Active-Copper-Promoted Expeditious N-Arylations in Aqueous Media under Microwave Irradiation

Lal Dhar S. Yadav,* Beerendra S. Yadav, Vijai K. Rai

Department of Chemistry, University of Allahabad, Allahabad 211 002, India
Fax +91(532)2545021; E-mail: ldsyadav@hotmail.com

Received 12 December 2005; revised 26 January 2006

Abstract: Active-copper-promoted mild and expeditious N-arylations of amines, amides, imides, and β-lactams with aryl halides under microwave irradiation conditions are reported. These reactions can be performed at 85–90 °C in aqueous media as well as under solvent-free conditions to give good yields. However, under solvent-free conditions, lower yields are obtained.

Key words: aqueous media, active copper, β-lactams, microwave, N-arylation, solvent-free

Aryl–nitrogen bonds are prevalent in many compounds that are of academic, pharmaceutical, and industrial interest. Transition-metal-mediated C–N bond-forming processes are important fundamental transformations and are extensively utilized for N-arylations. The Ullmann condensation has been a powerful method for the coupling of aryl halides with amines.[1–3] Typically, Ullmann coupling protocols necessitate the use of copper metal or copper salts, base, and high reactions temperatures. Recently, the palladium-catalyzed aryl amination has received attention as a synthetically useful method due to the lower temperature required.[4–6]

In the β-lactam field, the Ullmann-type condensation under basic conditions leads to decomposition of the starting material instead of the expected formation of penem and cephem analogues.[7–10] In about 100 years of study of Ullmann-type condensations, there have been only limited examples where no base is used and the copper metal or copper salt catalyst itself acts as the acceptor of halogen.[9–12] However, all of these reactions suffer from one or more disadvantages such as higher reaction temperatures, longer reaction times, and lower yields.

Microwave (MW) irradiation has now gained popularity as a powerful tool for rapid and efficient synthesis of a variety of organic compounds in various solvents as well as solvent-free conditions.[13–16] The application of MW irradiation to provide enhanced reaction rates and improved product yields in chemical synthesis has been extended to modern drug discovery processes,[17,18] and it is proving quite successful in the formation of carbon–heteroatom and carbon–carbon bonds.[19,20] Water is the cheapest, safest, and most non-toxic solvent in the world. It is a good absorber of microwave energy[21,22] and has been successfully employed as solvent for various organic syntheses.[23–27] Utilization of water as an eco-friendly reaction medium in conjunction with MW irradiation is gaining widespread acceptance.[28–32]

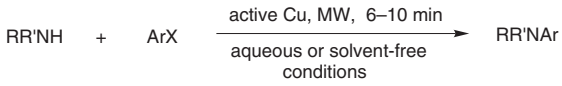
Considering the above valid points and in pursuing our work on the development of green synthetic processes,[33–36] we have devised active-copper-promoted mild and expeditious N-arylations with aryl halides under MW irradiation. These reactions can be preformed at 85–90 °C in aqueous media as well as under solvent-free conditions. However, the yields are lower under solvent-free conditions, especially in the case of β-lactam derivatives (Tables 1 and 2).

The present method in its entirety involves intermittent irradiation of an intimate mixture of an aryl halide, a R_2NH compound (an amine, amide, imide or β-lactam), and active copper[37] in neat conditions or their aqueous suspensions for two minutes in an MW oven at 100 W followed by thorough mixing for two minutes outside the oven. This intermittent irradiation-mixing cycle was repeated for the total irradiation time specified in Tables 1 and 2 to obtain the desired N-arylated products in good yields (Tables 1 and 2). For the comparison purposes the reactions were also carried out using a thermostated oil bath under the same conditions of time (Tables 1 and 2) and temperature (85–90 °C) as for the MW-assisted method. It was found that significantly lower yields (5–43%) were obtained using oil-bath heating rather than the MW-assisted method in both the cases, i.e. in neat conditions as well as in aqueous media. It is noteworthy that the present method is also successfully applicable to intramolecular N-arylation of β-lactam derivatives leading to penem and cephem analogues (Table 2) where most of the methods are unsuccessful and lead to the decomposition of the starting material because of the presence of a base.[7–10]

In summary, we have developed a general method for mild, rapid, and efficient N-arylations of amines, amides, imides and β-lactams with aryl halides. These N-arylations are promoted by active copper and are performed in the absence of a base employing microwave irradiation either under solvent-free conditions or in aqueous media.

