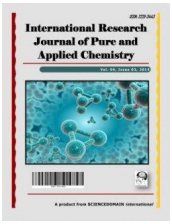

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Room Temperature Na_2CO_3-Catalysed One-pot Reaction of Benzaldehydes, Malononitrile and Phloroglucinol in Water, a Simple Green Synthetic Route to Antibacterial 2-Amino-4*H*-Benzopyrans

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Authors' contributions

This work was carried out in collaboration between both authors. Author IBM designed the study, participated in the interpretation of the spectral data and wrote the first draft of the manuscript. Author SOM performed the laboratory experiments, acquired and interpreted the spectral data and participated in editing the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

A simple and green room temperature Na_2CO_3-catalysed three-component reaction of benzaldehydes, malononitrile and phloroglucinol in water to give 2-amino-4*H*-benzopyrans in 70-96% yields is described. The reaction was tolerated by electron-donating and electron-withdrawing substituents on the benzaldehydes. Operational simplicity, use of readily available and safe reagents, easy work-up and high yields are some of the positive attributes of this method. The prepared compounds showed very good to promising activities against both gram negative and gram positive bacteria with minimum inhibitory concentrations of 0.25 to 25.0 mg/ml as compared to that of ciproflaxin at 0.25 mg/ml.

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Keywords: 2-aminochromene; malononitrile; phloroglucinol; benzaldehydes; three-component reaction.

1. INTRODUCTION

Water plays an essential role in life processes but its use as a solvent in organic synthesis has been limited. Despite the fact that it is the cheapest, safest and most nontoxic solvent in the world, its presence is generally avoided through the dehydrative drying of substrates and solvents. The use of water as a medium for organic reactions is therefore one of the latest challenges for modern organic chemists.

2-aminobenzopyrans or 2-aminochromenes are a class of compounds that have generated interest recently due to their biological activities [1-5]. These compounds are usually prepared by a base-catalysed three-component reaction of benzaldehydes, malononitrile and activated phenols. The basic catalysts that have been employed in these and related reactions include, NaOH [6], K_2CO_3 [5], $Na_2CaP_2O_7$ [7], Et_3N [8] and piperidine [9-11]. Most of these reported procedures for the synthesis of 2-aminochromenes required purification of the products, long reaction times, organic solvents and elevated temperatures.

As part of our interest in the synthesis of heterocyclic compounds [12-14] and green chemistry [15] we report a simple Na_2CO_3-catalysed one-pot reaction of benzaldehydes, malononitrile and phloroglucinol in water to give 4-phenyl-2-amino-4*H*-benzopyrans. Na_2CO_3 is produced in large quantities in Sua, Botswana and has extensive domestic use therefore relatively safe. The activities of the prepared 2-aminopyrans against gram positive and gram negative bacteria were assessed.

2. EXPERIMENTAL

2.1 General Reaction Conditions

Melting points were determined on a Stuart melting point apparatus SMP1 (UK) and are uncorrected. Infrared spectra were recorded neat on a Perkin Elmer FT-IR spectrophotometer 1000. ^{1}H, ^{13}C and 2D-NMR spectra were recorded on a Bruker Avance DPX 300 MHz NMR spectrometer in $CDCl_3$ (or acetone-d_6) with TMS as an internal standard at room temperature. Electron impact (EI) High resolution mass spectra (HR-MS) were carried out on GCT Premier Mass Spectrometer (Waters) ionisation energy 70 eV, at the Chemistry Department, University of Botswana. All reactions were monitored by TLC, which was carried out on 0.25 mm layer of Merck silica gel 60 F254 pre-coated on aluminium sheets. Laboratory grade chemicals and solvents available commercially in high purity were used. All the prepared compounds were identified by physical properties, IR, HRMS and NMR data. Yields reported are isolated yields unless indicated otherwise.

