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A highly efficient green synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives and their photophysical studies

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ABSTRACT

A task-specific ionic liquid, [Bmim]OH, has been used for an efficient synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones by one-pot cyclocondensation reaction of phthalhydrazide, aromatic aldehydes, and malononitrile or ethyl cyanoacetate under microwave irradiation. The advantages of this method include the use of green catalyst, no organic solvent, easy work-up and excellent yields. The photophysical properties for some 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives have been investigated for the first time.

Diversity-oriented synthesis (DOS) continues to be an area of importance at the interface of organic synthesis and chemical biology/material science.[1] At the heart of DOS are the methods needed for an efficient generation of functionally and diverse small molecules, especially those possessing skeletons found in natural products, drug-like molecules and materials.[2] Perhaps the most promising and powerful method for generating such molecules is by sequential multicomponent reactions (MCRs) with further increase in molecular complexity and diversity.[3] There is great current interest in microwave assisted organic synthesis (MAOS),[4] because such environmentally benign chemical methodologies are strongly required in the light of the paradigm shift to 'Green Chemistry'. According to the current synthetic requirements, environmentally benign multi-component procedures employing microwave (MW) methodology are particularly welcome due to their intrinsic advantages.[5] The use of a benign and recyclable catalyst/solvent with high activity and selectivity is an interesting and rapidly growing area of synthetic chemistry. Owing to their green credentials, ionic liquids (ILs) have attracted considerable interest as environmentally benign reaction media,[6–9] catalysts[9–11] and reagents.[12]

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to pharmaceuticals, agrochemicals, and functional materials are becoming more and more important.[13–15] Pyrazoles are an important class of compounds for new drug development, as they are the core structure of numerous biologically active compounds, including blockbuster drugs such as celecoxib, viagra, pyrazofurine, and many others.[16–19] Similarly, heterocycles containing a phthalazine moiety are of current interest due to their pharmacological and biological activities,[20–22] for example, pyrazolo[1,2-*b*]phthalazine-dione is described as anti-inflammatory, analgesic, anti-hypoxic, and anti-pyretic agent.[21] Phthalazine derivatives are also found to possess anticonvulsant,[23] cardiotonic[24] and vasorelaxant[25] activities. Present communication reports a one pot multicomponent, efficient and green synthesis of some 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives. The photophysical properties of some selected derivatives have also been studied showing medium to strong optical behavior.

A perusal of literature reveals that there exist only two multicomponent reports by Bazgir et al. for the synthesis of pyrazolo-[1,2-*b*]phthalazine-diones employing PTSA/BmimBr (100 °C, 3 h) and sonochemistry in the presence of Et_3N/EtOH (50 °C, 1 h).[26] However, the generality of the existing reports is somewhat vitiated by the severe reaction conditions, and the catalysts and solvents used are not acceptable in the context of green synthesis. Thus, the development of a new, efficient and green approach for the preparation of heterocycles containing a phthalazine ring fragment is highly desirable. In view of the above and as a part of our ongoing programme on multicomponent reactions,[27] an efficient and convenient synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione has been accomplished by the multicomponent reaction of phthalhydrazide, aromatic aldehydes, and malononitrile using controlled MW irradiation in the presence of [Bmim]OH at an ambient temperature of 45 °C (Scheme 1).

In order to optimize the reaction conditions, the catalytic activity of [Bmim]OH was tested for a typical multicomponent reaction

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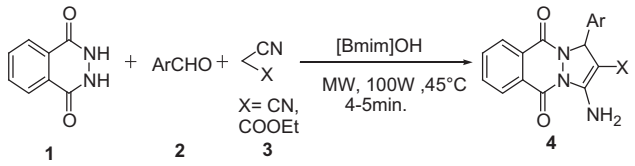

Scheme 1. [Bmim]OH catalyzed synthesis 1*H*-pyrazolo[1,2-*b*]phthalazine-5, 10-dione derivatives.

Table 1
[Bmim]OH mediated synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives **4a**–**z**[a]

Entry	Ar-CHO Ar	CN-CH_2-X X	Product	Time (min)	Yields (%)[b]
1	Ph	CN	**4a**	4	94
2	4-BrC_6H_4	CN	**4b**	4	92
3	3-BrC_6H_4	CN	**4c**	5	93
4	4-ClC_6H_4	CN	**4d**	4	96
5	3-ClC_6H_4	CN	**4e**	5	90
6	2-ClC_6H_4	CN	**4f**	5	91
7	4-$NO_2C_6H_4$	CN	**4g**	4	97
8	3-$NO_2C_6H_4$	CN	**4h**	4	95
9	2-$NO_2C_6H_4$	CN	**4i**	5	94
10	4-FC_6H_4	CN	**4j**	5	92
11	4-MeC_6H_4	CN	**4k**	5	91
12	4-$MeOC_6H_4$	CN	**4l**	5	89
13	2-Thienyl	CN	**4m**	5	92
14	Ph	COOEt	**4n**	4	95
15	4-BrC_6H_4	COOEt	**4o**	5	92
16	3-BrC_6H_4	COOEt	**4p**	5	91
17	4-ClC_6H_4	COOEt	**4q**	4	93
18	3-ClC_6H_4	COOEt	**4r**	5	91
19	2-ClC_6H_4	COOEt	**4s**	5	92
20	4-$NO_2C_6H_4$	COOEt	**4t**	4	98
21	3-$NO_2C_6H_4$	COOEt	**4u**	5	95
22	2-$NO_2C_6H_4$	COOEt	**4v**	5	95
23	4-FC_6H_4	COOEt	**4w**	4	93
24	4-MeC_6H_4	COOEt	**4x**	5	90
25	4-$MeOC_6H_4$	COOEt	**4y**	5	91
26	2-Thienyl	COOEt	**4z**	5	93

