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MILD AND EFFICIENT PROCEDURE FOR MICHAEL ADDITION OF N-HETEROCYCLES TO α,β-UNSATURATED COMPOUNDS USING ANHYDROUS K_3PO_4 AS CATALYST

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Imidazole, 1,2,4-triazole, indole, and benzotriazole undergo conjugate additions with α,β-unsaturated carbonyl compounds in the presence of anhydrous potassium phosphate at ambient temperature to afford the corresponding Michael adducts in excellent yields.

Keywords: Anhydrous potassium phosphate; N-heterocycle; imidazole; Michael addition

N-Substituted imidazoles and their derivatives, obtained through alkylation reactions[1] or Michael additions,[2] are of interest in pharmaceutical chemistry because of their pharmacodynamic properties. The Michael reaction, which is a conjugate addition reaction of nucleophiles to unsaturated carbonyl compounds, requires basic conditions[3] or acidic catalysts.[4] Recently, several Lewis acids were found to catalyze the conjugate addition of heterocyclic compounds to electron-deficient olefins, such as $BiNO_3$,[5] InX_3,[6] $AuCl_3$,[7] SmI_3,[8] $CeCl_3$,[9] and other metal salts of trifluoromethanesulfonate such as Bi(III), Yb(III), Hf(IV), Sc(III), Ga(III), and Cu(II) have also been successfully used.[10] Moreover, the use of metal complex (such as Sc, Au, Cu, Zn)[11] and enzyme[12] as the catalyst have also been reported.

However, there are only a few reports about the base-catalyzed conjugated addition of heterocyclic compounds to α,β-unsaturated carbonyl compounds, even though basic clays,[13] KF/Al_2O_3,[14] and guanidine[15] were reported. Unfortunately, under not only acidic conditions, but also basic ones, many of these catalytic procedures require long reaction times (several days), rigorous reaction conditions, or highly dangerous chemicals. Thus, development of a fast and facile protocol that could be performed at ambient temperature for the Michael addition of

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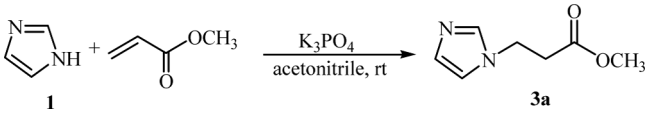
N-heterocycles to α,β-unsaturated compounds becomes particularly fascinating and remains a great challenge.

Professor Li's group has reported a simple one-pot procedure for the preparation of a different kind of β-electron-withdrawing group substituted ethyl dithiocarbamate by the Michael addition of an amine and carbon disulfide to electrophilic alkenes in the presence of anhydrous potassium phosphate under mild conditions in good yields.[16] Although heterocyclic compounds were not involved, we reasoned that the imidazole may work well using our method considering the specific structure of imidazole. Herein, we report the result of our efforts in this direction.

First, we selected the reaction of imidazole with methyl acrylate in the presence of anhydrous potassium phosphate as a model. In the initial studies of the screening of the volume of the catalyst, 100, 50, 25, and 10 mol% K_3PO_4 were screened. The reactions were quenched after 3 h. Their separated yields are 98, 97, and 86%, respectively, which shows that 25 mol% K_3PO_4 was the most suitable because of good yield and short reaction time. Different solvents [dimethylformamide (DMF), tetrahydrofuran (THF), acetone, CH_2Cl_2, MeCN] and reaction temperatures (0 °C to 40 °C) were examined. The reaction results were evaluated qualitatively by thin-layer chromatography (TLC). Rapid conversion was observed when the reaction was carried out in CH_3CN (97% yield) or DMF (96% yield). Poor conversion (17%) was obtained in CH_2Cl_2 when 50 mol% K_3PO_4 was used as catalyst. Moderate yield (65%) was achieved in THF. The reaction temperature has little influence on the reaction yield. It was revealed that the optimal reaction conditions were using 25 mol% K_3PO_4 as catalyst and CH_3CN as solvent at room temperature. The desired compound, 3-imidazol-1-yl-propionic acid methyl ester (**3a**), was obtained under the optimized reaction conditions after 3 h in 97% yield (Scheme 1).

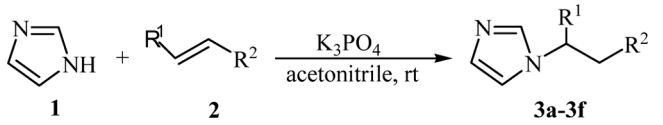
With the effective catalyst system in hand, the conjugate addition of imidazole to other α,β-unsaturated compounds was investigated (Scheme 2). As shown in Table 1, the catalytic system is suitable for a variety of α,β-unsaturated compounds including α,β-unsaturated esters, α,β-unsaturated amide, and α,β-unsaturated nitriles. The reaction of all α,β-unsaturated esters were completed within 3 h in good to excellent yields except for compound **3d**, which has methyl methacrylate as the substrate (entry 4). Even after 24 h, the conjugate addition of imidazole to methyl methacrylate still has a lesser isolated yield (47%), perhaps because of the steric effect of the methyl group in methyl methacrylate, which affected the attack of imidazole to the ester. Acrylamide and acrylonitrile (entries 5 and 6) were used as Michael acceptors and gave products **3e** and **3f** within 3 h in 98% and 99% yields, respectively.

