Microwave-Assisted One-Pot Synthesis of Functionalized Pyrimidines Using Ionic Liquid

Dushyant Singh Raghuvanshi and Krishna Nand Singh*

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221005, India
*E-mail: knsinghbhu@yahoo.co.in

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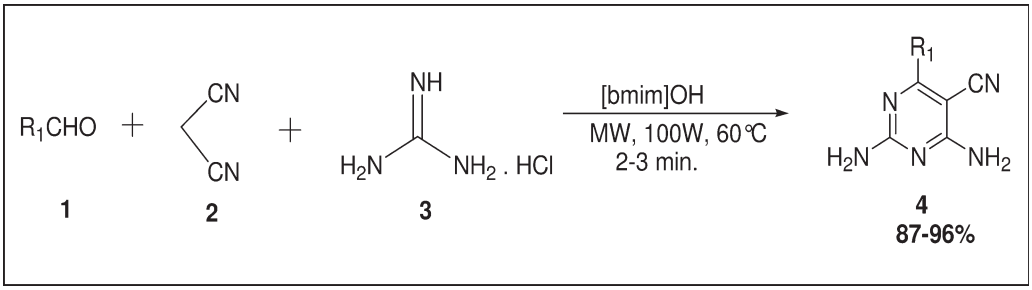

An efficient one-pot multicomponent synthesis of 2,4-diamino-5-pyrimidinecarbonitrile derivatives has been achieved in excellent yields by the condensation of aromatic aldehydes, malononitrile, and guanidine using ionic liquid under controlled microwave irradiation (100 W) at 60°C. This green approach offers a number of advantages in terms of methodology, high-product yield, short reaction time, mild reaction conditions, and easy workup.

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INTRODUCTION

Ionic liquids (ILs) have recently attracted a great deal of attention as a new class of more sustainable solvent system in organic synthesis [1]. Being composed entirely of ions, they possess unique advantages of negligible vapor pressure, a broad range of room temperature ionic compositions, excellent thermal and chemical stabilities, interesting physicochemical characteristics, and selective dissolvability to many organic and inorganic materials. A wide range of reactions have been reported using ILs as the reaction media for clean transformations and product selectivity [2,3].

In recent years, the combination of ''microwaves'' (MWs) and ''IL'' is becoming very popular due to the fact that a great variety of synthetic organic transformations can be carried out very efficiently and rapidly under these environmentally benign and green conditions. Consequently, it is highly desirable to develop environmentally benign MW-assisted processes that can be conducted in ILs.

Pyrimidine cores belong to one of the most important heterocycles and as such make attractive scaffolds in medicinal chemistry. Pyrimidine derivatives have diverse biological activities [4–11] and are found in many medicines as well as genetic materials including nucleosides and nucleotides. Pyrimidines are also reported to occur in some pesticides, herbicides, and plant growth regulators [12,13]. Consequently, synthetic methodologies for the synthesis of pyrimidines or pyrimidine-fused compounds are of paramount importance, particularly in the medicinal and agrochemical areas [14,15]. Although some pyrimidine synthetic routes have been known for a long time, the development of alternative and more efficient strategies is of considerable relevance [16–19].

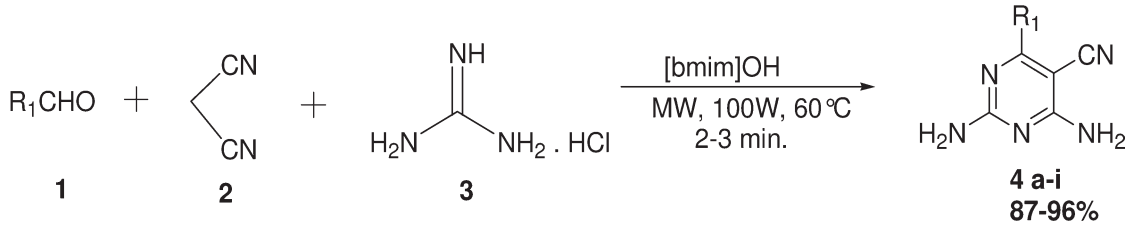
Multicomponent reactions (MCRs) have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [20–24]. There is great current interest in microwave-assisted organic synthesis [25–28], because such environmentally benign chemical methodologies are strongly required in light of the paradigm shift to ''*Green Chemistry*.'' According to the current synthetic requirements, environmentally benign multicomponent procedures using MW methodology are particularly welcome due to their intrinsic advantages [29–31].