[a] Microwave heating performed on 100 W at 45 °C.
[b] Isolated yield.

of phthalhydrazide **1**, benzaldehyde **2a,** and malononitrile **3** under controlled microwave in the presence and absence of ethanol. The use of [Bmim]OH (20 mol %) in ethanol promoted the reaction to a reasonable extent (70%) at 100 W and 80 °C; whereas the use of [Bmim]OH alone brought about an excellent conversion (92%) under the same set of MW conditions. Intrigued by this observation, the reaction was investigated in detail under controlled microwave by varying MW power (80, 100 and 150 W) and temperature (40, 45, 60 and 80 °C) in [Bmim]OH alone. It was observed that the maximum conversion to product **4a** (94%) was achieved using 100 W power output at 45 °C. A further increase in the MW power and temperature did not improve the product yield. It is interesting to note that the reactants, when simply stirred in [Bmim]OH at room temperature for 30 min, resulted in a sizable conversion to the product (50%).

Under the optimized set of controlled MW reaction conditions (100 W and 45 °C), a number of aromatic aldehydes **2** were allowed to undergo multicomponent reaction with malononitrile **3** and phthalylhydrazide **1** in a molar ratio of 1:1:1 in ionic liquid [Bmim]OH (0.2 mL) affording 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **4a**–**z** in excellent yields in 4–5 min (Table 1).[28] The physical and spectral data of all the products are in full agreement with the assigned structures**.** It is worthwhile to mention that the ionic liquid [Bmim]OH was recycled up to five times without any loss and diminution in its amount and efficacy. After each and every recycle, the purity of the ionic liquid was affirmed by spectroscopic data.

Electronic absorption and photoluminescent properties: out of all the 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **4a**–**z** synthesized, eight representative derivatives having variant structural features viz **4a**, **4g**, **4k,** and **4m** with cyano functionality; and **4n**, **4t**, **4y,** and **4z** containing ester linkage, were subjected to their possible photophysical studies. The photo physical parameters including the quantum yield and Stokes shift for all the examined compounds are given in Table 2.

The 5×10^{-5} M DMSO solution of compounds **4a**, **4g**, **4k,** and **4m** showed absorption bands at 360, 355, 351, and 354 nm, respectively (Fig. 1). Moreover, when these compounds were excited at their respective wavelengths, all the compounds (**4a**, **4k,** and **4m)** except **4g** exhibited a medium to strong photoluminescent emissions. Compound **4a** emits at two wavelengths at 438 and 522 nm, while **4k** and **4m** showed strong emission bands at 524 and 446 nm with a weak shoulder at 450 and 521 nm, respectively. The weak emission band (575 nm) observed in the case of **4g** is attributed to the electron-withdrawing nature of nitro substituent.

The photophysical behavior of the compounds containing the ester group is almost similar to that of the compounds with cyano substituent (Fig. 2). The compound **4n** showed two absorption bands at 310 and 364 nm, whereas **4z** absorbs at 332 and 365 nm. The compound **4x** absorbs strongly at 325 nm with a weak shoulder at 365 nm. Contrary to **4n**, **4x,** and **4z**; the compound **4t** absorbs at a single wavelength of 358 nm. When excited at 310 nm, **4n** emits at 519 nm; **4x** also emits around the same region at 517 nm upon excitement at 325 nm. Moreover, the excitation of **4t** at 358 nm showed comparatively weak intensity at 510 nm. The compound **4z** (thienyl substituent) showed an altogether different fluorescent behavior with two different emission bands at wavelengths 439 and 516 nm. In this series too, **4t** with the nitro substituent emits weakly in comparison to other examined derivatives.

