Synthesis of 1-[aryl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ols by *p*-toluenesulfonic acid catalysed reaction between 2-naphthol, aromatic aldehydes and 2-aminopyrimidine

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Three-component reaction between 2-naphthol, an aromatic aldehyde and 2-aminopyrimidine catalysed by *p*-toluenesulfonic acid provided a simple and efficient one-pot route for the synthesis of 1-[aryl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol derivatives in excellent yields.

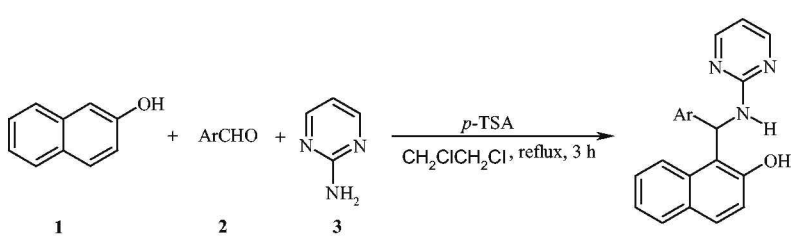
Keywords: 2-naphthol, aromatic aldehydes, 2-aminopyrimidine, three-component reaction, *p*-toluenesulfonic acid

Multi-component reactions (MCRs) have emerged as an important tool in organic synthesis in which carbon–carbon and carbon–heteroatom bond formation takes place in a tandem manner.[1-5]

The reaction of 2-naphthol with aromatic aldehydes in the presence of *p*-TSA, a Bronsted acid gives *ortho* quinone methides (*o*-QMs), which have been used in the building up of dibenzoxanthenes.[6] The same *o*-QMs, generated *in situ*, also react with amides[7] or acetonitrile[8] to form amidoalkyl naphthols. However, it has been reported[7,9] that no products were obtained from the reaction of *o*-QMs with anilines. In continuation of our previous work on three-component reactions between an aldehyde, an enolic system, such as substituted 2-naphthols, 4-hydroxycoumarin or acetophenone derivatives and a nucleophile,[8,10,11] we now report that a three-component reaction between 2-naphthol, aromatic aldehydes and 2-aminopyrimidine in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) afforded 1-[aryl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol derivatives in good yields. Thus, reaction between 2-naphthol, benzaldehyde and 2-aminopyrimidine in the presence of 0.1 equiv of *p*-TSA in refluxing 1,2-dichloroethane after 3 h afforded 1-[phenyl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol (**4a**) in 94% yield (Scheme 1). To determine the optimum quantity of *p*-TSA that was required, the reaction of 2-naphthol (1 equiv), benzaldehyde (1 equiv), and 2-aminopyrimidine (1 equiv) was carried out under the above conditions using different quantities of catalyst. The use of 5 mol% of catalyst resulted in the highest yield in 3 h. A slight excess of 2-aminopyrimidine was found to be advantageous, therefore the molar ratio of 2-naphthol, aldehyde, and 2-aminopyrimidine was kept at 1 : 1 : 1.1. Then, we examined the reaction of benzaldehyde derivatives with 2-naphthol and 2-aminopyrimidine in the presence of *p*-TSA catalyst under these reaction conditions. We prepared a range of 1-[aryl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol derivatives under the optimised reaction conditions: 2-naphthol (1 mmol), aryl aldehydes (1 mmol), and 2-aminopyrimidine (1.1 mmol) in the presence of *p*-TSA (0.05 mmol). In all cases, aromatic aldehydes with either electron-donating or electron-withdrawing groups gave the desired products in 90–97% yields after 3 h. We also examined the reaction between 2-naphthol, aliphatic aldehydes and 2-aminopyridine in the presence of *p*-TSA under the same conditions, but no products were isolated.

