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An efficient synthesis of 2-aminobenzochromene derivatives catalysed by tetrabutylammoniumbromide (TBABr) under microwave irradiation in aqueous medium

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TBABr efficiently catalyzes the three-component coupling of substituted aldehyde, α-naphthol or ß-naphthol and malononitrile to afford the corresponding 2-aminobenzochromene, the new protocol under microwave irradiation works in the absence of organic solvent, the yields are high and the reactions go to completion within 2-3 min.

Keywords: 2-Aminobenzochromene, aldehyde, α-naphthol, β-naphthol, malononitrile, TBABr, microwave irradiation, multi component reaction (MCR)

The use of microwave irradiation for carrying out organic reactions is a well-established procedure since reactions are clean, fast and economical. Coupling of the two techniques, that is, organic reactions using microwave irradiation has been a field, which has shown excellent results leading to the development of many reaction procedures, which are environmental friendly falling in the domain of green chemistry. The replacement of toxic organic solvents is one of the most important goals in green chemistry, which inevitably lead to solvent emission and/or waste. These not only avoid the use of solvents for carrying out reactions but also induce significant simplifications to the reaction procedures. The increasing attention during the last decades for environmental protection has led both modern academic and industrial groups to develop chemical processes with high yield and minimum cost whilst using non-toxic reagents, solvents and catalysts[1].

The ever-increasing demands of modern society for new and functional chemicals have led to the development of novel concepts that enable their production and screening at a greater rate than thought two decades ago. The traditional refinement and honing of individual chemical bond-forming steps as part of lengthy linear syntheses has been super seeded by technologies designed for the mass production of vast numbers of compounds, with great structural variation in breathtakingly short periods of time. This process was spearheaded mainly by the pharmaceutical and agrochemical industries which felt most painfully the need to synthesize bioactive molecules of sometimes considerable complexity in an efficient, resource and time sparing way and in compliance with the current stringent environmental legislation. Clearly, linear syntheses with more than ten individual steps, however selective and sophisticated they may be, were no longer an economically and ecologically justifiable option. While high throughput parallel synthesis offered a way out of the predicament of how to produce 'libraries' of thousands of compounds with slightly different structures at one stroke and at a scale, miniaturized enough to allow screening for biological activity, it was not intrinsically 'greener' or more economical than conventional one-compound-at-a-time approaches. An increase in efficiency is gained only if the relationship between structural complexity and the number of steps in a synthesis is improved significantly. In recent year the synthesis of 2-aminobenzochromene has gained acceptance and popularity. These types of derivative synthesized by the multi component reaction (MCR) strategy, one of the tools used to combine economic aspects with the environmental pollution, this process consists of two or more synthetic steps which are carried out without isolation of any intermediate thus reducing time, saving money, energy and raw materials[2].

2-Aminobenzochromene derivatives are widely used in the synthesis of many natural products[3]. These molecules are biological active and find application in pharmacological properties such as anticoagulant, spasmolytic, diuretic, antianaphylactin, anticancer agents[4]. Some 2-aminobenzochromene derivatives are useful cosmetics and pigments[5] and utilized as potential biodegradable agrochemicals[6]. The synthesis of 2-aminobenzochromene has gained acceptance and popularity, and a few conventional methods have been reported by the three component, one-pot condensation of arylaldehyde, α-naphthol or β-naphthol and malononitrile in the presence of basic alumina[7] (3 hr), KF/Al_2O_3 (ref. 8, 5–6 hr). The existing methods involve expensive reagents stoichiometric amount of catalyst longer reaction times, high temperatures, unsatisfactory yields, incompatibility with other functional groups, cumbersome product isolation and environmental pollution. Therefore, there is a need for versatile, simple and environmentally friendly processes for the synthesis of 2-aminobenzochromene. The development of alternative methods would extend the scope of this useful 2-aminobenzochromene.

