Microwave-assisted one-pot synthesis of α, β-unsaturated amides under solvent-free conditions

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Under microwave-assisted solvent-free conditions a one-pot reaction of triphenylphosphine, an aldehyde and N, N-diethyl chloroacetamide in the presence of zinc dust affords α, β-unsaturated amides stereoselectively in good yield. In comparison with the conventional heating method, the reaction was finished within five minutes under microwave irradiation.

Keywords: microwave irradiation, solvent-free conditions, α, β-unsaturated amides

Two pioneering papers[1-2] appeared in 1986 on the remarkable acceleration of many organic reactions upon irradiation with microwaves. Since then microwave-assisted organic synthesis has become increasingly popular in conventional and combinatorial synthesis, such as the Wittig reaction,[3,4] and the Suzuki reaction.[5] α,β-Unsaturated amides have been used as building blocks in organic synthesis[6-8] to prepare natural products.[9] Moreover, α, β-unsaturated amides show both biological and insecticide activity. Several methods for their synthesis have appeared, involving Rh-catalysed aminocarbonylation of alkynes,[10] Pt-catalysed aminocarbonylation of iodoalkenes or iodobenzene,[11-16] SmI_2 promoted elimination of α,β-epoxyamides[17] or 2-chloro-3-hydroxyamides,[18] the reaction of dichloroamide and aldehydes promoted by Rieke manganese,[19] Horner–Wadsworth–Emmons reaction,[20] Peterson reaction,[21] zinc-promoted reaction of bromoacetamide.[22] However, most reactions need a long time and the metallic reagents can be expensive or are difficult to handle.[23] Thus, there is a need to accelerate the reaction and to use inexpensive metallic reagents.

Our research group has been interested in the synthesis of α,β-unsaturated amides, and we have reported the synthesis of α,β-unsaturated amides by the Wittig reaction of phosphonium ylids. We report here the microwave-assisted one-pot reaction of α,β-unsaturated amides promoted by zinc under solvent-free conditions.

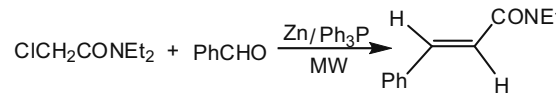
Initially we aimed to use the classical Reformastky-type condensation of N, N-diethylchloroacetamide and aldehyde promoted by zinc dust to obtian α,β-unsaturated amides. However, no product was formed in the reaction. The reaction occurred when triphenylphosphine was added. The reaction of triphenylphosphine, N, N-diethyl chloroacetamide, benzaldehyde was studied as the model reaction (Scheme 1) to explore different conditions.

We investigated the effect of different power and temperature of the microwave on the one-pot reaction. The results were summarised in Table 1.

As Table 1 shows, the yield improved with higher power and 1000W was the optimum 150 °C was the optimal temperature. There was no obvious change with higher temperatures. We also lengthened the reaction time from 5 to 10 min but no obvious change was apparent.

To test the generality of the reaction, several aldehydes were treated with triphenylphosphine, N,N-diethyl chloroacetamide and zinc under the optimised conditions (Scheme 2). The results are listed in Table 2.

In these experiments, it was found that the use of zinc dust increased the yield. In these experiments, it was found that not only aromatic aldehydes and aliphatic aldehydes but also heterocyclic aldehydes and the aldehyde with the double

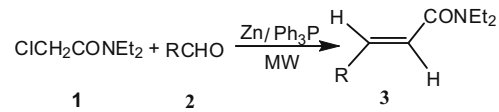


Scheme 1

Table 1 Results of different powers and temperatures with triphenylphosphine, N, N-diethyl chloroacetamide and benzaldehyde

Entry	Power/W	Temperature/°C	Time/min	Yield[a]/%
1	500	100	5	46
2	700	100	5	53
3	800	100	5	58
4	900	100	5	65
5	1000	100	5	69
6	1000	120	5	72
7	1000	130	5	76
8	1000	150	5	85
9	1000	160	5	86
10	1000	150	10	86

[a]Isolated yield.



Scheme 2

bond conjugated with the carbonyl group reacted smoothly under the same conditions. By comparison acetophenone was unreactive with the traditional thermal method, the reaction time was shortened from 16 h to 5 min under microwave irradiation.

The ratios of *Z*/*E* isomers were determined by ^{1}H NMR. By comparison with the literature data which reported the selective synthesis of the (*E*)-α, β-unsaturated amides, we found the chemical shifts of the vinyl and the ethyl protons of the (*E*)-isomer corresponded with that of major product of the reaction.