Products **4a–h** were all new compounds and their structures were deduced from their elemental analyses and spectroscopic data. The Mass spectrum of compound **4h** showed the molecular ion peak at 357. The ^{1}H NMR spectrum of compound **4h** displayed a sharp singlet at δ = 3.34 ppm for the methoxy protons, along with characteristic signals at δ = 6.65–8.07 ppm for the aromatic protons. The methine and NH protons were coupled to each other and two doublets were observed for them at 6.91 and 7.38 ppm, respectively. When the ^{1}H NMR spectrum was recorded after addition of some D_2O to the d6-DMSO solution of **4h** the doublet assigned to the NH proton disappeared and the doublet assigned to the methine proton was converted to a singlet. A singlet was observed at δ = 9.90 ppm, and assigned to an OH proton disappeared on addition of D_2O. The ^{13}C NMR spectrum of compound **4h** showed 21 distinct signals in agreement with the proposed structure. The methoxy and methine carbons resonated at δ 55.6 and 46.8 ppm, respectively.

A possible mechanism for the formation of 1-[aryl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ols **4a–h** has



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4	a	b	c	d	e	f	g	h
Ar	Ph	4-ClPh	4-BrPh	2-ClPh	3-NO_2Ph	4-NO_2Ph	4-CH_3OPh	2-CH_3OPh
%Yield*	94	93	95	90	93	95	90	97

*Yields refer to the pure isolated products.

Scheme 1

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been proposed in Scheme 2. As reported in the literature,[17-21] reaction of 2-naphthol with aromatic aldehydes in the presence of an acid catalyst gives orthoquinone methides (*o*-QMs). The same *o*-QMs, generated *in situ*, react with 2-aminopyrimidine by a conjugate addition to form 1-[aryl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol derivatives.

In summary, we report a simple and efficient one-pot synthesis of 1-[aryl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol derivatives by a three-component reaction between 2-naphthol, an aromatic aldehyde and 2-aminopyrimidine catalysed by *p*-toluenesulfonic acid. The advantages of this method are readily available starting materials, short reaction times, an easy and clean work-up and excellent yields.

Experimental

All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H, and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C NMR spectra were obtained on solution in d_6-DMSO using TMS as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

A magnetically stirred solution of 2-aminopyrimidine (1.1 mmol), 2-naphthol (1 mmol), aldehyde (1 mmol) and *p*-TSA (0.05 mmol) in 1,2-dichloroethane (15 mL) was refluxed for 3 h. The mixture was poured into water (50 mL). The solid product was filtered and recrystallised from ethyl acetate/hexane mixture to give the pure product.

1-[Phenyl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol (**4a**): White powder, m.p. 231–233 °C, IR (KBr) (ν_{max} cm^{-1}): 3480, 1621, 1591, 1567, 1507. Analyses: Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.22; H, 5.11; N, 13.05%. MS (*m/z*, %): 327 ($M^{+\cdot}$, 6). ^{1}H NMR (500 MHz, d_6-DMSO): δ 6.63 (1 H, t, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.23 (1 H, d, $^3J_{HH}$ = 8 Hz, NCH), 8.11 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 8.33 (2 H, d, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.28–7.32 (3 H, m, 3 C*H* of naphthol), 7.38 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.78 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.83 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.16 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of phenyl), 7.22–7.25 (2 H, m, 2 C*H* of phenyl), 7.49 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 C*H* of phenyl), 10.25 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 51.96 (*CH*), 108.35, 111.78, 119.57, 120.32, 123.49, 126.92, 127.10, 127.72, 128.94, 129.21, 129.49, 130.08, 133.11, 143.91, 153.88, 159.14 and 162.71 (aromatic).

1-[4-Chlorophenyl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol (**4b**): White powder, m.p. 228–230 °C, IR (KBr) (ν_{max} cm^{-1}): 3420, 1628, 1596, 1570, 1527. Analyses: Calcd for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61. Found: C, 69.93; H, 4.62; N, 11.75%. MS (*m/z*, %): 361 ($M^{+\cdot}$, 9). ^{1}H NMR (500 MHz, d_6-DMSO): δ 6.60 (1 H, t, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.20 (1 H, d, $^3J_{HH}$ = 8 Hz, NC*H*), 8.05 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 8.30 (2 H, d, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.21–7.32 (6 H, m, 6 C*H* of naphthol and phenyl), 7.75 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.78 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.46 (2 H, t, $^3J_{HH}$ = 8 Hz, 2 C*H* of phenyl), 10.26(1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 50.55 (*CH*), 111.95, 119.53, 119.87, 123.32, 123.55, 127.78, 128.81, 128.89, 129.23, 129.55, 130.31, 131.69, 133.01, 143.02, 153.94,159.13 and 162.61 (aromatic).

