

# Microwave-assisted *N*-Arylation of Indoles via $C(sp^2)$ – $N(sp^2)$ Bond Formation by Aromatic Nucleophilic Substitution Reactions

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*Z. Naturforsch.* **2008**, *63b*, 298 – 302; received October 7, 2007

Microwave-assisted nucleophilic aromatic substitution on aryl halides with different indoles is described. Moderate to good yields are obtained in short reaction time (25–40 min) when coupling indoles with fluoro- and chloro-substituted aryl halides under catalyst-free conditions.

**Key words:** *N*-Arylindoles, Aryl Halides, Microwave,  $S_NAr$  Reaction, Cross-coupling

## Introduction

The *N*-arylindole subunit is an important species in many biologically active and pharmaceutically important compounds, which display antiestrogen [1], analgesic [2], antiallergy [3], antimicrobial [4], and neuroleptic activity [5]. Although the traditional copper-catalyzed coupling of an aryl halide with a heteroatom-based nucleophile, the Ullmann-type coupling reaction, has remained a standard method for the construction of *N*-arylindoles, it requires high temperatures, generally 140 °C or more, and often the use of two or more equivalents of the aryl halide to obtain optimal yields. Buchwald reported some improved *N*-arylation of indoles, but still using expensive palladium or copper [6]. Another reaction of the CuOAc catalyzed *N*-arylation of indoles has been reported recently [7]. On the other hand, the nucleophilic aromatic substitution of aryl halides, activated by electron-withdrawing substituents, with indoles represents yet another route to *N*-arylindoles for certain substrate combinations. Smith has described the *N*-arylation of indole by aromatic nucleophilic substitution, however, this  $S_NAr$  reaction was catalyzed by 18-crown-6 at high temperature (120 °C), and no examples of reactions of substituted indoles were reported [8]. Maiorana described *N*-arylation of indoles by aromatic nucleophilic substitution on haloarenes, but using chromium tricarbonyl complexes [9]. Therefore, a simple and general method for  $S_NAr$  reactions, including easy work-up and a wide scope of substrates, for the preparation of *N*-arylindoles is highly desirable.

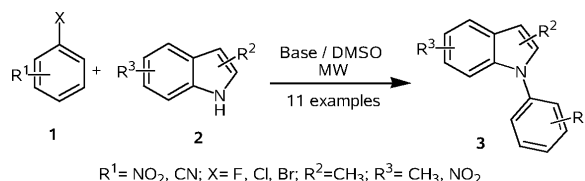


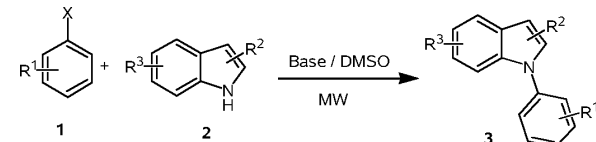
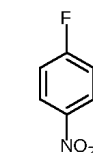
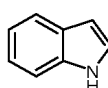
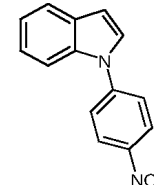
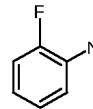
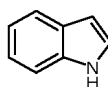
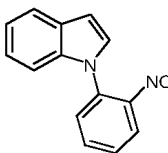
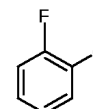
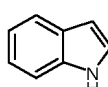
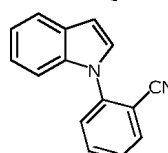
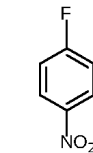
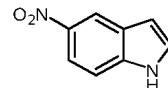
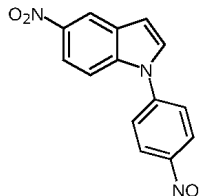
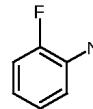
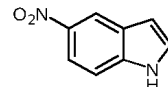
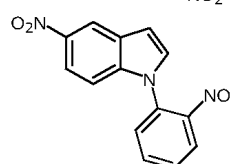
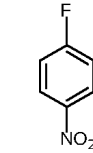
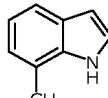
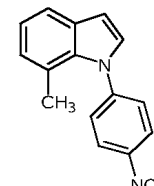
Fig. 1. Microwave-assisted synthesis of *N*-arylindoles via  $C(sp^2)$ – $N(sp^2)$  bond formation.