The possible mechanism of the reaction was investigated. When zinc powder, an aldehyde and *N*, *N*-diethylamidemethylenetriphenylphosphonium salt which could be synthesised easily by the reaction of triphenylphosphine and *N*, *N*-diethylchloroacetamide were added together under microwave irradiation, the α, β-unsaturated amide and triphenylphosphine oxide were obtained. We also used GCMS to follow the reaction, and observed the formation of *N*, *N*-diethylamidemethylene triphenylphosphorane ylid. It was noteworthy that the ylid was not found by GCMS when we added only the phosphonium salt and zinc powder together.

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Table 2 Synthesis of α,β-unsaturated amides

Entry	R	Product	Yield[a]/%	*Z*/*E*[b]
1	4-$NO_2C_6H_4$	**3a**	93	10:90
2	4-ClC_6H_4	**3b**	83	9:91
3	4-BrC_6H_4	**3c**	78	12:88
4	4-$CF_3C_6H_4$	**3d**	86	15:85
5	4-$CH_3C_6H_4$	**3e**	75	11:89
6	2-$NO_2C_6H_4$	**3f**	89	7:93
7	2-$CH_3OC_6H_4$	**3g**	79	13:87
8	C_6H_5	**3h**	85	11:89
9		**3i**	82	7:93
10		**3j**	84	10:90
11	$C_6H_5CH{=}CH$	**3k**	72	12:88
12	$C_6H_5CH_2CH_2$	**3l**	70	9:91
13	C_3H_7	**3m**	58	11:89
14	$PhCOCH_3$	**3n**	Trace	–

[a]Isolated yield, product characterised by ^{1}H NMR, ^{13}C NMR, IR, MS. [b]Ratio was determined by ^{1}H NMR (300 MHz, $CDCl_3$) analysis.

Thus, we think that it is possibe that the triphenylphosphonium salt was formed first, and then the corresponding ylid was formed in the presence of zinc powder, and the resulted ylid reacted with the aldehyde immediately to afford the α, β-unsaturated amides. At the same time, the reaction of ylid and aldehyde further promoted the formation of the product.

In conclusion, we have demonstrated a very simple and efficient stereoselective method for making α, β-unsaturated amides by the microwave-assisted one-pot reaction of triphenylphosphine, aldehyde and N, N-diethyl chloroacetamide in the presence of zinc dust under solvent-free conditions. The reaction does not require the use of any volatile organic solvents as well as expensive metallic reagents. Thus, this is an economical and environmentally friendly method for the synthesis of α, β-unsaturated amides, and the use of the microwaves significantly shortened the reaction time.

Experimental

All reactions were conducted in an XH-100A microwave synthesis/extraction instrument which was made by Beijing Xiang Hu Science and Technology Development Co. Ltd. Melting points were recorded on Digital Melting Point Apparatus WRS-1B and uncorrected. TLC was performed using precoated silica gel 60 GF_{254} (0.25 mm) and column chromatography was performed using silica gel (300–400 mesh).^{1}H NMR and ^{13}C NMR spectra were reported on a FT-Bruker AT-300 instrument using $CDCl_3$ as a solvent with tetramethylsilane (TMS) as the internal standard *J*-values are given in Hz. IR spectra were measured on a Bruker Vector55 instrument. MS were measured by the HP5989B instrument. GCMS was reported on QP-2010 Plus.

General procedure for the preparation of α, β-*unsaturated acetamide*

Triphenylphosphine (1.2 mmol), N, N-diethyl chloroacetamide (1.2 mmol), aldehydes (1.0 mmol) and Zn (1.2 mmol) were added into an oven-dried round-bottom flask (25 mL). The mixture was stirred under microwave irradiation which was set at 1000W, and 150 °C for 5 min. The product was purified by chromatography on silica gel with ethyl acetate and petroleum ether (60–90 °C). The physical and spectra data of all compounds are as follows.

N,N-diethyl-3-(4-nitrophenyl)acrylamide (**3a**): Pale yellow solid; m.p. 142–145 °C (Lit.[27] m.p. 151–152 °C); *Z*/*E* = 10:90. IR (KBr) (cm^{-1}): 2975, 1648, 1605, 975, 813, 725. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.26 (m, 6 H), 3.51 (m, 4 H), 6.95 (d, 1 H, *J* = 15.4 Hz), 7.65 (d, 2 H, *J* = 8.8 Hz), 7.73 (d, 1 H, *J* = 15.4 Hz), 8.23 (d, 2 H, *J* = 8.7 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.10, 15.14, 41.22, 42.39, 123.67, 124.09, 128.26, 139.55, 141,74, 143.99, 164.68. MS: *m/z* (%) 248 (M^+, 46), 233 (29) 176 (99), 130 (37), 102 (36), 77 (10), 58 (17). Elemental Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.05; H, 6.61; N, 11.41%.

