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A novel method for the synthesis of polysubstituted diaminobenzonitrile derivatives using controlled microwave heating

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ABSTRACT

A novel, simple and efficient method for the synthesis of polysubstituted diaminobenzonitriles has been developed that involves reaction of 1,1,3-tricyano-2-aminopropionitrile with nitroolefins under controlled microwave irradiation conditions.

Polysubstituted benzenes are of considerable interest in fields related to the organic and medicinal chemistry of natural products.[1] Based on the fact that these substances possess common structural features found in bioactive molecules, several polyfunctionalized benzenes have been employed as precursors for the synthesis of bioactive heterocycles.[2] Extensive effort has been devoted to the investigations of acceptor-donor-acceptor systems that can serve as potential mimics for photosynthesis.[3] Polysubstituted benzenes are generally synthesized by using aromatic substitution reactions, which introduce substituents at various arene centres.[4] This approach suffers from drawbacks of atom economy[5] and environmental impact. Alternatively, polysubstituted benzenes can be accessed starting with acyclic precursors by processes that have received growing interest owing to their concise nature and high regioselectivities.[6]

It is well documented that introduction of amino, cyano or ester groups onto the benzene ring is difficult.[7] For example, diaminobenzonitriles, which are useful in the synthesis of *N*-(2-cyano-3-aminophenyl)oxamate or *N*-(2-cyano-3-aminophenyl)tetrazole-5-carboxamide anti-allergy agents, are typically prepared using aromatic nucleophilic substitution reactions of 2,6-difluorobenzonitrile with amines. It is worth mentioning that in these processes harsh conditions (e.g., elevated temperature, and frequently pressure) are required for the displacement of the second fluorine. In addition, displacement of the first fluorine requires the use of a large excess of amine.[8] Recently, the results of an interesting study dealing with the synthesis of polysubstituted benzenes containing amino and cyano groups were described by Xue et al.[9] Specifically, these workers developed a one-pot, two-step procedure for the synthesis of polysubstituted benzenes that employed triethylamine-catalyzed vinylogous Michael addition reactions of vinyl malononitriles and nitroolefins followed by aromatization of the acyclic product promoted by heating in the presence of sodium ethoxide. Also, Su et al.[10] reported a convenient synthesis of polyfunctionalized benzenes that relied on $Cu(OTf)_2/Et_3N$-catalyzed cyclocondensation of vinyl malononitriles and ethyl vinylcyanoacetate with nitroolefins in refluxing acetonitrile. Wang et al.[11] described a similar reaction promoted by triethylbenzylammonium chloride (TEBAC) that utilized arylidenemalononitriles instead of nitroolefins and which occurred in aqueous media in the presence of K_2CO_3 at 50 °C. Although, these methods have specific merits, they sometimes require extended reaction times, expensive and environmentally harmful catalysts and/or lengthy procedures that consume excess reagents.

Extensive effort has been given to the adoption of green technologies in synthetic organic chemistry. One such technology involves microwave heating since it has advantageous features that include operational simplicity, enhanced reaction rates, and high yields and purities of products.[12] In continuation[13] of our studies on performing reactions using microwave heating we have developed an efficient one-pot method for the synthesis of polysubstituted diaminobenzonitrile derivatives from simple starting materials under controlled microwave heating conditions. The results are described below.

With the initial aim of optimizing the experimental conditions, we explored the reaction of 1,1,3-tricyano-2-aminopropionitrile (**1**) and (*E*)-(2-nitrovinyl)benzene (**2a**) in the presence of three

