agreement with the proposed structures. For example, the 1H NMR spectrum of **4a** displayed two signals for vicinal methine protons at δ = 4.76 and 4.90, which appeared as two doublets with 3JHH values of 11.8 Hz. The methoxy groups showed two singlet at δ = 3.75 and 3.82. Observation of $^{3}J_{HH}$ = 11.8 Hz for the vicinal methine protons in **4a** indicates the dominance of anti arrangement. Since compound **4** possesses two stereogenic centers, two diastereomers with anti HCCH arrangements are possible (Figure 2).


**Figure 2.** Anti arrangement of **4.**

The carbonyl groups resonances in the $^{13}C$ NMR spectra of **4a** are appeared at 170.8 (C=O), 171.6 (C=O) ppm. Also the mass spectra of **4a** displayed the molecular ion peak in the appropriate *m/z* values.

A proposed mechanism for the formation of compound **4** is shown in Scheme **2**. Apparently, the zwitterionic intermediate **5** formed from the reaction of primary amine **1** and isothiocyanate **2**. After adding ZnO-NR and dialkyl acetylenedicarboxylate produced intermediate **6** which undergo proton shifts to afford new zwitterionic **7**. Finally, intramolecular cyclization of **7** with elimination of ZnO-NR produces compound **4**.




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

## Conclusion

In conclusion, we investigate the reaction of dialkyl acetylenedicarboxylate with isothiocyanates and primary amines in the presence of catalytic amount of ZnO-NR that leads to a facile synthesis of some functionalized thiazoles in water at room temperature. In these reactions, purification and separation of product are very easy than procedure that is reported in the literature.

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