Compared to traditional processing of organic synthesis, microwave-enhanced chemistry saves significant time, very often improves yields and has attracted considerable attention in the past decade [10, 11]. To the best of our knowledge, however, the catalyst-free *N*-arylation of a variety of 3-, 5- and 7-substituted indoles with aryl halides by  $S_NAr$  reaction using high-speed microwave techniques has not been reported. In continuation of our research interest in the use of microwave irradiation [11], herein, we wish to describe our studies on the microwave-assisted construction of *N*-arylindoles via  $C(sp^2)$ – $N(sp^2)$  bond formation by  $S_NAr$  reaction at an irradiation power of 420 W (Fig. 1).

## Results and Discussion

From the results shown in Table 1 it can be seen that a range of indoles, including those with electron-deficient and electron-rich substituents, can be used in this  $C(sp^2)$ – $N(sp^2)$  cross-coupling  $S_NAr$  reaction with activated aryl halides ( $X = F, Cl, Br$ ) in the presence of  $K_2CO_3$  or  $Cs_2CO_3$  under microwave irradiation. For

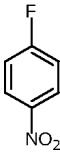
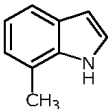
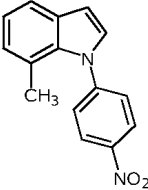
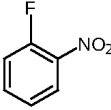
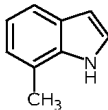
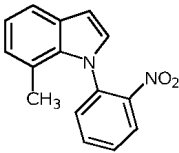
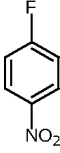
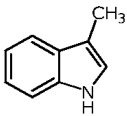
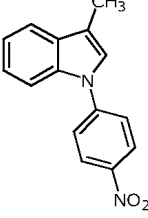
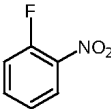
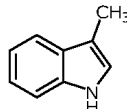
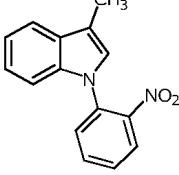
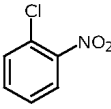
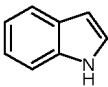
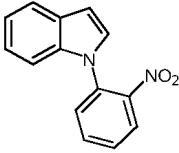
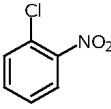
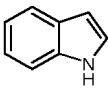
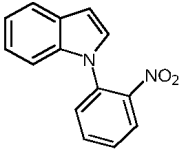
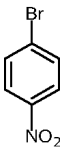
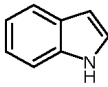
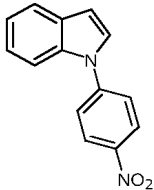
Table 1. Microwave-assisted synthesis of *N*-arylated indoles<sup>a</sup>.

|  |                                                                                     |                                                                                     |                                                                                     |                                |                         |                 |
|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------|-------------------------|-----------------|
| Entry                                                                              | Aryl halides (1)                                                                    | Indoles (2)                                                                         | <i>N</i> -Arylindoles (3)                                                           | Base                           | Time <sup>b</sup> (min) | Yield (%)       |
| a                                                                                  |    |    |    | K <sub>2</sub> CO <sub>3</sub> | 6 × 5                   | 79              |
| b                                                                                  |    |    |    | K <sub>2</sub> CO <sub>3</sub> | 6 × 5                   | 71              |
| c                                                                                  |    |    |    | K <sub>2</sub> CO <sub>3</sub> | 7 × 5                   | 52              |
| d                                                                                  |   |   |   | K <sub>2</sub> CO <sub>3</sub> | 6 × 5                   | 94              |
| e                                                                                  |  |  |  | K <sub>2</sub> CO <sub>3</sub> | 5 × 5                   | 91              |
| f                                                                                  |  |  |  | K <sub>2</sub> CO <sub>3</sub> | 6 × 5                   | NR <sup>c</sup> |