N,N-diethyl-3-(4-chlorophenyl)acrylamide (**3b**): Oil; *Z*/*E* = 9:91. IR (KBr) (cm^{-1}): 2975, 1648, 1606, 1489, 975, 817. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.22 (m, 6 H), 3.48 (m, 4 H), 6.79 (d, 1 H, *J* = 15.4 Hz), 7.33 (d, 2 H, *J* = 7.4 Hz), 7.43 (d, 2 H, *J* = 7.5 Hz), 7.64 (d, 1 H, *J* = 15.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.13, 15.04, 118.31, 128.87, 129.74, 133.91, 135.12, 140.80, 165.33. Elemental Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.84; H, 6.86, N, 6.02%. MS: *m/z* (%) 237 (M^+, 27), 222 (12) 165 (99), 137 (22), 102 (25), 75 (10), 44 (18).

N,N-diethyl-3-(4-bromophenyl)acrylamide (**3c**): Oil; *Z*/*E* = 12:88. IR (KBr) (cm^{-1}): 2975, 1648, 1605, 1489, 975, 813. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.22 (m, 6 H), 3.45 (m, 4 H), 6.80 (d, 1 H, *J* = 15.4 Hz), 7.28 (d, 2 H, *J* = 8.9 Hz), 7.46 (d, 2 H, *J* = 8.3 Hz), 7.62 (d, 1 H, *J* = 15.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.16, 15.08, 41.11, 42.29, 118.43, 123.48, 130.04, 131.94, 134.40, 140.96, 165.38. MS: *m/z* (%) 282 (M^+, 19), 209 (99), 181 (18), 126 (32), 102 (92), 77 (14), 58 (22).

N,N-diethyl-3-(4-(trifluoromethyl)phenyl)acrylamide (**3d**): Oil; *Z*/*E* = 15:85. IR (KBr) (cm^{-1}): 2975, 1648, 1606, 975, 813. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.23 (m, 6 H), 3.48 (m, 4 H), 6.89 (d, 1 H, *J* = 15.4 Hz), 7.65 (m, 4 H), 7.70 (d, 1 H, *J* = 15.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.06, 15.01, 41.11, 42.30, 120.32, 125.64, 127.81, 128.64, 138.88, 140.44, 165.06. MS: *m/z* (%) 271 (M^+, 48), 256 (26), 199 (100), 151 (82), 126 (43), 102 (20), 72 (34), 58 (54).

N,N-diethyl-3-p-tolylacrylamide (**3e**): Oil; *Z*/*E* = 11:89. IR (KBr) (cm^{-1}): 2975, 1647, 1605, 979, 813. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.21 (m, 6 H), 2.32 (s, 3 H), 3.46 (m, 4 H), 6.77 (d, 1 H, *J* = 15.4 Hz), 7.15 (d, 2 H, *J* = 7.4 Hz), 7.40 (d, 2 H, *J* = 7.7 Hz), 7.67 (d, 1 H, *J* = 15.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.21, 15.04, 21.36, 41.07, 42.28, 116.65, 127.71, 129.45, 132.71, 139.65, 142.30, 165.91. MS: *m/z* (%) 217 (M^+, 32), 202 (10), 145 (100), 115 (28), 91 (12), 72 (6). Elemental Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.50; H, 8.71; N, 6.71%.

N,N-diethyl-3-(2-nitrophenyl)acrylamide (**3f**): Oil; *Z*/*E* = 7:93. IR (KBr) (cm^{-1}): 2976, 1647, 1609, 1524, 968, 751. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.25 (m, 6 H), 3.48 (m, 4 H), 6.69 (d, 1 H, *J* = 15.3 Hz), 7.50 (m,1 H), 7.64 (m, 2 H), 8.02 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.06, 14.97, 40.94, 42.37, 123.41, 124.66, 128.53, 129.22, 129.52, 131.94, 133.29, 137.10, 148.24, 164.78. MS: *m/z* (%) 202 (69), 176 (45), 130 (100), 102 (27), 72 (38), 58 (10).

N,N-diethyl-3-(2-methoxyphenyl)acrylamide (**3g**): Oil; *Z*/*E* = 13 : 87. IR (KBr) (cm^{-1}): 2973, 1644, 1604, 1495, 984, 754. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.22 (m, 6 H), 3.50 (m, 4 H), 3.89 (s, 3 H), 6.95 (m, 3 H), 7.33 (m, 1 H), 7.50 (d, 1 H, *J* = 9 Hz), 7.97 (d, 1 H, *J* = 15.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.23, 15.04, 41.05, 42.24, 55.30, 114.02, 118.90, 120.91, 125,74, 136.27, 144.23, 160.65, 164.89. MS: *m/z* (%) 233 (M^+, 8), 202 (100), 161 (82), 146 (9), 118 (12), 105 (13), 77 (10).

