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# Green synthesis of oxazole derivatives using three component reactions of α-hydroxy carbonyls

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**Abstract:** An efficient synthesis of oxazole derivatives is described *via* an one-pot reaction between isothiocyanates, ammonium acetate, benzoin or 3-hydroxy-2-butanone and triethylamine.

**Keywords:** Acid chlorides, Ammonium thiocyanate, $Et_3N$, 3-Hydroxy-2-butanone, Oxazole.

## Introduction

The oxazole motif is one of the most widely occurring heterocycles in biologically active molecules and natural products and has attracted interest from both industry and academia [1]. In particular, 2,5-disubstituted and 2,4,5-trisubstituted oxazoles [2] are found in numerous natural products and pharmacologically active molecules such as the antimycobacterial natural product texaline [3], antipancreatic cancer agent PC046 [4], potent monoamine oxidase inhibitor pimpirinine,2f antidiabetic agent AD-5061,4 and peptide alkaloid (−)-muscoride A5 (Figure 1). Oxazoles also have applications as important structural motifs in fluorescent dyes [5, 6] and polymers. Heterocyclic compounds hold a prominent position in medicinal chemistry owing to their wide spectrum of biological activities such as antimalarial,[7] antimicrobial,[8] antitumor,[9] anticancer, [10] antidepressant,[11] antiviral,[12] antidiabetic,[13] anti-inflammatory [14] and anti-HIV[15]. Moreover, they also contribute in the field of material science, [16] dyes and pigment science [17] as well as agrochemistry [18]. Therefore, there is considerable thrust for the development of efficient synthetic strategies for producing these compounds.

MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [19, 20]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity. Therefore, we report an efficient synthetic route to ester derivatives. Thus, the reaction of isothiocyanate **1**, 3-hydroxy-2-butanone **2**, ammonium acetate **3** and catalytic amount of $Et_3N$ led to oxazole- derivatives **4** in excellent yields (Scheme **1**).

## Result and Discussion

Structures of compounds **4a–4h** were assigned by IR, $^1H$ NMR, $^{13}C$ NMR and mass spectral data. The $^1H$- and $^{13}C$-NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. Spectral data for these compounds are given in the experimental section. The reactions between acid chlorides and alcohol in the presence of alkali were reported in the literature, but large alcohol such as benzoin wasn't performed these reactions under similar conditions. In these reactions, $Et_3N$ is nucleophile and react with isothiocyanates as electrophiles.

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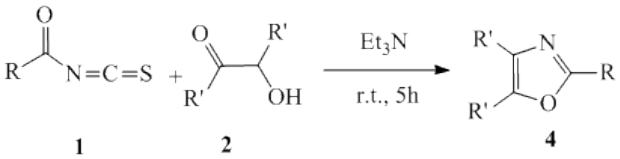
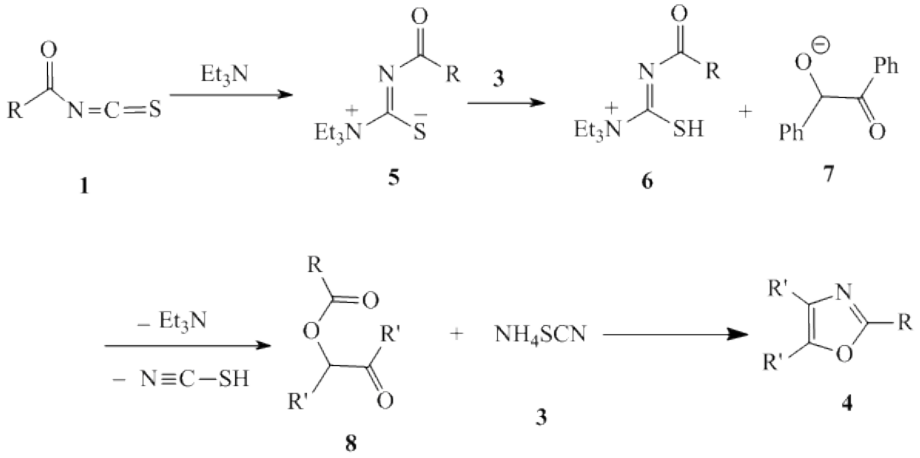



| 4 | R | R' | Yield (%) of 4 |
|---|---|---|---|
| a | Ph | Ph | 95 |
| b | 4-Me-$C_6H_4$ | Ph | 92 |
| c | 4-$NO_2$-$C_6H_4$ | Ph | 94 |
| d | 4-Br-$C_6H_4$ | Ph | 90 |
| e | 4-Cl-$C_6H_4$ | Ph | 85 |
| f | $(CH_3)_3CH$ | Ph | 87 |
| g | 4-Me-$C_6H_4$ | $CH_3$ | 83 |
| h | $(CH_3)_3CH$ | $CH_3$ | 75 |

