Note

Thiourea: An Efficient and Inexpensive Catalyst for the Knoevenagel Condensation of Pyrazole Derivates

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Received July 2, 2010; Accepted December 27, 2010; Published Online January 11, 2011

Thiourea is an inexpensive, efficient and mild catalyst for the synthesis of Knoevenagel condensation of pyrozoles derivate. In the presence of 10 mol% of thiourea, pyrazole aldehyde react with active methylene compound under microwave-assisted solvent-free conditions at 300 W for 2-5 min to give corresponding products in good yields.

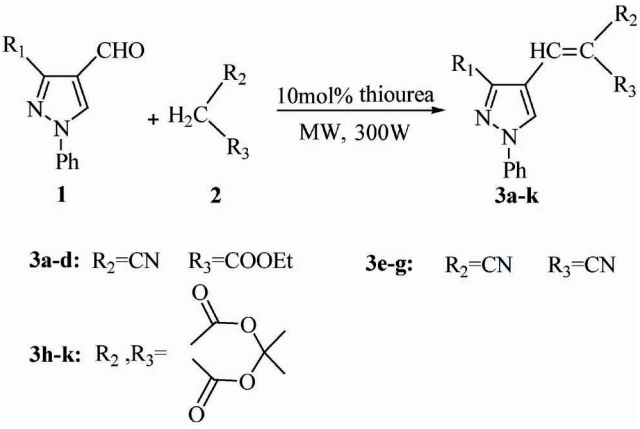
Keywords: Thiourea; Catalyst; Knoevenagel condensation; Pyrazole; Microwave-assisted solvent-free synthesis.

INTRODUCTION

The Knoevenagel condensation of aldehydes with active methylene compounds is an important and widely employed method for carbon-carbon bond formation in organic synthesis with numerous applications in the synthesis of fine chemicals,[1] hetero Diels-Alder reactions[2] and in synthesis of carbocyclic as well as heterocyclic[3] compounds of biological significance. The reaction is usually catalyzed by bases,[4] such as sodium hydroxide or sodium ethoxide in organic solvents. Lewis acids, such as $NbCl_5$ [5] and $ZnCl_2$,[6] silica gel[7] have also been employed to catalyze the reaction. Similarly, the use of ionic liquids[8] pave a new path for such organic synthesis. The use of environmentally benign solvents like water[9] and microwave-assisted solvent-free[10] reactions represent very powerful green chemical technology procedures from both the economical and synthetic point of view. They not only reduce the burden of organic solvent disposal, but also enhance the rate of many organic reactions. Therefore, efforts have been made to perform the Knoevenagel condensation in microwave-assisted solvent-free conditions which is usually catalyzed by Lewis acids or bases.

Recently, the Knoevenagel condesation about the pyrazole aldehyde as starting materials were reported. But these reactions are usually catalyzed by sodium acetate or piperidine in ethanol,[11-13] and the yield is low. Herein, we reported a genuienly green and mild Knoevenagel condensation containing pyrazole ring catalyzed by thiourea under microwave-assisted solvent-free conditions (Scheme I and Table 1).

Scheme I Reactions of pyrazole aldehyde with active methylene compounds



RESULTS AND DISCUSSION

An optimization study of the Knoevenagel condensation under microwave irradiation was tested. We took the reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde with malononitrile as a model to examine the effects of catalyst

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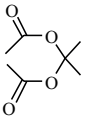
Table 1. Knoevenagel condensation catalyzed by thiourea under microwave-assisted solvent-free conditions

Entry	R_1	R_2	R_3	Product	Time/ min	Yield/%
1	C_6H_5	CN	COOEt	**3a**	4	75
2	p-$CH_3OC_6H_4$	CN	COOEt	**3b**	3	78
3	p-ClC_6H_4	CN	COOEt	**3c**	3	79
4	p-$CH_3C_6H_4$	CN	COOEt	**3d**	4	75
5	C_6H_5	CN	CN	**3e**	2	80
6	p-$CH_3OC_6H_4$	CN	CN	**3f**	2	82
7	p-ClC_6H_4	CN	CN	**3g**	2	80
8	p-$CH_3OC_6H_4$			**3h**	4	76
9	p-ClC_6H_4			**3i**	4	74
10	p-$CH_3C_6H_4$			**3j**	5	73
11	C_6H_5			**3k**	4	76

ranging from 0-20 mol% and microwave power at 100, 200, 300, 400, 500 W. The results were evaluated qualitatively through TLC. It was found that the quantitative yield was achieved when the reaction was carried out in the presence of 10 mol% thiourea at 300W under solvent-free conditions (Scheme I).