2.2 Typical Procedure

A mixture of benzaldehyde (0.30 g, 2.8 mmol), malononitrile (0.19 g, 2.8 mmol) and phloroglucinol (0.36 g, 2.8 mmol) was dissolved in methanol (1.0 cm^3) in a round bottom flask. A solution of Na_2CO_3 (0.09 g, 0.8 mmol) in water (19.0 cm^3) was then added to the round bottom flask and the resulting suspension was stirred at room temperature for 10 hrs. The solid formed was filtered off, washed with water followed by cold methanol and dried in an oven at 100 ^{o}C to give 2-amino-3-cyano-5,7-dihydroxy-4-phenyl-4*H*-chromene in 65% yield.

2.2.1 2-Amino-3-cyano-5,7-dihydroxy-4-henyl-4H-chromene (4)

White solid, 65%; mp 162-164 ^{o}C; IR (neat) v: 3331, 3203, 2188, 1654, 1618, 1468 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.48 (1H, s, H-4), 5.98 (1H, d, *J* = 1.5 Hz, H-6), 6.06 (1H, d, *J* = 1.5 Hz, H-8), 6.78 (2H, s, 2OH), 7.20 (5H, m, ArH), 9.57 (2H, br, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.8 (C-4), 58.0 (C-3), 94.2 (C-8), 99.3 (C-6), 102.8 (C-4a), 121.3 (CN), 126.6 (C-4'), 127.5 (C-2' and 6'), 128.6 (C-3' and 5'), 146.8 (C-1'), 150.9 (C-8a), 155.8 (C-7), 157.9 (C-5), 160.9 (C-2); HRMS-EI (*m/z*) calcd for $C_{16}H_{12}N_2O_3$: 280.2848; found, 280.2853.

2.2.2 2-Amino-3-cyano-5,7-dihydroxy-4-(4'-methoxyphenyl)-4H-chromene (4a)

Yellow solid, 75%; mp 211-212°C; IR (neat) v_{max}: 3460, 3226, 2994, 2191, 1648, 1602, 1583, 1409 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.71 (3H, s, OCH_3), 4.42 (1H, s, H-4), 5.96 (1H, d, *J* = 2.4 Hz, H-6), 6.06 (1H, d, J = 2.4 Hz, H-8), 6.80 (2H, dd, *J* = 8.8 and 2.3 Hz, H-3' and 5'), 7.07 (2H, dd, *J* = 8.8 and 2.3 Hz, H-2' and 6'), 9.55 (2H, br, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 35.8 (C-4),

54.3 (OCH_3), 58.5 (C-3), 93.9 (C-8), 98.6 (C-6), 103.3 (C-4a), 113.2 (C-3' and 5'), 120.9 (CN), 128.0 (C-2' and 6'), 138.3 (C-1'), 150.7 (C-8a), 155.5 (C-4'), 157.3 (C-7), 158.2 (C-5), 161.3 (C-2); HRMS-EI (*m/z*) calcd for $C_{17}H_{14}N_2O_4$: 310.3012; found, 310.3009.

2.2.3 2-Amino-3-cyano-5,7-dihydroxy-4-(4'-hydroxyphenyl)-4H-chromene (4b)

Yellow solid, 79%; mp 215-216 °C; IR (neat) ν_{max}: 3457, 3448, 2187, 1641, 1609, 1590, 1506, 1413 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 4.61 (1H, s, H-4), 6.05 (2H, br, 2OH), 6.13 (1H, d, *J* = 2.1 Hz, H-6), 6.21 (1H, d, *J* = 2.1 Hz, H-8), 6.75 (2H, dd, *J* = 9.3 and 2.7 Hz, H-3' and 5'), 7.06 (2H, dd, *J* = 9.3 and 2.7 Hz, H-2' and 6'), 8.60 (2H, br, NH_2); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 35.9 (C-4), 60.1 (C-3), 94.4 (C-8), 99.1 (C-6), 103.7 (C-4a), 114.9 (C-3' and 5'), 120.2 (CN), 128.4 (C-2' and 6'), 137.2 (C-1'), 150.8 (C-4'), 155.4 (C-8a), 155.8 (C-7), 157.8 (C-5), 160.5 (C-2); HRMS-EI (*m/z*) calcd for $C_{16}H_{12}N_2O_4$: 296.2837; found, 296.2841.

