*Iranian Journal of Organic Chemistry Vol. 14, No.3 (2022) 3417-3420*

# Synthesis of urea derivatives using multicomponent reactions of activated acetylene

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Received: May 2022; Revised: June 2022; Accepted: July 2022

**Abstract:** urea derivatives are obtained in good to excellent yields by proceeding through a simple, mild, and efficient procedure utilizing activated acetylens, primary amines and isocyanates in the presence of catalytic amount of *N-formylmorpholine* under solvent-free conditions.

**Keywords:** Acid chlorides, Potasium thiocyanate, *N*-formylmorpholine, Alcohol, Esterification.

## Introduction

Recently, multicomponent reactions (MCRs) are more interesting type of reaction due to mixing three or more reactants in one-pot and generating one product [1-2] and economically useful and environmentally secure than to multi-step methods. MCRs are very important in the synthesis of new drugs and agrochemicals [3-4]. In addition carrying out synthesis of organic compounds in water media is very interesting because of water is cheap solvent, more available with high amounts. For the reactions that starting compounds aren't solved in water, the rate of reaction improves. Separation of products in these reactions is very easy because of products aren't solved in water and separated by employing filtration [5-7]. MCRs are absolutely suited for combinatorial library synthesis and increased utilize in the finding procedure for new drugs and agrochemicals [8]. They supply a dominant tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [9].

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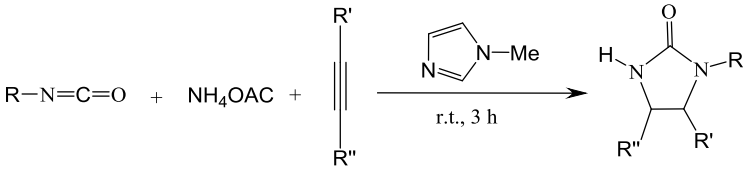
Green chemistry move towards hold out significant potential not only for reduction of byproducts, waste produced, and lowering of energy but also in the expansion of new methodologies toward before exclusive materials, using existing technologies [10]. Between existing part of chemistry, medicinal and pharmaceutical chemistry are possibly developed for greening [11]. Hence, we investigated a simple three-component reaction between activated acetylenic compounds, ammonium acetate and isothiocyanates in the presence of N-methylimidazole in water as green solvent at room temperature which afforded urea derivatives **4** in good isolated yields (Scheme **1**).

## Results and discussion

The $^{1}$H NMR spectrum of **4a** displayed signals for vicinal methine protons at δ = 4.78 and 4.92, which appeared as two set of doublets with $^{3}J_{HH}$ values of 12.4 Hz. The methoxy groups showed two separate singlet at δ = 3.78 and 3.85. Observation of $^{3}J_{HH}$ = 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** are appeared

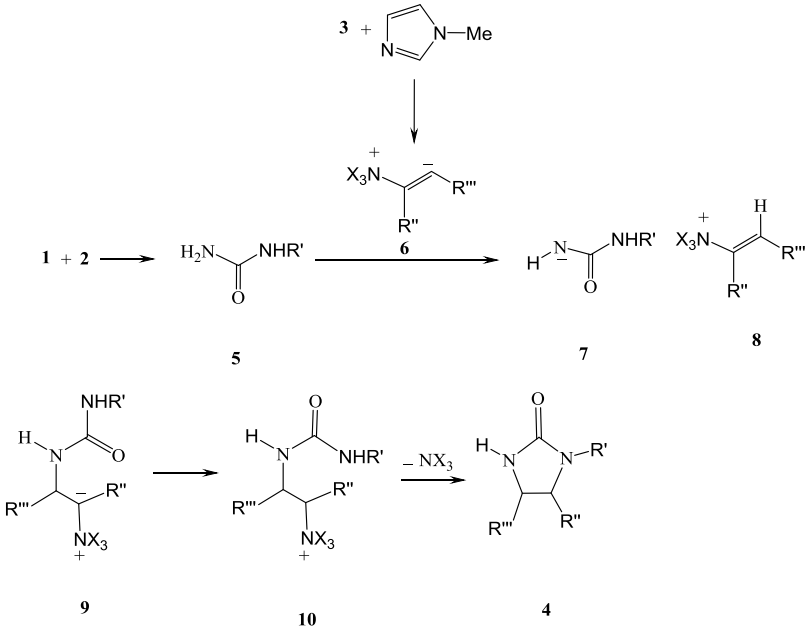
at 172.5 (C=O), 173.7 (C=O) ppm. Also the mass spectra of **4a** displayed the molecular ion peak in the appropriate m/z values.