SYNTHESIS 2006, No. 11, pp 1868–1872
Advanced online publication: 05.05.2006
DOI: 10.1055/s-2006-942369; Art ID: Z24205SS

Table 1 Active Copper-Promoted Intermolecular N-Arylations with Aryl Halides under MW Irradiation



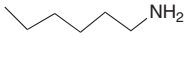
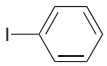
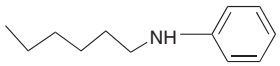
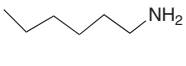
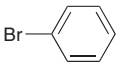
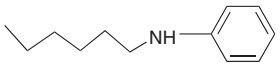
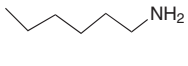
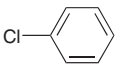
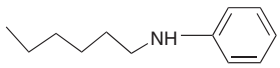
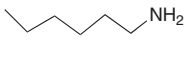
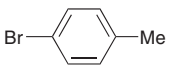
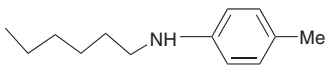
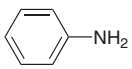
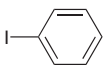
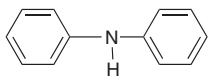
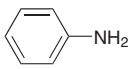
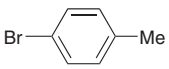
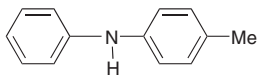
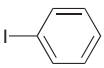
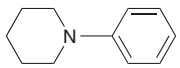
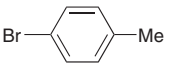
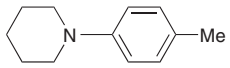
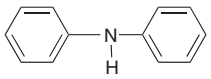
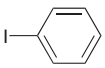
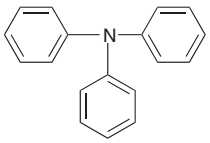
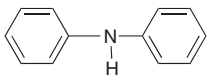
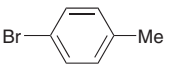
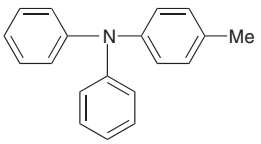
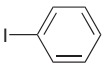
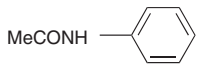
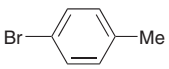
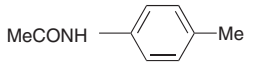
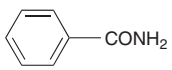
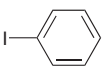
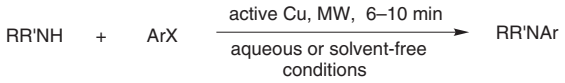
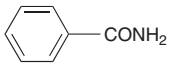
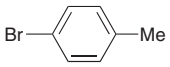
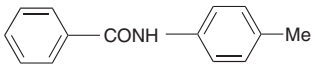
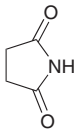
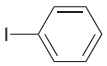
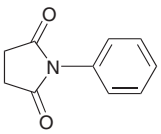
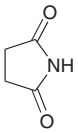
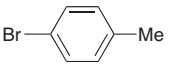
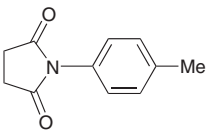
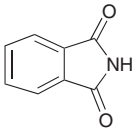
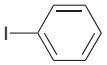
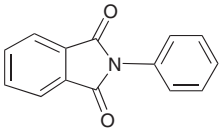
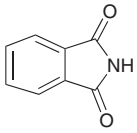
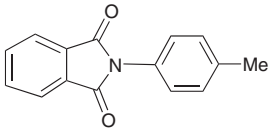
Entry	Substrates RR′NH	ArX	Time (min)[a]	Product RR′NH	Yield (%)[b,c]
1			6	 **1**	87 (84)
2			6	 **1**	84 (82)
3			8	 **1**	80 (77)
4			8	 **2**	78 (76)
5			6	 **3**	74 (71)
6			6	 **4**	71 (68)
7			6	 **5**	91 (87)
8			8	 **6**	87 (84)
9			6	 **7**	85 (83)
10			6	 **8**	81 (79)
11	$MeCONH_2$		8	 **9**	75 (72)
12	$MeCONH_2$		10	 **10**	72 (70)
13			8	 **11**	73 (71)