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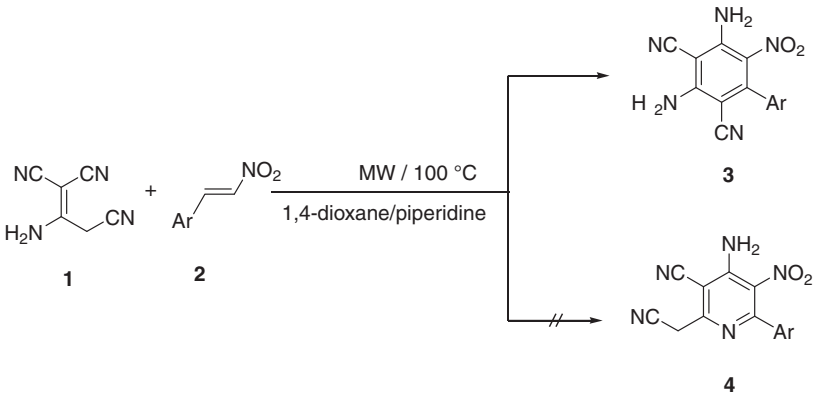
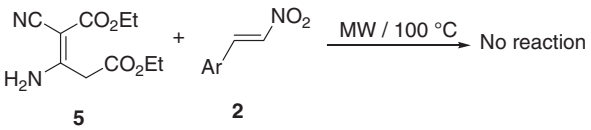


Scheme 1.

drops of piperidine as the catalyst (Scheme 1). The reaction promoted by microwave irradiation at 80 °C over 15 min did not occur when water was used as the solvent, while in ethanol the process led to a low yield of the target benzene derivative **3a**. 1,4-Dioxane was found to be the best solvent for this reaction. Other catalysts such as triethylamine and sodium ethoxide were screened but they resulted in low yielding reactions. To determine the role of the catalyst, the reaction of 1,1,3-tricyano-2-aminopropionitrile (**1**) and **2a** was carried out in the absence of catalyst under the same reaction conditions. In this case, **3a** was not formed even after prolonged microwave irradiation. This result indicates the requirement for the secondary amine catalyst in this transformation. Finally, irrespective of the aryl substituent, reactions utilizing a variety of nitroolefins took place in reasonable yields (Table 1).

Table 1
Microwave-promoted synthesis of diaminobenzonitiles[14]

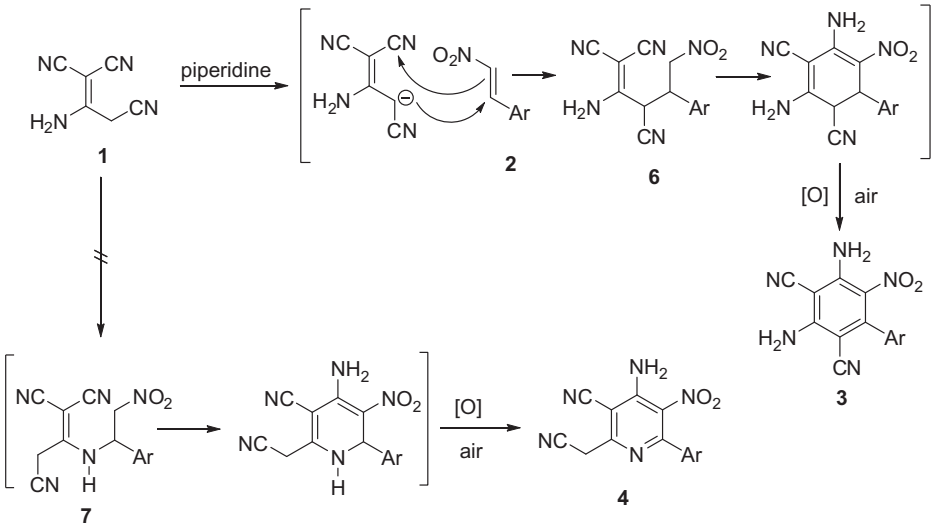
Entry	Ar	Product	Yield (%)
1	C_6H_5	**3a**	73
2	C_6H_4Cl-*p*	**3b**	70
3	C_6H_4–OMe-*p*	**3c**	72
4	C_6H_4–NO_2-*m*	**3d**	70
5	2-Furyl	**3e**	72
6	3,4-$Cl_2C_6H_3$	**3f**	70



Scheme 2.

