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Iodine-catalyzed three-component one-pot synthesis of naphthopyranopyrimidines under solvent-free conditions

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ABSTRACT

Iodine is found to be a highly efficient catalyst for the three-component coupling (3CC) of aldehydes, β-naphthol, and 1,3-dimethylbarbituric acid under solvent-free conditions to afford the corresponding 8,10-dimethyl-12-aryl-12*H*-naphtho[1′,2′5,6]pyrano[2,3-*d*]pyrimidine-9,11-diones in good yields with high selectivity. The use of readily available iodine makes this method very simple, convenient, and cost-effective.

The multi-component reactions are highly important because of their wide range of applications in pharmaceutical chemistry for the rapid generation of structural diversity in combinatorial libraries for drug discovery.[1] MCRs are extremely convergent, producing a remarkably high increase of molecular complexity in just one step.[2,3] Naphthopyranopyrimidine and its derivatives are important structural motifs in medicinal and pharmaceutical chemistry. They are known to exhibit promising physiological[4] and biological properties such as antimicrobial[5] and anticonvulsant behavior.[6] They are also known to possess antibacterial and antifungal activities.[7,8] Recently, Marugan et al. have reported the biological activity of these molecules (Fig. 1) as antagonists for neuropeptide S receptor (NPSR).[9] The NPSR represents a novel drug targets for the treatment of sleep, anxiety, and addiction disorders.[10]

Consequently, there have been some reports on the synthesis of dibenzoxanthene derivatives using acid catalysts such as $BF_3{\cdot}OEt_2$, $Sr(OTf)_2$, and TBAF, more recently with $InCl_3$.[11] However, some of these methods often involve long reaction times, harsh reaction conditions and expensive catalysts. Thus, there is a need to develop a simple and cost-effective protocol for the synthesis of naphthopyranopyrimidines of biological importance.

To the best of our knowledge, this is the first report on the synthesis of naphthopyranopyrimidines using molecular iodine under solvent-free conditions via a three-component reaction.

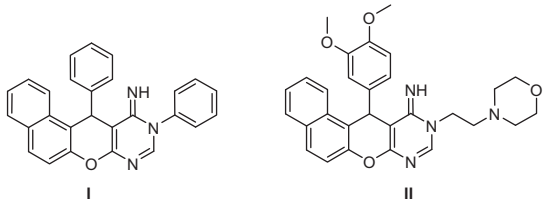

Figure 1. Representative examples of biologically interesting naphthopyranopyrimidines.

Recently, molecular iodine has received considerable attention as inexpensive, non-toxic, and readily available catalyst for various organic transformations affording the corresponding products with high selectivity and in excellent yields. The mild Lewis acidity associated with iodine has enhanced its use in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts.[12]

In continuation of our interest on catalytic application of molecular iodine,[13] and multi-component reactions (MCRs),[14] we herein report a simple and metal-free synthesis of naphthopyranopyrimidines via a three-component reaction under solvent-free conditions. Initially, we attempted the 3CC reaction between 2-naphthol, benzaldehyde, and 1,3-dimethylbarbutyric acid in the presence of 10 mol % molecular iodine in acetonitrile at room temperature (Scheme 1). However, no reaction was observed at room temperature either in acetonitrile or ethanol. Then the reaction

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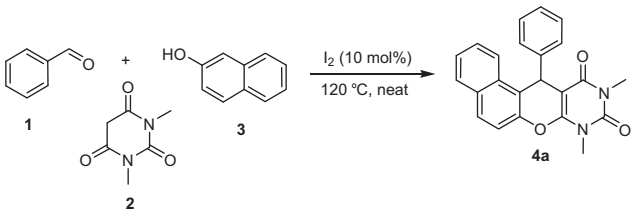

Scheme 1. 3CC Reaction of 2-naphthol, benzaldehyde and 1,3-dimethylbarbutyric acid.

was performed at 80 °C in both solvents, however the desired naphthopyranopyrimidine **4a** was obtained in very low yields along with phenyl-14*H*-dibenzo[*a,j*]xanthene after a long reaction time (8 h). It was found that keeping the reaction at lower temperature, that is, less than 100 °C, aryl-14*H*-dibenzo[*a,j*]xanthene was predominant even under solvent-free conditions using 10 mol % iodine. By increasing the temperature to 120 °C, the reaction went to completion within 60 min and the desired naphthopyranopyrimidine **4a** was obtained in 82% yield (Scheme 1).

