Indium-mediated microwave-assisted one-pot synthesis of *α,β*-unsaturated amides

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A stereoselective synthesis of *α,β*-unsaturated-*N,N*-diethyl amides was achieved by a one-pot reaction of triphenylphosphine, an aromatic aldehyde, and *N,N*-diethyl chloroacetamide in the presence of indium under microwave-assisted and solvent-free condition.

Keywords: indium, microwave irradiation, *α,β*-unsaturated amide, solvent-free

α,β-Unsaturated amides are a significant group of compounds found in many natural products,[1,2] and are useful substrates for many reactions such as conjugate additions with copper[3–4] and Grignard[5] reagents, and other transforamtions.[6–8] Indium-mediated or -catalysed reactions have attracted considerable attention since the discovery of its remarkable reactivity in organic or aqueous media.[9–11] Indium has also shown great potential for reactions such as Reformatsky reaction,[12] Michael addition reactions,[13–15] Barbier type alkylations,[16] allylations,[17] and cross-coupling reactions.[18–21] Compared with other metals such as zinc and iron, indium appears to be the metal of choice due to its lack of requirement for activation, fewer side reactions, and higher regio- and stereoselectivites. Microwave irradiation has also been employed in various reactions, as an effective method for reducing the reaction time, such as in Michael[22] and Diels–Alder reactions[23] As part of an ongoing study into the synthesis of *α,β*-unsaturated amides,[24] we report here a convenient, efficient, and selective indium-mediated, one-pot method starting from triphenylphosphine, an aromatic aldehyde, and *N,N*-diethyl chloroacetamide (**1**) under microwave-assisted and solvent-free conditions.

The study was initially carried out with the reaction of **1** and benzaldehyde (**2a**) to identify the optimal condition (Scheme 1). Factors that influenced the yield of the *α,β*-unsaturated amide **3a**, such as solvent effects, temperature, time, and microwave power, are summarised in Table 1. The results showed that the reactions carried out under solvent-free condition (entry 7) generally afforded much higher yields than those run in solvents (entries 1–6). Thus, solvent-free conditions were employed in the following reactions. Temperature (entries 7–10) and microwave power (entries 11 and 12) screening showed that 150 °C (entry 9) and 1000 W (entry 12) were the best. It was also found that reaction time could be reduced to only 5 minutes (entry 14). The conditions employed above did not affect the *E/Z* ratio in the product **3a** which were usually as high as 92/8.

Having identified the optimal reaction conditions, the scope of the reaction was then investigated. Various aldehydes **2** were reacted with *N,N*-diethyl chloroacetamide **1**, triphenylphosphine, and indium under the optimal condition (Scheme 2). The results are summarised in Table 2. It was found that aromatic and heterocyclic aldehydes all reacted quickly to form the target *α,β*-unsaturated amides in moderate to high yield with high *E/Z* selectivities (entries 1–11). Acetophenone (entry 12) did not react under these conditions. The *E/Z* ratios of the products **3** were determined by ^{1}H NMR analysis. By comparing with the literature data,[25] which also reported the selective synthesis of the (*E*)-*α,β*-unsaturated amides, the chemical shifts and coulping constants of the vinyl and ethyl protons in ^{1}H NMR spectra of the product **3** were in accordance with those of literature's (*E*)-isomers. Furthermore, comparing with the traditional methods which were run under heating, the reaction time was shortened to only 5 min under the present microwave irradiation conditions.

Table 1 Condition optimisation for the microwave-assisted one-pot synthesis of *α,β*-unsaturated amide

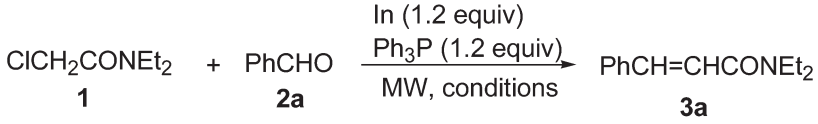
Entry	Solvent	Temp /°C	MW power /W	Time /min	Yield /%[a]
1	CH_2Cl_2	40	800	10	42
2	THF	60	800	10	46
3	DMF	100	800	10	51
4	CH_3OH	60	800	10	49
5	Toluene	100	800	10	54
6	CH_3CN	80	800	10	43
7	—	100	800	10	65
8	—	120	800	10	73
9	—	150	800	10	82
10	—	160	800	10	81
11	—	150	600	10	78
12	—	150	1000	10	88
13	—	150	1000	15	89
14	—	150	1000	5	88

[a] Isolated combined yields of (*E*)- and (*Z*)-isomers of **3a**, with *E/Z* ratios around 92/8.

In conclusion, we have developed a simple, efficient, and stereoselective method for the synthesis of *α,β*-unsaturated amides via indium-mediated microwave-assisted one-pot reaction from triphenylphosphine, an aldehyde and *N,N*-diethyl chloroacetamide under solvent-free conditions. The reaction did not require the use of any volatile organic solvents or expensive metallic reagents. Thus, it could be an economic and environmentally-friendly method for the synthesis of *α,β*-unsaturated amides.

