Indian Journal of Chemistry
Vol. 53B, October 2014, pp 1288-1294

Catalyst-free access to pseudo multi-component synthesis of benzopyranopyrimidines

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Received 23 August 2013; accepted (revised) 13 August 2014

A catalyst-free multi-component reaction of salicylaldehyde, malononitrile and secondary amine leads to the formation of benzopyranopyrimidines with intense fluorescence emission behavior is described. The method is simple, eco-friendly, economic, operable under mild conditions, having short reaction time, high yields and easy work-up procedure which suggests broad applicability of the protocol.

Keywords: Benzopyranopyrimidines, catalyst-free, eco-friendly, iminocoumarins, intense fluorescence emission, multi-component reaction (MCR)

The art of performing efficient chemical transformations that couple three or more components in a single operation under catalyst-free conditions, in eco-friendly solvent, avoiding expensive purification techniques, represents a fundamental challenge intended for modern organic synthesis[1]. In this context, multi-component reactions (MCRs) represent one of the powerful tools towards achieving this ideal goal. The MCRs involve construction of multi-bonds through a single step thus avoiding the necessity of separation and purification procedures after each step and achieve high atom economy, thus resulting in a minimization of waste, cost and labour[2]. The MCRs are suited uniquely for combinatorial library synthesis and thus have acquired an important place in the modern drug-discovery process[3]. The examples of approved therapeutic agents synthesized by MCR route include aminochromenes (a) (Ref 4a), benzo-pyranopyrimidines (b) (Ref 6), benzopyranopyridines (c) (Ref 4b), benzopyranopyrazoles (d) (Ref 4c), *etc*. which incorporate iminocoumarin framework **(Figure 1)**. Amongst them, benzopyrano[2,3-*d*]pyrimidine-4-one scaffolds represent an interesting class of heterocycles which exhibit *in vivo* anti-tumor activity in mice with P 388 lymphocytic leukemia[5]. More recently, a series of substituted benzopyrano[2,3-*d*]pyrimidines were tested for cytotoxic activity against a panel of cancer cell lines, and a number of them were shown to cause a significant perturbation in cell cycle kinetics[6]. Apart from this, benzopyranopyrimidines are known for their remarkable properties as emissive-dyes as well as possessing useful optical properties[7].

Despite diverse pharmacological properties associated with benzopyranopyrimidines, there are only three reports for the multi-component synthesis of benzo-pyranopyrimidines employing $LiClO_4$ (Ref 8a), [Bmim]BF_4 (Ref 8b) and APTES-MNPs (Ref 8c) as catalyst. Thus, the development of an efficient protocol for synthesis of benzopyranopyrimidines operable under catalyst-free conditions is highly warranted. The continued interest in the development of eco-benign methods for bioactive heterocycles[9] prompted the development of a catalyst-free, economic and eco-friendly method for the synthesis of benzopyranopyrimidines by a multi-component condensation between salicylaldehyde, secondary amine and malononitrile. To the best of knowledge this is the first report for catalyst-free, pseudo multi-component synthesis of benzopyranopyrimidines **(Scheme I)**.

Results and Discussion

Initially, the reaction of salicylaldehyde **1**, piperidine **2**, and malononitrile **3** [2:1:1] was carried out in ethanol medium at reflux conditions and corresponding benzopyrano[2,3-*d*]pyrimidine **4** **(Scheme I)** was obtained in 70% yield in 3 hr **(Table I)**. In continuation with our earlier experience with mixed solvent system[9], it was envisaged that H_2O:C_2H_5OH system could be suitable for increasing the yield of the present transformation and for carring out various sets of reactions **(Table I, entries 2-8)**. From **Table I** it is found that in C_2H_5OH:H_2O [80:20 v/v] the corresponding product was obtained in excellent yield (87%). Ethanol is required to increase the solubility of the substrate and water is highly essential to increase the yield of the product, therefore it was hypothesized that the corresponding transition

