Indian Journal of Chemistry
Vol. 49B, June 2010, pp. 826-829

Note

An efficient mono-mode MW controlled multicomponent synthesis of polysubstituted benzenes under solvent-free conditions

Krishna Nand Singh* & Satish Kumar Singh

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

Received 15 July 2009; accepted (revised)10 February 2010

Microwave-assisted, solvent-free one-step multicomponent and efficient synthesis of polysubstituted benzene derivatives has been achieved in reasonably good yield from ethylchloroacetate, aromatic aldehydes and malononitrile in the presence of pyridine.

Keywords: Multicomponent reactions, microwave synthesis, polysubstituted benzenes, solvent-free conditions, one-pot synthesis

The complexity and diversity of biologically important organic compounds has aroused the concern of chemical community to explore newer, more efficient and eco-safe synthetic tools. Multicomponent reactions (MCRs) constitute one approach to address this challenge, where three or more reactants are joined together in a one-pot reaction to afford the product with intrinsic atom economy and selectivity[1]. The MCR strategy offers significant advantages[2] and according to the current synthetic requirements, environmentally benign multicomponent procedures employing microwave methodology are particularly welcome[3].

Polysubstituted benzenes are highly useful compounds in organic chemistry, natural product chemistry, and material science. A variety of synthetic methodologies have been adopted for the preparation of substituted benzene derivatives employing $Cu(OTf)_2/Et_3N$-promoted cyclocondensation[4], DMAP catalyzed reaction[5], one-pot tandem reaction of vinyl malononitriles with nitro-olefins[6], Friedel-Crafts reactions[7], metalation-functionalization reaction[8], Reppe reaction[9], the Vollhardt protocol[10], the Diels-Alder strategy[11] and the Bergman cyclization[12]. The multicomponent syntheses of such benzenes has also been recently effected in acetonitrile under reflux[13], however, these procedures suffer from the drawbacks such as long reaction time, low yield of products and a lot of waste products.

In view of the above, we report herein an efficient, one-pot, multicomponent, solvent-free method for the synthesis of polysubstituted benzene derivatives in reasonably good yield under controlled microwave irradiation (**Scheme I**).

In order to optimize the reaction conditions, a mixture of benzaldehyde (**1a**, 2 mmoles), malononitrile (2 mmoles) and ethylchloroacetate (1 mmole) in the presence of pyridine (5 mmole) was used as reference and exposed to microwave irradiation under solvent-free conditions at different power (Watt), temperature and time. The outcome is given in **Table I**.

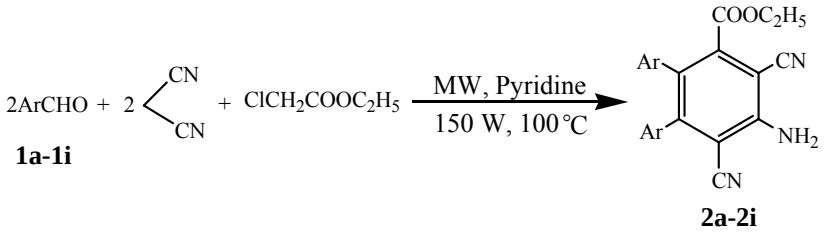
It is evident from **Table I** that the microwave irradiation has profound effect on the yield of the product with dramatic reduction in the reaction time; the best result is obtained using 150W at 100ºC in just 5 min. Under the same set of reaction conditions, different bases such as triethylamine, piperidine, morpholine, potassium carbonate and KF/alumina were used in place of pyridine, resulting in no significant reaction.

Under the optimized set of MW irradiation conditions (150W, 100ºC), various aromatic aldehydes **1a-i** were allowed to undergo multicomponent reaction with malononitrile and ethylchloroacetate in a molar ratio of 2:2:1 using excess of pyridine (5-10 mmoles, **Table II**).

In general, the reactions were facile and clean and afforded high yields of the products (63-85%); although a lower yield was observed in the case of *p*-nitrobenzaldehyde (36%). No side products were observed in any reaction. All the products were crystalline compounds and were fully identified by their melting point and spectral data (IR, ^{1}H NMR and ^{13}C NMR).