example, 4-fluoronitrobenzene (0.5 mmol) was coupled with indole (0.55 mmol) in DMSO (2 mL) at an irradiation power of 420 W mediated by K<sub>2</sub>CO<sub>3</sub> (1.5 mmol) for 6 × 5 min, *N*-(4-nitrophenyl)indole being obtained in 79 % yield (entry a). It is noteworthy that in our reaction the electron-poor 5-nitroindole could smoothly be coupled with 4-fluoronitrobenzene

and 2-fluoronitrobenzene (entries d and e), the corresponding yields being 94 % and 91 %, respectively. A steric effect was observed for this reaction. Although K<sub>2</sub>CO<sub>3</sub> was a good base for combining the activated fluoroarenes with indole, 5-nitroindole or 3-methylindole (entries a–e, i, j), it was ineffective in the coupling reaction with 7-methylindole. For example, when

Table 1 (continued).

| Entry | Aryl halides (1)                                                                    | Indoles (2)                                                                         | <i>N</i> -Arylindoles (3)                                                           | Base                            | Time <sup>b</sup> (min) | Yield (%) |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------|-------------------------|-----------|
| g     |    |    |    | Cs <sub>2</sub> CO <sub>3</sub> | 8 × 5                   | 62        |
| h     |    |    |    | Cs <sub>2</sub> CO <sub>3</sub> | 8 × 5                   | 46        |
| i     |    |    |    | K <sub>2</sub> CO <sub>3</sub>  | 7 × 5                   | 83        |
| j     |    |    |   | K <sub>2</sub> CO <sub>3</sub>  | 7 × 5                   | 94        |
| k     |  |  |  | K <sub>2</sub> CO <sub>3</sub>  | 8 × 5                   | NR        |
| l     |  |  |  | Cs <sub>2</sub> CO <sub>3</sub> | 5 × 5                   | 47        |
| m     |  |  |  | Cs <sub>2</sub> CO <sub>3</sub> | 5 × 5                   | 18        |

<sup>a</sup> All reactions were carried out with compounds **1** (0.5 mmol), **2** (0.55 mmol), and K<sub>2</sub>CO<sub>3</sub> (1.5 mmol) or Cs<sub>2</sub>CO<sub>3</sub> (1.0 mmol) in DMSO (2 mL) under microwave irradiation; <sup>b</sup> 6 × 5 means 6 times 5 min as reaction time; the progress of the reaction was checked by TLC at the end of each irradiation period; <sup>c</sup> NR = no reaction.

7-methylindole was coupled with 4-fluoronitrobenzene in the presence of K<sub>2</sub>CO<sub>3</sub> for 6 × 5 min, no tar-

get compound was monitored by TLC as the nitrogen atom of 7-methylindole is strongly hindered (entry f).

However, when we chose  $\text{Cs}_2\text{CO}_3$  as the base for the *N*-arylation of 7-methylindole with 4-fluoronitrobenzene and 2-fluoronitrobenzene, the corresponding yields were 62 % and 46 %, respectively (entries g and h).

Finally we investigated the microwave-assisted coupling of 2-chloronitrobenzene or 4-bromonitrobenzene with indole at an irradiation power of 420 W. Unfortunately, conditions employing  $\text{K}_2\text{CO}_3$  as the base were inefficient for the cross-coupling reaction (entry k). However, *N*-(2-nitrophenyl)indole and *N*-(4-nitrophenyl)indole were obtained in 47 and 18 % yields, respectively, in the presence of  $\text{Cs}_2\text{CO}_3$  (entries l and m).

## Conclusion

In summary, we have described an efficient  $\text{S}_{\text{N}}\text{Ar}$  reaction to synthesize *N*-arylindoles via  $\text{C}(\text{sp}^2)\text{--N}(\text{sp}^2)$  bond formation in the presence of  $\text{K}_2\text{CO}_3$  or  $\text{Cs}_2\text{CO}_3$  under a microwave irradiation power of 420 W. The reaction time was very short (25–40 min), and moderate to good yields (46–94 %) were achieved without any catalyst, when a wide substrate range of indoles were reacted with fluoro- and chloro-substituted aryl halides.

