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Microwave-assisted clean synthesis of 6-aryl-2,4-diamino-1,3,5-triazines in [bmim][PF$_6$]

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Abstract—An efficient and green approach was developed to prepare 6-aryl-2,4-diamino-1,3,5-triazines from corresponding arylnitriles and dicyanodiamide in ionic liquid [bmim][PF$_6$] under computer-controlled microwave irradiation. Particularly valuable features of this method included the short reaction time, good yield, convenient operation and eco-friendly solvent.

1. Introduction

6-Aryl-2,4-diamino-1,3,5-triazines, along with their derivatives, are a class of attractive compounds in modern chemical industry.[1] They are widely employed as flame-retardant additives in common resins,[2] or pivotal structural unit in fire-resistant polymers.[3] Chemically modified 6-aryl-2,4-diamino-triazines have also been reported as new ligands with potential multi-coordination modes,[4] crosslinkers in coatings,[5] capsule of vermin-repellent microcapsules with slow-release potentiality,[6] corrosion resistant agent on metal surfaces[7] and candidates of antiulcerous drugs[8] and allergy inhibitors.[9] More recently, the investigations concerning 6-substituted-2,4-diamino-1,3,5-triazines were focused in their properties in molecular recognition.[10] The syntheses of 6-aryl-2,4-diaminotriazines typically involve the condensation of arylnitriles with dicyandiamide in alcoholic solution in the presence of a strong base.[10b,c,11,12] Unfortunately, these transformations have traditionally suffered from long reaction times, for example, 24 h at 140 °C.[10b] Therefore, improved and environmentally friendly syntheses for such transformations are in demand.

Microwave irradiation is used as an alternative thermal energy source to conventional heating and has gained increasing popularity in recent years. Numerous successful reactions with great efficiency and dramatically enhanced reaction rates have been disclosed.[13] Automated and focused microwave flash heating, performed in closed vessels in a temperature and pressure controlled manner, has recently proven to be very effective in accelerating organic reactions and has been widely applied in parallel synthesis.[14] In the last decade, green chemistry has been recognized as a new approach in environmental protection.[15] Thus demands for substitutes for toxic and/or volatile molecular solvents are increasing. Room temperature ionic liquids, have received a great deal of attention in recent years as novel solvents systems for a range of organic reactions due to their polar nature, and attractive properties such as incombustibility, nonvolatility, unique phase behavior and good solubility.[16] To combine the advantages of microwave technique and ionic liquids, recently, several reactions such as olefin metathesis,[17] Heck reaction,[18] Kabachnik–Fields reaction,[19] catalytic transfer hydrogenation[20] and Beckmann rearrangement[21] have been carried out in ionic liquid under microwave irradiation.

Despite the successful application of microwave irradiation in organic synthesis, however, the preparation of 6-aryl-2,4-diamino-1,3,5-triazines using microwave techniques has not been described. Herein we wish to report our preliminary investigation in the microwave-assisted cyclization of dicyandiamide with various arylnitriles using ionic liquid [bmim][PF$_6$] as an eco-friendly solvent (Scheme 1). Employing computer-aided control of dielectric heating, the desired products were formed

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Keywords: Clean synthesis; Ionic liquids; Microwave; Triazines.

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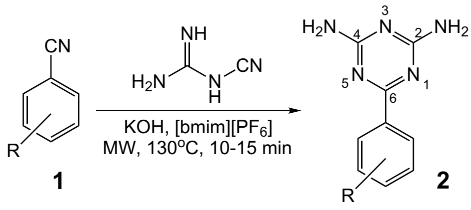

Scheme 1.

Table 1. Microwave-accelerated synthesis of 6-aryl-2,4-diamino-1,3,5-triazines in [bmim][PF_6]

Products	R	Time (min)	Yield[a] (%)
2a	H	12	87
2b	4-Cl	10	85
2c	4-F	15	80
2d	4-MeO	12	82
2e	4-Me	12	78
2f	4-NO_2	15	77
2g	2-Cl	15	70
2h	2,4-Cl_2	15	79
2i	3,4-CH_2OCH_2–	12	81

[a] Isolated yields of pure compounds.

efficiently and the reaction times in these reactions were shortened from 15–24 h to 15 min or even less. Successive reuse of the recovered solvent in the same reaction afforded the product in similar yields.