Result and Discussion

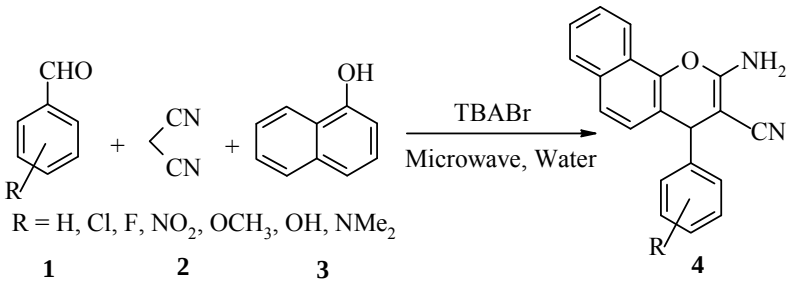
In continuation of the work on the synthesis of medicinally important molecules under environmentally safe conditions[9]. Recently the syntheses of 3,4-dihydropyrimidine-2(1*H*)-ones/-thiones from substituted arylaldehyde, β-keto ester and urea or thiourea under solvent-free condition in the presence of metal chlorides under microwave irradiation[10] have been reported. The utilization of microwaves has been extended for the synthesis of 2-aminobenzochromene **4** using catalytic amounts of TBABr for a three-component coupling of substituted arylaldehyde **1**, α-naphthol or β-naphthol **2** and malononitrile **3** under aqueous condition. While with TBABr the reaction is known to take about 6 hr for completion under reflux conditions[11]. The new protocol under microwave irradiation works in the absence of organic solvent, the yields are high and the reactions go to completion within 2-3 min. as shown in **Scheme I**.

In order to standardize the reaction conditions firstly the reaction was carried out with different amount of TBABr and temperature and the results are summarized in **Table I**. The effect of solvent was studied under different reaction conditions and the results are presented in **Table II**, from this table it is clear that, use of water as a solvent under microwave irradiation gives the best results. Under solvent-free condition, either the yield is low or the product gets charred (**Table II**, entry 4); in solvents such as methanol, ethanol or actetonitrile, the yields are low under microwave irradiation. To study the generality of the process (**Table II**, entry 3), several examples illustrating this method for the synthesis of polyfunctionalized 2-aminobenzochromene were studied and the results are summarized in **Table III**. The three-component cyclocondensation reaction proceeded smoothly under microwave irradiation to give the corresponding products **4** in excellent yields. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halides) or electron donating groups (hydroxy, dimethylamino group) were employed and reacted well to give the corresponding 2-aminobenzochromene in high to excellent yields.

Experimental Section

Melting points were determined on a Buchi melting point apparatus. IR, ^{1}H NMR, ^{13}C NMR, were recorded on a Nicolet 400D FT-IR Spectrophotometer, 300 MHz Brucker Spectrometer respectively. Substituted arylaldehydes, malononitrile, α-naphthol, β-naphthol and TBABr were all commercial products and were used without further purification. Solvents were distilled before use. Reactions were monitored on TLC with the authentic samples. For the microwave irradiation experiments a conventional (unmodified) household microwave oven was used (LG Microwave oven, Electronics India Private Limited). Yields refer to the isolated yields of the products.

General procedure for synthesis of 2-aminobenzochromene. A mixture of benzaldehyde (**1a**, 1.06 g, 10 mmoles), malononitrile (**2**, 0.66 g, 10 mmoles), α-naphthol (**3**, 1.44 g, 10 mmoles), catalytic amount of TBABr (0.80 g, 2.5 mmoles) and water (10 mL) are taken into a Pyrex cylindrical tube, heated in a microwave oven (320 W). At the end of irradiation [2 min, monitored on TLC] the contents were cooled to room temperature and extracted by diethyl ether and ethyl acetate. The combined organic layer was dried over anhyd. Na_2SO_4, concentrated *in vacuo* to afford the crude product, which was further purified by recrystallization using absolute alcohol to get pure 2-amino-3-cyano-4-phenyl-[*4H*]-benzochromene (**4a**, 2.80 g, 94%)