Table 1
I_2-catalyzed synthesis of naphthopyranopyrimidines via three-component reaction

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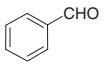
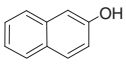
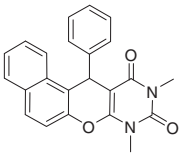
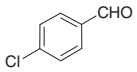
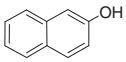
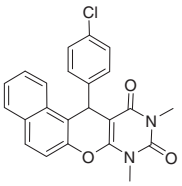
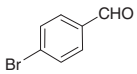
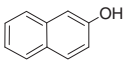
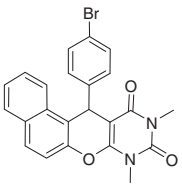
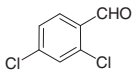
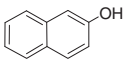
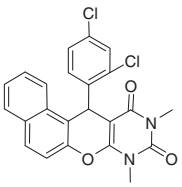
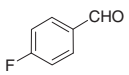
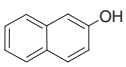
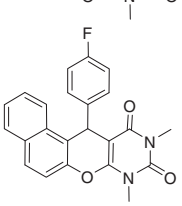
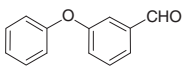
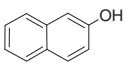
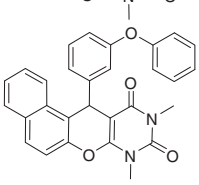
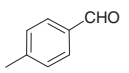
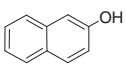
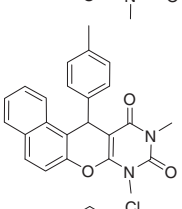
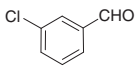
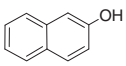
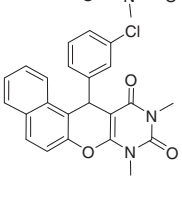
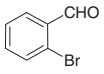
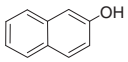
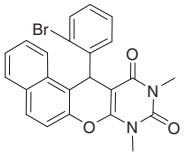
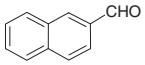
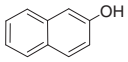
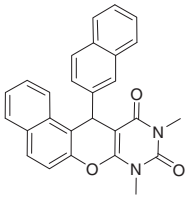
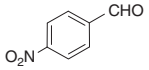
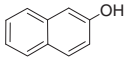
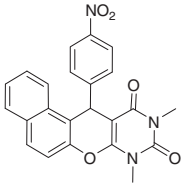
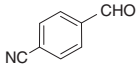
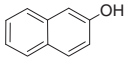
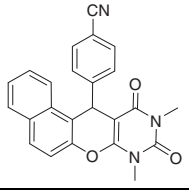
a				60	82
b				60	75
c				60	72
d				80	84
e				60	73
f				70	68
g				45	75
h				45	67

(*continued on next page*)

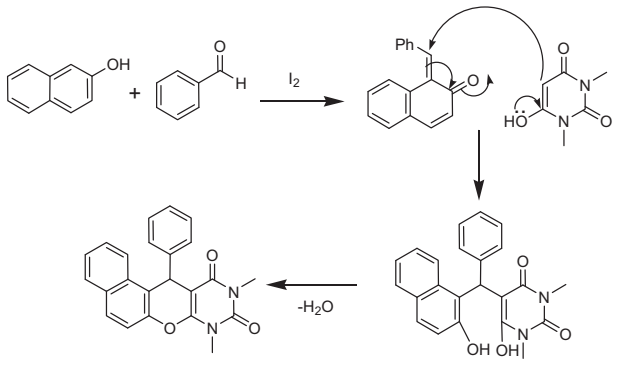
Table 1 (*continued*)

Entry	Aldehyde	2-Naphthol	Product[a]	Time (min)	Yield[b] (%)
i				70	65
j				55	59
k				55	86
l				60	72

[a] The products were characterized by NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after column chromatography.