In view of the above, an efficient and convenient synthesis of 2,4-diamino-5-pyrimidinecarbonitriles has been accomplished by the MCR of aromatic aldehydes, malononitrile, and guanidine using controlled MW irradiation in the presence of [bmim]OH at an ambient temperature of 60°C (Scheme 1).

RESULTS AND DISCUSSION

Although a few synthetic strategies have been adopted for the synthesis of pyrimidines using different bases [16–19]; however, these methods suffer from one or

Scheme 1



1 **2** **3** **4 a-i** **87-96%**

R_1= C_6H_5, 4-FC_6H_4, 4-BrC_6H_4, 2-furyl, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$N(CH_3)_2C_6H_4$, 4-MeC_6H_4, 3,4,5-$MeOC_6H_2$

another drawback such as low-product yield, cumbersome isolation, and long-reaction time. To develop a green and efficient approach and to avoid the use of alkaline catalysts, it was thought worthwhile to exploit the synthetic potential of [bmim]OH in the synthesis of of 2,4-diamino-5-pyrimidinecarbonitriles via three component reaction of aldehydes, malononitrile, and guanidine under controlled MW.

To optimize the reaction conditions, the catalytic activity of a number of catalysts viz., K_2CO_3, $NaHCO_3$, KF/alumina, NaOH, DBU and [bmim]OH in ethanol were observed in a typical MCR of benzaldehyde **1a**, malononitrile, and guanidine under conventional as well as MW irradiation conditions. The outcome is given in Table 1. The use of NaOH, DBU, KF/alumina, and [bmim]OH (Table 1, entries 7–10 and 14–17) in ethanol also promoted the reaction to a reasonable extent, but the other catalysts such as, K_2CO_3, $NaHCO_3$ in same solvent ethanol did not work well (Table 1, entries 3–6). As is evident from the table, the use of [bmim]OH as solvent without any catalyst stands best under the investigated set of reaction conditions affording **4a** in 72% yield under conventional conditions (Table 1, entry 12). Application of monomode MW irradiation at the same temperature, moreover, brought about a tremendous increase in the yield (94%) and a dramatic reduction in the reaction time. A further increase in the MW power and temperature starts diminishing the product yield (Table 1, entries 13).

Under the optimized set of controlled MW reaction conditions (100 W and 60°C), a number of aromatic aldehydes **1a–i** were allowed to undergo MCR with malononitrile and guanidine in a molar ratio of 1:1:1 in IL [bmim]OH (1 mL)affording 2,4-diamino-5-pyrimidinecarbonitriles **4a–i** in excellent yields in 2–3 min (Table 2). The physical and spectral data of all the products are in full agreement with the assigned structures. It is worthwhile to mention that the IL [bmim]OH was

Table 1

Optimization of reaction conditions for the multicomponent synthesis of **4a**.

			Microwave				Conventional		
S.NO.	Catalyst	Solvent	MW (W)	Temperature (°C)	Time (min)	Yield (%)[a]	Temperature (°C)	Time (min)	Yield (%)[a]
1	–	EtOH	80	60	20	–	60	120	–
2	–	EtOH	100	60	10	Trace	Reflux	120	–
3	K_2CO_3	EtOH	80	60	15	37	60	120	28
4	K_2CO_3	EtOH	100	80	10	55	Reflux	120	45
5	$NaHCO_3$	EtOH	80	60	10	25	60	120	20
6	$NaHCO_3$	EtOH	100	80	15	45	Reflux	90	35
7	NaOH	EtOH	80	60	15	50	60	120	40
8	NaOH	EtOH	100	80	10	69	Reflux	120	58
9	bmim[OH]	EtOH	80	60	10	52	60	60	45
10	bmim[OH]	EtOH	100	80	10	70	Reflux	60	65
11	–	bmim[OH]	80	60	05	85	RT	60	20
12	–	**bmim[OH]**	**100**	**60**	**02**	**94**	**60**	**90**	**72**
13	–	bmim[OH]	110	70	05	93	80	90	71
14	DBU	EtOH	80	60	10	42	60	60	30
15	DBU	EtOH	100	80	15	58	Reflux	120	54
16	KF/Al_2O_3	EtOH	80	60	10	43	60	120	35
17	KF/Al_2O_3	EtOH	100	80	15	62	Reflux	120	56

[a] Isolated yield based on aldehyde.

