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PAPER

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A series of functionalized pyrans fused with quinolones, naphthaquinones, coumarins and pyrones have been synthesized using three component reactions of arylglyoxal monohydrate, malononitrile, and a wide range of cyclic 1, 3-dicarbonyls under microwave irradiation. This method is a simple and straightforward method for the easy access of fused and functionalized pyrans tethered with aroyl group without involving any catalyst and column chromatographic purifications.

1. Introduction

Microwave-assisted multicomponent reactions are one of the preferred reaction strategy in organic synthesis.[1] Due to short reaction time and less energy consumptions in microwave heating as compared to the conventional heating process, microwave heating has gained tremendous popularity among organic, medicinal and material chemists.[2] In addition to these, performing reactions under catalyst-free conditions, provide additional benefits, such as no toxicity and cost for the catalyst. Considering these virtues, in recent times microwave-assisted catalyst-free MCRs have gained considerable interest in organic synthesis.[3]

Pyrans fused with other cyclic molecules are abundant in various natural and bioactive synthetic products.[4] Pyranoquinoline (pyran fused with quinoline) core is found in many alkaloids such as Flindersine , Oricine, Veprisine, and (+)–Orixalone D.[5] These bioactive alkaloids and their derivatives exhibit wide range of pharmacological activities such as antiallergic, anti inflammatory, psychotropic, and estrogenic activities.[6] Similarly, pyrans fused with nepthaquinone derivatives such as Kalafungin and Lapachone show anticancer, anti-inflammatory and antibacterial, activities.[7] Likewise, pyrans fused with coumarins (pyranocoumarins) possess broad pharmacological activities such as anticancer, anti-hepatitis B virus, anti HIV-1, anti-inflammatory, antimicrobial, and antiproliferative activity etc.[8] In addition, they are used as photoactive drugs for skin disorders.[9] Pyranocoumarins are also used as anti-hyperglycemic and anti-dyslipidemic agents.[10] Structures of a few representative bioactive fused pyrans are shown in Fig.1. Considering their widespread applications there is a continuing effort to synthesize either new fused pyrans or to develop new methodology for their synthesis.[11] In the literature, a few methods are known for the synthesis of coumarin fused pyrans having benzoyl substituent using multicomponent approach using various catalysts such as $NH_4H_2PO_4$,[12] Graphine oxide[13] etc. Although these methods are useful for the synthesis of coumarin fused pyrans still these methods are limited only towards the synthesis of pyranocoumarins whereas we were looking for a

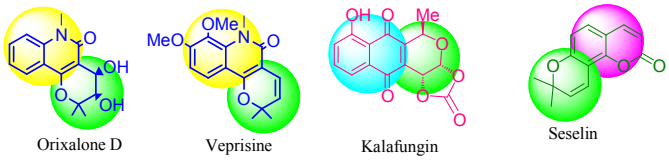

Figure 1. Structures of some biologically active pyrans fused with quinoline, nephthaquinone, and coumarins.

versatile and greener methodology for the construction of diverse functionalized pyrans fused with quinolone, naphthaquinone, pyrone as well as coumarins.

In continuation of our work on aryl glyoxal-based MCRs, so far we have shown the three component reactions of arylglyoxal with cyclic 1,3 dicarbonyls and various 1,3-binucleophiles to access a verity of functionalized five membered hetyerocycles.[3a,14] In this paper we are reporting a three component reaction involving arylglyoxal

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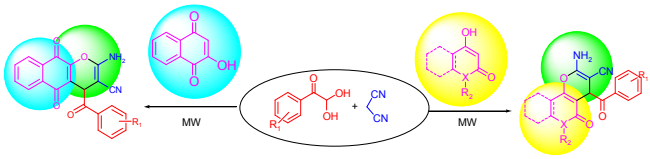
monohydrate, malononitrile, and cyclic 1,3-dicarbonyls such as 4-hydroxy-1-methyl-2(1H)-quinolone, 2-hydroxy naphtha quinone, and 4-hydroxyl coumarins as shown in Scheme 1.

Results and discussion

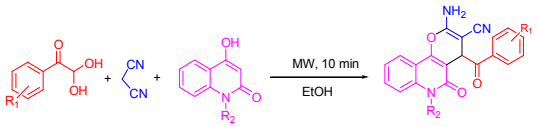
For our initial study, the reaction of phenylglyoxal monohydrate, (1.0 mmol), malononitrile (1.0 mmol) and 4-hydroxy-1-methyl-2(1H)-quinolone (1.0 mmol) was chosen as model reaction. This combination in water as reaction medium provided only trace amount of the desired three component product **1a** after 14 hours of stirring at room temperature. Interestingly, when the same reaction was tested in 2 ml ethanol-water (1:1 v/v) mix solvent at room temperature for the same duration, 15% yield was observed. After having this encouraging result, compound **1a** was initially characterized by IR, ^{1}H and ^{13}C NMR and by elemental analysis. Next, we tried to optimize the reaction conditions by varying the solvents and reaction temperatures. Interestingly, under the reflux conditions and ethanol as solvent, the model reaction provided 60% yield of the desired quinolone fused pyran within 12 hours. To our surprise, when we tried the reaction under microwave irradiation using the same solvent