In order to optimize the reaction conditions, initially, the effect of heating modes were studied. In our first experiment, condensation between benzonitrile and dicyandiamide (1.1 equiv) catalyzed by KOH (0.2 equiv) in [bmim][PF_6] was chosen as a prototype. Microwave-assisted reactions were conducted in septum-sealed reaction vessels in Emrys^{TM} Optimizer single-mode microwave parallel synthesizer. After the reaction had completed, the reaction mixture was cooled and precipitate was separated by filtration. Pure product was obtained after recrystallization.

Much longer reaction times were necessary under conventional thermal heating conditions (preheated oil bath). For example, transformation to **2a** required 8 h of heating at 130 °C in [bmim][PF_6], and the yield of the desired product was 79%. A remarkable rate acceleration was observed under the microwave conditions. Complete conversion was achieved within 12 min under same temperature, to afford the corresponding **2a** in 87% yield. These examples demonstrated the beneficial effect of microwaves as the energy source. The reaction system was very complicated under microwave irradiation at 180 °C for 10 min. Compound **2a** was isolated in 48% yield and other unknown products were detected by HPLC.

The effect of solvent was also examined. Reactions of benzonitrile with dicyandiamide were carried out under microwave irradiation (130 °C). The yield obtained in [bmim][PF_6] (reaction time 12 min, yield 87%) was found to be superior to [bmim][BF_4] (reaction time 12 min, yield 79%) and ethylene glycol monomethyl ether (reaction time 15 min, yield 76%). Therefore, [bmim][PF_6] was the solvent of choice.

Three bases were also examined employing the above-mentioned reaction. No significant difference was observed when the reaction was carried out by using KOH or NaOH, by which **2a** was obtained in 87% and 85% yield, respectively. However, reaction with relatively weaker base such as $Ba(OH)_2$ gave poor result (54%).

On the basis of these results, we next surveyed a structurally diverse group of substrates to explore the generality of this new protocol, and the results are summarized in Table 1. By using dielectric heating, satisfactory chemical yields (70–87%) and short reaction periods (10–15 min) were obtained in every case examined. Aromatic nitriles carrying either electron donating (entries d, e, i) or electron withdrawing (entries b, c, f, g, h) substituents all reacted well and gave satisfactory yields.

The ionic character of ionic liquids provides excellent coupling capability with microwave. However, to the organic reactions performed in ionic liquids, overheating is an ineluctable problem under consecutive microwave irradiation because of the nonvolatile nature of such solvents. By using computer-controlled microwave instruments, reactions in ionic liquids could be carried out under nearly steady temperature by temperature feedback power control device (Fig. 1).

The reusability of the ionic liquid was also checked in the synthesis of **2a** (Fig. 2). Since the products were springly soluble in the ionic phase, they were easily separated by simple filtration. After the first run, the recovered oily ionic liquid was thoroughly washed with water and ether successively, dried at 100 °C under vacuum, and then subjected to a second run of the reaction by charging with the same substrates and catalyst (KOH). The yields nearly the same in the five runs (87%, 82%, 85%, 86%, 83%).

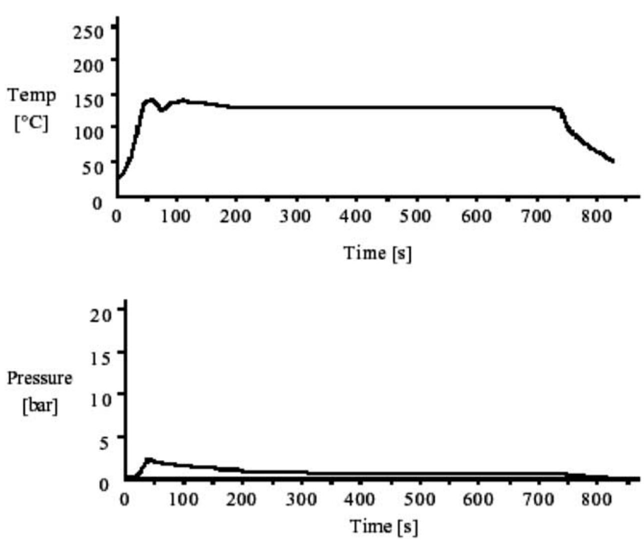

Figure 1. Temperature and pressure profiles in the synthesis of **2a**.

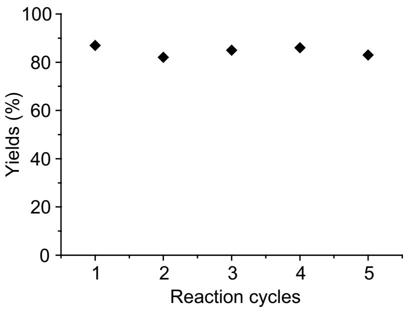

Figure 2. Recycling study of model reactions.