Table 1 Active Copper-Promoted Intermolecular N-Arylations with Aryl Halides under MW Irradiation (continued)



Entry	Substrates RR′NH	ArX	Time (min)[a]	Product RR′NH	Yield (%)[b,c]
14			10	 **12**	71 (68)
15			6	 **13**	87 (83)
16			6	 **14**	83 (81)
17			8	 **15**	81 (78)
18			10	 **16**	78 (74)

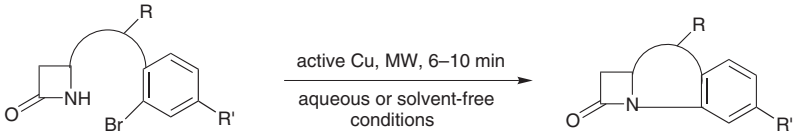
[a] Microwave irradiation time (power = 100 W).
[b] Yield of isolated and purified product in the case of the experiment performed in aqueous medium. Parentheses show the yield obtained in the case of the experiment performed under solvent-free conditions.
[c] Products were identified by their physical and spectral data. Selected ^{1}H and ^{13}C NMR spectral data are given in Table 3.

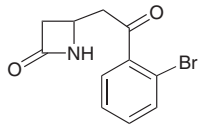
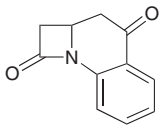
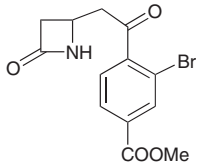
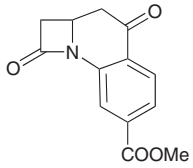
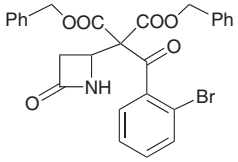
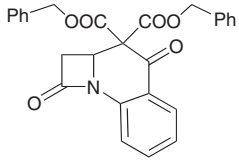
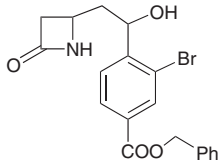
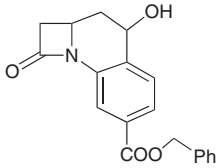
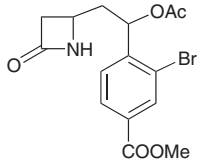
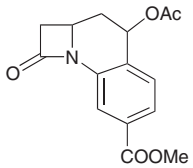
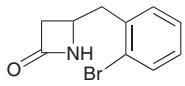
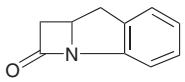
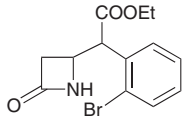
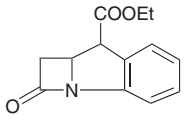
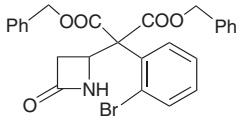
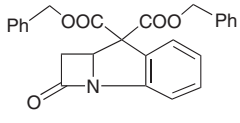
Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6 using TMS as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using the same solvent and internal reference. A CEM Discover Focused Microwave Synthesis System operating at 2450 MHz was used at an output of 100 W for all the experiments. All commercially available chemicals were used without further purification. Silica gel G was used for TLC.

N-Arylation of Amines, Amides, Imides and β-Lactams; General Procedure

Either an intimate mixture of a R_2NH compound (an amine, amide, imide or β-lactam) (1.0 mmol), an aryl halide (1.0 mmol) and active copper (5.0 mol equiv) in neat conditions or their aqueous suspensions in water (5 mL) was taken in a 20 mL vial and subjected to MW irradiation at 100 W for 2 min. The reaction mixture was then thoroughly mixed outside the MW oven for 2 min and again irradiated for another 2 min. This intermittent irradiation-mixing cycle was repeated for the total irradiation time (Tables 1 and 2). After completion of the reaction as indicated by TLC, the product was extracted with EtOAc (3 × 10 mL), the extract was filtered and the filtrate was evaporated under reduced pressure to leave the crude product, which was purified by column chromatography on silica gel (eluent: hexane–EtOAc) to obtain an analytically pure sample.

Table 2 Active Copper-Promoted Intramolecular N-Arylation of β-Lactam Derivatives under MW Irradiation



Entry	Substrate	Time (min)[a]	Product	Yield (%)[b,c]
1		10	 **17**	72 (61)
2		8	 **18**	75 (63)
3		10	 **19**	68 (60)
4		8	 **20**	88 (67)
5		10	 **21**	84 (62)
6		8	 **22**	69 (60)
7		8	 **23**	78 (62)
8		6	 **24**	86 (64)

[a] Microwave irradiation time (power = 100 W).