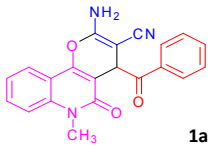
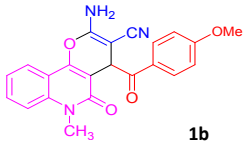
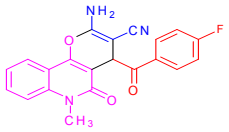
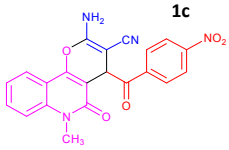
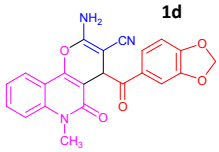
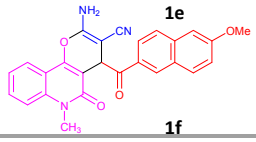


Scheme 1. Synthesis of fused and functionalized pyrans using three component reactions.

ethanol for 10 minutes the desired product 2-amino-4-benzoyl-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2c] quinoline-3-carbonitrile was obtained in very good yield (90%). Increasing reaction time under the same MW heating conditions did not provide any advantage in terms of yield obtained. Thus ethanol as solvent, and 10 minutes MW heating at 110 ^{o}C of the reaction mixture was considered as the optimized conditions. With this optimised conditions in hand,[15] we turned our attention to investigate the scope and general applicability of this procedure by varying the scope of phenylglyoxal monohydrate. Phenylglyoxals tethered with both electron donating and electron withdrawing groups provided the corresponding fused pyrans(**1b-1e**) in very good yields under the optimized conditions and the results are summarized in Table 1. Similar, to phenylglyoxals 6-methoxy naphthaylglyoxal also provided corresponding fused pyran (**1f**) in good yield. All these compounds were fully characterized by IR, ^{1}H, & ^{13}C NMR as well as by elemental analysis. For unambiguous determination of the structure of these

Table 1. MW-assisted three component synthesis of quinolone fused pyrans



Entry	Product	Yield	Melting Point
1.	 **1a**	90	264-266
2.	 **1b**	88	282-284
3.	 **1c**	85	264-266
4.	 **1d**	79	263-265
5.	 **1e**	93	277-280
6.	 **1f**	92	258-260

products single crystal XRD for one of the quinolone fused pyran (**1c**) was recorded as shown in Figure 2.

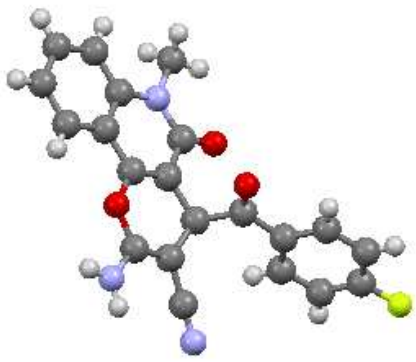
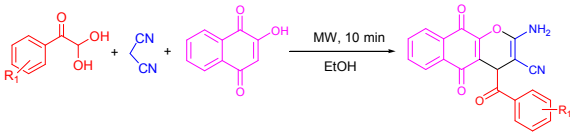
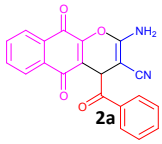
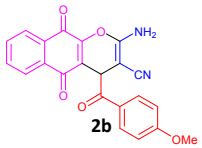
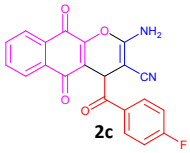
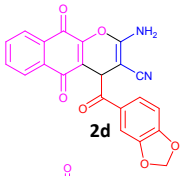
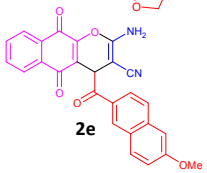


Fig. 2 Crystal structure of **1c** (CCDC 1450244)

In order to explore the versatility and scope of this methodology, next we wanted to explore 2-hydroxy-1,4-nepthaquinone for the preparation of nepthaquinone-fused pyrans using similar reaction strategy. When phenylglyoxal monohydrate was reacted with malononitrile and 2-hydroxy-1,4-nepthaquinone under the microwave irradiation, the corresponding fused pyran **2a** was obtained in very good yield. Next, variability of arylglyoxal was tested and in this case also it was observed that arylglyoxals tethered with electron donating or withdrawing groups as well as 6-methoxy napthyl glyoxal monohydrate provided the corresponding naphthaquinone fused pyran in good yield and the results are summarized in Table 2.

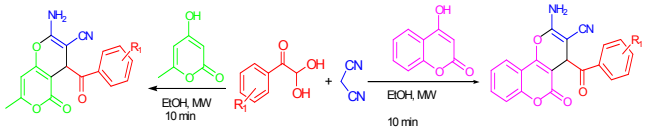
Table 2. MW-assisted three component synthesis of naphthaquinone fused pyrans

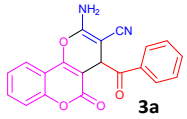
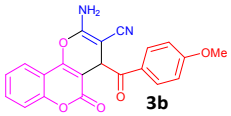
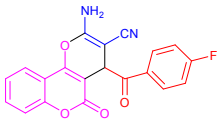
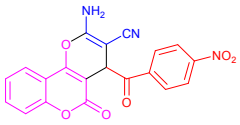
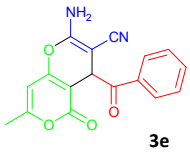


Entry	Product	Yield	Melting point
1.	 **2a**	91	233-245
2.	 **2b**	88	234-236
3.	 **2c**	79	254-256
4.	 **2d**	87	246-248
5.	 **2e**	91	238-240

Next, this methodology was extended to other cyclic 1,3-dicarbonyls such as 4-hydroxy coumarin and 4-hydroxy-6-methyl-2H-pyran-2-one. Interestingly, in these cases also the corresponding fused pyrans were obtained in good yields and the results are summarized in Table 3.