A proposed mechanism for the formation of compound **4** is shown in Scheme **2**. Apparently, the zwitterionic intermediate **6** which formed from the reaction of *N*-methylimidazole ($X_3N$) and electron deficient acetylenic ester **3** is protonated by the intermediate **5** that was generated in situ from the reaction of ammonium acetate **2** and isothiocyanate **1**, produce intermediates **7** and **8**. Nucleophilic attack of the conjugate base **7** on intermediate **8** leads to adduct **9** which undergo proton shifts to afford new zwitterionic **10**. Finally, intramolecular cyclization of **10** with elimination of NMI produces compound **4**.




| 1, 2, 3, 4 | R | R' | R'' | Yield (%) of **4** |
|---|---|---|---|---|
| **a** | Ph | $CO_2Me$ | $CO_2Me$ | 75 |
| **b** | 4-MeO-$C_6H_4$ | $CO_2Me$ | $CO_2Me$ | 72 |
| **c** | 4-MeO-$C_6H_4$ | $CO_2Et$ | $CO_2Et$ | 70 |
| **d** | 4-Me-$C_6H_4$ | $CO_2Et$ | $CO_2Et$ | 70 |
| **e** | 4-Br-$C_6H_4$ | $CO_2Me$ | $CO_2Me$ | 68 |

**Scheme 1:** Reaction of activated acetylenes, isothiocyanates and ammonium acetate




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

## Conclusion

In conclusion, we found that the reaction of activated acetylenic compounds with isothiocyanates and primary amines in the presence of catalytic amount of *N*-formylmorpholineleads to a facile synthesis of some functionalized urea under solvent-free conditions without using any catalyst.

## Experimental

All chemicals used in this work were prepared from Fluka (Buchs, Switzerland) and were used without further purification. Electrothermal 9100 apparatus is employed for measuring of melting points of products. Elemental analyses for C, H, and N were performed with Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. Measurement of IR spectra was performed by Shimadzu IR-460 spectrometer. $^1$H, and $^{13}$C NMR spectra were evaluated 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 4*

To a magnetically stirred mixture of activated acetylenes **3** (2 mmol) and *N-Methylimidazole* (5 mol%) was added mixture of isocyanates **1** and ammonium acetate **2** (2 mmol) at room temperature in water (5 mL). 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** and **12**.

### *Dimethyl 2-(methylimino)-3-phenyl-1,3- imidazole -4,5-dicarboxylate (4a):*

Yellow powder, m.p. 156-158°C, yield: 0.46 g (75%). 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, $CDCl_3$): $\delta$ 2.83 (3 H, s, NMe), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.78 (1 H, d, $^3J$ = 12.4, CH), 4.92 (1 H, d, $^3J$ = 12.4, 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, $CDCl_3$): $\delta$ 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), 172.5 (C=O), 173.7 (C=O) ppm. MS, *m/z* (%): 308 (M$^+$, 15), 277 (86), 77 (64), 31 (100).

### *Dimethyl 2-(ethylimino)-3-(4-methoxyphenyl)-1,3-imidazole -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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 14.2 ($CH_3$), 41.5 ($CH_2$), 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-imidazole -4,5-dicarboxylate (4c):*

White powder, m.p. 162-164 °C, yield: 0.70 g (83%). 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%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.19 (3H, t, $^3J$ = 7.2, $CH_3$), 1.22 (3H, t, $^3J$ = 7.4, $CH_3$), 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, $CDCl_3$): $\delta$ 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-imidazole-4,5-dicarboxylate (4d):*

Yellow powder, m.p. 164-166 °C, yield: 0.59 g (75%). 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%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 13.8 ($CH_3$), 14.2 ($CH_3$), 22.4 ($CH_3$), 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).

***Dimethyl 2-(methylimino)-3-(4-bromophenyl)-1,3-imidazole-4,5-dicarboxylate (4e):***

Yellow crystals, m.p. 183-185 $^o$C, yield: 0.62 g (80%). 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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).

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