## Experimental Section

The materials were used as purchased. Melting points were determined on a digital melting-point apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance DMX instrument ( $^1\text{H}$ : 400 MHz;  $^{13}\text{C}$ : 100 MHz) using TMS as internal standard and  $\text{CDCl}_3$  as solvent. HRMS and EIMS measurements were carried out with APEX II Bruker 4.7T AS and Thermo DSQ GC/MS instruments, respectively. Elemental analyses were determined with a Carlo-Erba 1106 CHN microanalyzer. Microwave irradiation was performed in a Galanz microwave oven, WG700CTL.

### General procedure

To a mixture of activated aryl halide ( $X = \text{F}, \text{Cl}, \text{Br}$ , 0.5 mmol), indole (0.55 mmol) and  $\text{K}_2\text{CO}_3$  (1.5 mmol) or  $\text{Cs}_2\text{CO}_3$  (1.0 mmol) was added DMSO (2 mL). The reaction was found not to be sensitive to air and moisture, hence DMSO was used directly without any additional purification, and there was no need for inert atmosphere. The mixture was placed in a microwave oven and irradiated at a power of 420 W for the appropriate time as shown in Table 1. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to r. t. and poured into ice water (20 mL). Then 40 mL of EtOAc was added to the mixture,

the organic layer was separated, and the aqueous layer was extracted with EtOAc ( $2 \times 40$  mL). The combined organic extracts were washed with 4 mol/L HCl ( $3 \times 20$  mL), brine ( $1 \times 40$  mL) and dried over anhydrous  $\text{MgSO}_4$ . After removal of the solvent under reduced pressure, the residue was purified by preparative thin-layer chromatography (PTLC) or silica gel column chromatography to give the pure *N*-arylindoles. All compounds were characterized by  $^1\text{H}$  NMR (400 MHz),  $^{13}\text{C}$  NMR (100 MHz), HRMS or elemental analysis, EIMS, and melting points.

**Compounds 3a and 3m:** Yellow solid, m.p. 109–109.5 °C. –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.77$  (1H, d,  $J = 3.2$  Hz), 7.21 (2H, m), 7.37 (1H, d,  $J = 3.6$  Hz), 7.64 (4H, m), 8.39 (2H, d,  $J = 8.8$  Hz). –  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 130.4, 127.0, 125.4, 123.3, 121.6, 121.5, 110.4, 110.1, 106.1$ . – GC/MS (EI, 70 eV):  $m/z$  (%) = 238 (100)  $[\text{M}]^+$ . – HRMS-ESI:  $m/z = 239.0818$  (calcd. 239.0815 for  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$ ,  $[\text{M}+\text{H}]^+$ ).

**Compounds 3b and 3l:** Orange solid, m.p. 69–70 °C. –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.72$  (1H, d,  $J = 3.2$  Hz), 7.11 (4H, m), 7.53 (2H, m), 7.68 (2H, m), 8.01 (1H, d,  $J = 8.4$  Hz). –  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 136.6, 133.6, 132.8, 129.7, 128.9, 128.3, 127.9, 125.4, 122.9, 121.3, 120.9, 109.4, 105.0$ . – GC/MS (EI, 70 eV):  $m/z$  (%) = 238 (100)  $[\text{M}]^+$ . – HRMS-ESI:  $m/z = 239.0818$  (calcd. 239.0815 for  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$ ,  $[\text{M}+\text{H}]^+$ ).

**Compound 3c:** White solid, m.p. 96–96.5 °C. –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.76$  (1H, d,  $J = 3.6$  Hz), 7.18 (2H, m), 7.33 (1H, d,  $J = 8.4$  Hz), 7.40 (1H, d,  $J = 3.2$  Hz), 7.46 (1H, m), 7.60 (1H, d,  $J = 8.4$  Hz), 7.69 (2H, m), 7.83 (1H, d,  $J = 7.6$  Hz). –  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 142.0, 134.5, 133.8, 129.3, 128.1, 127.4, 127.3, 122.8, 121.3, 121.1, 116.4, 110.2, 109.7, 105.0$ . – GC/MS (EI, 70 eV):  $m/z$  (%) = 218 (100)  $[\text{M}]^+$ . – HRMS-ESI:  $m/z = 219.0919$  (calcd. 219.0917 for  $\text{C}_{15}\text{H}_{10}\text{N}_2$ ,  $[\text{M}+\text{H}]^+$ ).