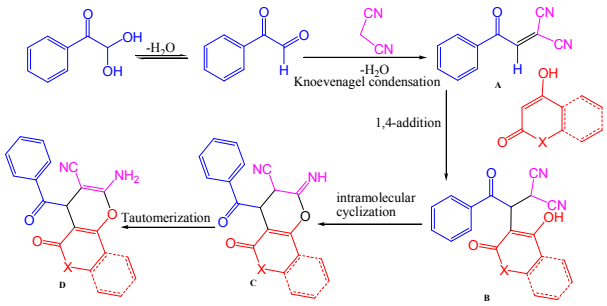
Table 3. MW-assisted three component synthesis of coumarin and pyrone fused pyrans



Entry	Product	Yield	Melting point
1.	 **3a**	79	266-268
2.	 **3b**	75	262-264
3.	 **3c**	77	251-253
4.	 **3d**	70	248-250
5.	 **3e**	85	268-270

It is noteworthy to mention that this methodology works for a diverse cyclic 1,3-dicarbonyls and aryl glyoxals and corresponding fused pyrans tethered with benzoyl group can be accessed in good yields within short time without using any catalyst. All the products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR and by elemental analysis.

Mechanistically we believe that this reaction goes via a Knoevenagel condensation of arylglyoxal monohydrate with malononitrile to provide the corresponding electron deficient alkene **A**. Then 1,4-addition of cyclic 1,3-dicarbonyls to this alkene takes place to provide intermediate **B** and followed by intramolecular cyclization to provide intermediate **C** which undergoes tautomerization and finally desired fused pyran **D** is formed (Scheme 2).



Scheme 2. Plausible mechanism for the synthesis of fused pyrans.

Conclusions

In conclusion, we have developed a straight forward one-pot three component reaction for the easy access of diverse fused pyrans tethered with amino, nitrile and benzoyl group. Due to the presence of these reactive functional groups on the synthesized fused pyrans, it is expected that further cyclization/modification of these molecules will be possible to synthesize new polycyclic heterocycles. The salient features of this methodology are: short reaction time, avoids column chromatographic purification and applicable to a wide range of substrates.

Experimental

General information

All starting materials were purchased from either Sigma Aldrich or Alfa Aesar and used without further purification. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. NMR spectra were recorded on Bruker 400 or 500 MHz for ^{1}H and 100 or 125 MHz for ^{13}C in $CDCl_3$/DMSO-d6, chemical shift values were reported in δ values ppm downfield from tetra methyl silane. Infrared spectra were recorded on a Shimadzu FTIR spectrometer. CHN analyses were carried out using Elementar, Vario micro cube elemental analyzer and melting points were recorded using SRS EZ- Melt automated melting point apparatus by capillary methods and uncorrected.

Typical experimental procedure for the synthesis of 1(a). Typical experimental procedure for the preparation of 1a: A mixture of phenylglyoxal monohydrate (1.0 mmol) and malononitrile (1.0 mmol) in ethanol (2 ml) was stirred at room temperature for 5 minutes. To this mixture 4-hydroxy-1-methyl-2(1H)-quinolone (1 mmol) was added and the resultant mixture was kept under microwave under sealed and stirring conditions for 10 minutes, keeping the temperature at 110 ^{o}C . After completion of the reaction, the reaction mixture was cooled to room temperature and solid product was separated by just filtration and purified by recrystallization from mixture of ethanol and THF. Using similar procedure all other products were prepared.

Spectral data

2-Amino-4-benzoyl-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile(1a) Light yellow solid ; m.p. 264-266 °C ; IR (ATR) 3449, 3319, 2192, 1673, 1622, 1593, 1447, 1377, 1332, 1260, 1218, 1154, 1034 cm^{-1}; ^{1}H NMR (400 MHz, DMSO - d_6 + $CDCl_3$): δ = 8.13 (d, *J* = 7.5 Hz, 2H, ArH), 8.0 (dd, *J* = 8.0 Hz, 1.3 Hz, 1H, ArH), 7.75-7.68 (m, 2H, ArH), 7.58 (d, *J* = 8.1 Hz, 2H, ArH), 7.57 (d, *J* = 7.5 Hz, 1H, ArH) 7.44 (bs, 2H, -NH_2), 7.40 (t, *J* = 7.8 Hz, 1H, ArH), 5.36 (s, 1H, CH), 3.57 (s, 3H, -NCH_3) ppm ; ^{13}C NMR (100 MHz, DMSO - d_6 + $CDCl_3$) : δ = 198.8, 160.1, 151.3, 138.6, 135.9, 133.5, 131.7, 128.8, 128.6, 122.3, 121.9, 119.1, 114.9, 112.6, 106.8, 51.8, 37.7, 29.3 ppm; Anal. Calcd. For $C_{21}H_{15}N_3O_3$ (357.36) : C, 70.58; H, 4.23; N, 11.76; Found: C, 70.61; H, 4.25; N, 11.82.