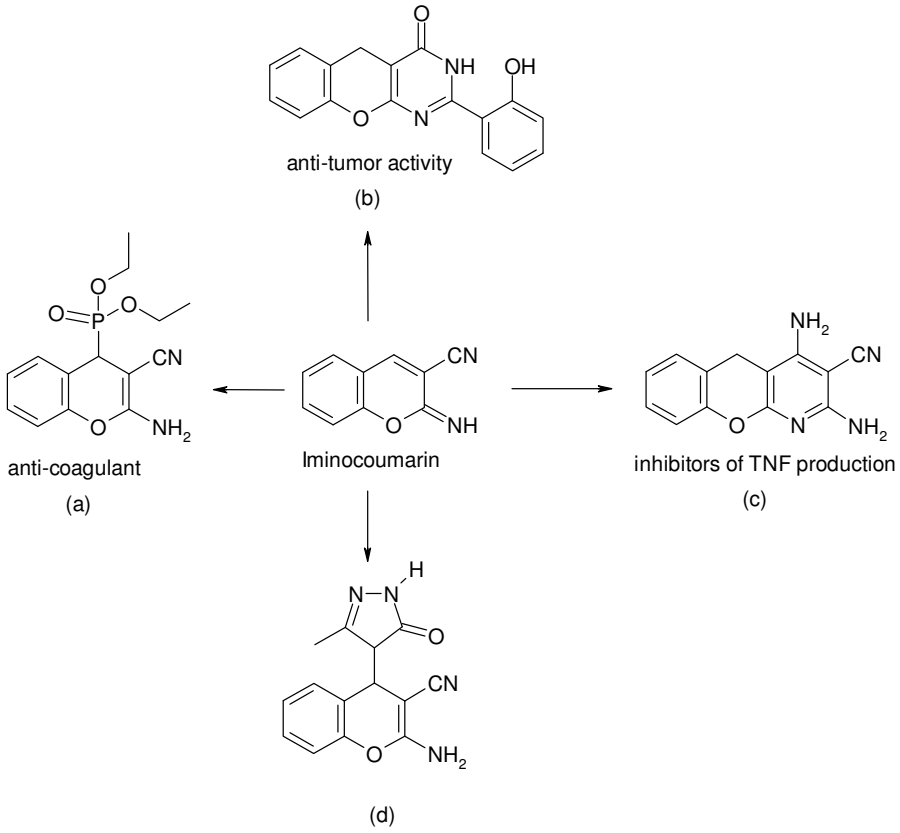
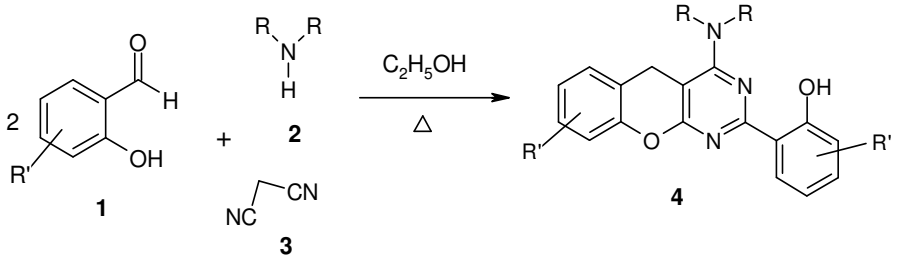


Figure 1 — Iminocoumarin derived biologically active heterocycles



Scheme I — Synthesis of benzopyrano[2,3-*d*]pyrimidines

states would be stabilized by water, which has a relatively high static permittivity (ε_T = 78.4) (Ref 10).

To probe the generality of the method, using the optimized reaction conditions, a range of substituted benzopyrano[2,3-*d*] pyrimidines **4a-l** were synthesized **(Table II)**. This method was found to be equally effective for salicylaldehydes bearing either electron donating or electron withdrawing substituents. Moreover, the variation in secondary amine *viz* morpholine, pyrolidine and piperidine could be successfully used for the synthesis of benzopyrano[2,3-*d*] pyrimidines.