In summary, for the first time, we have developed an efficient, convenient and practical conversion of arylnitriles into arylguanamines using computer-controlled microwave irradiation in conjunction with a green solvent [bmim][PF_6]. This new method has several advantages over its counterpart carried out in traditional organic solvents under conventional heating: (1) dramatically reduced reaction time, (2) good yields, (3) simple manipulation, and (4) safe reaction medium.

2. Experimental

Arylnitriles were purchased or prepared in good yields by standard dehydration method from aldoximes. Dicyandiamide and [bmim][PF_6] were obtained from commercial sources and used as received. Reactions were carried out on Emrys™ Optimizer single-mode microwave parallel synthesizer (Personal Chemistry Ltd., Uppsala, Sweden). All products were known compounds and gave physical (mps) and spectral (FT-IR, ^{1}H NMR and MS) data consistent with the assigned structures. Melting points were determined with a BÜCHI B-540 digital apparatus and were uncorrected. IR spectra were recorded in a Nicolet Nexus 470 FT-IR spectrophotometer in KBr. ^{1}H NMR spectra were measured in a Bruker AM 500 (500 MHz) spectrometer using TMS as the internal standard. MS spectra were recorded on a Hitachi M-80 mass spectrometer.

General procedure. A suspension of a mixture of arylnitrile (10 mmol), dicyandiamide (0.93 g, 11 mmol) and powdered KOH (0.11 g, 2 mmol) in [bmim][PF_6] (3 mL) was subjected to microwave irradiation (temperature setting: 130 °C) for an optimized period listed in Table 1. After cooling to room temperature, the precipitate was collected by filtration, washed with hot water and recrystallized from ethanol–DMF (5:1, v/v) to afford 6-aryl-2,4-diamino-1,3,5-triazine.

2,4-Diamino-6-phenyl-1,3,5-triazine (**2a**): mp = 229–230 °C (lit.:[11] 228 °C); ν_{max} (KBr, cm^{-1}): 3450, 3340, 1625, 1560; δ_H (DMSO-d_6): 6.55 (4H, s, NH_2), 7.44–7.56 (3H, m, Ph), 8.48 (2H, d, $J = 6.8$ Hz, Ph); MS (EI) m/z 187 (M^+).

2,4-Diamino-6-(4-fuorophenyl)-1,3,5-triazine (**2c**): mp = 251–252 °C (lit.:[11] 249 °C); ν_{max} (KBr, cm^{-1}): 3500, 3390, 1650, 1625; δ_H (DMSO-d_6): 6.76 (4H, s, NH_2), 7.27 (2H, t, $J = 8.9$ Hz, Ph), 8.25 (2H, t, $J = 8.9$ Hz, Ph); MS (EI) m/z 205 (M^+).

2,4-Diamino-6-(4-methylphenyl)-1,3,5-triazine (**2e**): mp = 244–245 °C (lit.:[11] 244 °C); ν_{max} (KBr, cm^{-1}): 3480, 3240, 1660, 1590. δ_H (DMSO-d_6): 2.30 (3H, s, CH_3)), 6.47 (4H, s, NH_2), 7.20 (2H, d, $J = 8.0$ Hz, Ph), 8.20 (2H, d, $J = 8.3$ Hz, Ph); MS (EI) m/z 201 (M^+).

2,4-Diamino-6-(2,4-dichloro-phenyl)-1,3,5-triazine (**2h**): mp = 206–207 °C (lit.:[22] 204–206 °C); ν_{max} (KBr, cm^{-1}): 3330, 3160, 1670, 1655; δ_H (DMSO-d_6): 6.58 (s, 2H, NH_2), 7.27–7.38 (m, 2H, ArH), 7.50–7.63 (m, 1H, ArH); MS (EI) m/z 256 (M^+).

2,4-Diamino-6-piperonyl-1,3,5-triazine (**2i**): mp = 260–261 °C (lit.:[23] 257–258 °C); ν_{max} (KBr, cm^{-1}): 3510, 3390, 1660, 1630, 1260; δ_H (DMSO-d_6): 6.25 (s, 2H, NH_2), 6.56 (s, 2H, OCH_2O), 6.75–6.93 (m, 3H, ArH); MS (EI) m/z 231 (M^+).

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