2-Amino-4-(4-methoxy-benzoyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile(1b) White solid; m.p . 282-284 °C ; IR (ATR) 3779, 3319, 2203, 1674, 1592, 1416, 1365, 1329, 1199, 1172, 1013 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6+$CDCl_3$): δ = 8.12 (d, *J* = 7.2Hz, 2H, ArH), 7.99 (dd, *J* = 8.0, 1.4 Hz, 1H, ArH), 7.75 (t, *J* = 7.75 Hz, 1H,ArH), 7.62 (d, *J* = 8.5 Hz, 1H, ArH), 7.44 (bs, 2H, -NH_2),), 7.43 (t, 1H, ArH), 7.11 (d, *J* = 7.08 Hz, 2H, ArH), 5.34 (s, 1H, CH), 3.89 (s, 3H, OCH_3), 3.56 (s, 3H, NCH_3) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$): δ = 179.1, 163.6, 160.1, 160.1, 151.2, 138.6, 131.8, 131.4, 128.7, 122.4, 121.9, 119.2, 115.1, 113.9, 112.6, 107.1, 55.6, 52.2, 37.2, 29.2 ppm ; Anal. Calcd. for $C_{22}H_{17}N_3O_4$ (387.39) : C, 68.21 ; H, 4.42 ; N, 10.85 ; Found : C, 68.23 ; H, 4.43 ; N, 10.89.

2-Amino-4-(4-fluoro-benzoyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile(1c) White solid ; m.p. 264-266°C; IR (ATR) 3779, 3435, 3259, 2188, 1825, 1654, 1590, 1418, 1367, 1268, 1217, 1201, 1173, 1043, cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6+$CDCl_3$): δ = 8.25-8.22 (m, 2H, ArH), 7.98 (dd, *J* = 7.96, 1.36 Hz, 1H, ArH), 7.74 (t, *J* = 7.16 Hz, 1H, ArH), 7.62 (d, *J* = 8.52 Hz, 1H, ArH), 7.51 (bs, 2H, NH_2), 7.4 (t, *J* = 8.76 Hz, 3H,ArH), 5.40 (s, 1H, CH), 3.56 (s, 3H, NCH_3) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$): δ = 197.7, 166.6, 164.1, 160.1, 151.2, 138.1, 132.8, 132.7, 132.1, 132.0, 131.9, 122.4, 121.8, 119.1, 115.9, 115.2, 112.5, 106.0, 51.7, 40.1 , 37.6, 29.3 ppm ; Anal. Calcd. for $C_{21}H_{14}FN_3O_3$ (375.35) : C, 67.20 ; H, 3.76 N,11.19 ; Found : C, 67.19 ; H, 3.74 ; N,11.22.

2-Amino-6-methyl-4-(4-nitro-benzoyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile(1d) Brown solid ; m.p. 263-265°C; IR (ATR) 3075, 2748, 2330, 1947, 1883, 1644, 1593, 1540, 1454, 1335, 1238, 1113, 1039, cm^{-1} ; ^1H NMR (400 MHz,DMSO – d_6+$CDCl_3$) : δ = 8.41- 8.35 (m, 4H, ArH) 8.01 (dd, *J* = 8.00, 1.36 Hz, 1H, ArH), 7.73-7.71 (m, 1H, ArH), 7.59 (d, *J* = 8.52Hz, 1H, ArH), 7.52 (s, 2H, NH_2), 7.40 (t, *J* = 7.92 Hz, 1H, ArH), 5.42 (s,1H, CH), 3.5 (s, 3H, NCH_3) ppm ; ^{13}C (100 MHz, DMSO-d_6+$CDCl_3$) : δ = 98.5, 160.2, 160.0, 151.3, 150.1, 140.9, 138.6, 131.8, 130.1, 123.6, 122.3, 122.1, 118.8, 114.9, 112.6, 106.3, 51.2, 38.5, 29.3 ppm ; Anal. Calcd. for $C_{21}H_{14}N_4O_5$ (402.36) : C, 62.69 ; H, 3.51 ; N, 13.92 ; Found : C, 62.71 ; H, 3.54 ; N, 13.95.

2-Amino-4-(benzo[1,3]dioxole-5-carbonyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile(1e) White solid ; m.p. 277-280°C ; IR (ATR) 3472, 3302, 3164, 2913, 2208, 2188, 1672, 1619, 1505, 1439, 1383, 1355, 1255, 1159, 1128, 1100, 1032 cm^{-1} ; ^1H NMR (400 MHz, DMSO - d_6+$CDCl_3$) : δ = 7.98 (dd, *J* = 8.0 Hz, 1H, ArH), 7.82 (dd, *J* = 8.32, 1.72 Hz, 1H, ArH), 7.75-7.72 (t, *J* = 8.64, 1H, ArH), 7.59 (d, *J* = 8.48, 1H, ArH), 7.55 (s, 1H, ArH), 7.43- 7.39 (m, 3H, NH_2 + ArH), 7.09 (d, 1H, ArH), 6.17 (s, 2H, OCH_2O), 5.31 (s, 1H, CH), 3.57 (s, 3H, N-CH_3) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$) : δ = 196.8, 160.1, 151.9, 151.2, 147.8, 138.6, 131.7, 130.5, 125.7, 122.3,121.9, 119.0, 114.9, 112.6, 108.1, 107.9, 106.9, 102.1, 52.2, 37.4, 29.2 ; Anal. Calcd. for $C_{22}H_{15}N_3O_5$ (401.37): C, 65.83; H, 3.77; N, 10.47; Found : C, 65.81; H, 3.75; N, 10.52.