As evident from Table 2, a large Stokes shift and low quantum yield for all the examined derivatives are observed. The Stokes shifts

Table 2
UV-Visible and fluorescence data of the examined derivatives of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione

Compound	λ^{abs} (nm)	λ^{ext} (nm)	λ^{em} (nm)	ε (M^{-1} cm^{-1})	$\Delta\nu$ (cm^{-1})	Φ_f[a]	τ (μs)[b]
4a	360	360	438, 522	25000	4946.73, 8620.69	0.057	328
4g	355	355	575	13000	10857.29	0.051	227
4k	351	351	524, 450 (s)	25400	9085.04, 5946.79	0.045	279
4m	354	354	446, 521 (s)	17400	6068.51, 9296.17	0.080	225
4n	310, 364 (s)	310	519	16800	12990.24	0.136	225
4t	358	358	510	22400	8325.12	0.049	212
4x	325, 365 (s)	325	517	30000	11426.87	0.063	222
4z	332, 365 (s)	332	439, 516	20200	7341.44, 10740.64	0.075	227

λ_{abs} = absorbance maxima, λ_{ext} = excitation wavelength, λ_{em} = fluorescence maxima, ε = molar absorptivity, $\Delta\nu$ = Stoke's lines, Φ_f = quantum yield.
[a] Quantum yield was calculated with respect to naphthalene in DMSO.
[b] Fluorescence decay time was carried out at room temperature using the 355 nm wavelength from a 7 ns pulsed Nd:YAG laser (Innolas, Spitlight 600, Germany) and the data were acquired using an oscilloscope (analog digital scope-HM1507) with software SP107.

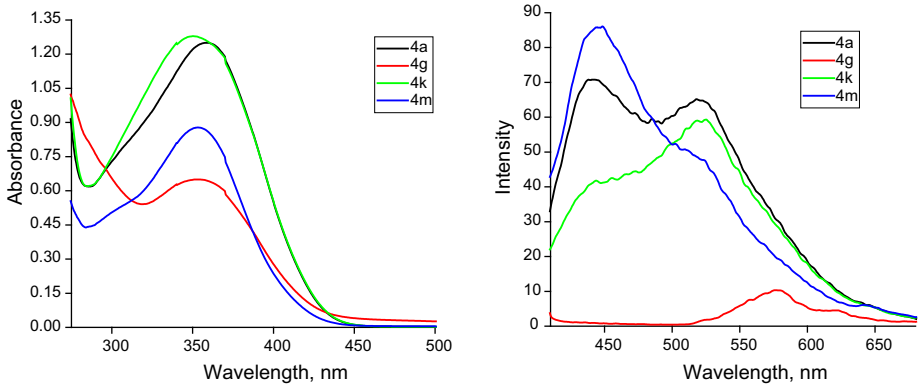

Figure 1. Absorption and emission spectra of **4a**, **4g**, **4k** and **4m** derivatives.

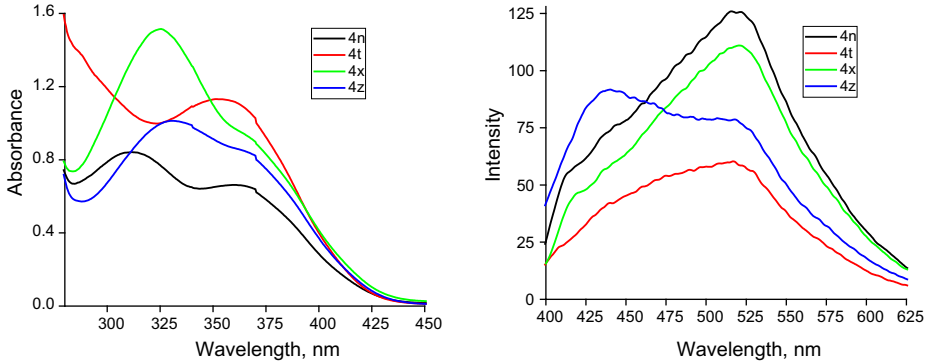

Figure 2. Absorption and emission spectra of **4n**, **4t**, **4x** and **4z** derivatives.

have been determined as the difference $\Delta E = E_{abs} - E_{flu}$ (in cm^{-1}) and have been found to range from 4946.73 to 10857.29 cm^{-1} for the cyano derivatives **4a**, **4g**, **4k,** and **4m**, and from 7341.44 to 12990.24 cm^{-1} for the ester derivatives **4n**, **4t**, **4y,** and **4z**. Thus, the Stokes shifts for the cyano compounds are lower as compared to that of the ester derivatives. This may be explained as a consequence of involvement of amino group in hydrogen bonding with the O-atom of the ester group, which is absent in the case of first series of compounds.

In conclusion, a one-pot high yielding synthetic protocol has been developed for achieving 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones using an environmentally benign and recyclable catalyst [Bmim]OH. The observed fluorescent behavior of these derivatives further opens its amenability as a new series of fluorescent molecules.

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28. *General procedure for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione:* Phthalhydrazide (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol) and [Bmim]OH (0.2 mL) were put in a pressure regulation 10-mL pressurized vial with 'snap-on' cap and the reaction mixture was subjected to irradiation in a single-mode microwave synthesis system at 100 W power and 45 °C for 4–5 min. After completion of the reaction as indicated by TLC, water (5 mL) was added and the product was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, evaporated under reduced pressure and recrystallized from ethanol to afford pure 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **4**. After isolation of the product, the remaining aqueous layer containing the ionic liquid was washed with ether (10 mL) to remove any organic impurity, and then dried under vacuum at 90–95 °C for 15 h to afford [Bmim]OH, which was used in the subsequent runs without further purification.