Zinc-mediated facile synthesis of α,β-unsaturated primary amides

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A general method for the synthesis of α,β-unsaturated primary amides was achieved by an one-pot, triphenylphosphine- and zinc powder-promoted Wittig reaction of bromoacetamide and aldehydes under solvent-free conditions.

Keywords: unsaturated primary amide, solvent-free, zinc powder, triphenylphosphine

α,β-Unsaturated amides have been used as building blocks in the preparation of deplancheine, tacamonine and paroxetine.[1] A number of synthetic acrylamide derivatives have also shown important biological and insecticidal activities.[2] Many methods for the synthesis of α,β-unsaturated primary amides have been developed,[3–11] including the condensation of α,β-unsaturated carboxylic acid and carbonyl compounds with different reagents,[4–8] the hydrolysis of α,β-unsaturated nitriles,[9] the coupling reaction of acrylamides with aryl halides,[10] and the rearrangement of oximes.[11] However, in many cases these methods were of limited scope. The Wittig reaction[12] is one of the most important general methods for the construction of carbon–carbon double bonds, and as a part of our studies on developing new Wittig reactions,[13–16] we considered developing a general route to α,β-unsaturated primary amide via a Wittig method.

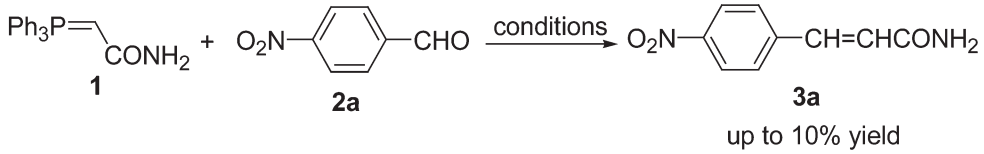
Since there has been no report of the Wittig synthesis of α,β-unsaturated primary amides from an amidomethylene triphenylphosphorane ylide **1** with aldehydes, we initially investigated the reaction by mixing **1** with 4-nitrobenzaldehyde **2a** under the usual conditions (Scheme 1). However, the product **3a** was only obtained in less than 10% yield even after a series of modifications to the conditions. Satoshi and coworkers's have reported that more complicated phosphines could be employed to replace triphenyl phosphine to improve the reactivity of the ylid.[17] Consequently we concluded that it might not be a good method to use **1** as the starting material, since it might be too stable and thus difficult to react with aldehydes. Various modifications were attempted including changing the substrates. Subsequently, we found that the reaction using bromoacetamide **4** as the substrate to react with aryl aldehydes in the presence of triphenylphosphine and metal powders was a direct and efficient method (Scheme 2). Zinc powder was the metal of choice (see Table 1).

As shown in Table 1, the reaction did not occur in the absence of a metal (entry 1). However, when Fe, Zn, or Zn-Cu powder was added, there was a low yield at 60 °C in CH_2Cl_2 when the reactions were carried out in a sealed tube (entries 2–4). Zinc powder was then used in the following modifications of the conditions to examine the solvent and temperature effects (entries 5–10). Firstly, prolonged reaction time gave no obvious enhancement in product yield. Then other solvents were investigated and it was found the reaction was best run under solvent-free conditions (entry 10). Later 150 °C (entry 12) was found to be a better temperature than lower or higher ones (entries 10–13), giving high yield of **3a**. As to the stereoselectivity of the reaction, it has been reported that the chemical shifts of the vinyl protons of (*Z*)-α,β-unsaturated

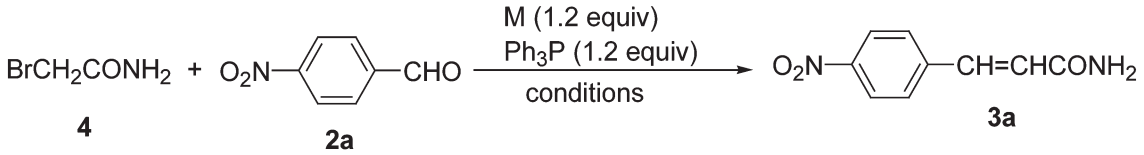
Table 1 Condition optimisation for the metal-mediated synthesis of α,β-unsaturated primary amides