2-Amino-4-(6-methoxy-nepthalene-2-carbonyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbontrile(1f) Grey solid ; m.p. 258- 260°C; IR (ATR) 3455, 3304, 2193, 1673, 1620, 1593, 1478, 1464, 1379, 1262, 1191, 1151, 1124, 1030 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$) : δ = 8.11 (d, *J* = 9.0 Hz, 1H, ArH), 8.02 (t, *J* = 8.84 Hz, 2H, ArH), 7.94 (d, *J* = 8.72 Hz, 1H, ArH), 7.75 (t, *J* = 5.8 Hz, 1H, ArH), 7.63 (d, *J* = 8.52Hz, 1H, ArH), 7.48 -7.45 (m, 4H, ArH), 7.32-7.29 (dd, *J* = 8.96, 2.52 Hz, 2H, ArH), 5.57 (s, 1H, CH), 3.9 (s, 3H, OCH_3), 3.57 (s, 3H, N-CH_3) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$) : δ = 198.3, 160.13, 159.6, 151.3, 138.6, 137.2, 131.8, 131.5, 131.4, 131.0, 127.4, 127.1, 124.8, 122.4, 121.9, 119.5, 119.2, 119.15, 115.1, 112.6, 107.0, 106.1, 55.1, 52.2, 37.3, 29.3 ppm ; anal. Calcd. for $C_{26}H_{19}N_3O_4$ (437.14): C, 71.39, H, 4.38, N, 9.61; Found : C, 71.41, H, 4.35, N, 9.64.

2-Amino-4-benzoyl-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile(2a) Red solid ; m.p. 233 - 235 °C ; IR (ATR) 3779, 3341, 2194, 1685, 1662, 1589, 1408, 1363, 1246, 1206, 1046 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$) : δ = 8.16 (d, *J* = 7.28 Hz, 2H, ArH), 8.12 - 8.01 (m, 1H, ArH), 7.95- 7.89 (m, 3H, ArH), 7.75 (t, *J* = 7.48 Hz,1H, ArH), 7.63 (t, *J* = 7.9 Hz, 2H, ArH), 7.62 (bs, 2H, NH_2), 5.5 (s, 1H, CH) ; ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$) : δ = 197.8, 182.5, 176.5, 159.8, 149.9, 135.1, 134.8, 134.6, 134.1, 130.5, 130.4, 129.2, 128.9, 126.4, 125.9, 121.1, 118.6, 51.4, 37.2 ppm ; anal. Calcd. for $C_{21}H_{12}N_2O_4$ (356.33) : C, 70.78; H, 3.39; N, 7.86; Found : C, 70.75; H, 3.41; N, 7.89.

2-Amino-4-(4-methoxy-benzoyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile(2b) Brown solid ; m.p. 234- 236 °C ; IR (ATR) 3776, 3319, 2203, 1719, 1655, 1592, 1416, 1365, 1245, 1199, 1172, 1042 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$) : δ = 8.14 (d, *J* = 7.0 Hz, 2H, ArH), 8.11 – 8.10 (m, 1H, ArH), 7.95- 7.88 (m, 3H, ArH), 7.57 (s, 2H, NH_2), 7.14 (d, *J* = 9.84 Hz, 2H, ArH), 5.45 (s, 1H, CH), 3.90 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$) : δ = 195.9, 182.5, 176.5, 163.9, 159.8, 149.9, 134.8, 134.5, 131.7, 130.5, 130.4, 127.8, 126.3, 125.9, 121.2, 118.7, 114.2, 55.7, 51.8, 36.8 ppm ; Anal. Calcd. for $C_{22}H_{14}N_2O_5$ (386.36) : C, 68.39; H, 3.65; N, 7.25 ; Found : C, 68.37; H, 3.66; N, 7.27.

2-Amino-4-(4-fluoro-benzoyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile(2c) Red solid ; m.p. 254-256°C ; IR (ATR) 3779, 3338, 2188, 1654, 1590, 1417, 1367, 1268, 1246, 1156, 1043 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$): δ = 8.28- 8.25 (m, 2H, ArH), 8.11 – 8.09 (m, 1H, ArH), 7.95- 7.89 (m, 3 H, ArH), 7.62 (bs, 2H, NH_2), 7.46 (t, *J* = 8.8 Hz, 2H, ArH), 5.5 (s, 1H, CH) ppm ; ^{13}C NMR (400 MH_Z, DMSO-d_6+$CDCl_3$) δ = 196.5, 182.5, 176.5, 159.8, 149.9, 134.9, 134.6, 132.4, 132.3, 130.5, 130.4, 126.4, 126.0, 120.9, 118.6, 116.2, 115.9, 51.3, 37.2, Anal .calcd. for $C_{21}H_{11}FN_2O_4$ (374.32): C, 67.38 ; H, 2.96 ; N, 7.48 ; Found : C, 67.36 ; H, 2.98 ; N, 7.51.