Benzopyranopyrimidines are analogous to rhodols, rhodamines, and fluoresceins[11] that constitute a well-known class of dyes. Hence, it was expected that synthesized benzopyranopyrimidines might possess fluorescence properties. To verify this assumption, absorption and emission study of these derivatives was carried out. Gratifyingly, within substituted benzopyrano[2,3-*d*]pyrimidines **(Table II, 4a-l)**, compound **4j** bearing a methoxy group at 7-position, displayed an absorption at 350 nm in $CHCl_3$ **(Figure 2)** and strong fluorescence emission centered at 500 nm in $CHCl_3$ **(Figure 2)**, with a fluorescence quantum yield of 0.75 ± 0.04. This is illustrated by the red-shift of the absorption maximum (in chloroform) of reported[11] iminocoumarin **(I, Figure 3**), oxo-benzo-

Table I — Optimization of reaction conditions in terms of solvent for the synthesis of benzopyrano[2,3-*d*]pyrimidines

Entry	Solvent	Yield (%)
1	C_2H_5OH: H_2O (100: 00)	75
2	C_2H_5OH: H_2O (90:10)	83
3	C_2H_5OH: H_2O (80:20)	87
4	C_2H_5OH: H_2O (70:30)	84
5	C_2H_5OH: H_2O (60:40)	79
6	C_2H_5OH: H_2O (50:50)	65
7	C_2H_5OH: H_2O (40:60)	56
8	C_2H_5OH: H_2O (30:70)	50
9	C_2H_5OH: H_2O (20:80)	43
10	C_2H_5OH: H_2O (10:90)	35
11	C_2H_5OH: H_2O (00:100)	28

Reaction conditions: salicyladehyde (2 mmol), secondary amine (1 mmol), malononitrile, (1mmol), solvent (5 mL), reflux temp

pyranopyrimidine **(II, Figure 3)** and compared with benzopyranopyrimidine **4j (III, Figure 3)**. Hence the variation in the acceptor strength and the extension of the electron conjugated system induce changes in the optical properties.

Experimental Section

Various substituted salicylaldehydes (Sigma-Aldrich), malononitrile (Alfa Aesar) and secondary amines *viz* piperidines, morpholine, pyrolidine (Thomas Baker) were used as received. Melting points recorded were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR-783 spectrophotometer. NMR spectra were recorded on Bruker AC-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard and δ values are expressed in ppm. HRMS were recorded on Q-TOF mass spectrometer. UV-Vis absorption spectra were recorded on a Shimadzu UV-Visible-1800 spectrophotometer. The emission spectrum was recorded on a spectrofluorimeter, Jasco Model-F.P.-750. The fluorescence quantum yield was determined using quinine sulfate in chloroform (Φ = 0.55) as the standard.

Typical procedure for catalyst-free synthesis of benzopyranopyrimidines

A mixture of a salicylaldehyde (2 mmol), malononitrile (1 mmol) and a secondary amine (1.1 mmol) in 20% ethanol (5 mL) was stirred under reflux conditions and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water and filtered to yield the corresponding benzopyranopyrimidines. These products were characterized by usual spectral techniques. (*i.e.* IR, ^{1}H and ^{13}C NMR, HRMS).

Spectral analysis of some representative compounds

4a (Table II): m.p. 220°C; IR (KBr): 3448, 2939, 1602, 1581, 1239 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.46 (s, 1H,-OH), 8.42 (dd, 1H, Ar-H, *J* = 1.8Hz, *J* = 8.1Hz), 6.89-7.38 (m, 7H, Ar-H), 3.92 (s, 2H,-CH_2), 3.43 (s, 4H,-2CH_2), 1.77 (s, 6H,-3CH_2); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.34, 25.63, 25.92, 49.53, 97.50, 117.08, 117.53, 118.60, 118.80, 119.56, 124.37, 128.18, 128.52, 129.20, 132.79, 150.64, 160.42, 162.02, 164.46, 165.23.