2.2.4 2-Amino-3-cyano-5,7-dihydroxy-4-(4-hydroxy-3-methoxyphenyl)-4H-chromene (4c)

Yellow solid, 70%; mp 239-240 °C; IR (neat) ν_{max}: 3447, 3354, 2194, 1657, 1906, 1506, 1480 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 3.76 (3H, s, OCH_3), 4.61 (1H, s, H-4), 6.02 (2H, s, 2OH), 6.11 (1H, d, *J* = 2.1 Hz, H-6), 6.21 (1H, *J* = 2.1 Hz, H-8), 6.64 (1H, dd, *J* = 8.1 and 1.8 Hz, H-6'), 6.73 (1H, d, *J* = 8.1 Hz, H-5'), 6.86 (1H, d, *J* = 2.1 Hz, H-2'), 8.56 (2H, br, NH_2); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 36.3 (C-4), 55.4 (OCH_3), 60.1 (C-3), 94.5 (C-8), 99.1 (C-5), 103.6 (C-2'), 111.2 (C-4a), 114.7 (C-5'), 119.7 (CN), 120.1 (C-6'), 137.7 (C-1'), 145.1 (C-4'), 147.1 (C-3'), 150.9 (C-8a), 155.4 (C-5), 157.4 (C-7) 160.4 (C-2); HRMS-EI (*m/z*) calcd for $C_{17}H_{14}N_2O_5$: 326.3003; found, 326.3299.

2.2.5 2-Amino-4-(benzo[d][1,3]dioxol-5-yl)-3-cyano-5,7-dihydroxy-4H-chromene (4d)

Yellow solid, 72%; mp 231-232 °C; IR (neat) ν_{max}: 3463, 3361, 2191, 1657, 1631, 1593, 1487 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.49 (1H, s, H-4), 5.95 (2H, s, OCH_2O), 5.97 (1H, d, *J* = 2.2 Hz, H-6), 6.08 (1H, d, *J* = 2.2 Hz, H-8), 6.59 (1H, dd, *J* = 7.8 and 2.1 Hz, H-6'), 6.77 (1H, d, *J* = 7.8 Hz, H-5'), 6.82 (1H, d, *J* = 2.1 Hz, H-2'), 9.58 (2H, br, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.5 (C-4), 58.1 (C-3), 94.2 (C-8), 99.3 (C-5), 101.2 (OCH_2O), 107.9 (C-5'), 108.4 (C-2'), 120.4 (C-4a), 121.3 (CN), 140.9 (C-6'), 146.0 (C-1'), 147.5 (C-4'), 150.8 (C-3'), 155.7 (C-8a), 157.9 (C-5 and 7), 160.9 (C-2); HRMS-EI (*m/z*) calcd for $C_{17}H_{12}N_2O_5$: 324.2946; found, 324.2948.

2.2.6 2-Amino-3-cyano-5,7-dihydroxy-4-(o-tolyl)-4H-chromene (4e)

Yellow solid, 78%; mp 220-221 °C; IR (neat) ν_{max}: 3454, 3332, 2194, 1661, 1622, 1596, 1465 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.53 (3H, s, CH_3), 4.95 (1H, s, H-4), 6.02 (1H, d, *J* = 2.1 Hz, H-6), 6.18 (1H, d, *J* = 2.1 Hz, H-8), 6.94-7.12 (4H, m, ArH); ^{13}C NMR (75 MHz, CD_3OD) δ 18.4 (CH_3), 32.3 (C-4), 58.2 (C-3), 93.9 (C-8), 98.6 (C-6), 103.4 (C-4a), 121.1 (CN), 125.7 (C-6'), 125.9 (C-4'), 128.0 (C-5'), 129.6 (C-3'), 134.8 (C-2'), 144.7 (C-1'), 150.9 (C-8a), 155.6 (C-7), 157.3 (C-5) 160.8 (C-2); HMRS-EI (*m/z*) calcd for $C_{17}H_{14}N_2O_3$: 294.3004; found, 294.3011.