Table 2

[bmim]OH-mediated synthesis of 2,4-diamino-5-pyrimidinecarbonitriles (**4a–i**).

Entry	Product	R_1	Microwave (100 W, 80°C) Time (min)	Yield (%)[a]	M.p. (°C)
1	**4a**	C_6H_5	2	94	235–237
2	**4b**	4-FC_6H_4	2	96	243–245
3	**4c**	4-BrC_6H_4	3	93	263–265
4	**4d**	2-Furyl	2	92[b]	265–267
5	**4e**	4-$MeOC_6H_4$	3	90	238–240
6	**4f**	4-ClC_6H_4	3	87	233–235
7	**4g**	4-$N(CH_3)_2C_6H_4$	2	90	263–265
8	**4h**	4-MeC_6H_4	3	91	228–230
9	**4i**	3,4,5-$(OMe)_3C_6H_2$	2	96	190–192

[a] Isolated yield based on aldehyde.
[b] Average yield of five recycles.

recycled up to five times with no loss and diminution in its amount and efficacy (cf. Table 2, entry 4). After each and every recycle, the purity of the IL was affirmed by spectroscopic data.

In conclusion, this report demonstrates an efficient use of [bmim]OH and MW combination for a convenient multicomponent synthesis of 2,4-diamino-5-pyrimidinecarbonitriles by the condensation of aromatic aldehydes, malononitrile, and guanidine. The advantages include excellent yields, easier work-up, lesser reaction time, and application of green methodology.

EXPERIMENTAL

IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer, whereas NMR was run on a JEOL AL300 FTNMR spectrometer. The chemical shifts are given in δ ppm with respect to TMS as internal standard. Elemental analysis (C, H, and N) of final compounds were performed on a Model CE-440 CHN Analyzer. The TLC spots were detected using iodine chamber. MW irradiation was made using a CEM Discover single mode MW reactor (Benchmate Model, USA) with infrared temperature probe and adjustable 0–300 W output power. All the chemicals used were purchased from Aldrich and E. Merck. The IL [bmim]OH was prepared adopting a literature report [3], and its purity was checked by IR and ^{1}H-NMR.

General microwave procedure for 2,4-diamino-5-pyrimidinecarbonitriles (4a–h). Aromatic aldehyde (1 mmol), malononitrile (1 mmol), guanidine (1 mmol), and [bmim]OH (1 mL) were put in a pressure regulation 10-mL pressurized vial ''snap-on'' cap, and the reaction mixture was subjected to irradiation in a single-mode MW synthesis system at 100 W power and 60°C for 2–3 min. After completion of the reaction as indicated by TLC, 10 mL of water was added and the product was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and were evaporated under reduced pressure to afford the crude product, which was recrystallized from ethanol to afford pure 2,4-diamino-5-pyrimidinecarbonitriles **4**. After isolation of the product, the remaining aqueous layer containing the IL was washed with ether (10 mL) to remove any organic impurity, dried under vacuum at 90°C to afford [bmim]OH, which was used in subsequent runs without further purification.

Physical and spectral data of the products. ***2,4-Diamino-6-phenyl-5-pyrimidinecarbonitrile (4a).*** Yellow crystals; M.p.: 235–237°C; IR (KBr): 3426, 3377, 2203, 1691, 1617, 1548 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.12 (4H, broad, 2NH_2), 7.53–7.76 (5H, m, Ar) ppm; ^{13}C-NMR (DMSO-d_6): δ = 79.21, 116.25, 128.03, 128.56, 130.72, 136.18, 162.87, 164.92, 169.05 ppm; Anal. Calcd. for $C_{11}H_9N_5$: C, 62.55; H, 4.29; N, 33.16. Found: C, 62.43; H, 4.32; N, 33.02.