The 3CC reaction was also performed using various amounts of iodine. Initially, 5 mol % iodine was used to perform the reaction. But it requires slightly long reaction time. Therefore, the loading of the catalyst was gradually increased from 5 mol % to 50 mol %. It was found that 10 mol % of I_2 is optimal to carry out the reactions in a short duration (45–80 min). The use of excess of catalyst did not alter either reaction time or yield of the product. Thus, the use of 10 mol % iodine at 120 °C is ideal to achieve the desired product in good yields. However, in the absence of 1,3-dimethylbarbutyric acid, aryl-14*H*-dibenzo[*a*,*j*]xanthene was formed exclusively in good yields. Next, we examined the reactivity of various catalysts such as $FeCl_3$, $Mn(OAc)_3{\cdot}2H_2O$ and ceric ammonium nitrate. Of these, molecular iodine was found to be superior in terms of conversion. For example, 2-naphthol underwent smooth electrophilic nitration along with the formation of desired naphthopyranopyrimidine when CAN was used. Similarly, a mixture of naphthopyranopyrimidine and aryl-14*H*-dibenzo[*a*,*j*] xanthene was obtained with $Mn(OAc)_3{\cdot}2H_2O$. However, in the presence of $FeCl_3$, the dimerization of 2-naphthol was prominent than the expected product. Next, we decided to study the scope of the reaction with respect to various aldehydes under optimized conditions. Interestingly, a variety of aromatic aldehydes bearing substitutions at *ortho*-, *meta*-, and *para*-positions participated well in this 3CC reaction (Table 1). [15] This method was successful with pharmacologically most prevalent substrates such as halogenated aldehydes. Notably, sterically hindered *ortho* substituted aldehydes also participated effectively in this reaction. Both electron rich as well as electron deficient substrates are found to be equally effective for this conversion.

Mechanistically, we assume that the reaction proceeds via the formation of *ortho*-quinonemethide from β-naphthol and aldehyde. Subsequent Michael addition of 1,3-dimethylbarbutyric acid followed by cyclodehydration would give the desired naphthopyranopyrimidine (Scheme 2).



Scheme 2. A plausible reaction pathway.

In summary, we have demonstrated a metal-free approach for the Biginelli-type three-component reaction for the synthesis of a variety of pharmacologically potent naphthopyranopyrimidines using a catalytic amount of molecular iodine. The advantages of this method are short reaction times, good conversions, high selectivity, and easy availability of the catalyst at low costs. Further studies to extend such easy-to-handle protocols are still in progress in our laboratory.