Experimental Section

All the chemicals were procured from Aldrich, USA, and E. Merck, Germany and were used as received. IR spectra were recorded on a JASCO FT-IR-5300 spectrophotometer. NMR spectra were run on a JEOL AL300 FT NMR spectrometer; chemical shifts are given in δ (ppm), relative to TMS as internal standard. Melting points were measured in open capillaries and are uncorrected. The microwave irradiation was effected using the CEM's Discover



1a-1i **2a-2i**

Scheme I — Synthesis of polysubstituted benzenes **2**

Table I — Optimization of reaction conditions using compound **1a**

Entry	MW (W)	Temp (ºC)	Time (min)	Yield (%)
1	50	80	10	-
2	50	100	10	Trace
3	70	80	10	10
4	100	80	10	12
5	100	100	10	20
5	120	80	10	27
6	120	100	10	34
7	150	80	8	46
8	150	100	5	63
9	180	100	5	62

BenchMate single-mode microwave synthesis system using safe pressure regulation 10-mL pressurized vials with "snap-on" cap.

General procedure for the preparation of 2a-i

A mixture of pyridine (5-10 mmoles), ethyl chloroacetate (1 mmole, 0.128 g), aromatic aldehyde (2 mmoles) and malononitrile (2 mmoles, 0.132 g) were taken in a sealed pressure regulation 10 mL pressurezed vials with "snap-on" cap and was irradiated in the single-mode microwave synthesis system at 150W power and 100ºC temperature for 5-20 min. After the completion of reaction (TLC in UV chamber), the mixture was cooled and the product was extracted by ethyl acetate (5 mL). Evaporation of the solvent and recrystallisation of the resulting crude solid in ethanol furnished the pure product. The products were fully characterized by their spectroscopic (IR, ^{1}H and ^{13}C NMR) data.

Ethyl 5-amino-4,6-dicyano-2,3-diphenylbenzoate, 2a: IR (KBr): 3435, 3354, 3252, 2221, 1724, 1647, 1565, 1449, 1377, 1229, 1114, 1028, 754, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15-7.27 (m, 3H, Ar-H), 7.09-7.13 (m, 3H, Ar-H), 6.91-7.07 (m, 4H, Ar-H), 5.36 (s, 2H, NH_2), 4.08 (q, J = 6.9 Hz, 2H, CH_2), 0.97 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.44, 150.83, 150.76, 135.95, 135.84, 130.06, 129.90, 129.29, 128.84, 128.18, 127.88, 127.66, 114.94, 114.17, 99.84, 94.50, 62.54, 13.47.

Ethyl 5-amino-4,6-dicyano-2,3-di(*p*-methylphenyl)benzoate, 2b: IR (KBr): 3464, 3356, 3255, 2221, 1741, 1646, 1564, 1447, 1377, 1232, 1023, 794, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04 (d, J = 7.8 Hz, 2H, Ar-H), 6.94 (d, J = 7.8 Hz, 4H, Ar-H), 6.80 (d, J = 7.8 Hz, 2H, Ar-H), 5.34 (s, 2H, NH_2), 4.10 (q, J = 6.9 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.01 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.59, 151.03, 150.67, 141.65, 138.71, 137.29, 133.08, 132.87, 129.84, 129.18, 128.87, 128.57, 115.17, 114.26, 99.84, 94.10, 62.43, 21.29, 21.14, 13.48.

Ethyl 5-amino-4,6-dicyano-2,3-di(*p*-fluorophenyl)benzoate, 2c: IR (KBr): 3477, 3352, 3248, 2222, 1739, 1644, 1567, 1454, 1378, 1224, 1023, 838, 807 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96-7.05 (m, 4H, Ar-H), 6.86-6.93 (m, 4H, Ar-H), 5.39 (s, 2H, NH_2), 4.12 (q, J = 6.9 Hz, 2H, CH_2), 1.04 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.18, 160.49, 150.89, 149.78, 141.72, 131.82, 131.70, 131.24, 128.62, 115.77, 115.48, 115.30, 115.01, 114.74, 113.94, 99.75, 94.65, 62.68, 13.55.

Ethyl 5-amino-4,6-dicyano-2,3-di(*o*-fluorophenyl)benzoate, 2d: IR (KBr): 3426, 3351, 3247, 2225, 1733, 1647, 1570, 1454, 1381, 1226, 1023, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02-7.19 (m, 4H, Ar-H), 6.81-6.98 (m, 4H, Ar-H), 5.48 (s, 2H, NH_2), 4.13 (q, J = 6.9 Hz, 2H, CH_2), 1.02 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.60, 160.63, 157.87, 156.73, 151.17, 145.90, 141.31, 131.55, 130.83, 130.50, 130.27, 124.71, 124.26, 123.52, 116.09, 115.80, 115.35, 114.52, 113.99, 95.66, 62.62, 13.40.