[b] Yield of isolated and purified product in the case of MW irradiation in aqueous medium. Parentheses show the yield obtained in the case of solvent-free MW irradiation.

[c] Products were identified by comparison of their physical and spectral data with those reported in the literature.[10] Selected ^{1}H and ^{13}C NMR spectral data are given in Table 3.

Table 3 Selected ^{1}H and ^{13}C NMR Spectral Data of Products

Product	^{1}H NMR (DMSO-d_6, TMS), δ	^{13}C NMR (DMSO-d_6, TMS), δ
1	0.92 (t, *J* = 6.6 Hz, 3 H, 6′-H), 1.30–1.46 (m, 6 H, 2′-H, 3′-H, 4′-H), 1.54–1.66 (m, 2 H, 5′-H), 3.08 (t, *J* = 6.9 Hz, 2 H, 1′-H), 3.56 (br s, 1 H, NH exch. D_2O), 7.08–7.59 (m, 5 H_{arom})	14.7, 27.4, 30.2, 32.4, 44.7, 63.8, 120.5, 124.0, 128.6, 140.7
2	0.91 (t, *J* = 6.6 Hz, 3 H, 6′-H), 1.29–1.50 (m, 6 H, 2′-H, 3′-H, 4′-H), 1.56–1.66 (m, 2 H, 5′-H), 2.31 (s, 3 H, Me) 3.10 (t, *J* = 6.9 Hz, 2 H, 1′-H), 3.55 (br s, 1 H, NH exch. D_2O), 7.09–7.60 (m, 4 H_{arom})	14.5, 21.1, 27.2, 29.9, 32.5, 44.6, 63.5, 120.3, 124.3, 133.6, 138.0
10	2.04 (s, 3 H, COMe), 2.32 (s, 3 H, Me), 8.04 (br s, 1 H, NH, exch. D_2O), 7.10–7.58 (m, 4 H_{arom})	17.7, 21.0, 120.2, 129.5, 133.3, 137.7, 168.3
13	2.75 (s, 4 H, CH_2CH_2), 7.04–7.68 (m, 5 H_{arom})	26.2, 120.3, 124.1, 128.6, 140.9, 173.8
16	2.37 (s, 3 H, Me), 7.08–8.10 (m, 8 H_{arom})	20.9, 120.2, 127.5, 129.4, 131.4, 132.5, 133.2, 135.3, 166.5
17	2.71 (dd, *J* = 13.0, 15.5 Hz, 1 H, $COCH_2$), 3.03 (dd, *J* = 2.5, 15.5 Hz, 1 H, $COCH_2$), 3.05 (dd, *J* = 4.5, 15.5 Hz, 1 H, $NCOCH_2$), 3.49 (dd, *J* = 5.0, 15.5 Hz, 1 H, $NCOCH_2$), 4.25 (m, 1 H, NCH), 7.07–7.91 (m, 4 H_{arom})	32.5, 43.2, 47.6, 120.5, 124.0, 128.6, 129.2, 133.2, 141.0, 169.8, 197.7
19	3.38 (dd, *J* = 5.5, 16.0 Hz, 1 H, $NCOCH_2$), 3.97 (dd, *J* = 2.8, 16.0 Hz, 1 H, $NCOCH_2$), 4.75 (dd, *J* = 2.8, 5.5 Hz, 1 H, NCH), 5.12 (s, 4 H, OCH_2), 6.08–7.91 (m, 14 H_{arom})	32.4, 43.8, 72.3, 79.1, 120.4, 124.2, 127.1, 127.7, 128.4, 129.0, 129.6, 133.3, 140.6, 141.2, 169.9, 171.9, 197.8
21	1.80 (ddd, *J* = 2.75, 12.5, 14.0, 1 H, CH_2), 2.1 (s, 3 H, Me), 2.57 (ddd, *J* = 3.0, 3.0, 14.0, 1 H, CH_2), 2.99 (dd, *J* = 2.5, 15.5 Hz, 1 H, $NCOCH_2$), 3.7 (dd, *J* = 5.0, 15.5 Hz, 1 H, $NCOCH_2$), 3.97 (s, 3 H, Me), 4.19 (m, 1 H, NCH), 6.19 (dd, *J* = 2.75, 3.0 Hz, 1 H, OCH) 7.55–8.02 (m, 3 H_{arom})	17.6, 32.3, 40.9, 43.4, 51.0, 72.5, 120.2, 124.0, 128.6, 129.4, 133.8, 141.1, 165.6, 171.3, 172.3
24	2.67 (dd, *J* = 3.5, 17.0 Hz, 1 H, $NCOCH_2$), 3.43 (dd, *J* = 6.0, 17.0 Hz, 1 H, $NCOCH_2$), 4.36 (m, 1 H, NCH), 5.14 (s, 4 H, OCH_2), 7.2.0–7.78 (m, 14 H_{arom})	32.1, 44.2, 67.8, 72.1, 120.5, 121.3, 124.0, 125.5, 126.2, 128.2, 129.0, 130.4, 140.6, 153.2, 169.7, 171.8