To check the scope of the N-heterocyclic compounds in this reaction, we extended this K_3PO_4 catalyst system to the conjugate addition of 1,2,4-1*H*-triazole (**4**), indole (**5**), and 1*H*-benzotriazole (**6**) to methyl acrylate (Scheme 3). As expected,



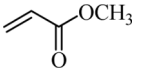
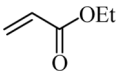
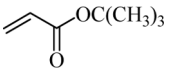
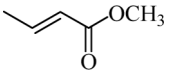
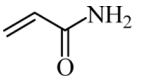
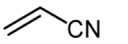
1 3a

Scheme 1. The optimized reaction condition.

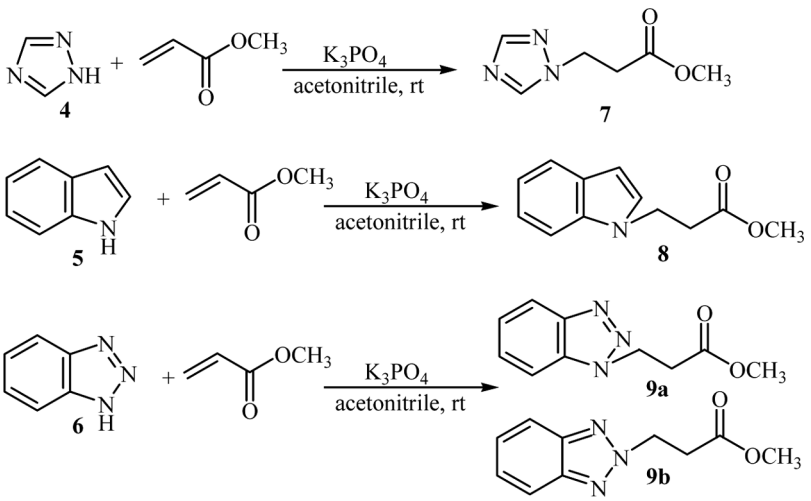


Scheme 2. The conjugate addition of imidazole to various α,β-unsaturated compounds.

Table 1. Conjugate addition of imidazole **1** to α,β-unsaturated carbonyl compounds **3a**–**3f**

Entry	**2**	Product	Yield (%)[a]	Reaction time (h)
1		**3a**	97	3
2		**3b**	95	2.5
3		**3c**	98	3
4		**3d**	47	24
5		**3e**	98	2
6		**3f**	99	3

[a]Isolated yield by silica-gel column chromatography.



Scheme 3. The conjugate addition of other N-heterocyclic compounds with methyl acrylate.

Table 2. Attempts on other heterocycles in the presence of anhydrous K_3PO_4

Entry	Heterocycle	Product	Yield (%)[a]	Reaction time (h)
1	Imidazole	**3a**	97	3
2	1-*H*-1,2,4-Triazole	**7**	92	3
3	Indole	**8**	68	24
4	1-*H*-Benzotriazole	**9a**	67	6
5	1-*H*-Benzotriazole	**9b**	21	6

[a]Isolated yield by silica-gel column chromatography.

the K_3PO_4-catalyzed conjugate addition reaction of 1,2,4-1*H*-triazole (**4**) to methyl acrylate was very fast and afforded 3-[1,2,4]triazole-1-yl-propionic acid methyl ester (**7**) in 92% isolated yield (Table 2). The reaction of indole with methyl acrylate was very slow, and 3-indole-1-yl-propionic acid methyl ester (**8**) was obtained in 68% yield after 2 days. Further research on the reaction of 1*H*-benzotriazole with methyl acrylate gave a mixture of 3-benzotriazole-1-yl-propionic acid methyl ester (**9a**) and 3-benzotriazole-2-yl-propionic acid methyl ester (**9b**) in 67% and 21% yields, respectively (Table 2, entry 4). The formation of **9b** may be because of the resonant structure of 1*H*-benzotriazole under the basic conditions. Changing the solvent from CH_3CN to DMF or increasing the reaction temperature cannot improve the ratio of **9a** and **9b**.

In conclusion, we have demonstrated the first use of anhydrous K_3PO_4 as catalyst for the Michael addition of N-heterocycles to a series of α,β-unsaturated compounds. The catalyst is cheaper, milder, and more efficient. The reactions were carried out at room temperature to afford the desired products in good yields in short reaction times. This strategy is quite general, and it works with a broad range of N-heterocycles, including imidazole, triazole, indole, and benzotriazole.

Melting points were measured on a Büchi B-540 apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Varian Inova-400 spectrometer, using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal standard. Electrospray ionization (ESI) mass spectra were recorded using a Waters ZQ4000/2690 LC–MS spectrometer (solvent: methanol; positive mode). Thin-layer chromatography (TLC) was carried out on precoated GF254 silica-gel plates. Column chromatography was performed using G60 H silica gel. Anhydrous potassium phosphate was obtained from dehydration of $K_3PO_4 \cdot 3H_2O$. The other reagents and solvents were of commercial quality and used without further purification.