**Compound 3d:** Yellow solid, m.p. 220–221 °C. –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.95$  (1H, d,  $J = 3.6$  Hz), 7.53 (1H, d,  $J = 3.2$  Hz), 7.61 (1H, d,  $J = 8.8$  Hz), 7.70 (2H, d,  $J = 8.4$  Hz), 8.18 (1H, dd,  $J = 8.8$  Hz,  $J = 2.0$  Hz), 8.46 (2H, d,  $J = 8.8$  Hz), 8.66 (1H, d,  $J = 2.0$  Hz). –  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 144.0, 130.4, 129.4, 125.7, 124.4, 118.8, 118.5, 110.4, 107.5$ . – GC/MS (EI, 70 eV):  $m/z$  (%) = 283 (28)  $[\text{M}]^+$ . –  $\text{C}_{14}\text{H}_9\text{N}_3\text{O}_4$  (283): calcd. C 59.36, H 3.18, N 14.84; found C 59.71, H 3.42, N 14.48.

**Compound 3e:** Orange solid, m.p. 104.5–106 °C. –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.90$  (1H, d,  $J = 3.2$  Hz), 7.10 (1H, d,  $J = 9.2$  Hz), 7.32 (1H, d,  $J = 3.2$  Hz), 7.59 (1H, dd,  $J = 8.0$  Hz,  $J = 0.8$  Hz), 7.68 (1H, m), 7.81 (1H, m), 8.08 (2H, m), 8.63 (1H, d,  $J = 1.6$  Hz). –  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 142.7, 139.6, 134.1, 131.3, 130.0, 129.8, 128.2, 125.8, 118.5, 118.3, 109.6, 106.6$ . – GC/MS (EI, 70 eV):  $m/z$  (%) = 283 (100)  $[\text{M}]^+$ . – HRMS-ESI:  $m/z = 284.0592$  (calcd. 284.0588 for  $\text{C}_{14}\text{H}_9\text{N}_3\text{O}_4$ ,  $[\text{M}+\text{H}]^+$ ).

**Compound 3g:** Yellow solid, m.p. 121–122 °C. –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.09 (3H, s), 6.71 (1 H, d,  $J$  = 3.2 Hz), 7.01 (1 H, d,  $J$  = 7.2 Hz), 7.11 (2H, m), 7.49 (2H, dd,  $J$  = 6.8 Hz,  $J$  = 1.6 Hz), 7.54 (1 H, d,  $J$  = 8.0 Hz), 8.33 (2H, dd,  $J$  = 6.4 Hz,  $J$  = 1.6 Hz). –  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 146.8, 130.3, 130.1, 127.3, 125.8, 124.2, 121.4, 119.3, 105.2, 20.4. – GC/MS (EI, 70 eV):  $m/z$  (%) = 252 (100)  $[\text{M}]^+$ . –  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2 \cdot 0.5\text{H}_2\text{O}$  (261): calcd. C 68.96, H 4.98, N 10.73; found C 69.28, H 4.57, N 11.20.

**Compound 3h:** Orange solid, m.p. 96.5–97 °C. –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.94 (3H, s), 6.67 (1 H, d,  $J$  = 3.2 Hz), 6.92 (1 H, d,  $J$  = 6.8 Hz), 7.05 (2H, m), 7.49 (2H, m), 7.66 (2H, m), 7.97 (1H, dd,  $J$  = 8.0 Hz,  $J$  = 1.2 Hz). –  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 134.8, 132.6, 131.7, 130.0, 129.2, 125.2, 124.4, 120.8, 119.3, 104.4, 18.5. – GC/MS (EI, 70 eV):  $m/z$  (%) = 252 (95)  $[\text{M}]^+$ . – HRMS-ESI:  $m/z$  = 253.0973 (calcd. 253.0972 for  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$ ,  $[\text{M}+\text{H}]^+$ ).

