Bismuth triflate catalysed one-pot synthesis of tetrahydrochromanoquinolines

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An efficient one-pot synthesis of tetrahydrochromano[4,3-*b*]quinolines using bismuth triflate as the catalyst at room temperature is described.

Keywords: bismuth triflate, tetrahydrochromanoquinolines

Cycloaddition reactions are important synthetic routes for the fast assembly of polycyclic structures.[1] The [4+2] Diels–Alder reaction between *N*-aryl amines and electron rich dienophiles is a powerful synthetic strategy for *N*-containing six membered heterocyclic compounds and in the synthesis of natural products.[2] In particular intramolecular hetero Diels–Alder reactions provide multiple opportunities for the stereoselective construction of tetrahydroquinolines and their derivatives, which have attracted considerable interest recently due to their wide range of biological activities[3] such as psychotropic, anti-allergic, and anti-inflammatory activities. Consequently, syntheses of these compounds has gained much importance and numerous methods have been developed for the synthesis of tetrahydroquinolines by inter and intramolecular Diels–Alder reactions using either Lewis acids[4] or Bronsted acids.[5] Recently perchlorates[6] were also found to affect the intramolecular cyclisation reactions of aldimines derived from aromatic amines and *O*-prenyl derivatives of salicylaldehydes.

However, some of these reagents suffer from certain drawbacks such as low yields and long reaction times. Lewis acids[7] promote these reactions but require more than stoichiometric amounts and these acids are decomposed or deactivated during the imine formation by the elimination of water. Thus there is a need to develop milder reaction conditions, better yields and environmentally friendly and catalytic processes.

We now report a highly efficient and one-pot synthesis of tetrahydrochromano[4,3-*b*]quinolines from anilines and *O*-prenyl derivatives of salicylaldehydes via intramolecular cyclisation of imines in the presence of catalytic amount of bismuth triflate (Scheme 1). Bismuth triflate is a highly efficient catalyst and is found to retain its activity even in the presence of small quantities of amines and water. Recently bismuth compounds have become attractive candidates as reagents in organic syntheses due to their low toxicity[8] and reactivity in both dry and wet organic solvents.[9] Bismuth triflate is not commercially available but can easily be prepared according to the literature procedure.[10]

Initially, we examined this reaction with *p*-chloroaniline (**1d,** 0.52 mmol) and the *O*-prenyl derivative of salicylaldehyde (**2d,** 0.52 mmol) with a catalytic amount of $Bi(OTf)_3$ (10 mol%) in acetonitrile at room temperature. After addition of catalyst, the reaction mixture immediately turned dark yellow. The reaction was complete within 5–10 min (TLC) and resulted in the formation of tetrahydroquinolines (**3d** and **4d**) as *trans* and *cis* isomers in a 1:1 ratio, which were separated by column chromatography. The *cis* and *trans* isomeric products were determined from the ^{1}H NMR spectrum of the crude products and the diastereomers were well characterised by IR, ^{1}H NMR and MS. Under similar conditions several examples with various substituents were studied and the results tabulated in the Table clearly indicate the formation of *trans* and *cis* isomers in 1:1 ratio. The known compounds were compared with those reported in the literature[6a] and unknown compounds were fully characterised.

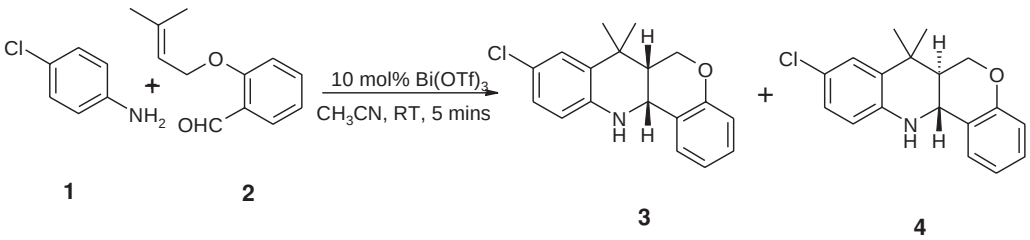
In summary, the present paper demonstrates the simple and highly efficient one-pot synthesis of tetrahydrochromano [4,3-*b*] quinolines from anilines and O-prenyl derivatives of salicylaldehydes via intramolecular cyclisation of imines in the presence of a catalytic amount of $Bi(OTf)_3$. In addition to its simplicity, milder reaction conditions, the method offers several advantages including high yields, short reaction times and operational simplicity which make this an attractive alternative process for the synthesis of tetrahydroquinolines to the existing methods.