GENERAL SYNTHETIC PROCEDURE

N-Heterocycles (1 mmol) and α,β-unsaturated carbonyl compounds (1.2 mmol) were added to a 10-mL flask containing anhydrous K_3PO_4 (0.25 mmol), and the mixture was stirred at room temperature for a period of time. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by flash-column chromatography (silica gel, petroleum ether–ethyl acetate) to obtain the corresponding Michael adducts.

All compounds can be stored at rt for several months without decomposition.

3-Imidazole-1-yl-propionic Acid Methyl Ester (3a)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.750$ (t, 2H, $J = 6.8$ Hz), 3.660 (s, 3H), 4.237 (t, 2H, $J = 6.6$ Hz), 6.900 (s, 1H), 7.008 (s, 1H), 7.475 (s, 1H). ESI-MS: $m/z = 155$ (M + 1).

3-Imidazole-1-yl-propionic Acid Ethyl Ester (3b)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.245$ (t, 3H, $J = 7.6$ Hz), 2.769 (t, 2H, $J = 6.2$ Hz), 4.162 (d, d, 2H, $J = 7.2$ Hz, 14.4 Hz), 4.271 (t, 2H, $J = 6.6$ Hz), 6.935 (s, 1H), 7.050 (s, 1H), 7.511 (s, 1H). ESI-MS: $m/z = 169$ (M + 1).

3-Imidazole-1-yl-propionic Acid *t*-Butyl Ester (3c)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.423$ (s, 9H), 2.680 (t, 2H, $J = 6.8$ Hz), 4.220 (t, 2H, $J = 6.8$ Hz), 6.930 (t, 1H, $J = 1.2$ Hz), 7.041 (t, 1H, $J = 1.1$ Hz), 7.499 (s, 1H). ESI-MS: $m/z = 197$ (M + 1).

3-Imidazole-1-yl-butyric Acid Methyl Ester (3d)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.184$ (d, 3H), 2.875 (m, 1H), 3.667 (s, 3H), 4.007 (m, 1H), 4.238 (m, 1H), 6.878 (d, 1H, $J = 0.8$ Hz), 7.263 (s, 1H), 7.448 (s, 1H). ESI-MS: $m/z = 169$ (M + 1).

3-Imidazole-1-yl-propionamide (3e)

White solid; mp 139–140 °C. ^{1}H NMR (400 MHz, DMSO): $\delta = 2.524$ (t, 2H, $J = 6.8$ Hz), 4.151 (t, 2H, $J = 6.8$ Hz), 6.846 (t, 1H, $J = 1.2$ Hz), 6.922 (s, 1H), 7.108 (t, 1H, $J = 1.2$ Hz), 7.377 (s, 1H), 7.558 (s, 1H). ESI-MS: $m/z = 140$ (M + 1).

3-Imidazole-1-yl-propionitrile (3f)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.814$ (t, 2H, $J = 6.8$ Hz), 4.268 (t, 2H, $J = 6.8$ Hz), 7.018 (s, 1H), 7.119 (s, 1H), 7.566 (s, 1H). ESI-MS: $m/z = 122$ (M + 1).

3-[1,2,4]-Triazole-1-yl-propionic Acid Methyl Ester (7)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.908$ (t, 2H, $J = 6.4$ Hz), 3.671 (s, 3H), 4.463 (t, 2H, $J = 6.4$ Hz), 7.915 (s, 1H), 8.131 (s, 1H). ESI-MS: $m/z = 156$ (M + 1).

3-Indole-1-yl-propionic Acid Methyl Ester (8)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.802$ (t, 2H, $J = 6.8$ Hz), 3.640 (s, 3H), 4.430 (t, 2H, $J = 6.8$ Hz), 6.477 (m, 1H), 7.084 (t, 1H, $J = 1.2$ Hz), 7.207 (m, 1H), 7.319 (m, 1H), 7.623 (m, 1H). ESI-MS: $m/z = 204$ (M + 1).

3-Benzotriazole-1-yl-propionic Acid Methyl Ester (9a)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.102$ (t, 2H, $J = 6.8$ Hz), 3.647 (s, 3H), 4.902 (t, 2H, $J = 6.8$ Hz), 7.353 (m, 1H), 7.492 (m, 1H), 7.612 (m, 1H), 8.043 (m, 1H). ESI-MS: $m/z = 206$ $(M + 1)$.

3-Benzotriazole-2-yl-propionic Acid Methyl Ester (9b)

White solid, mp 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.198$ (t, 2H, $J = 6.8$ Hz), 3.727 (s, 3H), 5.043 (t, 2H, $J = 6.8$ Hz), 7.379 (d, d, 2H, $J = 13.6$, 6.8 Hz), 7.861 (d, d, 2H, $J = 13.6$, 6.8 Hz). ESI-MS: $m/z = 206$ $(M + 1)$.

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