Acknowledgements

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15. General procedure: A mixture of aldehyde (1.1 mmol), β-naphthol (1.0 mmol), 1,3-dimethylbarbutyric acid (1.0 mmol) and 10 mol % of iodine was mixed in a 10 mL flask. The resulting mixture was stirred in preheated oil bath at 120 °C for the appropriate time (Table 1). After completion, the mixture was quenched with 15% solution of sodium thiosulfate and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel (Acme, 60–120 mesh, ethyl acetate/*n*-hexane) to afford the pure product. In few cases, the products were recrystallized from methanol. Spectral data for the products. **4a**: White solid, mp 223–225 °C; IR (KBr): *ν* 2922, 2853, 1706, 1667, 1644, 1593, 1486, 1233, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.91 (d, *J* = 8.3 Hz, 1H), 7.82–7.76 (m, 2H), 7.48–7.28 (m, 5H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.11–7.04 (m, 1H), 5.76 (s, 1H), 3.59 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.9, 152.2, 150.6, 147.1, 143.8, 131.7, 130.9, 129.5, 129.0, 128.4, 128.2, 127.4, 126.7, 125.4, 123.9, 117.3, 116.2, 91.4, 35.9, 29.0, 28.1; MS-ESI: *m*/*z*: 371 (M+H); HRMS calcd for $C_{23}H_{18}N_2O_3Na$: 393.1215, found: 393.1230. **4b**: White solid; mp 274–276 °C; IR (KBr): *ν* 2923, 2852, 1704, 1675, 1591, 1226, 1174, 1087, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.04 (d, *J* = 8.5 Hz, 1H), 7.87–7.78 (m, 2H), 7.48–7.40 (m, 2H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 5.75 (s, 1H), 3.60 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.9, 152.2, 150.5, 147.1, 142.3, 132.5, 131.7, 130.7, 129.7, 129.6, 128.5, 127.5, 125.6, 123.7, 116.7, 116.3, 90.9, 35.4, 29.0, 28.2; MS-ESI: *m*/*z*: 405 (M+H); HRMS calcd for $C_{23}H_{18}N_2O_3Cl$: 405.1005, found: 405.1001. **4c**: White solid; mp 243–245 °C; IR (KBr): *ν* 2923, 2853, 1707, 1669, 1644, 1593, 1483, 1226, 506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.85–7.77 (m, 3H), 7.43 (m, 2H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 5.71 (s, 1H), 3.58 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.9, 152.2, 150.5, 147.1, 142.8, 131.7, 131.5, 130.7, 130.0, 129.7, 128.5, 127.5, 125.6, 123.7, 120.6, 116.6, 116.2, 90.8, 35.5, 29.0, 28.2; MS-ESI: *m*/*z*: 471 (M+Na); HRMS calcd for $C_{23}H_{17}N_2O_3NaBr$: 471.0320, found: 471.0323. **4d**: White solid; mp 219–221 °C; IR (KBr): *ν* 3057, 2925, 1710, 1647, 1594, 1482, 1228, 1178, 749, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.05 (d, *J* = 8.3 Hz, 1H), 7.82–7.76 (m, 2H), 7.53–7.39 (m, 2H), 7.32–7.29 (m, 2H), 7.22 (s, 1H), 7.08 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.01 (s, 1H), 3.63 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.6, 152.4, 150.4, 146.8, 139.7, 133.7, 133.0, 132.3, 131.5, 130.9, 129.9, 129.6, 128.6, 127.6, 127.4, 125.5, 123.7, 116.2, 89.9, 33.7, 29.0, 28.1; MS-ESI: *m*/*z*: 439 (M+H); HRMS calcd for $C_{23}H_{17}N_2O_3Cl$: 439.0616, found: 439.0615. **4e**: White solid; mp 305–307 °C; IR (KBr): *ν* 3064, 2922, 1707, 1672, 1645, 1596, 1484, 1450, 1228, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.88–7.78 (m, 3H), 7.48–7.39 (m, 2H), 7.37–7.24 (m, 3H), 6.86 (t, *J* = 8.7 Hz, 2H), 5.75 (s, 1H), 3.60 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): *δ* 161.9, 152.2, 150.6, 147.1, 139.6, 131.8, 130.7, 129.8, 129.7, 128.6, 127.5, 125.6, 123.8, 117.0, 116.3, 115.4, 115.1, 91.2, 35.3, 29.1, 28.2; MS-ESI: *m*/*z*: 389 (M+H); HRMS calcd for $C_{23}H_{18}N_2O_3F$: 389.1301, found: 389.1313. **4f**: White solid; mp 177–179 °C; IR (KBr): *ν* 2923, 2854, 1703, 1652, 1450, 1229, 1170, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.92 (d, *J* = 8.1 Hz, 1H), 7.8 (d, *J* = 8.7 Hz, 2H), 7.5–7.39 (m, 2H), 7.33 (d, *J* = 8.9 Hz, 