In this paper, several substituted pyrazole aldehyde with three active methylene compounds reacted under the microwave-assisted solvent-free conditions catalyzed by thiourea. The results are summarized in Table 1, which indicated that the reactions gave yields of 73-82%. 2,2-Dimethyl-1,3-dioxane-4,6-dione (Entry 8-11) showed much faster reaction rate than literature.[14] Comparatively, malononitrile proved to be of higher reactivity than ethyl cyanoacetate and 2,2-dimethyl-1,3-dioxane-4,6-dione. The presence of electronwithdrawing groups on active methylene compounds resulted in the corresponding products in high yield and in short reaction times (Entry 5-7). Besides, the reaction rate and yield were not significantly affected by the position and the properties of substituted groups on the pyrazole aldehyde. Furthermore, we also try some other methylene compounds such as difluoromethane, dichloromethane, dibromomethane and dimethoxymethane. However, no desired product was obtained. Perhaps because these methylene compounds are not very active.

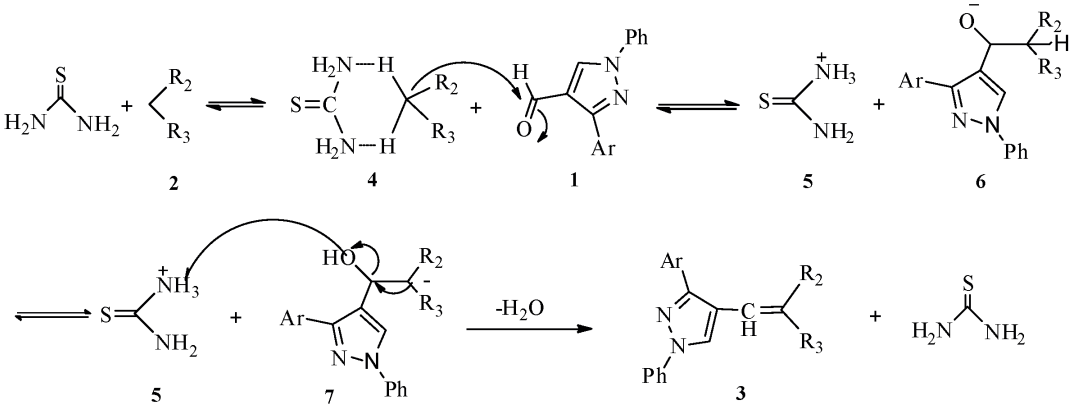
The possible mechanism of thiourea catalyzed Knoevenagel reaction has been proposed in Scheme II. At first, thiourea reacts with active methylene compound **2** to form a six-membered cyclic intermediate **4**. Because the active hydrogen of **2** is pulled by the more electronegative nitrogen atom in intermediate, it is easier for active methylene compound to add nucleophilically to the pyrazole aldehydes **1**. Then the intermediate **5** and **6** are obtained. There is an equilibrium between **6** and **7**. At last, the target product **3** is afforded along with removeing one mole of H_2O, and regenerate the thiourea.

In conclusion, thiourea has been used efficiently to catalyze the Knoevenagel condensation reaction between active methylene compounds and pyrazole aldehydes. A microwave-assisted solvent-free reaction conditions with a shorter time and inexpensive and easily available catalyst are the key features involved in the present protocol. These features will enable this protocol to find widespread applications in the field of organic synthesis.

EXPERIMENTAL SECTION

Melting points were determined with a XRC-1 micromelting point apparatus and were uncorrected. NMR spectra were measured on a Bruker DPX 400 M, respectively, using TMS at internal standard and $CDCl_3$ as solvent.

Scheme II Possible mechanism of thiourea catalyzed Knoevenagel reaction



Chemical shift (δ) were expressed in ppm downfield from internal standand TMS and coupling constants *J* were given in Hz. Mass spectra were performed on a Bruker-Esquire 3000 Mass spectrometer. Elemental analysis was performed on PE-2400 Analyzer. The experiment was carried out with Galanz microwave oven (750 W). Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. The starting material, 1-phenyl-3-aryl-1H-pyrazole-4-carbaldehyde (**1**) was prepared according to Ref. 15.

General procedure for the Knoevenagel condensation

To a mixture of pyrazole aldehyde (1 mmol), active methylene compound (1.1 mmol), and the thiourea (10 mol%), was mixed in an agate mortar and exposed to microwave irradiation for appropriate time (see Table 1) under solvent-free conditions. The power of the microwave oven is 300 W. The end of the reaction was tested by TLC. After the reaction was complete, the crude products were purified by column chromatography (petroleum ether: ethyl acetate = 10:1).