**Scheme 1**: Synthesis of oxazole derivatives

Mechanistically, the reaction starts with formation of intermediate **5** from the reaction of isothiocyanate **1** with triethylamine followed by addition of $\alpha$-hydroxycarbonyles **2** to generate the intermediate **6** and **7**. Intermediate **7** react with **6** to produced intermediate **8** followed the reaction with ammonium acetate **3** to produced compounds **4** (Scheme **2**).




**Scheme 2**: Proposed mechanism for the synthesis of **4**

## Conclusion

In summary, the results obtained in the one-pot reaction of isothiocyanates, ammonium acetate, α-hydroxy carbonyls and catalytic amount of $Et_3N$ are depicted in Scheme **1**. All these reactions yielded a mixture of only **4a-h** as major products, which could be easily purified by recrystalization with diethyl ether. The ester derivatives were isolated in high yield and to the best of our knowledge this strategy has not yet applied to the synthesis of such compounds. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials without solvent. The

simplicity of the present procedure makes it an interesting alternative to other approaches.

## Experimental

Chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for the C and H were performed using a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values. Mass spectra were recorded on a FINNIGAN-MATT 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-500 AVANCE spectrometer at 500.1 and 125.8 MHz.

### *General Procedure for the Preparation of* 4**:**

A stirred mixture of isothiocyanaes **1** (0.15 g, 2 mmol) and $Et_3N$ 2 (2 mmol) was reacted in a water for 5 min and 3-hydroxy-2-butanone **3** (0.18 g, 2 mmol) was added slowly. The mixture was allowed to react in r.t. and ammonium acetate **3** (2 mmol) was added. The reaction mixture was stirred for 3 h at room temperature, and then poured into 15 mL of water. The resulting precipitate was separated by filtration and recrystallized by $Et_2O$ (2 mL) to afford the pure title compounds.

### *2-oxo-1, 2-diphenylethyl oxazole (4a):*

White powders; m.p. 170-171 ºC; yield: 0.57 g (95%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1701, 1697, 1585, 1449, 1275, 1112. $^{1}$H NMR (500.13 Hz, $CDCl_3$): $\delta$ = 7.15 (1 H, s, CH), 7.36-7.46 (8 H, m, 8 CH), 7.57 (1 H, m, CH), 7.61 (2 H, d, $^{3}J$ = 7.4 Hz, 2 CH), 8.04 (2 H, d, $^{3}J$ = 7.8 Hz, 2 CH), 8.16 (2 H, d, $^{3}J$ = 7.8 Hz, 2 CH) ppm. $^{13}$C NMR (125.7 Hz, $CDCl_3$): $\delta$ = 78.0 (CH), 128.4 (2 CH), 128.7 (CH), 128.8 (2 CH), 129.1 (2 CH), 129.3 (2 CH), 130.0 (2 CH), 130.8 (2 CH), 131.5 (CH), 132.0 (C), 132.7 (CH), 133.9 (C), 134.8 (C), 166.0 ($CO_2$), 193.7 (CO) ppm. Anal. Calc. for $C_{21}H_{16}O_3$ (316.35): C, 79.73; H, 5.10 found: C, 79.68; H, 4.98%.