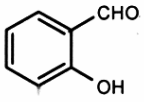
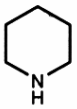
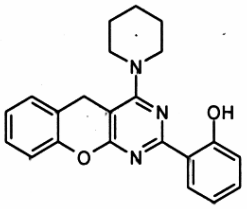
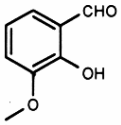
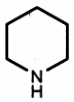
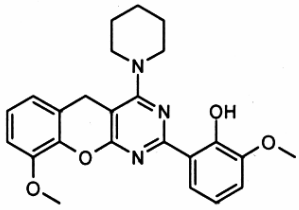
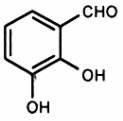
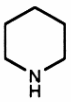
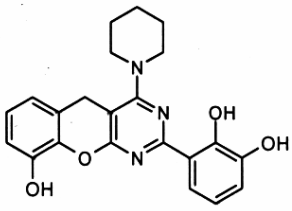
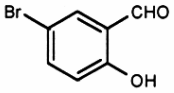
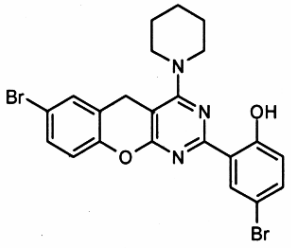
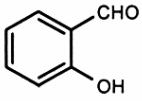
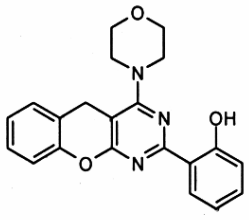
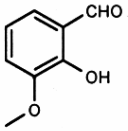
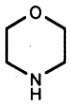
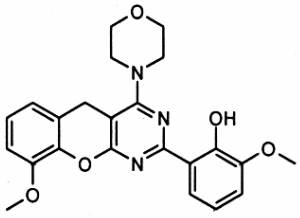
4b (Table II): m.p. 195°C; IR (KBr): 3432, 2933, 1572, 1544, 1237 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.99 (s, 1H,-OH), 8.10 (dd, 1H, Ar-H, *J* = 1.5Hz, *J* = 7.8Hz), 6.76-7.05 (m, 5H, Ar-H), 3.93 (s, 2H,-CH_2), 3.90 (s, 3H,-OCH_3), 3.89 (s, 3H,-OCH_3), 3.43 (m, 4H,-2CH_2), 1.76 (m, 6H,-3CH_2); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.31, 25.69, 25.88, 49.57, 56.03, 56.05, 97.52, 110.54, 113.88, 117.73, 118.74, 119.82, 120.48, 121.15, 124.12, 140.22, 148.17, 148.68, 150.78, 162.20, 164.56, 164.97.

4i (Table II): m.p. 256°C; IR (KBr): 3433, 2974, 1604, 1544, 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.69 (s, 1H,-OH), 8.38 (dd, 1H, Ar-H, *J* = 1.5Hz, *J* = 7.8Hz), 6.86-7.35 (m, 7H, Ar-H,), 4.20 (s, 2H,-CH_2), 3.77-3.81 (m, 4H,-2CH_2), 1.97-2.01 (m, 4H,-2CH_2); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 25.47, 49.85, 91.36, 116.93, 117.38, 118.60, 118.64, 119.18, 124.04, 128.04, 128.12, 128.62, 129.14, 132.52, 150.19, 160.27, 160.49, 161.73.

4j (Table II): m.p. 247°C; IR (KBr): 3445, 2957, 1615, 1575, 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.32 (s, 1H,-OH), 7.90 (d, 1H, Ar-H, *J* = 3.0Hz), 7.26 (s, 1H, Ar-H), 7.08 (d, 1H, Ar-H, *J* = 9.0Hz), 6.97-6.86 (m, 1H, Ar-H), 6.77 (dd, 1H, Ar-H, *J* = 9.0Hz and *J* = 3.0Hz), 6.64 (d, 1H, Ar-H, *J* = 2.7Hz), 4.21 (s, 2H,-CH_2), 3.85 (s, 3H,-OCH_3), 3.82 (s, 3H,-OCH_3), 3.78-3.79 (m, 4H,-2CH_2), 1.99-2.03 (m, 4H,-2CH_2); ^{13}C NMR ($CDCl_3$,75 MHz): δ 25.50, 25.89, 49.89, 55.63, 56.07, 90.92, 111.78, 113.06, 113.76, 117.74, 118.24, 118.48, 119.86, 120.62, 144.14, 152.06, 154.88, 155.97, 161.55, 163.82; HRMS: Calcd for $C_{23}H_{23}N_3O_4$ + Na: *m/z* 428.1586 (M+Na). Found: 428.1593.