2-Amino-4-(benzo[1,3]-dioxole-5-carbonyl)-5,10-dioxo-5,10-dihydro-4Hbenzo[g]chromene-3-carbonitrile(2d) Orange solid ; m.p. 246-248 °C ; IR (ATR) 3470, 3335, 3088, 2195, 1677, 1647, 1062, 1589, 1503, 1438, 1353, 1268, 1249, 1209, 1100, 1038, 949, 869, 797, 726 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$): δ = 8.09 - 8.07 (m, 1H, ArH), 7.94 - 7.91 (m, 1H, ArH), 7.89-7.83(m, 3H, ArH), 7.58-7.57 (m, 1H, ArH), 7.54 (bs, 2H, NH_2) , 7.11 (d, J = 8.56, 1H, ArH), 6.19 (s, 2H, CH_2) , 5.4 (s, 1H, CH) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$) : δ = 195.5, 182.4, 176.5, 159.8, 152.3, 149.8, 148.1, 134.7, 134.4, 130.5, 130.3, 129.6, 126.3, 126.2, 125.9, 121.2, 118.6, 108.2, 108.1, 102.2, 51.8, 36.9 ppm ; Anal. Calcd. for $C_{22}H_{12}N_2O_6$ (400.34): C, 66.00; H, 3.02; N, 7.00; Found: C, 66.02; H, 3.05; N, 7.08.

2-Amino-4-(6-methoxy-naphthalene-2-carbonyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3carbonitrile(2e) Pale yellow solid ; m.p. 238-240°C ; IR (ATR) 3303, 3189, 2200, 1962, 1677, 1623, 1480, 1367, 1298, 1242, 1197, 1170, 1045, 1016 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6+$CDCl_3$): δ = 8.89 (s, 1H, ArH), 8.12- 8.02 (m, 3H, ArH), 7.96-7.86(m, 4H, ArH), 7.57 (bs, 2H, NH_2), 7.45 (s,1H, ArH), 7.31 (dd, *J* = 8.92, 2.52 Hz, 1H, ArH), 5.6 (s, 1H, CH), 3.95 (s, 3H, OCH_3) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$) : δ = 197.0, 182.5, 176.5, 159.9, 159.8, 150.0, 137.4, 134.8, 134.4, 131.8, 131.4, 130.6, 130.4, 130.2, 127.4, 127.2, 126.3, 125.9, 124.8, 121.2, 119.6, 118.7, 106.1, 55.4, 51.8, 36.9 ppm ; Anal. calcd. for $C_{26}H_{16}N_2O_5$ (436.42) : C, 71.56; H, 3.70; N, 6.42; Found : C, 71.57; H, 3.72; N, 6.45.

2-Amino-4-benzoyl-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile(3a) White solid ; m.p. 266-268 °C, IR (ATR) 3400 ,2814, ,1831, 1708, 1672, 1600, 1579, 1458, 1372, 1221, 1112, 1063 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$) : δ = 8.13 (d, *J* = 8.6 Hz, 2H, ArH) ; 7.90 (dd, *J* = 7.92, 1.48 Hz, 1H, ArH), 7.75 - 7.69 (m, 2H, ArH), 7.59 (t, *J* =7.68 Hz, 2H, ArH), 7.59 (bs, 2H, NH_2), 7.51- 7.46 (m, 2H, ArH), 5.34 (s, 1H, CH) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$): δ = 197.8, 160.0, 159.6, 154.8, 152.1, 135.4, 133.8, 133.1, 129.0, 128.7, 124.7, 122.2, 118.5, 116.6, 112.6, 101.8, 51.90, 37.2 ppm ; Anal. Calcd. for $C_{20}H_{12}N_2O_4$ (344.32): C, 69.76; H, 3.51; N, 8.14; Found : C, 69.78; H, 3.53; N, 8.16.

2-Amino-4-(4-methoxy-benzoyl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile(3b) White solid; m.p. 262-264 °C ; IR (ATR) 3456, 3311, 2192, 1668, 1594, 1379, 1258, 1158, 1025, 945, 802 ,782 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$) δ = 8.12 (d, *J* = 8.92, 2H, ArH), 7.88 (d, *J* = 7.72 Hz, 1H, ArH), 7.73- 7.69 (m, 1H, ArH), 7.57 (bs, 2H, NH_2), 7.47 (t, *J* = 8.8 Hz, 2H, ArH), 7.09 (d, *J* = 8.8 Hz, 2H, ArH), 5.29 (s, 1H, CH), 3.88 (s, 3H, OCH_3) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) ; δ = 196.0, 163.8, 159.9, 159.5, 154.7, 152.1, 133.0, 131.5, 128.1, 124.7, 122.1, 118.5, 116.6, 113.9, 112.6, 102.0, 55.5, 52.2, 36.7 ppm ; Anal. Calcd. for $C_{21}H_{14}N_2O_5$ (374.35) : C, 67.38; H, 3.77; N, 7.48; Found : C 67.36; H, 3.78; N, 7.51.

2-Amino-4-(4-fluoro-benzoyl)-5-oxo-4H, 5H-pyrano[3,2-c]chromene-3-carbonitrile(3c) White solid, m.p. 251-253°C ; IR (ATR) 3473, 3329, 2186, 1719, 1677, 1589, 1509, 1386, 1329, 1222, 1072, 946, 866, 753 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$) : δ = 8.31 – 8.27 (m, 2H, ArH), 7.92 (dd, *J* = 8.2, 1.44 Hz, 1H, ArH), 7.80 (t, *J* = 8.4 Hz, 1H, ArH), 7.73 (bs, 2H, NH_2), 7.59 - 7.55 (m, 2H, ArH), 7.49 (t, *J* = 8.84 Hz, 2H, ArH), 5.47 (s, 1H, CH), ; ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ = 196.2, 166.8, 164.3, 160.1, 159.6, 154.8, 152.2, 132.8, 132.02,132.00, 131.9, 124.6, 122.3, 118.5, 116.5, 115.8, 115.5, 112.6, 101.5, 51.8, 37.2, ppm ; anal. Calcd. for $C_{20}H_{11}FN_2O_4$ (362.31) : C, 66.30; H, 3.06; N, 7.73; Found C, 66.32; H, 3.08; N, 7.75