Experimental

All reactions were conducted with an XH-100A microwave synthesis/extraction instrument which was made by Beijing Xiang Hu Science



Scheme 1

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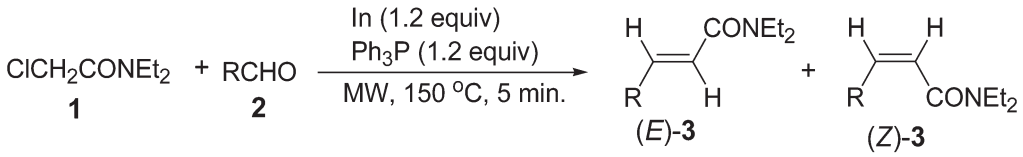
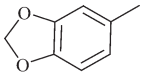


Scheme 2

Table 2 Indium-mediated microwave-assisted one-pot synthesis of α, β-unsaturated amides

Entry	R	Product	Yield /%[a]	*E/Z*[b]
1	C_6H_5	**3a**	88	92/8
2	4-ClC_6H_4	**3b**	90	88/12
3	4-BrC_6H_4	**3c**	85	91/9
4	4-$CH_3C_6H_4$	**3d**	84	89/11
5	4-$CH_3OC_6H_4$	**3e**	82	96/4
6	2-$NO_2C_6H_4$	**3f**	93	95/5
7	4-$NO_2C_6H_4$	**3g**	95	93/7
8		**3h**	95	93/7
9		**3i**	88	93/7
10	$C_6H_5CH{=}CH$	**3j**	70	88/12
11	$C_6H_5CH_2CH_2$	**3k**	65	88/12
12	$PhCOCH_3$	**3l**	Trace	—

[a] Isolated combined yield of (*Z*)- and (*E*)-isomers.
[b] *E/Z* Ratios determined by ^{1}H NMR analysis.

and Technology Development Co. Ltd. Melting points were recorded on a Digital Melting Point Apparatus WRS-1B and arenot corrected. TLC was performed using precoated silica gel 60 GF254 (0.25 mm) and column chromatography was performed using silica gel (300–400 mesh). ^{1}H NMR spectra were measured on a Bruker Avance 300 instrument using $CDCl_3$ as solvent with tetramethylsilane (TMS) as the internal standard. *J* values in ^{1}H NMR spectra were given in Hz. IR spectra were measured on a Bruker Vector 55 instrument. MS spectra were measured by an HP5989B instrument. GC–MS were measured on a Shimadzu GCMS-QP2010 Plus spectrometer (EI).

Preparation of **3a–k***; general procedure*

The mixture of triphenylphosphine (1.2 mmol), *N,N*-diethyl chloroacetamide (1.2 mmol), the aldehyde (1.0 mmol), and indium (1.2 mmol) in an oven-dried round-bottomed flask (25 mL) was stirred under microwave irradiation which was set at 1,000 W and 150 °C for 5 min. The products were purified by column chromatography on silica gel using ethyl acetate and petroleum ether (60–90 °C) as the eluent. Ratios of the (*E*)- and (*Z*)-isomers were determined by ^{1}H NMR analysis of the combined column-purified mixtures. It was not possible to separate the isomers by chromatography.

N,N-diethylcinnamamide (**3a**):[24] Solid. *E/Z* =92/8. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.23 (m, 6 H), 3.46 (m, 4 H), 6.81 (d, 1 H, *J* = 15.4 Hz), 7.36 (m, 3 H), 7.50 (m, 2H), 7.70 (d, 1 H, *J* = 15.4 Hz) ppm. MS: *m/z* (%) 203 (M^+, 33), 131 (100), 103 (60), 77 (22). IR (KBr) (cm^{-1}): 2979, 1697, 1652, 1523, 985, 764.

N,N- diethyl -3-(4-chlorophenyl)acrylamide (**3b**):[26] Oil. *E/Z* =88/12. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.28 (m, 6 H), 3.52 (m, 4 H), 6.82 (d, 1 H, *J* = 15.4 Hz), 7.36 (d, 2 H, *J* = 7.4 Hz), 7.46 (d, 2 H, *J* = 7.5 Hz), 7.67 (d, 1 H, *J* = 15.4 Hz) ppm. IR (KBr) (cm^{-1}): 2983, 1656, 1614, 1497, 983, 825.

N,N- diethyl-3-(4- bromophenyl)acrylamide (**3c**):[24] Oil. *E/Z* =91/9. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.29 (m, 6 H), 3.51 (m, 4 H), 6.84 (d, 1 H, *J* = 15.4 Hz), 7.39 (d, 2 H, *J* = 8.5 Hz), 7.51 (d, 2 H, *J* = 8.5 Hz), 7.66 (d, 1 H, *J* = 15.4 Hz) ppm. MS: *m/z* (%) 281 (M^+, 26), 209 (100), 181 (30), 126 (36), 102 (79), 77 (20). IR (KBr) (cm^{-1}): 2983., 1656, 1613, 1497, 983, 821.