Experimental

Melting points were measured in a Buchi-510 apparatus and are un corrected. The ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard. IR spectra were recorded on a Nicolet 740 FT IR spectrometer and mass spectra on a VG micro mass 7070H.

Typical experimental procedure: $Bi(OTf)_3$ (0.034g, 0.01mmol) was added at room temperature to a mixture of *p*-chloroaniline (**1d,** 0.067g, 0.52 mmol) and the *O*-prenyl derivative of salicylaldehyde (**2d,** 0.1g, 0.52 mmol) in acetonitrile (5ml). The reaction mixture was stirred at room temperature for 5mins. After completion of the reaction (TLC), the reaction mixture was concentrated, extracted with ethyl acetate (10 ml) and washed with water (5 ml). The organic layer was separated, dried over Na_2SO_4, concentrated and purified by column chromatography (100-200 mesh, hexane-EtOAc, 99:1) to afford **3d** and **4d** in 94% yield.

Compound (**3e**): Pale yellow solid, m.p. 118–120^0 C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.96–2.04 (dt, 1H, H-6a, *J* = 11.0, 3.6 Hz), 3.76 (t, 1H, H-6, *J* = 11.2 Hz),



Scheme 1

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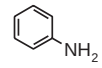
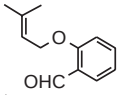
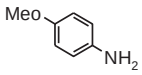
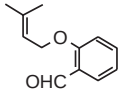
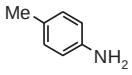
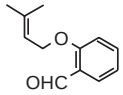
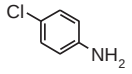
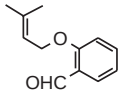
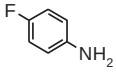
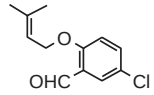
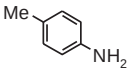
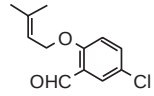
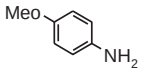
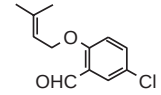
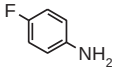
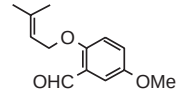
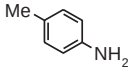
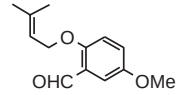
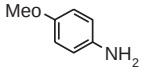
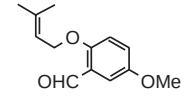
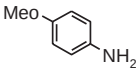
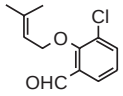
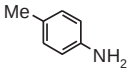
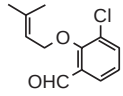
Table 1 $Bi(OTf)_3$ catalysed one-pot synthesis of tetrahydrochro-manoquinolines[a]

Entry	Aniline **1**	Salicylaldehyde derivative **2**	Time/min	Yield[b] **3**	**4**	Overall yield/% [Ref]
a			5	46	44	90[6a]
b			10	45	47	92[6a]
c			8	43	47	90[6a]
d			5	48	46	94[6a]
e			10	40	45	85
f			15	38	42	80
g			15	45	42	87
h			15	44	46	90
I			20	38	40	78
j			25	35	40	75
k			30	34	36	70
l			20	42	38	80

[a]All the products were characterised by IR, ^1H NMR, MS and compared with reported data. [b]Yield refers to the 1:1 diastereomeric products **3 and 4** in pure form by column chromatography.