2.2.7 2-Amino-3-cyano-5,7-dihydroxy-4-(m-tolyl)-4H-chromene (4f)

Yellow solid, 83%; mp 181-182 °C; IR (neat) ν_{max}: 3452, 3329, 2192, 1659, 1601, 1459 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 229 (3H, s, CH_3), 4.56 (H-4), 6.09 (2H, s, H-6 and 8), 6.95 (3H, m, H-2', 4' and 6'), 7.16 (1H, dd, *J* = 7.5 and 6.9 Hz, H-5'); ^{13}C NMR (75 MHz, CD_3OD) δ 20.2 (CH_3), 36.5 (C-4), 58.3 (C-3), 93.9 (C-8), 98.6 (C-6), 103.0 (C-4a), 121.0 (CN), 124.1 (C-6'), 126.6 (C-4'), 127.6 (C-5'), 127.7 (C-2'), 137.3 (C-3'), 145.9 (C-1'), 150.8 (C-8a), 155.5 (C-7), 157.5 (C-5), 161.1 (C-2); HRMS-EI (*m/z*) calcd for $C_{17}H_{14}N_2O_3$: 294.3004; found, 294.2998.

2.2.8 2-Amino-3-cyano-5,7-dihydroxy-4-(p-tolyl)-4H-chromene (4g)

Yellow solid, 79%; mp 132-124 °C; IR (neat) ν_{max}: 3449, 3338, 2193, 1660, 1599, 1452 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 2.27 (3H, s, CH_3), 4.64 (1H, s, H-4), 6.04 (2H, s, 2OH), 6.14 (1H, d, *J* = 2.1 Hz, H-8), 6.22 (1H, d, *J* = 2.1 Hz, H-6), 7.08 (4H, m, ArH), 8.64 (2H, br, NH_2); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 20.2 (CH_3), 36.4 (C-4), 60.0 (C-3), 94.4 (C-8), 99.1 (C-6), 103.4 (C-4a), 120.0 (CN), 127.3 (C-3' and 5'), 128.7 (C-2' and 6'), 135.5 (C-4'), 143.2 (C-1'), 150.9 (C-8a), 155.5 (C-7) 157.6 (C-5), 160.4 (C-2); HRMS-EI (*m/z*) calcd for $C_{17}H_{14}N_2O_3$: 294.3004; found, 294.3010.

2.2.9 2-Amino-3-cyano-5,7-dihydroxy-4-(4-nitrophenyl)-4H-chromene (4h)

Yellow solid, 96%; mp 268-270 ^{o}C; IR (neat) ν_{max}: 3399, 3180, 2206, 1651, 1587, 1512, 1409 cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 4.82 (1H, s, H-4), 6.16 (1H, d, *J* = 2.1 Hz, H-8), 6.22 (1H, d, *J* = 2.1 Hz, H-6), 6.25 (2H, s, 2OH), 7.48 (2H, d, *J* = 8.7 Hz, H-2' and 6'), 8.18 (2H, d, *J* = 8.7 Hz, H-3' and 5'), 8.85 (2H, br, NH_2); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 36.9 (C-4), 58.3 (C-3), 94.6 (C-8), 99.1 (C-6), 101.6 (C-4a), 119.4 (CN), 123.4 (C-3' and 5'), 128.5 (C-2' and 6'), 146.6 (C-4'), 150.7 (C-1'), 153.7 (C-8a), 155.6 (C-7), 158.3 (C-5), 160.5 (C-2); HRMS-EI (*m/z*) calcd for $C_{16}H_{11}N_3O_5$: 325.2799; found, 325.2802.

2.2.10 2-Amino-4-(4-chlorophenyl)-3-cyano-5,7-dihydroxy-4H-chromene (4i)

Yellow solid, 73%; mp 142-144 ^{o}C, IR (neat) ν_{max}: 3606, 3460, 3301, 2994, 2192, 1649, 1608, 1579 cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 4.65 (1H, s, H-4), 6.11 (3H, m, H-8 and 2OH), 6.19 (1H, d, *J* = 3.6 Hz, H-6), 7.22 (2H, d, *J* = 8.7 Hz, H-2' and 6'), 7.32 (2H, d, J = 8.7 Hz, H-3' and 5'), 8.95 (2H, br, NH_2); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 36.3 (C-4), 59.2 (C-3), 94.4 (C-8), 99.1 (C-6), 119.4 (C-4a), 128.1 (C-3' and 5'), 129.1 (C-2' and 6'), 130.9 (C-4'), 145.2 (C-1'), 151.2 (C-8a), 155.5 (C-7), 157.9 (C-5), 160.4 (C-2); HRMS-EI (*m/z*) calcd for $C_{16}H_{11}ClN_2O_3$: 314.7214; found, 314.7220.