N,N-diethyl-3-p-tolylacrylamide (**3d**):[24] Oil. *E/Z* =89/11. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.26(m, 6 H), 2.34 (s, 3 H), 3.49 (m, 4 H), 6.80 (d, 1 H, *J* = 15.4 Hz), 7.17 (d, 2 H, *J* = 7.4 Hz), 7.42 (d, 2 H, *J* = 7.7 Hz), 7.70 (d, 1 H, *J* = 15.4 Hz) ppm. MS: *m/z* (%) 217 (M^+, 23), 202 (30), 145 (100), 115 (19), 91 (12). IR (KBr) (cm^{-1}): 2983, 1655, 1613, 987, 819.

N,N-diethyl-3-(4-methoxyphenyl)acrylamide (**3e**):[24] Oil. *E/Z* = 96/4. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.20 (m, 6 H), 3.45 (m, 4 H), 3.76 (s, 3 H), 6.68 (d, 1 H, *J* = 15.3 Hz), 6.85 (d, 2 H, *J* = 8.5 Hz), 7.44 (d, 2 H, *J* = 8.4 Hz), 7.59 (d, 1 H, *J* = 15.5 Hz) ppm. MS: *m/z* (%) 233 (M^+, 21), 202 (100), 161 (66), 146 (19), 118 (12), 105 (31), 77 (10). IR (KBr) (cm^{-1}): 2981, 1652, 1612, 1503, 992, 762.

N,N-diethyl-3-(2-nitrophenyl)acrylamide (**3f**):[24] Oil. *E/Z* =95/5. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.27 (m, 6 H), 3.52 (m, 4 H), 6.72 (d, 1 H, *J* = 15.3 Hz), 7.50 (m,1 H), 7.66 (m, 2 H), 8.01 (m, 2 H) ppm. MS: *m/z* (%) 248 (69), 176 (45), 130 (100), 102 (27). IR (KBr) (cm^{-1}): 2983, 1655, 1617, 1530, 976, 759.

N,N-diethyl-3-(4-nitrophenyl)acrylamide (**3g**):[27] Pale yellow solid. *E/Z* = 93/7. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.21 (t, 3 H, *J* = 7.1 Hz), 1.29 (t, 3 H, *J* = 7.1 Hz), 3.53 (m, 4 H), 6.98 (d, 1 H, *J* = 15.4 Hz), 7.67 (d, 2 H, *J* = 8.8 Hz), 7.76 (d, 1 H, *J* = 15.4 Hz), 8.25 (d, 2 H, *J* = 8.8 Hz) ppm. MS: *m/z* (%) 248 (M^+ , 53), 233 (17) 176 (100), 130 (33), 102 (39), 77 (20). IR (KBr) (cm^{-1}): 2983, 1656, 1615, 985, 821, 733.

3-(benzo[d][1,3]dioxol-5-yl)-N,N-diethylacrylamide (**3h**):[24] Oil. *E/Z* = 93/7. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.24 (m, 6H), 3.44 (m, 4H), 5.95 (s, 2H), 6.64 (d, 1H, *J* = 15.4 Hz), 6.77 (d, 1H, *J* = 7.9 Hz), 7.00 (m, 2H), 7.64 (d, 1H, *J* = 15.4 Hz) ppm. MS: *m/z* (%) 247(M^+, 34), 75 (100), 145 (46), 117 (21). IR (KBr) (cm^{-1}): 2983, 1651, 1601, 1501, 984, 819.

N,N-diethyl-3-(furan-2-yl)acrylamide (**3i**):[26] Oil. *E/Z* =93/7. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.23 (m, 6 H), 3.45 (m, 4 H), 6.50 (m, 2 H), 6.72 (d, 1 H *J* = 15.1 Hz), 7.45 (m, 2 H) ppm. MS: *m/z* (%) 193 (M^+, 32), 121 (100), 72 (25). IR (KBr) (cm^{-1}): 2988, 1653, 1604, 988, 823.

N,N-diethyl-5-phenylpenta-2,4-dienamide (**3j**):[28] Oil. *E/Z* =88/12. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.18 (m, 6 H), 3.45 (m, 4 H), 6.38 (d, 1 H, *J* = 15.1 Hz), 6.88 (d, 1 H, *J* = 15.1 Hz), 7.47, (m, 7 H) ppm. MS: *m/z* (%) 229 (M^+, 37), 157 (100), 128 (37), 115 (21), 77 (11). IR (KBr) (cm^{-1}): 2978, 1663, 1623, 983, 768.

N,N-diethyl-5-phenylpent-2-enamide (**3k**):[29] Oil. *E/Z* = 88/12. ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-isomers: δ 1.12 (m, 6 H), 2.51 (m, 2 H), 2.77 (m, 2 H), 3.39 (m, 4 H), 6.15 (d, 1 H, *J* = 15.9 Hz), 6.89 (m, 1 H), 7.25 (m, 5 H). MS: *m/z* (%) 231(M^+, 46), 159 (30), 126 (37), 91 (100). IR (KBr) (cm^{-1}): 2983, 1663, 1618, 978, 768.

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