2-Amino-4-(4-nitro-benzoyl)-5-oxo-4H, 5H-pyrano[3,2-c]chromene-3-carbonitrile(3d) Yellow solid ; m.p. 248-250°C; IR (ATR) 3456, 3332, 2192, 1717, 1699, 1679, 1588, 1515, 1381, 1325, 1217, 1172, 1068 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$): δ = 8.46 (q, *J* = 14.4 Hz, 4H, ArH), 7.94 (d, *J* = 8.16 Hz, 1H, ArH), 7.85-7.81 (m, 2H, NH_2+ 1H, ArH), 7.62 - 7.58 (m, 2H, ArH), 5.54 (s, 1H, CH) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$): δ = 197.2, 160.1, 159.6, 154.9, 152.1, 150.2, 140.3, 133.1, 130.2, 124.7, 123.6, 122.3, 118.3, 116.6, 112.5, 101.1, 51.1, 37.9 ppm ; Anal. Calcd. for $C_{20}H_{11}N_3O_6$ (389.32): C, 61.70; H, 2.85; N, 10.79; Found : C, 61.73; H, 2.87; N, 10.83.

2-Amino-4-benzoyl-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile(3e) Brown solid; m.p. 168-170°C, IR (ATR) 3779, 3145, 2197, 1709, 1673, 1611, 1390, 1263, 1223, 1142, 1047 cm^{-1} , ^1H NMR (400 MHz, DMSO-d_6+$CDCl_3$): δ = 8.07 (d, *J* = 8.6 Hz, 2H, ArH), 7.67 (t, *J* = 7.4 Hz, 1H, ArH), 7.55 (t, *J* = 7.5 Hz, 2H, ArH), 7.35 (bs, 2H, NH_2), 6.25 (s, 1H, =CH), 5.14 (s, 1H, CH), 2.25 (s, 3H, CH_3) ppm ; ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) :δ = 198.1, 162.9, 161.7, 159.6, 159.5, 135.5, 133.6, 128.8, 128.6, 118.6, 98.6, 97.9, 51.9, 36.6, 19.3 ppm ; Anal. Calcd. for $C_{17}H_{12}N_2O_4$ (308.29) C, 66.23; H, 3.92; N, 9.09; Found : C, 66.25; H, 3.95; N, 9.14.

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References and notes

1. (a) H.M. Hügel, *Molecules*., 2009, **14**, 4936-4972; (b) W.S. Bremner and M. G. J. Organ, *Comb. Chem.,* 2007, **9**, 14-16; (c) C. E. Bella, A. Y. Shawb, F. D. Molinerb and C. Hulme, *Tetrahedron* 2014, **70**, 54-59.
2. (a) C. O. Kappe, *Angew. Chem. Int. Ed.* 2004, **43**, 6250 -6284; (b) C. O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry,* 1st Ed. 2005. (c) R. Hoogenboom and U.S. Schubert *Macromol. Rapid Commun*. 2007, **28**, 368-386. (d) M.B. Gawande, S. N. Shelke,R. Zboril and R. S. Varma, *Acc. Chem. Res.* 2014, **47**, 1338-1348; (e) A. Kruithof, E. Ruijter and R.V.A. Orru, *Curr Org Chem*. 2011, **15**, 204-236.
3. (a) S. Karamthulla, S. Pal, M. N. Khan and L.H. Choudhury, *RSC Adv.,* 2014, **4**, 37889-37899; (b), G. M. Shelke, V. K. Rao, M. Jha, T. S. Cameron and A. Kumar, *Synlett.,* 2015, **26,** 404-407; (c) M. M. Kabachnik, E.V. Zobnina and I. P. Beletskaya, *Synlett.,* 2005, **9,** 1393-1396.