2.3 Antibacterial Activity

Antibacterial activities of the prepared compounds were assessed using the broth macro dilution method [16,17]. Preparation of the stock solutions of the prepared compounds involved dissolving each of the compounds (250 mg) in DMSO (1.0 ml). This solution was then transferred to a 10 ml volumetric flask and filled to the mark with DMSO to make the 25 mg/ml stock solutions. Serial dilution was then employed to come with solutions of concentrations 12.5, 2.5, 1.25 and 0.25 mg/ml. These concentrations were then tested against two gram negative bacteria *S. aureus* (ATCC 9144) and *E. coli* (ATCC 11229) and two gram positive bacteria *B. subtilis* (ATCC 6633) and *P. aeruginosa* (NCTC 10332) obtained from the Department of Biological Science, University of Botswana. All the tests were done in triplicates. Ciprofloxacin was used as a positive standard while DMSO was used as a negative standard. The antibacterial activity was recorded as the minimum inhibitory concentration (MIC) of the test compound that inhibited an observable growth of the bacteria.

3. RESULTS AND DISCUSSION

Our initial experiments were focused on the Na_2CO_3-catalysed reaction of benzaldehyde **1**, malononitrile **2** and phloroglucinol **3**. Thus, reaction of equimolar mixture of these three reagents in a mixture of H_2O and MeOH (95:5; v/v) at room temperature for 10 h afforded 2-aminobenzopyran **4** as a white solid in 65% yield, Scheme 1. This product was found to be pure enough to allow characterization without further purification. The structure of **4** was confirmed by mass spectrometry, IR, ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of **4** (Fig. 1) exhibited a characteristic singlet at δ 4.48 due to H-4, two doublets at δ 5.98 and 6.06 due to H-6 and H-8 and a broad signal at δ 9.57 integrating for two protons due to -NH_2. The IR spectrum spectrum of **4** showed the presence of the OH and NH_2 functionalities at 3331-3203 cm^{-1} and the cyano group at 2188 cm^{-1}.

The mechanism of the reaction is thought to involve an aldol reaction of benzaldehyde **1** and malononitrile **2** to give **5**. Subsequent Michael addition of **3** to the aldol product **5** gives intermediate **6**. Cyclisation of intermediate **6** proceed to give imine **7** followed by imine-enamine tautomerism to afford the desired product **4**, Scheme 1.

To explore the scope and generality of the reaction, our research work was extended to various substituted benzaldehydes. Thus, the reaction of benzaldehyde **1a** with an electron-donating methoxy group, malonitrile **2** and phloroglucinol **3** proceeded smoothly to afford aminobenzopyran **4a** in 75% yield. 4-hydroxybenzaldehyde **1b** also participated in this three-component reaction to give benzopyran **4b** in 79% yield, Scheme 2. This result suggests that free hydroxyl groups on the benzaldehyde have no significant effect on this reaction. In addition, disubstituted benzaldehyde derivatives **1c** and **1d** also participated in the three-component reaction to give the corresponding 2-aminobenzopyrans **4c** and **4d** in 72 and 70% yield respectively. The reactions described thus far involved benzaldehyde derivatives with substituents that donating electron to the aromatic ring by resonance and these were well tolerated by the three-component reaction. To

investigate the tolerance of the procedure to groups that donate electrons by inductive effect, methylbenzaldehydes **1e-g** were used in the three-component reaction and this afforded the corresponding benzopyrans **4e-g** in 78-83% yields, Scheme 2. In almost all of the studied examples, no considerable effects of electron-donating groups on the reaction were observed.