Scheme I

Table I—Optimization of the catalytic activity of TBABr and reaction conditions[a] and the yield of 2-amino-3-cyano-4-(4-methoxyphenyl)-4H-benzochromene

Entry	Amount of TBABr (mmole)	MW (W)[a]	Temp.	Time (min)	Yield (%)[b]
1	10	160	80-85	3	95
2	10	320	97-99	2	98
3	5	160	80-85	3	95
4	5	320	98-100	2	98
5	2.5	160	87	3	95
6	2.5	320	99-102	2	98
7	1	160	88	3	65
8	1	320	98	2	65
9	0.5	320	98	4	60
10	0.1	160	87	3+2	50
11	0.1	320	102	3+2	50
13	None	320	99	3+2	35<

Reaction conditions: 4-methoxybenzaldehyde (10 mmoles), malononitrile (10 mmoles), α-naphthol (10 mmoles) and TBABr catalyst stable, [a]Reaction temperature was measured by immersing a glass thermometer into the reaction mixture immediately after exposure to microwaves; [b]Isolated product

Table II—Comparative study on the effect of various solvents on the synthesis 2-amino-3-cyano-4-(4-methoxyphenyl)-4*H*-benzochromene **4b** in the presence of TBABr under different conditions

Entry	Solvent	Condition[a]	Time	Yield(%)[b]
1	H_2O	Reflux[11]	6h	91
2	None	Reflux	8h	30<
3	H_2O	MW	2 min	98
4	None	MW[c]	2+2 min	60
5	EtOH	MW	3+2 min	75
6	MeOH	MW	3+2 min	78
7	CH_3CN	MW	3+2 min	60

[a]Reaction conditions: 4-methoxybenzaldehyde (10 mmoles), malononitrile (10 mmoles), α-naphthol (10 mmoles) and TBABr (2.5 mmoles), [b]Isolated and unoptimized yields; [c]gave charred product.

Data of some selected compounds

2-Amino-3-cyano-4-(phenyl)-4*H*-benzochromene 4a: IR(KBr): 3455, 3320, 3020, 2932, 2210, 1660, 1613, 1575, 1462, 1381, 1269, 1100, 1023, 820, 754 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO): δ 4.96 (s, 1H), 7.13 (s, 2H), 7.10–7.16 (m, 6H), 7.51–7.68 (m, 3H), 7.94 (d, *J* = 8.5, 1H), 8.23 (d, *J* = 8.4, 1H); Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.54; H, 4.70; N, 9.39. Found: C, 80.42; H, 4.73; N, 9.36%.

2-Amino-3-cyano-4-(4-methoxyphenyl)-4*H*-benzochromene 4b: IR (KBr): 3426, 3336, 2187, 1642, 1591, 1509, 1407, 1233, 1214, 1181, 1141, 1081, 1035, 817, 797, 763, 748, 731 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO): δ 3.71 (s, 3H), 4.84 (s, 1H), 6.87 (d, *J* = 8 Hz, 2H), 7.08–7.10 (m, 3H) 7.16–8.23 (m, 7H), Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.89; H, 4.91; N, 8.53. Found: C, 76.83; H, 4.95; N, 8.52%.

2-Amino-3-cyano-4-(4-nitrophenyl)-4*H*-benzochromene 4c: IR (KBr): 3460, 3335, 2196, 1665, 1600, 1575, 1536, 1500, 1346, 1270, 1195, 1100, 770 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO): δ 5.12 (s, 1H), 7.29 (s, 2H), 7.05 (d, *J* = 8.4, 1H), 7.51–7.72 (m, 3H), 7.52 (d, 2H), 7.90 (d, *J* = 8.4, 1H), 8.15 (d, 2H), 8.27 (d, *J* = 8.4, 1H); Anal. Calcd for $C_{20}H_{13}N_3O_3$: C, 69.97; H, 3.79; N, 12.24. Found: C, 70.05; H, 3.92; N, 12.16%.