N,N-diethylcinnamamide (**3h**): Solid; m.p. 60–62 °C (Lit.[27] m.p. 67–68 °C); *Z*/*E* = 11:89. IR (KBr) (cm^{-1}): 2971, 1689, 1644, 1515, 977, 756. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.18 (m, 6 H), 3.45 (m, 4 H), 6.80 (d, 1 H, *J* = 15.4 Hz), 7.37 (m, 3 H), 7.50 (m, 2H), 7.69 (d, 1 H, *J* = 15.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.19, 15.05, 41.06, 42.28, 117.78, 128.31, 128.75, 129.40, 135,47, 142.24, 165.68. MS: *m/z* (%) 203 (M^+, 21), 131 (100), 103 (43), 77 (28), 44 (15). Elemental Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.99; H, 8.61; N, 7.03%.

3-(benzo[d][1,3]dioxol-5-yl)-N,N-diethylacrylamide (**3i**): Oil; *Z*/*E* = 7:93. IR (KBr) (cm^{-1}): 2975, 1643, 1593, 1493, 976, 811. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.24 (m, 6H), 3.46 (m, 4H), 5.97 (s, 2H), 6.66 (d, 1H, *J* = 15.4 Hz), 6.79 (d, 1H, *J* = 7.9), 6.99 (m, 2H), 7.62 (d, 1H, *J* = 15.4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.21, 15.04, 41.07, 42.25, 101.37, 106.34, 108.48, 115.74, 123.67, 129.88, 142.02, 148.15, 148.84, 165.80. MS: *m/z* (%) 247(M^+, 44), 75 (100), 145 (45), 117 (16), 89 (26), 63 (9). Elemental Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.19; H, 7.07; N, 5.80%.

N,N-diethyl-3-(furan-2-yl)acrylamide (**3j**): Oil; *Z*/*E* = 10:90. IR (KBr) (cm^{-1}): 2980, 1645, 1595, 980, 815. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.21 (m, 6 H), 3.47 (m, 4 H), 6.55 (m, 2 H), 6.73 (d, 1 H), 7.45 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.20, 15.05, 41.06, 42.25, 112.07, 113.50, 115.32, 129.08, 143.67, 151.81, 165.53. MS: *m/z* (%) 193(M^+, 20), 121 (100), 72 (15), 65 (32).

N,N-diethyl-5-phenylpenta-2,4-dienamide (**3k**): Oil; *Z*/*E* = 12:88. IR (KBr) (cm^{-1}): 2970, 1655, 1615, 975, 760. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.18 (m, 6 H), 3.45 (m, 4 H), 6.38 (d, 1 H, *J* = 15 Hz), 6.88 (d, 1 H, *J* = 15 Hz), 7.47, (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.19, 14.96, 41.05, 42.27, 120.90, 126.95, 128.56, 128.86, 130.00, 136.43, 138.83, 142.54, 165.93. MS: *m/z* (%) 229 (M^+, 31), 157 (100), 128 (67), 115 (13), 77 (11), 58 (7).

N,N-diethyl-5-phenylpent-2-enamide (**3l**): Oil; *Z*/*E* = 9:91. IR (KBr) (cm^{-1}): 2975, 1655, 1610, 970, 760. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 1.10 (m, 6 H), 2.52 (m, 2 H), 2.75 (m, 2 H), 3.34 (m, 4 H), 6.15 (d, 1 H, *J* = 15 Hz), 6.89 (m, 1 H), 7.23 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.12, 14.74, 30.88, 34.65, 40.80, 42.13, 121.21, 122.82, 126.13, 128.38, 141.11, 165.92. MS: *m/z* (%) 231(M^+, 44), 159 (19), 126 (51), 100 (24), 91 (100), 72 (43), 58 (39).

N,N-diethylhex-2-enamide (**3m**):Oil; *Z*/*E* = 16:84. IR (KBr) (cm^{-1}): 2969, 1656, 1615, 1447, 974, 820. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 0.96 (m, 3H), 1.20 (m, 6H), 1.44 (m, 2H), 2.14 (q, 2H), 3.47 (m, 4H), 6.15 (d, 1H, *J* = 16 Hz), 6.88 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.07, 14.50, 14.70, 23.15, 34.20, 40.75, 42.08, 120.93, 140.89, 165.41. MS: *m/z* (%) 169 (M^+,65), 154 (100), 126 (80), 97 (75), 72 (36), 58 (55), 55 (85).

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