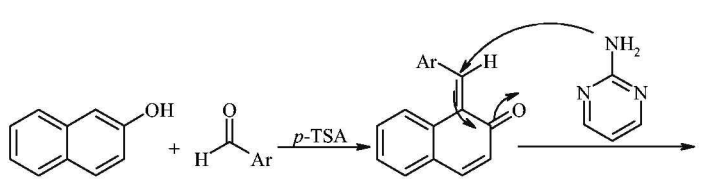
1-[4-Bromophenyl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol (**4c**): White powder, m.p. 216–218 °C, IR (KBr) (ν_{max} cm^{-1}): 3423, 1629, 1592, 1571, 1525. Analyses: Calcd for $C_{21}H_{16}BrN_3O$: C, 62.08; H, 3.97; N, 10.34. Found: C, 62.21; H, 4.07; N, 10.25%. MS (*m/z*, %): 405 ($M^{+\cdot}$, 8). ^{1}H NMR (500 MHz, d_6-DMSO): δ 6.61 (1 H, t, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.21 (1 H, d, $^3J_{HH}$ = 8 Hz, NC*H*), 8.03 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 8.32 (2 H, d, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.23–7.31 (6 H, m, 6 C*H* of naphthol and phenyl), 7.74 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.76 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.44 (2 H, t, $^3J_{HH}$ = 8 Hz, 2 C*H* of phenyl), 10.28 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 50.53 (*CH*), 111.98, 119.56, 119.85, 123.34, 123.52, 127.76, 128.83, 128.86, 129.25, 129.58, 130.36, 131.64, 133.11, 143.07, 153.92,159.17 and 162.63 (aromatic).

1-[2-Chlorophenyl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol (**4d**): White powder, m.p. 201–203 °C, IR (KBr) (ν_{max} cm^{-1}): 3405, 1621, 1595, 1566, 1514. Analyses: Calcd for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61. Found: C, 69.93; H, 4.62; N, 11.75%. MS (*m/z*, %): 361 ($M^{+\cdot}$, 6). ^{1}H NMR (500 MHz, d_6-DMSO): δ 6.60 (1 H, t, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.16 (1 H, d, $^3J_{HH}$ = 8 Hz, NC*H*), 8.11 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 8.29 (2 H, d, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.23–7.42 (7 H, m, 7 C*H* of naphthol and phenyl), 7.62 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.75 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.80 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol moiety), 10.01 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 50.51 (*CH*), 111.80, 118.34, 119.63, 123.25, 123.65, 127.25, 127.34, 129.13, 129.32, 129.50, 130.15, 130.34, 130.66, 133.49, 133.56, 140.74, 154.55, 158.98 and 162.23 (aromatic).

1-[3-Nitrophenyl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol (**4e**): White powder, m.p. 234–236 °C, IR (KBr) (ν_{max} cm^{-1}): 3395, 1625, 1594, 1571, 1522. Analyses: Calcd for $C_{21}H_{16}N_4O_3$: C, 67.73; H, 4.33; N, 15.05. Found: C, 67.88; H, 4.50; N, 15.25%. MS (*m/z*, %): 372 ($M^{+\cdot}$, 10) ^{1}H NMR (500 MHz, d_6-DMSO): δ 6.68 (1 H, t, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.25 (1 H, d, $^3J_{HH}$ = 8 Hz, NCH), 8.06 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 8.36 (2 H, d, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.32 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.45 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.54 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.61 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.82 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.85 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.50 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of phenyl), 7.68 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of phenyl), 8.14 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 C*H* of phenyl), 10.39(1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 50.71 (*CH*), 112.22, 119.28, 119.47, 121.39, 122.28, 123.28, 123.67, 127.93, 129.23, 129.61, 130.60, 130.79, 132.94, 133.77, 146.59, 148.62, 154.08, 159.18 and 162.58 (aromatic).