2-Amino-3-cyano-4-(3-chlorophenyl)-4*H*-benzochromene 4d: IR (KBr) 3459, 3343, 3025, 2935, 2210, 1650, 1600, 1580, 1470, 1378, 1030, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO): δ 4.98 (s, 1H), 7.24 (s, 2H), 7.12–7.38 (m, 4H), 7.23 (s, 1H), 7.56–7.66 (m, 3H), 7.89 (d, *J* = 8.4, 1H), 8.26 (d, *J* = 8.4, 1H); Anal. Calcd for $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.91; N, 8.42. Found: C, 72.09; H, 4.05; N, 8.44%.

2-Amino-3-cyano-4-(2-chlorophenyl)-4*H*-benzochromene 4e: IR (KBr) 3475, 3318, 2917, 2195, 1670, 1600, 1410, 1360, 1275, 1180, 1040, 805, 750 cm^{-1}; ^1H NMR($CDCl_3$/DMSO): δ 5.41 (s, 1H), 7.20 (s, 2H), 7.01 (d, *J* = 8.4, 1H), 7.25–7.31 (m, 3H), 7.45 (d, *J* = 8.4, 1H), 7.56–7.67 (m, 3H), 7.89 (d, *J* = 8.4, 1H), 8.24 (d, *J* = 8.4, 1H); Anal. Calcd for $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.91; N, 8.42. Found: C, 72.10; H, 4.02; N, 8.35%.

2-Amino-3-cyano-4-(4-flurophenyl)-4H-benzochromene, **4f**: IR (KBr): 3465, 3356, 2191, 1659, 1590, 1529, 1410, 1349, 1260, 1217, 1178, 1081, 1028, 903, 859, 812, 762, 738, 725 cm^{-1}; ^1H NMR

Table III—TBABr catalysed synthesis of 2-amino-benzochromenes

Entry	R^1	Phenol	Product[a]	Yields[b]	Melting point (°C)	
	1	**3**	**4a-k**	(%)	Found	Reported
1	H	1-Naphthol	**4a**	94	206	206-207
2	4-OCH_3	1-Naphthol	**4b**	98	185	182-83
3	4-NO_2	1-Naphthol	**4c**	92	240	239-41
4	3-Cl	1-Naphthol	**4d**	95	220	216-18
5	2-Cl	1-Naphthol	**4e**	94	235	236-37
6	4-F	1-Naphthol	**4f**	93	234	235-37
7	4-Me_2N	1-Naphthol	**4g**	92	206	203-05
8	4-NO_2	2-Naphthol	**4h**	81	185	185-86
9	3-NO_2	2-Naphthol	**4i**	81	178	179-82
10	4-Cl	2-Naphthol	**4j**	84	208	206-08
11	4-OCH_3	2-Naphthol	**4k**	83	193	190-91

[a]All the products are known, characterized by IR, ^{1}H NMR spectral analysis and compared with the authentic samples.[b]Isolated yields. [c]Melting points of compounds are consistent with reported values (references 7, 8 and 11).

($CDCl_3$/DMSO): δ 4.95 (s, 1H), 7.09–7.12 (m, 2H), 7.15 (s, 2H), 7.21–8.23 (m, 8H); Anal. Calcd for $C_{20}H_{13}FN_2O$: C 75.94, H 4.14, N 8.86; Found C 76.12, H 4.11, N 8.77%.

Amino-3-cyano-4-(4-dimethylaminophenyl)-4*H*-benzochromene 4g: IR (KBr): 3465, 3340, 3090, 2955, 2863, 2806, 2193, 1662, 1605, 1570, 1522, 1400, 1380, 1342, 1262, 1190, 1100, 800, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO): δ 2.84 (s, 6H), 4.75 (s, 2H), 7.03–7.10 (m, 3H), 6.65 (d, J = 8.4, 2H), 7.06 (d, J = 8.4, 2H), 7.53-7.64 (m, 3H), 7.88 (d, J = 8.4, 1H), 8.24 (d, J = 8.4, 1H); Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.42; H, 5.57; N, 12.32. Found: C, 77.36; H, 5.60; N, 12.23%.

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