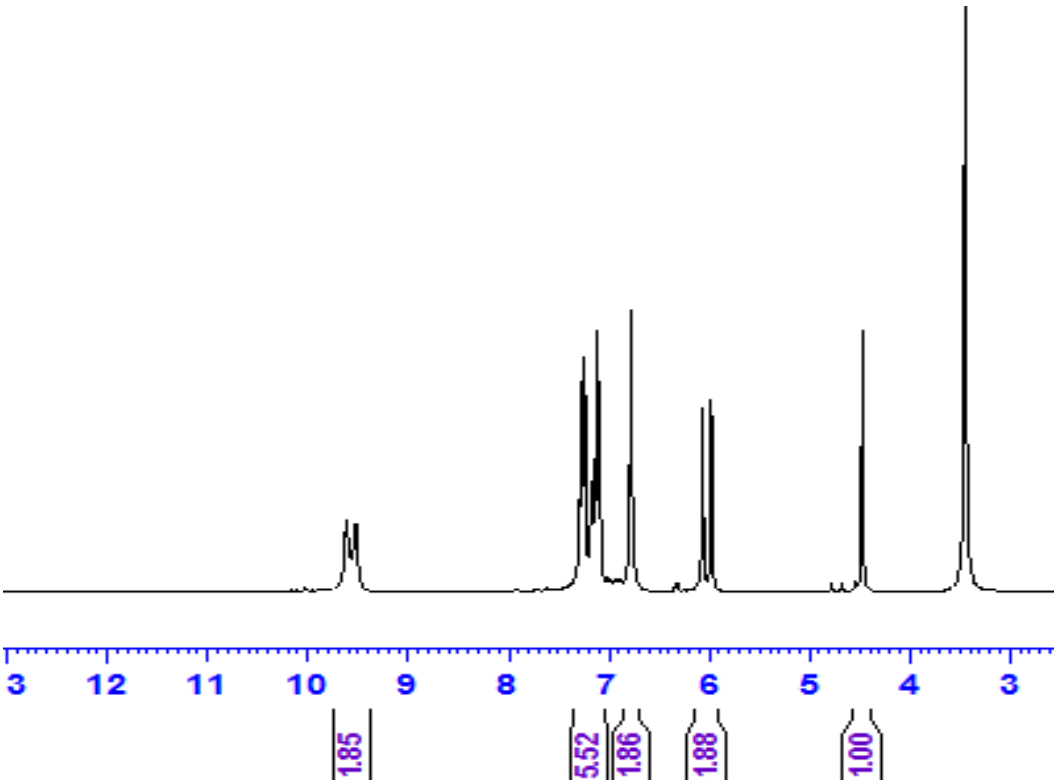
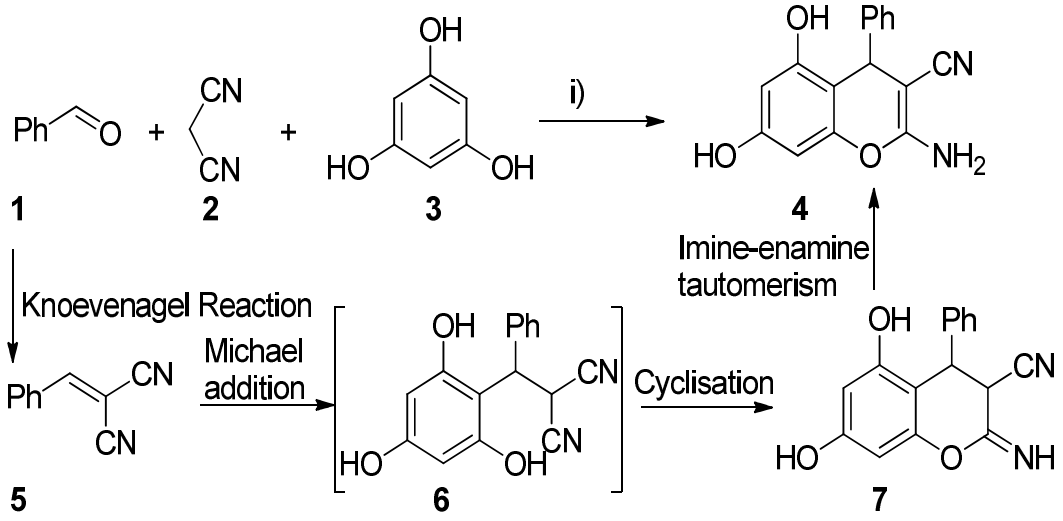