Entry	Solvent	Temp /°C	Metallic reagent	Time /h	Yield /%[a]
1	CH_2Cl_2	60	—	3	—
2	CH_2Cl_2	60	Fe	3	25
3	CH_2Cl_2	60	Zn	3	43
4	CH_2Cl_2	60	Zn-Cu	3	42
5	CH_2Cl_2	60	Zn	6	44
6	CH_3OH	60	Zn	3	42
7	THF	80	Zn	3	44
8	CH_3CN	80	Zn	3	40
9	DMF	120	Zn	3	41
10	—	120	Zn	3	50
11	—	140	Zn	3	75
12	—	150	Zn	3	90
13	—	160	Zn	3	86

[a] Isolated combined yield of (*E*)- and (*Z*)-isomers of **3a**, with *E/Z* ratios around 88/12.



Scheme 1



Scheme 2

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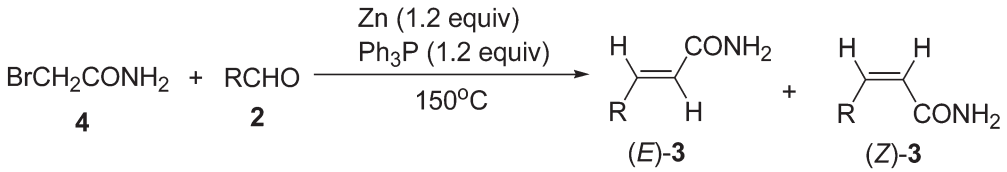

Scheme 3

amides were usually at lower field than the corresponding (*E*)-isomers.[18] Thus, chemical shifts of vinyl protons of (*E*)-4-nitrocinnamamide **3a** (6.65 ppm) and the (*Z*)-isomer (6.24 ppm) obtained in present reactions were in accordance with the literature data.[18] The conditions employed as above did not alter the (*E*)- and (*Z*)-isomer ratios, which were usually 88/12.

The method was then applied to various substrates to investigate the scope of the reaction for the synthesis of different *α*,*β*-unsaturated primary amides (Scheme 3). As shown in Table 2, all aromatic aldehydes reacted well under the optimal solvent-free condition, giving moderate to high product yields (entries 1–8). The reaction of aliphatic aldehydes was not always successful (entry 10), and a vinylic aldehyde gave moderate yield (entry 9). The results also showed that more electrophilic aldehydes bearing electon-withdrawing groups (entries 1–5) gave higher yields (86–90%). Benzaldehyde gave only a moderate yield (72%, entry 6), and aromatic aldehydes with electron-donating groups (entries 7–8) even lower yields (61–63%). All products were identified by MS, IR and ^{1}H NMR spectra. The *E/Z* ratios of the isomers were determined by ^{1}H NMR spectra but it was not possible to separate the isopmers.

In conclusion, *α*,*β*-unsaturated primary amides, which could not be obtained by a normal Wittig reaction using an ylid, could be easily Obtained through a direct, one-pot, zinc- and triphenylphosphine-mediated reaction with bromoacetamide and aldehydes under solvent-free conditions. The reaction did not require the use of any volatile organic solvents and expensive metallic reagents. Thus, it could be an economic, convenient, and environmentally-friendly-friendly method for the synthesis of *α*,*β*-unsaturated primary amides.

Experimental

Starting materials were obtained from commercial suppliers and used without further purification. DMF was distilled from calcium hydride and THF was distilled from sodium/benzophenone prior to use. ^{1}H NMR (300 MHz) spectra were recorded on a Bruker Avance (300 MHz) spectrometer, using d_6-DMSO as the solvent and TMS as internal standard. Mass spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. IR spectra were recorded on a Shimadzu IR-408 spectrometer.

Table 2 Zinc-mediated synthesis of *α*,*β*-unsaturated primary amides

Entry	Product	R	Yield /%[a]	*E/Z*[b]
1	**3a**	4-$NO_2C_6H_4$	90	88/12
2	**3b**	2-$NO_2C_6H_4$	89	90/10
3	**3c**	4-BrC_6H_4	88	70/30
4	**3d**	4-ClC_6H_4	86	70/30
5	**3e**	4-$CF_3C_6H_4$	89	83/17
6	**3f**	C_6H_5	72	70/30
7	**3g**	4-$CH_3C_6H_4$	65	75/25
8	**3h**	2-$CH_3OC_6H_4$	63	80/20
9	**3i**	C_6H_5CH=CH	61	88/12
10	**3j**	C_3H_7	—	—

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

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

The mixture of triphenylphosphine (0.314 g, 1.2 mmol), bromoacetamide (0.164 g, 1.2 mmol), aldehydes (1.0 mmol) and zinc (1.2 mmol) in a sealed oven-dried tube was heated at 150 °C for 3 h. The products were purified by chromatography on silica gel using ethyl acetate and petroleum ether (60–90 °C) as the eluent but the *E/Z* isomers could not be separated.