1H), 7.25–7.18 (m, 2H), 7.16–7.08 (m, 2H), 7.04–6.97 (m, 1H), 5.74 (s, 1H), 3.59 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.8, 157.0, 156.8, 152.2, 150.6, 147.0, 145.8, 131.7, 130.8, 139.8, 129.5, 129.4, 128.5, 127.4, 125.4, 123.8, 123.2, 123.1, 119.0, 118.6, 117.0, 116.6, 116.3, 91.1, 35.8, 29.0, 28.2; MS-ESI: *m*/*z*: 463 (M+H); HRMS calcd for $C_{29}H_{23}N_2O_4$: 463.1657, found: 463.1650. **4g**: White solid; mp 200–202 °C; IR (KBr): *ν* 2922, 2854, 1700, 1639, 1487, 1230, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.92 (d, *J* = 8.3 Hz, 1H), 7.81–7.75 (m, 2H), 7.47–7.32 (m,3H), 7.21–7.16 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 5.71 (s, 1H), 3.58 (s, 3H), 3.31 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.5, 151.8, 150.3, 147.1, 140.9, 136.0, 131.7, 130.1, 129.3, 129.2, 128.4, 128.1, 127.4, 125.4, 124.2, 117.7, 116.1, 91.5, 35.5, 28.9, 28.1, 21.1; MS-ESI: *m*/*z*: 407 (M+Na); HRMS calcd for $C_{24}H_{20}N_2O_3Na$: 407.1371, found: 407.1388. **4h**: White solid; mp 222–224 °C; IR (KBr): *ν* 2923, 1707, 1641, 1594, 1482, 1430, 1230, 1177, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.89–7.79 (m, 3H), 7.51–7.39 (m, 4H), 7.18–7.05 (m, 3H), 5.75 (s,1H), 3.61 (s, 3H), 3.33 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.8, 152.3, 150.5, 147.1, 145.7, 134.3, 131.8, 130.7, 129.8, 129.5, 128.6, 128.2, 127.6, 127.0, 126.7, 125.6, 123.7, 116.5, 116.3, 90.8, 35.8, 29.1, 28.2; MS-ESI: *m*/*z*: 405 (M+H); HRMS Calcd for $C_{23}H_{18}N_2O_3Cl$: 405.1005, found: 405.0997. **4i**: White solid; mp 217–219 °C; IR (KBr): *ν* 2923, 1708, 1652, 1595, 1456, 1235, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.22 (d, *J* = 8.3 Hz, 1H), 7.77 (m, 2H), 7.53–7.46 (m, 2H), 7.43–7.17 (m, 3H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.98–6.91 (m, 1H), 6.03 (s, 1H), 3.63 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.4, 157.2, 150.4, 146.8, 142.9, 133.5, 132.4, 132.0, 131.7, 131.3, 129.8, 128.5, 128.2, 127.7, 127.6, 125.6, 124.6, 123.7, 117.4, 90.7, 36.6, 29.1, 28.2; MS-ESI: *m*/*z*: 449 (M+H); HRMS calcd for $C_{23}H_{18}N_2O_3Br$: 449.0500, found: 449.0504. **4j**: White solid; mp 193–195 °C; IR (KBr): *ν* 3066, 2924, 1704, 1644, 1587, 1486, 1444, 1238, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.99 (d, *J* = 7.7 Hz, 1H), 7.87–7.62 (m, 6H), 7.46–7.31 (m, 6H), 5.93 (s, 1H), 3.62 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.8, 152.2, 150.6, 147.2, 141.2, 133.3, 132.4, 131.8, 131.0, 129.6, 128.5, 128.3, 128.0, 127.54, 127.48, 127.0, 126.3, 125.9, 125.6, 125.5, 124.0, 117.4, 116.2, 91.3, 36.2, 29.0, 28.2; MS-ESI: *m*/*z*: 421 (M+H), 295; HRMS calcd for $C_{27}H_{21}N_2O_3$: 421.1551, found: 421.1555. **4k**: White solid; mp 291–293 °C; IR (KBr): *ν* 2923, 1709, 1669, 1596, 1516, 1345, 1229, 1177 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.07 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.85–7.60 (m, 2H), 7.51 (d, *J* = 8.9 Hz, 2H), 7.47–7.43 (m, 2H), 7.40 (d, *J* = 8.9 Hz, 1H), 5.87 (s, 1H), 3.61 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.8, 152.4, 150.8, 150.4, 147.1, 146.5, 131.8, 130.5, 130.2, 129.2, 128.7, 127.8, 125.8, 123.7, 123.3, 116.3, 115.7, 90.0, 36.0, 29.1, 28.2; MS (ESI): 416 (M+H). **4l**: White solid; mp 276–280 °C; IR (KBr): *ν* 2922, 2853, 2230, 1707, 1668, 1598, 1454, 1227, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.89–7.75 (m, 3H), 7.52–7.43 (m, 6H), 7.38 (d, *J* = 9.1 Hz, 1H), 5.82 (s, 1H), 3.61 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 161.8, 152.4, 150.4, 148.8, 147.2, 132.3, 131.8, 130.5, 130.2, 129.1, 128.7, 127.7, 125.8, 123.4, 118.7, 116.3, 115.8, 110.6, 90.2, 36.2, 29.1, 28.2; MS-ESI: *m*/*z*: 396 (M+H); HRMS calcd for $C_{24}H_{18}N_3O_3$: 396.1348, found: 396.1340.