Ethyl 5-amino-4,6-dicyano-2,3-di(*o*-chlorophenyl)benzoate, 2e: IR (KBr): 3426, 3350, 3249, 2224, 1728, 1650, 1569, 1444, 1375, 1231, 1029, 863, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.36 (m, 4H, Ar-H), 6.96-7.15 (m, 4H, Ar-H), 5.44 (s, 2H, NH_2), 4.12 (q, J = 7.2 Hz, 2H, CH_2), 1.01 (t, J = 7.2

Table II — Solvent-free, MW-assisted one-pot synthesis of polysubstituted benzenes **2**

Entry	Ar	Reaction conditions			Yield (%)[a]	m.p. (ºC)	
		Temperature (ºC)	Time (min)	MW power (W)		Obs.	Lit.[13]
1	Ph **1a**	100	5	150	63	152-53	151-52
2	*p*-$CH_3C_6H_4$ **1b**	100	7	150	73	189-90	190-91
3	*p*-FC_6H_4 **1c**	100	6	150	74	180-81	-
4	*o*-FC_6H_4 **1d**	100	7	150	68	137-38	-
5	*o*-ClC_6H_4 **1e**	100	7	150	71	172-73	-
6	*m*-ClC_6H_4 **1f**	100	5	150	81	183-85	201-02
7	*p*-BrC_6H_4 **1g**	100	5	150	85	251-52	252-53
8	*m*-BrC_6H_4 **1h**	100	5	150	78	187-88	187-88
9	*p*-$NO_2C_6H_4$ **1i**	100	20	150	36	158-59	-

[a] isolated mass yield based on **1**.

Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.48, 150.94, 134.30, 134.00, 133.34, 132.66, 131.43, 130.97, 130.62, 130.44, 130.10, 129.71, 129.47, 129.34, 128.72, 126.73, 126.29, 126.03, 125.70, 114.36, 114.13, 62.61, 13.37.

Ethyl 5-amino-4,6-dicyano-2,3-di(*m*-chlorophenyl)benzoate, 2f: IR (KBr): 3470, 3348, 3238, 2223, 1726, 1635, 1568, 1447, 1374, 1239, 1030, 779 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13-7.29 (m, 4H, Ar-H), 6.79-7.10 (m, 4H, Ar-H), 5.43 (s, 2H, NH_2), 4.15 (q, *J* = 7.2 Hz, 2H, CH_2), 1.05 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.86, 151.02, 148.93, 141.57, 137.20, 137.15, 134.36, 133.97, 129.99, 129.70, 129.29, 129.26, 129.19, 128.30, 128.13, 128.08, 127.37, 114.39, 113.80, 99.62, 95.08, 62.79, 13.51.

Ethyl 5-amino-4,6-dicyano-2,3-di(*p*-bromophenyl)benzoate, 2g: IR (KBr): 3467, 3350, 3242, 2220, 1742, 1640, 1561, 1446, 1378, 1218, 1072, 787 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.1 Hz, 2H, Ar-H), 6.92 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.79 (d, *J* = 8.1 Hz, 2H, Ar-H), 5.40 (s, 2H, NH_2), 4.13 (q, *J* = 6.9 Hz, 2H, CH_2), 1.05 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.02, 150.98, 149.24, 141.61, 134.45, 131.73, 131.55, 131.33, 130.77, 128.18, 123.70, 122.33, 114.61, 113.85, 99.54, 94.91, 62.80, 13.52.

Ethyl 5-amino-4,6-dicyano-2,3-di(*m*-bromophenyl)benzoate, 2h: IR (KBr): 3462, 3341, 3235, 2222, 1725, 1636, 1564, 1448, 1374, 1235, 1073, 778, 683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.34 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.13-7.21 (m, 3H, Ar-H), 6.83-7.07 (m, 3H, Ar-H), 5.43 (s, 2H, NH_2), 4.15 (q, *J* = 7.2 Hz, 2H, CH_2), 1.06 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.83, 150.94, 148.82, 141.55, 137.37, 132.86, 132.23, 132.08, 131.07, 129.92, 129.51, 128.73, 128.07, 127.80, 122.35, 122.01, 114.39, 113.78, 99.61, 95.11, 62.83, 13.56.