2,4-Diamino-6-(4-fluorophenyl)-5-pyrimidinecarbonitrile (4b). Yellow shining crystals; M.p.: 243–245°C; IR (KBr): 3413, 3383, 3145, 2202, 1678, 1615, 1550 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.05–7.85 (m, Ar and NH_2) ppm; ^{13}C-NMR (DMSO-d_6): δ = 75.84, 115.07, 115.36, 117.92, 130.57, 133.61, 162.96, 165.02, 168.31 ppm; Anal. Calcd. for $C_{11}H_8FN_5$: C, 57.64; H, 3.52; N, 30.55. Found: C, 57.49; H, 3.43; N, 30.48.

2,4-Diamino-6-(4-bromophenyl)-5-pyrimidinecarbonitrile (4c). Yellow crystals; M.p.: 263–265°C; IR (KBr): 3425, 3375, 3152, 2203, 1680, 1614, 1548 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.16–7.71 (m, Ar and NH_2) ppm; ^{13}C-NMR (DMSO-d_6): δ = 76.05, 118.12, 128.45, 130.47, 134.79, 136.32, 163.23, 165.50, 168.56 ppm; Anal. Calcd. for $C_{11}H_8BrN_5$: C, 45.54; H, 2.78; N, 24.14. Found: C, 45.38; H, 2.69; N, 23.97.

2,4-Diamino-6-(2-furyl)-5-pyrimidinecarbonitrile (4d). Brown crystals; M.p.: 265–267°C IR (KBr): 3419, 3369, 3154, 2204, 1678, 1628, 1542 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.71–7.93 (m, Ar and NH_2) ppm; ^{13}C-NMR (DMSO-d_6): δ = 72.51, 112.28, 114.16, 117.43, 145.57, 150.15, 157.22, 162.96, 165.02 ppm; Anal. Calcd. for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81. Found: C, 53.56; H, 3.46; N, 34.69.

2,4-Diamino-6-(4-methoxyphenyl)-5-pyrimidinecarbonitrile (4e). Yellow crystals; M.p.: 238–240°C; IR (KBr): 3422, 3379, 3160, 2201, 1670, 1610, 1550 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.94–7.78 (m, Ar and NH_2) ppm; ^{13}C-NMR (DMSO-d_6): δ = 55.31, 75.21, 113.51, 118.32, 129.33, 129.85, 160.94, 162.94, 165.21, 168.56; Anal. Calcd. for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.63; H, 4.48; N, 28.94.

2,4-Diamino-6-(4-chlorophenyl)-5-pyrimidinecarbonitrile (4f). White crystals; M.p.: 233–235°C; IR (KBr): 3482, 3370, 3182, 2210, 1675, 1612, 1553 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.15–7.76 (m, Ar and NH_2) ppm; ^{13}C-NMR (DMSO-d_6): δ = 76.15, 117.23, 128.52, 131.04, 135.51, 136.72, 163.30, 165.28, 168.65 ppm; Anal. Calcd. for $C_{11}H_8ClN_5$: C, 53.78; H, 3.28; N, 28.51. Found: C, 53.61; H, 3.19; N, 28.38.

2,4-Diamino-6-[4-(dimethylamino)phenyl]-5-pyrimidinecarbonitrile (4g). Yellow crystals; M.p.: 263–265°C; IR (KBr): 3410, 3300, 2924, 2197, 1688, 1622, 1545 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.05 (s, 6H, N—$(CH_3)_2$), 6.74–7.78 (m, Ar and NH_2) ppm; ^{13}C-NMR (DMSO-d_6): δ = 40.50, 75.8, 110.87, 120.20, 123.75, 129.42, 151.70, 162.86, 165.44, 169.50 ppm; Anal. Calcd. for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.51; H, 5.43; N, 32.92.