**Compound 3i:** Yellow solid, m.p. 137–139 °C. –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.39 (3H, s), 7.18 (1H, s), 7.24 (2H, m), 7.63 (2 H, d,  $J$  = 8.4 Hz), 7.64 (2H, d,  $J$  = 8.8 Hz), 8.36 (2H, d,  $J$  = 8.8 Hz). –  $^{13}\text{C}$  NMR (100 MHz,

$\text{CDCl}_3$ ):  $\delta$  = 145.0, 125.4, 124.4, 123.4, 122.6, 121.1, 119.7, 116.0, 110.4, 9.5. – GC/MS (EI, 70 eV):  $m/z$  (%) = 252 (100)  $[\text{M}]^+$ . –  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$  (252): calcd. C 71.42, H 4.76, N 11.11; found C 71.54, H 4.52, N 10.98.

**Compound 3j:** Red liquid. –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.35 (3H, s), 6.90 (1H, s), 7.11 (3H, m), 7.43 (2H, m), 7.61 (2H, m), 7.94 (1H, dd,  $J$  = 8.0 Hz,  $J$  = 1.2 Hz). –  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 145.9, 136.6, 133.5, 132.9, 129.6, 129.3, 127.6, 125.4, 125.1, 122.8, 120.3, 119.3, 114.3, 109.3, 9.5. – GC/MS (EI, 70 eV):  $m/z$  (%) = 252 (80)  $[\text{M}]^+$ . – HRMS-ESI:  $m/z$  = 253.0971 (calcd. 253.0972 for  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$ ,  $[\text{M}+\text{H}]^+$ ).

#### Acknowledgements

This work was supported by the Program for New Century Excellent Talents in University (NCET-06-0868), State Education Ministry, China, and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (No.14110101). We also acknowledge Northwest A&F University for the financial assistance within the program for excellent young talents.

- [1] E. von Angerer, J. Strohmeier, *J. Med. Chem.* **1987**, *30*, 131–136.
- [2] E. J. Glamkowski, J. M. Fortunato, T. C. Spaulding, J. C. Wilker, D. B. Ellis, *J. Med. Chem.* **1985**, *28*, 66–73.
- [3] P. C. Unangst, M. E. Carethers, K. Webster, G. M. Janik, L. J. Robichaud, *J. Med. Chem.* **1984**, *27*, 1629–1633.
- [4] A. G. Kamat, G. S. Gadaginamath, *Indian J. Chem.* **1994**, *33B*, 255–259.
- [5] J. Perregaard, J. Arnt, K. P. Boegesoe, J. Hyttel, C. Sanchez, *J. Med. Chem.* **1992**, *35*, 1092–1101.
- [6] a) D. W. Old, M. C. Harris, S. L. Buchwald, *Org. Lett.* **2000**, *2*, 1403–1406; b) J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688.
- [7] F. Bellina, C. Calandri, S. Cauteruccio, R. Rossi, *Eur. J. Org. Chem.* **2007**, 2147–2151.
- [8] W. J. Smith III, J. S. Sawyer, *Tetrahedron Lett.* **1996**, *37*, 299–302.
- [9] S. Maiorana, C. Baldoli, P. Del Buttero, M. Di Ciolo, A. Papagni, *Synthesis* **1998**, *5*, 735–738.
- [10] a) D. S. Li, S. Komarneni, *Z. Naturforsch.* **2006**, *61b*, 1566–1572; b) E. K. Ahmed, M. A. Ameen, F. F. Abdel-Latif, *Z. Naturforsch.* **2005**, *60b*, 221–226; c) D. Bogdal, M. Lukasiewicz, J. Pielichowski, S. Bednarz, *Synth. Commun.* **2005**, *23*, 2973–2983.
- [11] H. Xu, H. F. Li, *Z. Naturforsch.* **2007**, *62b*, 1183–1186.