Physical properties and spectral data

Ethyl 2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylate 3a

White crystal; mp. 134 ~ 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.382 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.327 ~ 4.380 (m, 2 H, CH_2), 7.412 (t, *J* = 7.2 Hz, 1 H, ArH), 7.501 ~ 7.558 (m, 5 H, ArH), 7.621 (d, *J* = 6.4 Hz, 2 H, ArH), 7.837 (d, *J* = 8.0 Hz, 2 H, ArH), 8.313 (s, 1 H, N-CH), 9.145 (s, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.20, 62.40, 99.80, 114.94, 116.71, 119.93, 128.51, 129.01, 129.15, 129.26, 129.37, 129.68, 130.82, 138.84, 146.27, 156.38, 162.68; MS (*m/z*): 343.9 (M^+). Anal. Calcd. for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.49; H, 4.82; N, 12.28.

Ethyl 2-cyano-3-[3-(4-methoxyphenyl)-1-p-henyl-1H-pyrazol-4-yl]acrylate 3b

White crystal; mp. 155 ~ 157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.383 (t, *J* = 7.0 Hz, 3 H, CH_3), 3.884 (s, 3 H, OCH_3), 4.327 ~ 4.381 (m, 2 H, CH_2), 7.051 (d, *J* = 8.4 Hz, 2 H, ArH), 7.383 ~ 7.422 (t, *J* = 7.8 Hz, 1 H, ArH), 7.498 ~ 7.566 (m, 4 H, ArH), 7.827 (d, *J* = 8.0 Hz, 2 H, ArH), 8.300 (s, 1 H, N-CH), 9.116 (s, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.21, 55.40, 62.36, 99.43, 114.48, 114.83, 119.91, 123.22, 128.07, 129.20, 129.61, 130.43, 130.81, 138.88, 146.49, 156.25, 160.57, 162.79; MS (*m/z*): 373.9 (M^+). Anal. Calcd. for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.89; H, 5.22; N, 11.11.

Ethyl 2-cyano-3-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]acrylate 3c

Light yellow crystal; mp. 117 ~ 119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.387 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.335 ~ 4.388 (m, 2 H, CH_2), 7.421 (t, *J* = 6.8 Hz, 1 H, ArH), 7.499 ~ 7.577 (m, 7 H, ArH), 7.819 (d, *J* = 8.0 Hz, 2 H, ArH), 8.242 (s, 1 H, N-CH), 9.130 (s, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.20, 62.50, 100.22, 114.87, 116.56, 119.95, 128.30, 129.28, 129.37, 129.72, 130.36, 135.65, 138.75, 145.66, 155.13, 162.56; MS (*m/z*): 377.8 (M^+). Anal. Calcd. for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 66.67; H, 4.38; N, 11.01.

Ethyl 2-cyano-3-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-acrylate 3d

White crystal; mp. 136 ~ 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.377 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.437 (s, 3 H, $ArCH_3$), 4.321 ~ 4.374 (m, 2 H, CH_2), 7.331 (d, *J* = 7.6 Hz, 2 H, ArH), 7.400 (t, *J* = 7.4 Hz, 1 H, ArH), 7.516 (t, *J* = 7.4 Hz, 4 H, ArH), 7.827 (d, *J* = 8.0 Hz, 2 H, ArH), 8.306 (s, 1 H, N-CH), 9.122 (s, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.21, 21.37, 62.35, 99.56, 114.92, 116.76, 119.93, 127.91, 128.08, 129.02, 129.22, 129.65, 129.70, 138.88, 139.43, 146.45, 156.49, 162.73; MS (*m/z*): 357.8 (M^+). Anal. Calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.09; H, 5.45; N, 11.69.

2-[(1,3-Diphenyl-1H-pyrazol-4-yl)methylene]malononitrile 3e

Light yellow solid; mp. 158 ~ 160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.455 (d, *J* = 7.6 Hz, 1 H, ArH), 7.524 ~ 7.564 (m, 7 H, ArH), 7.803 (s, 1 H, N-CH), 7.811 ~ 7.834 (m, 2 H, ArH), 9.064 (s, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.50, 113.85, 113.89, 114.99, 120.07, 128.65, 129.17, 129.20, 129.26, 129.81, 129.84, 130.09, 138.54, 151.11, 156.36; MS (*m/z*): 296.9 (M^+). Anal. Calcd. for $C_{19}H_{12}N_4$: C, 77.01; H, 4.08; N, 18.91. Found: C, 77.23; H, 4.01; N, 18.82.