The structures of compounds **3** could be established on the basis of analytical and spectral data. Mass spectra of **3c** showed M^+ peak at 309.2 (100%). ^1H NMR revealed a broad singlet at δ = 5.04 ppm due to the four D_2O exchangeable hydrogens of the two amino functions. In addition it showed two doublets at δ = 7.07 and 7.39 ppm (J = 5.2 Hz) for aromatic protons and a singlet at δ = 3.82 ppm for OCH3 group. This excludes the possible formation of the acyclic adducts **6** and **7** either by the addition of active methylene or amino function in **1** to the activated double bond in **2c** or the pyridine derivative **4** produced from cyclization of **7** and aromatization. ^{13}C NMR measurements further confirm this conclusion as no signals for sp^3 carbons were found.

An attempt to extend the scope of this process to condensations of ethyl cyanoacetate dimer **5** and nitroolefins **2** was unsuccessful. Starting materials were recovered even after prolonged microwave irradiation (Scheme 2). This could be a consequence of the comparatively weaker electron-withdrawing ability of CO_2Et compared to CN.



Scheme 3.

A plausible mechanism for the formation of **3**, displayed in Scheme 3, involves Michael addition of the carbanion produced from **1** to the activated double bond of the nitroolefin yielding Michael adduct intermediate **6** followed by cyclization and aromatization via aerial oxidation. Addition of the enamine nitrogen in **1** to the activated double bond in **2** would result in the formation of acyclic adduct **7** which upon cyclization and aerial oxidation would produce pyridine derivative **4**

In conclusion, the method described above represents a simple and convenient protocol for the microwave irradiation promoted synthesis of polysubstituted diaminobenzonitrile derivatives from simple starting materials.