4k (Table II): m.p. 260°C; IR (KBr): 3444, 2972, 1616, 1586, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.56 (s, 1H,-OH), 8.18 (d, 1H, Ar-H, *J* = 1.8Hz),

Table II — Catalyst-free synthesis of benzopyrano[2,3-d] pyrimidines **4**

Entry	Substrate 1	Substrate 2	Product 4	Time (h)	Yield (%)[a,b]
a				1.5	87
b				1.0	91
c				2.0	81
d				2.0	75
e				1.5	88
f				1.0	90

Contd —

Table II — Catalyst-free synthesis of benzopyrano[2,3-d] pyrimidines **4** — *Contd*

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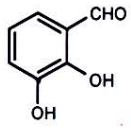
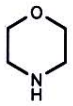
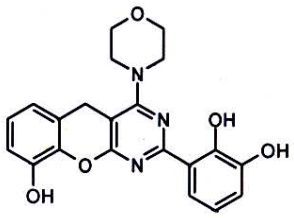
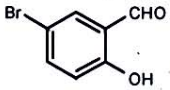
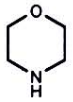
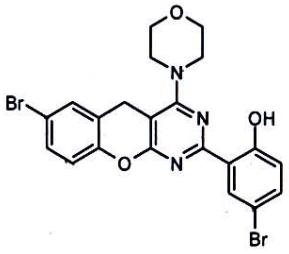
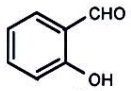
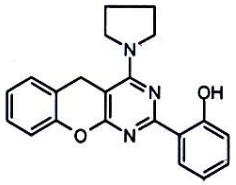
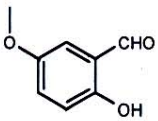
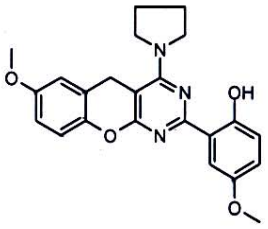
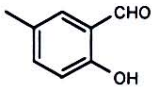
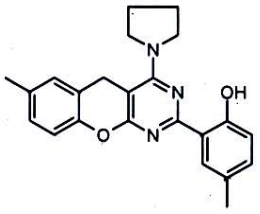
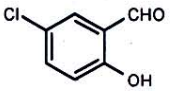
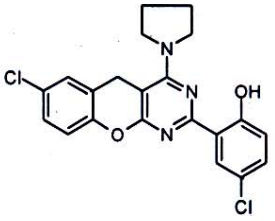
g				2.0	79
h				2.0	77
i				1.5	89
j				1.0	92
k				1.0	79
l				2.0	71

[a]All products showed satisfactory spectroscopic data (IR, ^{1}H and ^{13}C NMR, HRMS); [b] Yields refer to pure, isolated products.

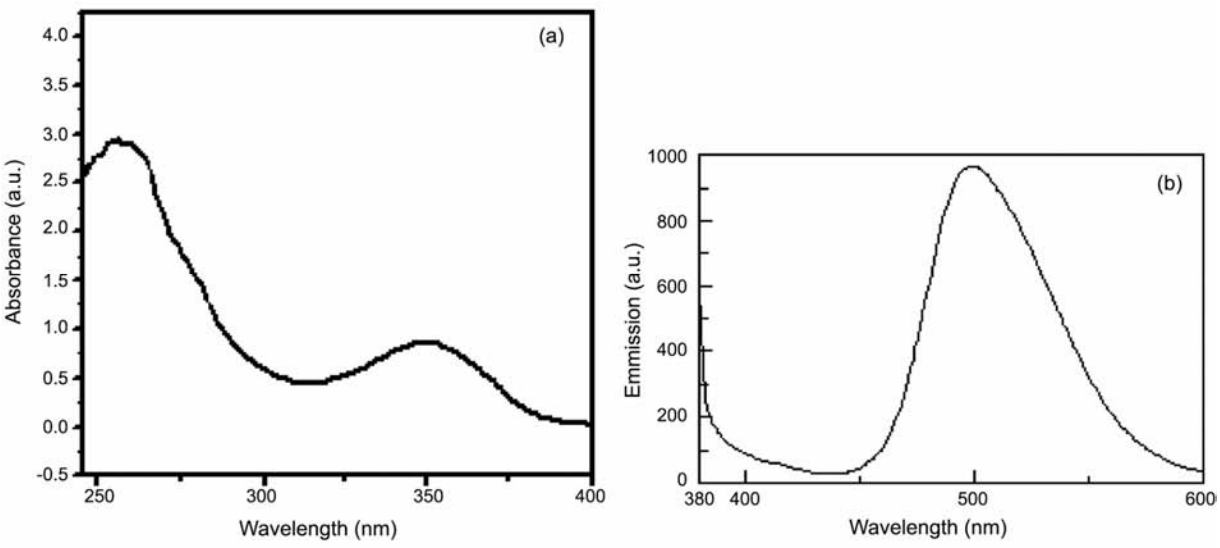
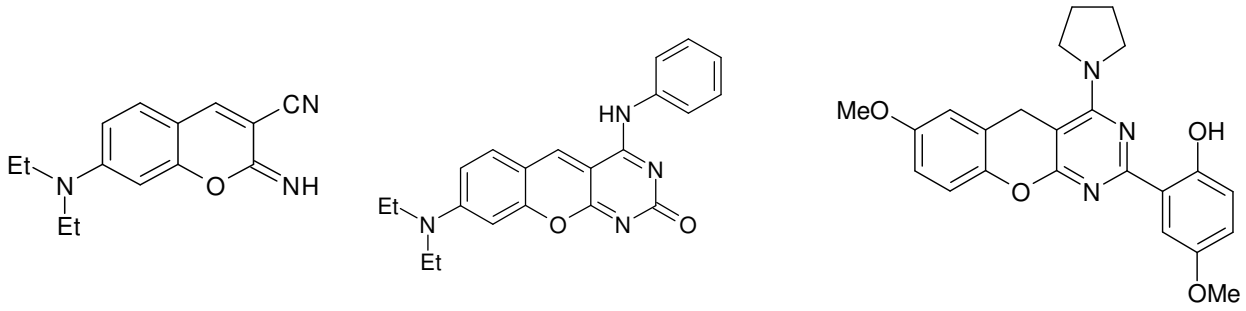