4.18–4.24 (dd, 1H, H-6, *J* = 2.4, 10.6 Hz), 4.36 (d, 1H, H-12a, *J* = 3.6 Hz), 6.34 (d, 1H, *J* = 4 Hz, Ar), 6.60–7.14 (m, 5H, Ar). IR (KBr):3380, 2870, 1240, 753 cm^{-1}. MS (*m/z*): 317 (M^+). Anal. Calcd for $C_{18}H_{17}FClNO$: C, 68.03; H, 5.35; N, 4.40. Found: C, 68.12; H, 5.39; N, 4.32.

Compound (**4e**): Yellow solid, m.p. 130–134^0 C, ^1H NMR ($CDCl_3$, 200 MHz): δ1.20 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.72–1.82 (td, 1H, H-6a, *J* = 11.6, 3.2 Hz), 3.88 (t, 1H, H-6, *J* = 10.8 Hz), 4.26 (d, 1H, H-12a, *J* = 11.8 Hz), 4.40–4.54 (dd, 1H, H-6, *J* = 12.4, 3.4 Hz), 6.38 (d, 1H, *J* = 4 Hz, Ar), 6.62–7.18 (m, 5H, Ar). IR (KBr): 3386, 2874, 1238, 756 cm^{-1}. MS (*m/z*): 317 (M^+). Anal. Calcd for $C_{18}H_{17}FClNO$: C, 68.03; H, 5.35; N, 4.40. Found: C, 68.09; H, 5.26; N, 4.37.

Compound (**3f**): White solid, m.p. 110–114^0 C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.92–2.00 (dt, 1H, H-6a, *J* = 10.8, 3.4 Hz), 2.22 (s, 3H, Me), 3.76 (brs, NH), 3.86 (t, 1H, H-6, *J* = 11.6 Hz), 4.18–4.28 (dd, 1H, H-6, *J* =2.6, 10.8 Hz), 4.58 (d, 1H, H-12a, *J* = 3.6 Hz), 6.36 (d, 1H, *J* = 10 Hz, Ar), 6.72–6.82 (m, 2H, Ar), 6.92 (s, 1H, Ar), 7.14–7.20 (m, 2H, Ar). IR (KBr): 3384, 2876, 1248, 752 cm^{-1}. MS (*m/z*): 313 (M^+). Anal. Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.37; N, 4.46. Found: C, 72.69; H, 6.39; N, 4.38

Compound (**3g**): Yellow solid, m.p. 115–117^0 C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.38 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.84–2.02 (dt, 1H, H-6a, *J* = 3.4, 10.6 Hz), 3.80 (brs, 1H, NH), 3.82 (t, 1H, H-6, *J* = 10.6 Hz), 3.84 (s, 3H, OMe), 4.18–4.26 (dd, 1H, H-6, *J* = 3.2, 10.8 Hz), 4.44 (d, 1H, H-12a, *J* = 3.5 Hz), 6.38 (d, 1H, *J* = 3.2 Hz, Ar), 6.60 (d, 1H, *J* = 6.0 Hz, Ar), 6.68–6.82 (m, 2H, Ar), 7.12–7.20 (m, 2H, Ar). IR (KBr): 3375, 2885, 1610, 1210, 745 cm^{-1}. MS (*m/z*): 329. (M^+). Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.06; N, 4.24. Found; C, 69.15; H, 6.02; N, 4.16.