2,4-Diamino-6-(4-methylphenyl)-5-pyrimidinecarbonitrile (4h). Yellow crystals; M.p.: 228–230°C; IR (KBr): 3426, 3377, 3156, 2203, 1681, 1547 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.41 (3H, s, CH_3), 7.09–7.85 (m, Ar and NH_2) ppm; ^{13}C-NMR (DMSO-d_6): δ = 21.93, 80.73, 118.57, 128.59, 130.62, 134.80, 140.53, 163.45, 165.56, 169.67 ppm; Anal. Calcd. for $C_{12}H_{11}N_5$: C, 63.99; H, 4.92; N, 31.09. Found: C, 63.80; H, 4.83; N, 30.95.

2,4-Diamino-6-(3,4,5-trimethoxyphenyl)-5-pyrimidinecarbonitrile (4i). Yellow crystals; M.p.: 194–196°C; IR (KBr): 3428, 3375, 3162, 2205, 1671, 1615, 1552 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.70 (3H, s, OCH_3), 3.79 (6H, s, OCH_3), 6.70–7.25 (m, Ar and NH_2) ppm; ^{13}C-NMR (DMSO-d_6): δ = 52.35, 55.97, 80.10, 106.32, 116.24, 118.97, 131.04, 138.89, 152.52, 157.91, 165.11, 167.39 ppm; Anal. Calcd. for $C_{14}H_{15}N_5O_3$: C, 55.81; H, 5.02; N, 23.24. Found: C, 55.60; H, 4.93; N, 23.12.

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REFERENCES AND NOTES

[1] (a) Welton, T. Chem Rev 1999, 99, 2071; (b) Wasserscheid, P.; Keim, W. Angew Chem Int Ed Engl 2000, 39, 3772; (c) Sheldon, R. Chem Commun 2001, 2399; (d) Wilkes, J. S. Green Chem 2002, 4, 73; (e) Yao, Q. Org Lett 2002, 4, 2197; (f) Zerth, H. M.; Leonard, N. M.; Mohan, R. S. Org Lett 2003, 5, 55; (g) Kumar, A.; Pawar, S. S. J Org Chem 2004, 69, 1419.

[2] (a) Boon, J. A.; Levinsky, J. A.; Pflug, J. I.; Wilkes, J. S. J Org Chem 1986, 51, 480; (b) Harjani, J. R.; Nara, S. J.; Salunkhe, M. M. Tetrahedron Lett 2002, 43, 1127; (c) Namboodiri, V. V.; Varma, R. S. Chem Commun 2002, 342; (d) Sun, W.; Xia, C.-G.; Wang, H.-W. Tetrahedron Lett 2003, 44, 2409.

[3] (a) Ranu, B. C.; Dey, S. S. Tetrahedron 2004, 60, 4183; (b) Ranu, B. C.; Banerjee, S. J Org Chem 2005, 70, 4517; (c) Ranu, B. C.; Banerjee, S. Org Lett 2005, 7, 3049.

[4] Slee, D. H.; Zhang, X.; Moorjani, M.; Lin, E.; Lanier, M. C.; Chen, Y.; Rueter, J. K.; Lechner, S. M.; Markison, S.; Malany, S.; Joswig, T.; Santos, M.; Gross, R.; Williams, J. P.; Castro-Palomino, J. C.; Crespo, M. I.; Prat, M.; Gual, S.; Diaz, J. L.; Wen, J.; O'Brien, Z.; Saunders, J. J Med Chem 2008, 51, 400.

[5] Vidal, B.; Nueda, A.; Esteve, C.; Domenech, T.; Benito, S.; Reinoso, R. F.; Pont, M.; Calbet, M.; Lopez, R.; Cadavid, M. I.; Loza, M. I.; Cardenas, A.; Godessart, N.; Beleta, J.; Warrellow, G.; Ryder, H. J Med Chem 2007, 50, 2732.

[6] Atwal, K. S.; O'Neil, S. V.; Ahmad, S.; Doweyko, L.; Kirby, M.; Dorso, C. R.; Chandrasena, G.; Chen, B.; Zhao, R.; Zahler, R. Bioorg Med Chem Lett 2006, 16, 4796.