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References and notes

1. (a) Wang, J. O.; Gao, M.; Miller, K. D.; Slede, G. W.; Zheny, Q. H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4102; (b) Kaiah, T.; Lingaiah, B. P. V.; Marsiah, B.; Shireesha, B.; Kumar, B. A.; Gururag, S.; Pathasarathy, T.; Sirdhar, B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3445; (c) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cara, G. L.; Preti, D.; Fruttarolo, F.; Parani, M. G.; Tabrizi, M. A.; Tolomeo, M.; Grimando, S.; Cristina, A. D.; Balazarim, J.; Hadfield, J. A.; Brancale, A.; Hamel, E. *J. Med. Chem.* **2007**, *50*, 2273.
2. (a) Warshakoon, N. C.; Sheville, J.; Bhatt, R. T.; Ji, W.; Mendez-Andino, J. L.; Meyers, K. M.; Kim, N.; Wos, J. A.; Mitchell, C.; Paris, J. L.; Pinney, B. B.; Reizes, O.; Hu, X. E. *Bioorg. Med. Chem.* **2006**, *16*, 5207; (b) Zhong, W.; Liu, H.; Kaller, M. R.; Henley, C.; Madal, E.; Nguyen, T.; Osslund, T. D.; Powers, D.; Rzasa, R. M.; Wang, H.-L.; Wang, W.; Xiong, X.; Zhang, J.; Norman, M. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5384.
3. Kurreck, H.; Huber, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 849.
4. (a) Olah, G.. In *Friedel–Crafts and Related Reactions*; Wiley Interscience: New York, 1963; Vols. I–IV, (b) Pearson, D. E.; Buehler, C. A. *Syntheses* **1972**, 533; (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemarire, M. *Chem. Rev.* **2002**, *102*, 1359; (d) Smith, M. B.; March, J. In *Advanced Organic Chemistry*, 5th ed.; Wiley-Intersciences: New York, 2001; p 850. Chapter 13; (e) Buncel, E.; Dust, J. M.; Terrier, F. *Chem. Rev.* **1995**, *95*, 2261; (f) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
5. (a) Trost, B. M. *Science* **1991**, *254*, 1471; (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
6. For a review see: Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.
7. (a) Milart, P.; Wilamowshi, J.; Sepiol, J.-J. *Tetrahedron* **1998**, *54*, 15643; (b) Gewald, K.; Schill, W. *J. Prakt. Chem.* **1971**, *313*, 678; (c) Wang, X. S.; Zhang, M. M.; Li, Q.; Yao, C. S.; Tu, S. T. *Tetrahedron* **2007**, *63*, 5265.
8. Klaubert, D. H.; Bell, P. S. C. U.S. 1985, 4, 504, 660; *Chem. Abstr.* **1985**, *103*, 6048.
9. Xue, D.; Li, J.; Zhang, Z.-T.; Deng, J.-G. *J. Org. Chem.* **2007**, *72*, 5443.
10. Su, W.; Ding, K.; Chen, Z. *Tetrahedron Lett.* **2009**, *50*, 636.
11. Wang, X.-S.; Zhang, M.-M.; Li, Q.; Yao, C.-S.; Tu, S.-J. *Tetrahedron* **2007**, *63*, 5265.
12. (a) Richard, D.; Carpenter, K. S. L.; Mark, J. K. *J. Org. Chem.* **2007**, *72*, 284; (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403; (c) Mayetich, G.; Wheless, K. In *Microwave-Enhanced Chemistry*; Kinsington, H. M., Haswell, S. J., Eds.; American Chemical Society: Washington, DC, 1997; p 455.
13. (a) Barsy, M. A.; Abdel Ltif, F. M.; Aref, A. M.; Sadek, K. U. *Green Chem.* **2002**, *4*, 196; (b) Mekheimer, R. A.; Sadek, K. U. *J. Heterocycl. Chem.* **2009**, 295; (c) Mekheimer, R. A.; Abdel-Hameed, A.; Sadek, K. U. *Green Chem.* **2008**, *10*, 592; Sadek, K. U.; Al-Qalay, F.; Abdelkhalik, M. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2010**, *47*, 284.
14. *General procedure for the synthesis of polysubstituted diaminobenzonitrile derivatives* **3**. A solution of 1,1,3-tricyano-2-aminopropionitrile **1** (1 mmol) and nitroolefin **2** (1 mmol) in 1,4-dioxane (15 mL) and piperidine (three drops) was heated under reflux in a Milestone Microwave Labstation at 100 °C for 15 min. The solvent was evaporated under reduced pressure and the residue was triturated with ice cold water and neutralized with HCl. The solid product was collected by filtration and crystallized from EtOH. Spectral data for selected products.
3,5-Diamino-6-nitrobiphenyl-2,4-dicarbonitrile (**3a**). Greenish yellow powder, mp 305–306 °C, yield: 73%. ^{1}H NMR (400 MHz, DMSO-d_6): δ: 7.31–7.29 (m, 4H, integrated for 2H on D_2O exchange); 7.39 (br s, 2H, D_2O exchangeable); 7.47–7.45 (m, 3H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ: 86.0, 86.4, 115.6, 117.2, 125.3, 127.6, 127.7, 129.4, 136.2, 150.8, 159.7. IR (KBr) ν_{max}: 3437, 3350, 3320, 3215, 2923, 2215, 1638 cm^{-1}. MS (EI): m/z (%) = 279.1 (100). Anal. Calcd for $C_{14}H_9N_5O_2$: C, 60.21; H, 3.25; N, 25.08. Found: C, 60.11; H, 3.37; N, 25.13.
3,5-Diamino-4′-methoxy-6-nitrobiphenyl-2,4-dicarbonitrile (**3c**). Greenish yellow powder, mp 266–267 °C, yield: 72%. ^{1}H NMR (400 MHz, DMSO-d_6): δ: 3.82 (s, 3H), 5.07 (br s, 4H, D_2O exchangeable); 7.07 (d, J = 5.2 Hz, 2H), 7.39 (d, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ: 55.6, 86.0, 86.4, 114.7, 115.9, 117.3, 125.2, 128.9, 130.2, 141.1, 150.7, 159.5, 159.9. IR (KBr) ν_{max}: 3435, 3340, 3322, 2924, 2215, 1633 cm^{-1}. MS (EI): m/z (%) = 309.2 (100). Anal. Calcd for $C_{15}H_{11}N_5O_3$: C, 58.25; H, 3.58; N, 22.64. Found: C, 58.19; H, 3.63; N, 22.60.