4. P. Magiatis, E. Melliou, A. L. Skaltsounis, S. Mitaku, S. Leons, P. Renard, A. Pierre and G. Atassi, *J. Nat. Prod.,* 1998, **61**, 982-986.
5. (a) B.V.S. Reddy, M. Durgaprasad and B. Sridhar, *J. Org. Chem.,* 2013, **78**, 8161−8168 (b) S. S. Irudayaraji, A. Stalin, V. Duraipandiyan and S. Ignacimuthu, *Int. J. Comput. Biol.,* 2014, **3,** 18-23; (c) X. Wang, Y.R. Lee, *Synthesis.,* 2007, **19**, 3044-3050.
6. (a) N. Yamada, S. Kadowaki, K. Takahashi and K. Umezu, *Biochem. Pharmacol*., 1992, **44,** 1211–1213.; (b) K. Faber, H. Stueckler and T. Kappe, *J. Heterocycl. Chem.,* 1984, **21**, 1177–1181.; (c) J.V. Johnson, B.S. Rauckmann, D.P. Baccanari and B. Roth, *J. Med. Chem.,* 1989, **32**, 1942–1949.
7. (a) S.B. Ferreira, K. Salomao, F. C. Silva, A. V. Pinto, C. R. Kaiser, A. C. Pinto, V. F. Ferreira and S. L. Castro, *Eur. J. Med. Chem.* 2011, **46**, 3071-3077; (b) R. J. Karwoski, M. Jackson, R. J. Theriault, J. F. Prokop, M. L. Maus, C. F. Hansen and D. M. Hansey, *J. Antibiot*. 1988, **9,** 1205-1211; (c) N. Kongkathip, B. Kongkathip, P. Siripong, C. Sangma, S. Luangkamin, M. Niyomdecha, S. Pattanapa, S. Piyaviriagulb and P. Kongsaeree, *Bioorg. Med .Chem*. 2003, **11**, 3179-3191.
8. (a) J.Y.C. Wu, W.F. Fong, J.X. Zhang, C.H. Leung, H. L. Knong, M.S. Yang, D. Li and H.Y. Cheung, *Eur.J. Pharmacol*., 2003, **473**, 9-17.; (b) Ch.-R. Su, S.F. Yeh, C.M. Liu, A.G. Damu, T.-H. Kuo, P.-Ch. Chiang, K.F. Bastow, K.-H. Lee and T.-Sh. Wu, *Bioorg. Med. Chem.,* 2009, **17**, 6137-6143.; (c) D. Schillaci, F. Venturella, F. Venoti and F. Plescia, *J. Ethonopharmacol.* 2003, **87**, 99-101.; (d) T. Symeondid, K.C. Fylaktakidou, D.J. Hadjipavlou-Latina and K.E. Litinas, *Eur. J. Med. Chem.,* 2009, **44**, 5012-5017.
9. R. S. Mali, N. A. Pandhare and M.D. Sindkhedkar, *Tetrahedron Lett.* 1995, **36,** 7109-7110.
10. A. Kumar, R.A Maurya, S. Sharma, P. Ahmad, A.B. Singh, G. Bhatia and A. K. Srivastava, *Bioorg. Med. Chem. Lett*., 2009, **19**, 6447-6451.
11. (a) S. Ahadi, M. Zolghadr, H. R. Khavasi and A. Bazgir, *Org. Biomol. Chem.,* 2013, **11**, 279-286.; (b) V.F. Ferreira, S.B. Ferreira and F. C. da Silva, *Org. Biomol. Chem.,* 2010, **8,** 4793-4802.;(c) A. Saha, S. Payra and S. Banerjee, *RSC Adv.* 2015, **5**, 101664-101671.;(d) M. V. Reddy, B.S. Kumar, K. T. Lim, B. G. Cho and Y.T. Jeong, *Tetrahedron Lett.* 2016, **57**, 476-478.; (e) P.T. Moshapo, M. Sokamisa, E. M. Mmutlane, R.M. Mampa and H.H Kinfe, *Org. Biomol. Chem.,* 2016, doi: 10.1039/C5OB02536B.; (f) A. A. Esmaeili, F. Salehan, A. Habibi, and A.R. Fakhari, *Tetrahedron Lett.* 2016, **57**, 100-102.
12. S. Khodabakhshi, B. Karami, K. Eskandari and M. Farahi, Tetrahedron *Lett.* 2014, **55,** 3753-3755.
13. S. Khodabakhsi and B. Karami, *New J. Chem.,* 2014, **38**, 3586-3590.
14. (a) S. Karamthulla, M. N. Khan and L. H. Choudhury, *RSC Adv.*, 2015, **5**, 19724-19733. (b) S. Karamthulla, S. Pal, M.N. Khan and L. H. Choudhury, *Synlett.* 2014, **25**, 1926-1936.
15. Typical experimental procedure for the preparation of **1a**: A mixture of phenylglyoxal monohydrate (1.0 mmol) and malononitrile (1.0 mmol) in ethanol (2 ml) was stirred at room temperature for 5 minutes. To this mixture 4-hydroxy-1-methyl-2(1H)-quinolone (1 mmol) was added and the resultant mixture was kept under microwave irradiation with sealed and stirring conditions for 10 minutes, keeping the temperature at 110 ^{o}C. After completion of the reaction, the reaction mixture was cooled to room temperature and solid product was separated by just filtration and purified by recrystallization from mixture of ethanol and THF.

Graphical abstract

Catalyst-free microwave assisted arylglyoxal-based multicomponent reactions for the synthesis of fused pyrans

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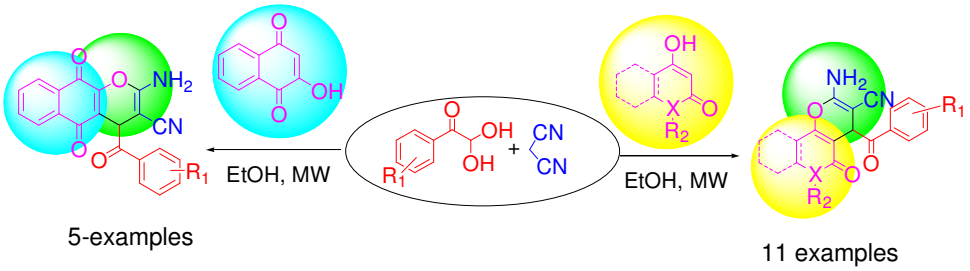
A simple and straight forward method has been reported for the synthesis of fused pyrans from the three component reactions of arylglyoxals, cyclic 1,3-dicarbonyls and malononitrile under microwave and catalyst free conditions.



- Short reaction time
- Catalyst-free reaction
- No column chromatography