4-Nitrocinnamamide **(3a):**[18] ^{1}H NMR (300 MHz, DMSO) of (*E*)-isomers: δ 6.22 (d, *J* = 15 Hz, 1H), 6.80 (d, *J* = 15 Hz, 1H), 7.80–7.84 (m, 2H), 8.16–8.26 (m, 2H). EI-MS *m/z* (%): 51.10 (14.50), 77.15 (22.91), 152.15 (11.67), 183.05 (14.69), 192.05 (M^+, 24.63). IR (cm^{-1}): 3370, 3175, 1665, 1520, 1340, 980.

2-Nitrocinnamamide **(3b):**[19] ^{1}H NMR (300 MHz, DMSO) of (*E*)-isomers: δ 6.61 (d, *J* = 16.0 Hz, 1H), 7.54–7.78 (m, 5H). EI-MS *m/z* (%): 51.10 (53.70), 59.60 (0.15), 65.15 (72.51), 77.15 (59.50), 92.15 (65.59), 102.15 (46.21), 117.15 (49.94), 192.20 (M^+, 100). IR (cm^{-1}): 3453, 3145, 1624, 1392, 966, 861.

4-Bromocinnamamide **(3c):**[20] ^{1}H NMR (300 MHz, DMSO) of (*E*)-isomers: δ 6.62 (d, *J* = 16.0 Hz, 1H), 7.35–7.65 (m, 5H); EI-MS *m/z* (%): 51.10 (31.56), 58.65 (5.88), 76.15 (22.97), 130.20 (12.52), 226.05 (M^+, 27.33). IR (cm^{-1}): 3340, 3163, 1671, 1386, 987, 820.

4-Chlorocinnamamide **(3d):**[18] ^{1}H NMR (300 MHz, DMSO) of (*E*)-isomers: δ 6.61 (d, *J* = 16.0 Hz, 1H), 7.37–7.65 (m, 5H). EI-MS *m/z* (%): 51.10 (45.29), 58.65 (11.76), 76.10 (17.57), 128.20 (14.03), 137.15 (72.66), 181.10 (M^+, 52.89). IR (cm^{-1}): 3335, 3150, 1670, 1090, 990, 830.

4-Trifluoromethylcinnamamide **(3e):**[21] ^{1}H NMR (300 MHz, DMSO) of (*E*)-isomers: δ 6.74 (d, *J* = 16.0 Hz, 1H), 7.45–7.64 (m, 5H). EI-MS *m/z* (%): 51.10 (10.46), 58.65 (1.55), 77.10 (3.67), 102.15 (23.88), 151.15 (68.31), 215.10 (M^+, 42.79), 215.10 (48.18). IR (cm^{-1}): 3341, 3169, 1669, 1395, 987, 835.

Cinnamamide **(3f):**[22] ^{1}H NMR (300 MHz, DMSO) of (*E*)-isomers: δ 6.62 (d, *J* = 16.0 Hz, 1H), 7.29–7.78 (m, 5H). EI-MS *m/z* (%): 51.10(11.61), 65.15(22.32), 77.15(6.43), 147.20 (M^+, 50.18). IR (cm^{-1}): 3370, 3165, 1664, 1598, 967, 760.

4-Methylcinnamamide **(3g):**[18] ^{1}H NMR (300 MHz, DMSO) of (*E*)-isomers: δ 2.29 (s, 3H), 6.53 (d, *J* = 16.0 Hz, 1H), 7.18–7.43 (m, 5H). EI-MS *m/z* (%): 51.10 (11.61), 65.15 (22.32), 77.15 (6.43), 91.15 (42.95), 145.20 (53.90), 161.20 (M^+, 56.76); IR (cm^{-1}): 3320, 3145, 1665, 1390, 990, 820.