1-[4-Nitrophenyl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol (**4f**): White powder, m.p. 238–240 °C, IR (KBr) (ν_{max} cm^{-1}): 3420, 1627, 1592, 1568, 1513. Analyses: Calcd for $C_{21}H_{16}N_4O_3$: C, 67.73; H, 4.33; N, 15.05. Found: C, 67.56; H, 4.30; N, 15.00%. MS (*m/z*, %): 372 ($M^{+\cdot}$, 8). ^{1}H NMR (500 MHz, d_6-DMSO): δ 6.68 (1 H, t, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.25 (1 H, d, $^3J_{HH}$ = 8 Hz, NCH), 8.09 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 8.35 (2 H, d, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.32 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.43–7.54 (5 H, m, 5 C*H* of naphthol and phenyl), 7.82 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.84 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 8.13 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 C*H* of phenyl), 10.37 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 50.71 (*CH*), 112.21, 119.37, 119.43, 123.33, 123.64, 124.22, 128.03, 128.13, 129.25, 129.61, 130.68, 132.96, 146.90, 152.32, 154.07, 159.19 and 162.58 (aromatic).

1-[4-Methoxyphenyl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol (**4g**): White powder, m.p. 211–213 °C, IR (KBr) (ν_{max} cm^{-1}): 3455, 1624, 1597, 1566, 1523. Analyses: Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.11; H, 5.19; N, 11.92%. MS (*m/z*, %): 357 ($M^{+\cdot}$, 6). ^{1}H NMR (500 MHz, d_6-DMSO): δ 3.67 (3 H, s, OCH_3), 6.61 (1 H, t, $^3J_{HH}$ = 5 Hz, pyrimidine), 7.20 (1 H, d, $^3J_{HH}$ = 8 Hz, NC*H*), 8.09 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 8.32 (2 H, d, $^3J_{HH}$ = 5 Hz, pyrimidine), 6.80–6.82 (2 H, m, 2 C*H* of naphthol), 7.22–7.59 (6 H, m, 6 C*H* of naphthol and phenyl), 7.75 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol), 7.81 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of naphthol),



Scheme 2

10.42 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 50.72 (*C*H), 55.84 (OCH_3), 111.63, 114.35, 119.82, 120.23, 123.32, 123.52, 127.54, 128.17, 129.08, 129.45, 129.86, 133.09, 135.86, 154.19, 158.66, 159.01 and 162.67(aromatic).

1-[2-Methoxyphenyl-(pyrimidin-2-ylamino)-methyl]-naphthalen-2-ol (**4h**): White powder, m.p. 207–209 °C, IR (KBr) (ν_{max} cm^{-1}): 3420, 1620, 1593, 1568, 1516. Analyses: Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.65; H, 5.41; N, 11.99%. MS (*m/z*, %): 357 (M^{+}, 9). ^{1}H NMR (500 MHz, d_6-DMSO): δ 3.34 (3 H, s, OCH_3), 6.36 (1 H, t, $^3J_{HH}$ = 5 H_Z, pyrimidine), 6.91 (1 H, d, $^3J_{HH}$ = 8 H_Z, NC*H*), 7.38 (1 H, d, $^3J_{HH}$ = 8 H_Z, N*H*), 8.07 (2 H, d, $^3J_{HH}$ = 5 H_Z, pyrimidine), 6.65–6.68 (2 H, m, 2 *C*H of naphthol), 6.93–7.27 (5 H, m, 5 *C*H of naphthol and phenyl), 7.48 (1 H, d, $^3J_{HH}$ = 8 H_Z, *C*H of naphthol), 7.57 (1 H, d, $^3J_{HH}$ = 8 H_Z, *C*H of naphthol), 8.15 (1 H, d, $^3J_{HH}$ = 8 H_Z, *C*H of phenyl), 9.90 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 46.80 (*C*H), 55.60 (OCH_3), 111.13, 119.14, 119.75, 120.18, 122.82, 123.90, 126.39, 128.16, 128.56, 128.66, 129.26, 130.84, 132.81, 134.69, 145.88, 153.71, 157.09,158.58 and 161.92(aromatic).

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