Figure 2 — (a) UV-visible absorption and (b) fluorescence spectra



I
λ= 430 nm

II
λ = 494 nm

III
λ = 500 nm

Figure 3 — Red shift in UV-Vis absorption of iminocoumarin and its derivatives

7.26 (s, 1H, Ar-H), 7.13 (dd, 1H, Ar-H, *J* = 8.1Hz and *J* = 2.1Hz), 6.97-7.05 (m, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 6.84 (d, 1H, Ar-H, *J* = 8.1Hz), 4.16 (s, 2H,-CH_2), 3.76-3.81 (m, 4H,-2CH_2), 2.31 (s, 3H,-CH_3), 2.28 (s, 3H,-CH_3), 1.97-2.01 (m, 4H,-2CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.49, 20.69, 25.49, 25.50, 49.87, 91.26, 116.66, 117.12, 118.12, 118.73, 127.71, 128.70, 128.90, 128.94, 133.46, 133.53, 148.02, 158.29, 160.24, 161.80; HRMS: Calcd for $C_{23}H_{23}N_3O_2$ + Na: *m/z* 396.1688 (M+Na). Found: 396.1683.

4l (Table II): m.p. 280°C; IR (KBr): 3434, 2972, 1602, 1545, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.58 (s, 1H,-OH), 8.33 (d, 1H, Ar-H, *J* = 2.4Hz), 7.06-7.27 (m, 4H, Ar-H), 6.88 (d, 1H, Ar-H, *J* = 9.0Hz), 4.20 (s, 2H,-CH_2), 3.77-3.82 (m, 4H,-2CH_2), 2.00-2.05 (m, 4H,-2CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.39, 25.48, 49.96, 91.04, 116.18, 118.30, 118.94, 119.61, 120.68, 123.61, 128.31, 128.35, 129.07, 132.44, 148.68, 159.06, 160.27, 160.85; HRMS: Calcd for $C_{21}H_{17}N_3O_2Cl_2$ + Na: *m/z* 436.0596 (M+Na). Found: 436.0601.

Conclusion

A catalyst-free, pseudo four-component reaction of salicylaldehydes, malononitrile, and secondary amines has been portrayed leading to formation of benzopyrano [2,3-*d*] pyrimidines. The major advantages of this multi-component approach are (i) catalyst as well as toxic organic solvents are not required, (ii) no purification is needed avoiding the waste generated by silica gel column chromatography, (iii) 100% carbon atom economy and (iv) benzopyrano[2,3-*d*] pyrimidine possessing methoxy substituent show intense fluorescence emission wavelength. It is believed that these observations

portend significant gains toward achieving ideal transformations.

Acknowledgement

Author DMP thanks UGC, New Delhi, India for financial assistance [F. No.42-394/2013 (SR)].

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