### *2-oxo-1, 2-diphenylethyl 4-methyloxazole (4b):*

Pale yellow powders; mp: 175-177ºC; yield: 0.61 g (92%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1690, 1683, 1595, 1276, 1245, 1176, 1101. $^{1}$H NMR (500.13 Hz, $CDCl_3$): $\delta$ = 2.40 (3 H, s, Me), 7.15 (1 H, s, CH), 7.25 (2 H, d, $^{3}J$ = 8.0 Hz, 2 CH), 7.35-7.43 (5 H, m, 5 CH), 7.51 (1 H, t, $^{3}J$ = 7.3 Hz, CH), 7.62 (1 H, d, $^{3}J$ = 7.1 Hz CH), 8.06 (4 H, t, $^{3}J$ = 8.3 Hz, 4 CH) ppm. $^{13}$C NMR (125.7 Hz, $CDCl_3$): $\delta$ = 21.7 (Me), 77.8 (CH), 126.8 (C), 128.6 (2 CH), 128.7 (2 CH), 128.8 (CH), 129.1 (2 CH), 129.2 (2 CH), 129.3 (2 CH), 130.0 (2 CH), 133.4 (CH), 134.0 (C), 134.9 (C), 144.1 (C), 166.1 ($CO_2$), 193.9 (CO) ppm. MS: *m*/*z* (%) = 330 ($M^+$, 10), 211 (70), 119 (100), 105 (98), 77 (64). Anal. Calc. for $C_{22}H_{18}O_3$ (330.38): C, 79.98; H, 5.49 found: C, 79.85; H, 4.35%.

### *2-oxo-1, 2-diphenylethyl 4-nitrooxazole (4c):*

Yellow crystal; m.p. 190-192 ºC; yield: 0.68 g (94%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1711, 1685, 1515, 1341, 1275, 1244, 1091. $^{1}$H NMR (500.13 Hz, $CDCl_3$): $\delta$ = 7.15 (1 H, s, CH), 7.38-7.45 (5 H, m, 5 CH), 7.54 (1 H, d, $^{3}J$ = 7.5 Hz, CH), 7.58 (2 H, m, 2 CH), 7.99 (2 H, d, $^{3}J$ = 7.3 Hz, 2 CH), 8.29 (4 H, t, $^{3}J$ = 8.0 Hz, 4 CH) ppm. $^{13}$C NMR (125.7 Hz, $CDCl_3$): $\delta$ = 78.8 (CH), 123.5 (2 CH), 128.7 (2 CH), 128.8 (CH), 129.3 (2 CH), 129.6 (2 CH), 131.0 (2 CH), 133.1 (C), 133.7 (2 CH), 133.4 (CH), 134.4 (C), 134.8 (C), 150.7 (C), 164.1 ($CO_2$), 192.8 (CO) ppm. Anal. Calc. for $C_{21}H_{15}NO_5$ (361.35): C, 69.80; H, 4.18; N, 3.88 found: C, 69.75; H, 4.15; N, 3.84%.

### *2-oxo-1, 2-diphenylethyl 4-bromooxazole (4d):*

Pale yellow powders; m.p. 185-187 ºC; yield: 0.71 g (90%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1708, 1683, 1580, 1398, 1347, 1247, 1099. $^{1}$H NMR (500.13 Hz, $CDCl_3$): $\delta$ = 7.11 (1 H, s, CH), 7.36-7.43 (5 H, m, 5 CH), 7.53 (1 H, t, $^{3}J$ = 7.4 Hz, CH), 7.58 (4 H, m, 4 CH), 8.00 (4 H, t, $^{3}J$ = 8.0 Hz, 4 CH) ppm. $^{13}$C NMR (125.7 Hz, $CDCl_3$): $\delta$ = 78.2 (CH), 128.4 (2 CH), 128.5 (C), 128.7 (CH), 128.8 (2 CH), 128.9 (2 CH), 129.2 (2 CH), 129.4 (2 CH), 131.5 (C), 131.8 (2 CH), 133.5 (CH), 133.6 (C), 134.7 (C), 165.3 ($CO_2$), 193.4 (CO) ppm. Anal. Calc. for $C_{21}H_{15}BrO_3$ (395.25): C, 63.82; H, 3.83 found: C, 63.78; H, 3.80%.