Ethyl 5-amino-4,6-dicyano-2,3-di(*p*-nitrophenyl)benzoate, 2i: IR (KBr): 3446, 3368, 3234, 2197, 1723, 1633, 1598, 1518, 1344, 1223, 1177, 1019, 856 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37-8.45 (m, 4H, Ar-H), 8.15-8.31(m, 4H, Ar-H), 5.54 (s, 2H, NH_2), 4.28 (q, *J* = 6.9 Hz, 2H, CH_2), 1.08 (t, *J* = 6.9 Hz, 3H, CH_3).

Conclusion

A facile, efficient and controlled microwave assisted multi-component preparation of poly substituted benzene derivatives under solvent-free conditions is developed.

Acknowledgement

The authors are thankful to the Department of Biotechnology, New Delhi for financial assistance.

References

1 (a) Zhu J & Bienayme H, *Multicomponent reactions* (Wiley-VCH, Weinheim), **2005**; (b) Domling A & Ugi I, *Angew Chem, Int Ed (Engl)*, 39, **2000**, 3168; (c) Weber L, *Drug Discovery Today*, 7, **2002**, 143.

2 (a) Ye F & Alper H, *J Org Chem*, 72, **2007**, 3218; (b) Groenendaal B, Vugts D J, Schmitz R F, de Kanter F J J, Ruijter E, Groen M B & Orru R V A, *J Org Chem*, 73, **2008**, 719; (c) Nefzi A, Ostresh J M & Houghten R A, *Chem Rev*, 97, **1997**, 449.

3 (a) Caddick S & Fitzmaurice R, *Tetrahedron*, 65, **2009**, 3325; (b) Kappe C O, *Angew Chem, Int Ed (Engl)*, 43, **2004**, 6250; (c) Dallinger D & Kappe C O, *Chem Rev*, 107, **2007**, 2563; (d) Chow W S & Chan T H, *Tetrahedron Lett*, 50, **2009**, 1286.

4 Su W, Ding K & Chen Z, *Tetrahedron Lett*, 50, **2009**, 636.

5 Nair V, Vidya N, Biju A T, Deepthi A, Abhilash K G & Suresh E, *Tetrahedron*, 62, **2006**, 10136.

6 Xue D, Li J, Zhang Z-T & Deng J-G, *J Org Chem*, 72, **2007**, 5443.

7 (a) Eyley S C, *Comprehensive organic synthesis*, edited by B M Trost & I Fleming (Pergamon, New York, NY), 2, **1991**, 707; (b) Heaney H, *Comprehensive Organic Synthesis*, edited by B M Trost & I Fleming (Pergamon, New York, NY), 2, **1991**, 733; (c) Olah G A, *Friedel-Crafts Chemistry* (Wiley, New York, NY), **1973**.

8 Snieckus V, *Chem Rev*, 90, **1990**, 879.

9 Suzuki D, Urabe H & Sato F, *J Am Chem Soc*, 123, **2001**, 7925.

10 (a) Vollhardt K P C, *Angew Chem, Int Ed (Engl)*, 23, **1984**, 539; (b) Bonaga L V R, Zhang H-C, Moretto A F, Ye H, Gauthier D A, Li J, Leo G C & Maryanoff B E, *J Am Chem Soc*, 127, **2005**, 3473.

11 (a) Sato S, Isobe H, Tanaka T, Ushijima T & Nakamura E, *Tetrahedron*, 61, **2005**, 11449; (b) Xi C, Chen C, Lin J & Hong X, *Org Lett*, 7, **2005**, 347; (c) Yamamoto Y, Ishii J, Nishiyama H & Itoh K, *J Am Chem Soc*, 126, **2004**, 3712.

12 (a) Jones R R & Bergman R G, *J Am Chem Soc*, 94, **1972**, 660; (b) Bergman R G, *Acc Chem Res*, 6, **1973**, 25.

13 (a) Yan C G, Song X K, Wang Q F, Sun J, Siemeling U & Bruhn C, *Chem Commun*, **2008**, 1440; (b) Yan C G, Wang Q F, Song X K & Sun J, *J Org Chem*, 74, **2009**, 710.