[7] Giblin, G. M. P.; O'shaughnessy, C. T.; Nayor, A.; Mitchell, W. L.; Eatherton, A. J.; Slingsby, B. P.; Rawlings, A.; Goldsmith, P.; Brown, A. J.; Haslam, C. P.; Clayton, N. M.; Wilson, A. W.; Chessell, I. P.; Wittington, A. R.; Green, R. J Med Chem 2007, 50, 2597.

[8] Epple, R.; Azimioara, M.; Russo, R.; Bursulaya, B.; Tian, S. S.; Gerken, A.; Iskandar, M. Bioorg Med Chem Lett 2006, 16, 2969.

[9] Russowsky, D.; Canto, R. F. S.; Sanches, S. A. A.; D'Oca, M. G. M.; de Fátima, F.; Pilli, R. A.; Kohn, L. K.; Antônio, M. A.; de Carvalho, J. E. Bioorg Chem 2006, 34, 173.

[10] Cannito, A.; Pemmsin, M.; Lnu-Due, C.; Hoguet, F.; Gaultier, C.; Narcisse, J. Eur J Med Chem 1990, 25, 635.

[11] Smith, P. A. S.; Kan, R. O. J Org Chem 1964, 29, 2261.

[12] Vega, S.; Alonso, J.; Diaz, A.; Junquera, F. J Heterocycl Chem 1990, 27, 269.

[13] Shishoo, C. J.; Jain, K. S. J Heterocycl Chem 1992, 29, 883.

[14] Peters, J.-U.; Hunziker, D.; Fischer, H.; Kansy, M.; Weber, S.; Kritter, S.; Muller, A.; Ricklin, F.; Boehringer, M.; Poli, S. M.; Csato, M.; Loeffler, B. M. Bioorg Med Chem Lett 2004, 14, 3575.

[15] Peters, J.-U.; Weber, S.; Kritter, S.; Weiss, P.; Wallier, A.; Zimmerli, D.; Boehringer, M.; Steger, M.; Loeffler, B. M. Bioorg Med Chem Lett 2004, 14, 3579.

[16] Wu, Y.-C.; Zou, X.-M.; Hu, F.-Z.; Yang, H.-Z. J Heteocycl Chem 2005, 42, 609.

[17] Spivey, A. C.; Srikaran, R.; Diaper, C. M.; Turner, D. J Org Biomol Chem 2003, 1, 1638.

[18] Bratušek, U.; Meden, A.; Svete, J.; Stanovnik, B. ARKIVOC 2003, (v), 77.

[19] (a) Bowman, M. D.; Jeske, R. C.; Blackwell, H. E. Org Lett 2004, 6 2019; (b) Sheibani, H.; Saljoogi, A. S.; Bazgirb A. ARKIVOC 2008, (ii), 115; (c) Deshmukh, M. B.; Anbhule, P. V.; Jadhav, S. D.; Jagpat, S. S.; Patil, D. R.; Salunkhe, S. M.; Sankpal, S. A. Indian J Chem 2008, 47B, 792.

[20] Zhu, J.; Bienayme, H. Multicomponent Reactions; Wiley-VCH: Weinheim, 2005.

[21] Tejedor, D.; Garcia-Tellado, F. Chem Soc Rev 2007, 36, 484.

[22] Dömling, A. Chem Rev 2006, 106, 17.

[23] Orru, R. V. A.; de Greef, M. Synthesis 2003, 10, 1471.

[24] Dömling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168.

[25] Caddick, S.; Fitzmaurice, R. Tetrahedron 2009, 65, 3325.

[26] Dallinger, D.; Kappe, C. O. Chem Rev 2007, 107, 2563.

[27] Loupy, A. Microwaves in Organic Synthesis, 2nd ed.; Wiley-VCH: Weinheim, 2006.

[28] Kappe, C. O. Angew Chem Int Ed Engl 2004, 43, 6250.

[29] Shore, G.; Morin, S.; Organ, M. G. Angew Chem Int Ed Engl 2006, 45, 2761.

[30] Kappe, C. O.; Stadler, A. Microwaves in Organic and Medicinal Chemistry; Wiley-VCH: Weinheim, 2005; p 182.

[31] Comer, E.; Organ, M. G. A. J Am Chem Soc 2005, 127, 8160.