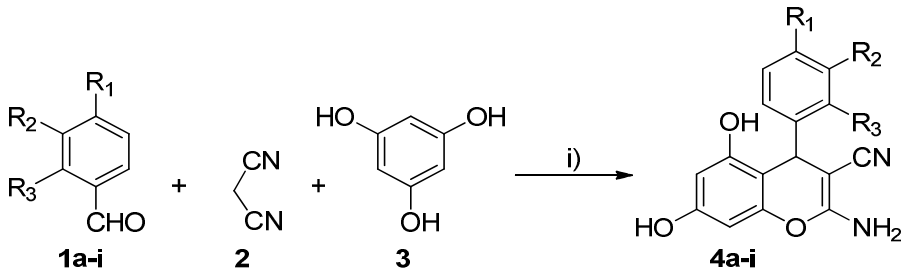
Fig. 1. ^{1}H spectrum of compound 4 in DMSO-d_6



Scheme 1: Reagents and conditions: i) Na_2CO_3 (30 mol%), H_2O/MeOH (95:5 v/v), 25 ^oC, 10 h, 65%

Electron-withdrawing groups on the benzaldehyde were also well tolerated by the three-component reaction. Benzaldehyde **1h** with the electron withdrawing nitro group reacted with malononitrile **2** and phloroglucinol **3** under the conditions described above to give benzopyrans **4h** in 96%. Likewise, Chlorobenzaldehyde **1i** participated in the reaction to afford the corresponding benzopyran **4i** in 73% yields, Scheme 2.

The antibacterial activities of the prepared compounds are presented in Table 1. Benzopyran **4h** with a nitro group showed activity comparable to that of the standard positive control against all four test organisms while benzopyran **4i** showed that kind of activity against gram negative bacteria. Compound **4b** showed activities comparable for that of the ciprofloxacin against *E. coli*, *B. subtilis* and *P. aeruginosa* while **4d** showed comparable activities against *E. coli* and *B. subtilis*. It is important to note that both benzopyrans **4b** and **4d** have a free hydroxyl group on the 4-phenyl group. The rest of the compounds showed promising activity against all the test bacteria with minimum inhibitory concentrations ranging mostly from 12.5 to 1.25 mg/ml.



1a-i **2** **3** **4a-i**

Aldehyde	R_1	R_2	R_3	Yield (%)
1a	OMe	H	H	75
1b	OH	H	H	79
1c	OCH_2O		H	72
1d	OH	OMe	H	70
1e	Me	H	H	79
1f	H	Me	H	83
1g	H	H	Me	78
1h	NO_2	H	H	96
1i	Cl	H	H	73

Scheme 2: Reagents and conditions: i) Na_2CO_3 (30 mol%), H_2O/MeOH (95:5 v/v), 25 ^oC, 10 h

Table 1. Antibacterial activities of compounds 4-4i

	Minimum inhibitory concentration (MIC; mg/ml)			
Compound No.	***S. aureus***	***E. coli***	***B. subtilis***	***P. aeruginosa***
4	12.5	1.25	25.0	25.0
4a	12.5	2.50	2.50	2.50
4b	1.25	**0.25**	**0.25**	**0.25**
4c	12.5	2.50	2.50	2.50
4d	1.25	**0.25**	**0.25**	1.25
4e	12.5	2.50	2.50	12.5
4f	12.5	2.50	2.50	2.50
4g	12.5	2.50	12.5	12.5
4h	0.25	0.25	0.25	0.25
4i	0.25	0.25	2.50	2.50
Ciprofloxacin	0.25	0.25	0.25	0.25

4. CONCLUSION

A one-pot Na_2CO_3-catalysed reaction of benzaldehydes, malononitrile and phloroglucinol to give 2-amino-4*H*-benzopyran derivatives that avoid the use of hazardous organic solvents has been described. The advantage of this procedure is that the products are isolated from the reaction mixture in pure form and therefore eliminates the need for chromatographic purification. Arrays of substituents on benzaldehyde were well tolerated by the reaction. The prepared 2-aminobenzopyrans showed very good to good antibacterial activities.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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