### *2-oxo-1, 2-diphenylethyl 4-chlorooxazole (4e):*

White powders; m.p. 174-176 ºC; yield: 0.59 g (85%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1710, 1675, 1512, 1345, 1300, 1295, 1109. $^{1}$H NMR (500.13 Hz, $CDCl_3$): $\delta$ = 7.22 (1 H, s, CH), 7.42-7.48 (5 H, m, 5 CH), 7.62 (1 H, t, $^{3}J$ = 7.4 Hz, CH), 7.68 (4 H, m, 4 CH), 8.10 (4 H, t, $^{3}J$ = 8.0 Hz, 4 CH) ppm. $^{13}$C NMR (125.7 Hz, $CDCl_3$): $\delta$ = 78.5 (CH), 127.9 (2 CH), 128.4 (C), 128.8 (CH), 128.7 (2 CH), 129.4 (2 CH), 129.6 (2 CH), 130.0 (2 CH), 131.2 (C), 132.0 (2 CH), 133.8 (CH), 134.2 (C), 134.9 (C), 166.2 ($CO_2$), 195.4 (CO) ppm. Anal. Calc. for $C_{21}H_{15}ClO_3$ (350.80): C, 71.90; H, 4.31 found: C, 71.86; H, 4.25%.

### *2-oxo-1, 2-diphenylethyl pivalate (4f):*

White powders; m.p. 145-147 ºC; yield: 0.52 g (87%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1725, 1645, 1557, 1445, 1227, 1112. $^1$H NMR (500.13 Hz, $CDCl_3$): $\delta$ = 1.23 (9 H, s, 3 Me), 7.27 (1 H, s, CH), 7.43 (3 H, m, 2 CH), 7.50 (1 H, m, CH), 7.58 (2 H, d, $^3J$ = 7.4 Hz, 2 CH), 7.95 (2 H, d, $^3J$ = 7.8 Hz, 2 CH), 8.14 (2 H, d, $^3J$ = 7.8 Hz, 2 CH) ppm. $^{13}$C NMR (125.7 Hz, $CDCl_3$): $\delta$ = 27.5 (3 Me), 37.5 (C), 78.2 (CH), 123.4 (C), 124.7 (2CH), 127.6 (CH), 128.4 (2 CH), 128.6 (2 CH), 129.1 (2 CH), 131.7 (CH), 134.7 (C), 168.2 ($CO_2$), 197.5 (CO) ppm. Anal. Calc. for $C_{19}H_{20}O_3$ (296.36): C, 77.00; H, 6.80 found: C, 76.95; H, 6.78%.

***1-methyl-2-oxopropyl 4-methyloxazole (4g):***

Yellow powders; m.p. 168-170 ºC; yield: 0.34 g (83%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1734, 1625, 1498, 1427, 1200, 1015. $^1$H NMR (500.13 Hz, $CDCl_3$): $\delta$ = 1.28 (6 H, d, $^3J$ = 7.5 Hz, 2 Me), 2.15 (Me), 2.36 (Me), 5.42 (1 H, q, $^3J$ = 7.5 Hz, CH), 7.58 (2 H, d, $^3J$ = 7.5 Hz, 2 CH), 7.75 (2 H, d, $^3J$ = 7.5 Hz, 2 CH) ppm. $^{13}$C NMR (125.7 Hz, $CDCl_3$): $\delta$ = 16.5 (Me), 21.7 (Me), 24.3 (Me), 75.7 (CH), 127.6 (C), 127.8 (2CH), 128.4 (2 CH), 138.7 (C), 168.8 ($CO_2$), 200.6 (CO) ppm. Anal. Calc. for $C_{12}H_{14}O_3$ (206.24): C, 69.89; H, 6.84 found: C, 69.85; H, 6.79%.

***1-methyl-2-oxopropyl pivalate (4h):***

Yellow oil; yield: 0.26 g (75%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1767, 1638, 1354, 1154, 1028. $^1$H NMR (500.13 Hz, $CDCl_3$): $\delta$ = 1.14 (9 H, s, 3 Me), 1.25 (3 H, d, $^3J$ = 7.3 Hz, Me), 2.24 (Me), 5.32 (1 H, q, $^3J$ = 7.3 Hz, CH) ppm. $^{13}$C NMR (125.7 Hz, $CDCl_3$): $\delta$ = 17.2 (Me), 24.8 (Me), 27.6 (3 Me), 41.5 (C), 76.8 (CH), 178.8 ($CO_2$), 204.2 (CO) ppm. Anal. Calc. for $C_9H_{16}O_3$ (172.22): C, 62.77; H, 9.36 found: C, 62.68; H, 9.26%.

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