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Synthesis of urea derivatives in the presence of *N*-formylmorpholine as a solvent

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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

Multicomponent reactions (MCRs), with three or more reactants join in a one-pot procedure to afford a single product [1-3]. They are economically and environmentally useful because multi-step synthesis produce large amounts of trash frequently because of complex isolation actions frequently involving comfortable, toxic, and hazardous solvents after each step [4-7]. 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]. 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].

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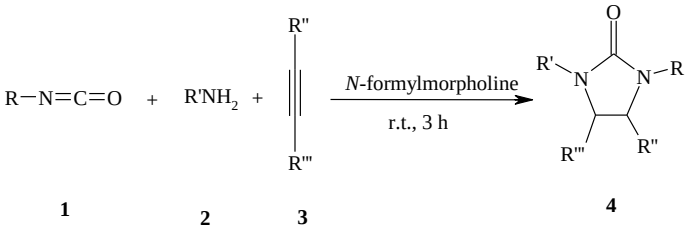
Hence, we investigated a simple three-component reaction between activated acetylenic compounds, primary amines and isothiocyanates in the presence of *N*-formylmorpholine as solvent-free conditions at room temperature which afforded urea derivatives **4** in good isolated yield**s**. With propargylic esters yield of reactions is low (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*-formylmorpholine (X_3N) and electron

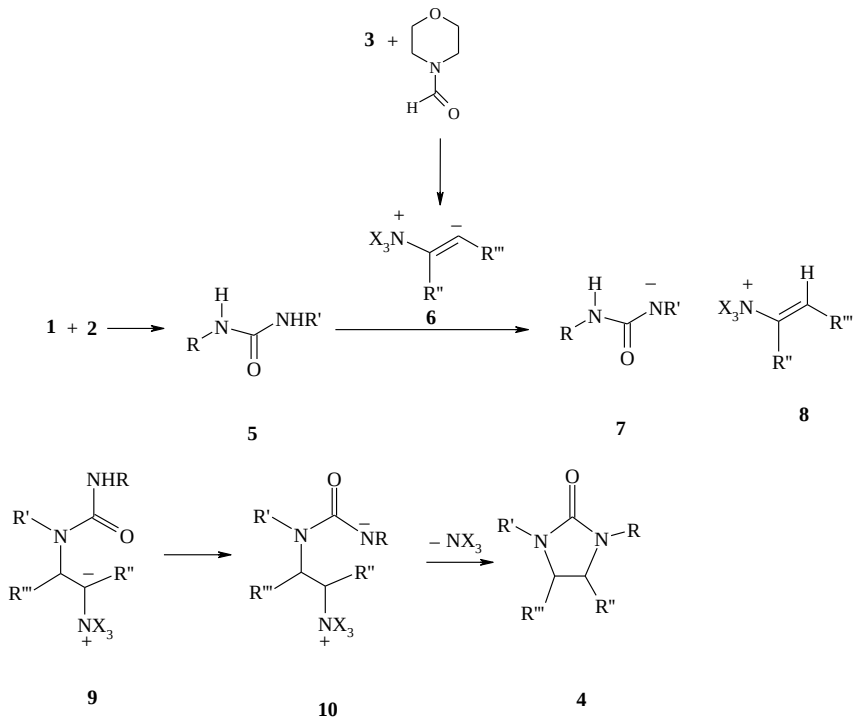
deficient acetylenic ester **3** is protonated by the intermediate **5** that was generated in situ from the reaction of primary amine **2** and isothiocyanate **1**, produce intermediates **7** and **8**. Nucleophilic attack of the conjugate base **7** on intermediate **8** leads to adduct **9** which undergo proton shifts to afford new zwitterionic **10**. Finally, intramolecular cyclization of **10** with elimination of *N*-formylmorpholine produces compound **4**.



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

1, 2, 3, 4	R	R'	R''	R'''	Yield (%) of **4**
a	Ph	Me	CO_2Me	CO_2Me	75
b	4-MeO-C_6H_4	Et	CO_2Me	CO_2Me	72
c	4-MeO-C_6H_4	n-Bu	CO_2Et	CO_2Et	70
d	4-Me-C_6H_4	^{t}Bu	CO_2Et	CO_2Et	70
e	4-Br-C_6H_4	Me	CO_2Me	CO_2Me	68

Scheme 1: Reaction of activated acetylenes, isothiocyanates and primary amins



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-formylmorpholine*(5 mol%) was added mixture of isocyanates **1** and primary amines **2** or secondary amine **11** (2 mmol) at room temperature. The reaction mixture was then stirred. After completion of the reaction [TLC (AcOEt/hexane 1:7) monitoring], 15 mL H_2O was poured into the reaction mixture. 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) (ν_{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), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.78 (1 H, d, ^{3}J = 12.4, CH), 4.92 (1 H, d, ^{3}J = 12.4, CH), 7.23 (1 H, t, ^{3}J = 7.4, CH), 7.35 (2 H, d, ^{3}J = 7.6, 2 CH), 7.54 (2 H, t, ^{3}J = 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), 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 ^{o}C, yield: 0.59 g (87%). IR (KBr) (ν_{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, ^{3}J = 7.3, CH_3), 3.27 (2 H, q, ^{3}J = 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, ^{3}J = 12.2, CH), 4.87 (1 H, d, ^{3}J = 12.2, CH), 7.14 (2 H, d, ^{3}J = 7.8, 2 CH), 7.28 (2 H, d, ^{3}J = 7.6, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 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 ^{o}C, yield: 0.70 g (83%). IR (KBr) (ν_{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, $CDCl_3$): δ 1.19 (3H, t, ^{3}J = 7.2, CH_3), 1.22 (3H, t, ^{3}J = 7.4, CH_3), 1.28 (3H, t, ^{3}J = 7.3, CH_3), 1.68 (2 H, q, ^{3}J = 7.3, CH_2), 1.78 (2 H, m, CH_2), 2.83 (2 H, t, ^{3}J = 6.8, NCH_2), 3.75 (3 H, s, MeO), 4.12 (2 H, q, ^{3}J = 7.3, CH_2O), 4.23 (2 H, q, ^{3}J = 7.3, CH_2O), 4.62 (1 H, d, ^{3}J = 11.7, CH), 5.02 (1 H, d, ^{3}J = 11.7, CH), 7.12 (2 H, d, ^{3}J = 7.6, 2 CH), 7.32 (2 H, d, ^{3}J = 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-imidazole-4,5-dicarboxylate (4d):

Yellow powder, m.p. 164-166 ^{o}C, yield: 0.59 g (75%). IR (KBr) (ν_{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, $CDCl_3$): 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 (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) (ν_{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).

References

[1] Do¨mling, A. *Comb. Chem. High T. Screen.* **1998**, *1*, 1.

[2] Do¨mling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169.

[3] Weber, L. *Drug Disc. Today* **2002**, *7*, 143.

[4] Multicomponent Reactions; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, **2005**.

[5] Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1779.

[6] Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101.

[7] Jacobi von Wangelin, A.; Neumann, H.; Gordes, D.; Klaus, S.; Strubing, D.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 4286.

[8] (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (b) Ugi, I.; Domling, A. *Endeavour* **1994**, *18*, 115; (c) Heck, S.; Domling, A. Synlett 2000, 424.

[9] Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085.

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

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