2-{[3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-methylene}malononitrile 3f

Kelly crystal; mp. 176 ~ 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.898 (s, 3 H, OCH_3), 7.069 (d, *J* = 8.8 Hz, 2 H, ArH), 7.436 (t, *J* = 7.4 Hz, 1 H, ArH), 7.494 ~ 7.556 (m, 4 H, ArH), 7.788 (s, 1 H, N-CH), 7.810 (d, *J* = 8.0 Hz, 2 H, ArH), 9.036 (s, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.46, 78.07, 113.92, 114.01, 114.67, 114.93, 120.04, 122.40, 128.57, 129.19, 129.79, 130.48, 138.56, 151.29, 156.23, 160.91; MS (*m/z*): 326.9 (M^+). Anal. Calcd. for $C_{20}H_{14}N_4O$: C, 73.61; H, 4.32; N, 17.17. Found: C, 73.42;

H, 4.15; N, 17.26.

2-{[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-methylene}malononitrile 3g

Light yellow solid; mp. 217 ~ 218 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.453 (t, J = 7.2 Hz, 1 H, ArH), 7.504 ~ 7.566 (m, 6 H, ArH), 7.744 (s, 1 H, N-CH), 7.794 ~ 7.817 (t, J = 4.6 Hz, 2 H, ArH), 9.055 (s, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.99, 113.72, 114.88, 120.07, 128.58, 128.78, 129.38, 129.50, 129.85, 130.37, 136.21, 138.44, 150.50, 155.09; MS (*m/z*): 330.8 (M^+). Anal. Calcd. for $C_{19}H_{11}ClN_4$: C, 68.99; H, 3.35; N, 16.94. Found: C, 68.95; H, 3.23; N, 3.52.

5-{[3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-methylene}-2,2-dimethyl-1,3-dioxane-4,6-dione 3h

Mp. 193 ~ 195 °C; Lit[14]: 194 ~ 196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.785 (s, 6 H, 2 CH_3), 3.890 (s, 3 H, OCH_3), 7.070 (d, J = 8.4 Hz, 2 H, ArH), 7.420 (d, J = 6.0 Hz, 1 H, ArH), 7.507 ~ 7.581 (m, 4 H, ArH), 7.865 (d, J = 8.0 Hz, 2 H, ArH), 8.514 (s, 1 H, N-CH), 9.717 (s, 1 H, C=CH).

5-{[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-methylene}-2,2-dimethyl-1,3-dioxane-4,6-dione 3i

Mp. 174 ~ 175 °C; Lit[14]: 172 ~ 174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.787 (s, 6 H, 2 CH_3), 7.426 (t, J = 6.8 Hz, 1 H, ArH), 7.519 ~ 7.589 (m, 6 H, ArH), 7.857 (d, J = 7.6 Hz, 2 H, ArH), 8.451 (s, 1 H, N-CH), 9.729 (s, 1 H, C=CH).

2,2-Dimethyl-5-[(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-methylene]-1,3-dioxane-4,6-dione 3j

Mp. 202 ~ 204 °C; Lit[14]: 201 ~ 203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.797 (s, 6 H, 2 CH_3), 2.460 (s, 3 H, $ArCH_3$), 7.366 (d, J = 8.0 Hz, 2 H, ArH), 7.424 (t, J = 7.4 Hz, 1 H, ArH), 7.543 (t, J = 7.4 Hz, 4 H, ArH), 7.882 (t, J = 4.2 Hz, 2 H, ArH), 8.531 (s, 1 H, N-CH), 9.741 (s, 1 H, C=CH).

2,2-Dimethyl-5-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-1,3-dioxane-4,6-dione 3k

Mp. 206 ~ 208 °C; Lit[14]: 205 ~ 207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.787 (s, 6 H, 2 CH_3), 7.418 (t, J = 7.0 Hz, 1 H, ArH), 7.517 ~ 7.569 (m, 5 H, ArH), 7.626 (t, J = 3.8 Hz, 2 H, ArH), 7.875 (d, J = 7.6 Hz, 2 H, ArH), 8.518 (s, 1 H, N-CH), 9.746 (s, 1 H, C=CH).

ACKNOWLEDGMENTS

This work was supported by the National Natural Sciences Foundation of China (2087 2029).

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