2-Methoxycinnamamide **(3h):**[23] ^{1}H NMR (300 MHz, DMSO) of (*E*)-isomers: δ 3.85 (s, 3H), 6.61 (d, *J* = 16.0 Hz, 1H), 7.05–7.67 (m, 5H). EI-MS *m/z* (%): 59.15 (2.14), 77.15 (15.81), 89.15 (14.46), 105.20 (13.12), 118.15 (16.58), 177.15 (M^+, 100). IR (cm^{-1}): 3374, 3174, 1658, 1400, 975, 753.

5-Phenylpenta-2,4-dienamide **(3i):**[24] ^{1}H NMR (300 MHz, DMSO) of (*E*)-isomers: δ 6.12 (d, *J* = 16.0 Hz, 1H), 7.03–7.65 (m, 8H). EI-MS *m/z* (%): 51.10 (16.01), 59.65 (1.85), 77.15 (16.04), 96.15 (24.03), 102.15 (12.09), 173.15 (M^+, 22.61). IR (cm^{-1}): 3342, 3145, 1666, 1391, 1001, 752.

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References

1 S. Wang, R. Li, W. Liu, X. Xu and Y. Guan, *Youji Huaxue*, 1988, **8**, 217.
2 K. Takasu, N. Nishida, A. Tomimura and M. Ihara, *J. Org. Chem.*, 2005, **70**, 3957.
3 C. Marrano, P. Macedo and J.W. Keillor, *Bioorg. Med. Chem.*, 2001, **9**, 1923.

4 M.A. Bailen, R. Chinchilla, D.J. Dodsworth and C. Najera, *Tetrahedron Lett.*, 2000, **41**, 9809.
5 K.N. Ali, Z. Abdolkarim, P. Abolfath, R.M.N. Soltan and N.G. Reza, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2007, **182**, 657.
6 L. Cao, J. Ding, M. Gao, Z. Wang, J. Li and A. Wu, *Org. Lett.*, 2009, **11**, 3810.
7 T. Jun and K.D. Moeller, *Org. Lett.*, 2005, **7**, 5381.
8 M. Cai, Q. Xu and J. Jiang, *Journal of Molecular Catalysis A: Chemical*, 2006, **260**, 190.
9 V. Cadierno, J. Francos and G. Jose., *Chem. Eur. J.*, 2008, **14**, 6601.
10 R.B. Sanjay and B.W. Suresh, *Tetrahedron Lett.*, 2008, **49**, 3423.
11 N.A. Owston, A.J. Parker and J.M.J. Williams, *Org. Lett.* 2007, **9**, 3599.
12 M.L. Kantam, K.B.S. Kumar, V. Balasubramanyam, G.T. Venkanna and F. Figueras, *Journal of Molecular Catalysis A: Chemical*, 2010, **321**, 10.
13 A. Ren, X. Yang, J. Hong and X. Yu, *Synlett*, 2008, 2376.
14 S. Jiang, K. Yang and X. Yu, *Syn. Commun.*, 2009, **39**, 1759.
15 Z. Zhang, Y. Xie and X. Yu, *J. Chem. Res.*, 2009, 140.
16 S. Jiang, Y. Xie and Yu, X. *J. Chem. Res.*, 2009, 24.
17 K. Satoshi, K. Kazuhiro, M. Shiro, U. Keiichiro and K. Akiba, *Chem. Lett.*, 2002, **2**, 170.
18 M. Cai, H. Zhao and W. Wu, *Chin. J. Chem.*, 2005, **23**, 443.
19 C.S. Reddy, M. Raghu and A. Nagaraj, *Indian J. Chem., B: Org. Chem. Med. Chem.*, 2008, **47B**, 315.
20 Z. Zhang, Y. Pan, H. Hu, T. Kao, *Syn. Commun.*, 1990, **20**, 3563.
21 F. Rampf and M. Eckert, *PCT Int. Appl.*, 2003, 38.
22 H. Zhao, M. Cai and C. Peng, *J. Chem. Res. (S)*, 2002, 28.
23 F. Hollywood, H. Suschitzky and R. Hull, *Synthesis*, 1982, 662.
24 E.V. Burgaz, M. Yilmaz, A.T. Pekel and A. Oektemer, *Tetrahedron*, 2007, **63**, 7229.