Acknowledgment

We sincerely thank SAIF, Punjab University, Chandigarh, for providing microanalyses and spectra.

References

(1) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382.
(2) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
(3) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemairc, M. *Chem. Rev.* **2002**, *102*, 1359.
(4) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.
(5) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
(6) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
(7) Oida, S.; Yashida, A.; Hayashi, T.; Naikayama, E.; Sato, S.; Okhi, E. *Tetrahedron Lett.* **1980**, *21*, 619.
(8) McCombie, S. W.; Ganguly, A. K.; Girijavallabhan, V. M.; Jeffrey, P. D.; Lin, S.; Pinto, P.; McPhail, A. T. *Tetrahedron Lett.* **1981**, *22*, 3489.
(9) Joyeau, R.; Dugenet, Y.; Wakselman, M. *J. Chem. Soc., Chem. Commun.* **1983**, 431.
(10) Joyeau, R.; Yadav, L. D. S.; Wakselman, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1899.
(11) Yamamoto, T.; Kurata, Y. *Chem. Ind. (London)* **1981**, 737.
(12) Yamamoto, T.; Kurata, Y. *Can. J. Chem.* **1983**, *61*, 86.
(13) Varma, R. S. *Green Chem.* **1999**, *1*, 43.
(14) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.
(15) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
(16) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.
(17) Strohmeier, G. A.; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 154.
(18) Alexandre, F. R.; Domon, L.; Frere, S.; Testard, A.; Thiery, V.; Besson, T. *Mol. Diversity* **2003**, *7*, 273.
(19) Varma, R. S. *J. Heterocycl. Chem.* **1999**, *36*, 1565.
(20) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717.
(21) Hayes, B. L. In *Microwave Technology Chemistry at the Speed of Light*; CEM Publishing: Mathews NC, **2002**, 29.
(22) Varma, R. S. In *Microwave Technology Chemical Applications: Kirk–Othmer Encyclopedia of Chemical Technology*, 5th ed.; John Wiley & Sons: New York, **2004**.
(23) Li, J.; Chan, T. H. *Organic Reaction in Aqueous Media*; John Wiley & Sons: New York, **1997**.
(24) Grieco, A. P. *Organic Synthesis in Water*; Blackie Academic and Professional: London, **1998**.
(25) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209.
(26) Wei, W.; Keh, C. C. K.; Li, C. J.; Varma, R. S. *Clean Tech. Environ. Policy* **2005**, *7*, 62.
(27) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751.
(28) An, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505.
(29) Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83.
(30) Ju, Y.; Varma, R. S. *Green Chem.* **2004**, *6*, 219.
(31) Dandia, A.; Arya, K.; Sati, M. *Synth. Commun.* **2004**, *34*, 1141.
(32) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409.
(33) Yadav, L. D. S.; Kapoor, R. *J. Org. Chem.* **2004**, *69*, 8118.
(34) Yadav, L. D. S.; Singh, A. *Tetrahedron Lett.* **2003**, *44*, 5667.
(35) Yadav, L. D. S.; Singh, S. *Synthesis* **2003**, 63.
(36) Yadav, L. D. S.; Yadav, S.; Rai, V. K. *Tetrahedron* **2005**, *61*, 10013.
(37) Gore, P. H.; Hughes, G. K. *J. Chem. Soc.* **1959**, 1615.