Compound (**4g**): Yellow solid, 125–128^0 C ^1H NMR ($CDCl_3$, 200 MHz): δ 1.98 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.92–2.08 (td, 1H, H-6a, *J* = 11.4, 3.6 Hz), 3.68 (s, 3H, OMe), 3.82 (s, 1H, NH), 3.86 (t, 1H, H-6, *J* =11.8 Hz), 4.30 (d, 1H, H-12a, *J* = 10.8 Hz), 4.40–4.54 (dd, 1H, H-6, *J* = 11.0, 3.0 Hz), 6.64 (d, 2H, *J* = 2.0 Hz, Ar), 6.80–6.86 (m, 2H, Ar), 7.14 (d, 1H, *J* = 2.2 Hz, Ar), 7.38 (d, 1H, *J* = 2.8 Hz). IR (KBr): 3365, 2880, 1620, 1525, 1180, 775 cm^{-1}.

MS (*m/z*) 329. (M^+). Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.06; N, 4.24. Found: C, 69.23; H, 6.18; N, 4.29

Compound (**3h**): Pale yellow solid, m.p. 124–128^0 C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.96–2.08 (dt, 1H, H-6a, *J* = 3.5,10.5 Hz), 3.76 (t, 1H, H-6, *J* = 10.8 Hz), 3.80 (brs, 1H, NH), 3.80 (s, 3H, OMe), 4.18–4.24 (dd, 1H, H-6, *J* = 3.4,10.6 Hz), 4.46 (d, 1H, H-12a, *J* = 3.6 Hz), 6.26–6.38 (m, 1H, Ar), 6.64–6.88 (m, 5H, Ar). IR (KBr): 3365, 2885, 1610, 1510, 1175, 765 cm^{-1}. MS (*m/z*) 313 (M^+). Anal. Calcd for $C_{19}H_{20}FNO_2$: C, 72.84; H, 6.38; N, 4.47. Found: C, 72.78; H, 6.35; N, 4.45.

Compound (**4h**): Yellow solid, m.p. 132–134^0 C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.22 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.98–2.14 (td, 1H, H-6a, *J* = 11.2, 3.2 Hz), 3.82 (s, 3H, OMe), 3.92 (t, 1H, H-6, *J* = 11.6 Hz), 4.06 (brs, 1H, NH), 4.38 (d, 1H, H-12a, *J* = 12 Hz), 4.42–4.34 (dd, 1H, H-6, *J* = 11.0, 3.2 Hz), 6.62–7.02 (m, 6H, Ar). IR (KBr): 3374, 2875, 1625, 1520, 1240, 765 cm^{-1}. MS (*m/z*) 313 (M^+). Anal. Calcd for $C_{19}H_{20}FNO_2$: C, 72.84; H, 6.38; N, 4.47. Found: C, 72.88; H, 6.42; N, 4.51.

Compound (**3i**): Yellow solid, m.p. 116–118^0 C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.96–2.02 (dt, 1H, H-6a, *J* = 11.4, 3.4 Hz), 2.22 (s, 3H, Me), 3.74 (t, 1H, H-6, *J* = 11.0 Hz), 3.80 (s, 3H, OMe), 4.16–4.22 (dd, 1H, H-6, *J* = 3.2, 10.2 Hz), 4.52 (d, 1H, H-12a, *J* = 3.2 Hz), 6.34 (d, 1H, *J* = 12 Hz, Ar), 6.74–6.82 (m, 3H, Ar), 6.98 (s, 1H, Ar), 7.20 (d, 1H, *J* = 4 Hz, Ar). IR (KBr): 3384, 2870, 1620, 1246, 750 cm^{-1}. MS (*m/z*) 309 (M^+). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.66; H, 7.44; N, 4.53. Found: C, 77.62; H, 7.38; N, 4.37.

Compound (**3j**): Yellow liquid, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.38 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.96–1.98 (dt, 1H, H-6a, *J* = 11.0, 3.2 Hz), 3.76 (t, 1H, H-6, *J* = 11.6 Hz), 3.80 (s, 6H, 2xOMe), 4.18–4.22 (dd, 1H, H-6, *J* = 2.8, 10.4 Hz), 4.46 (d, 1H, H-12a, *J* = 3.8 Hz), 6.38 (d, 1H, *J* = 2 Hz, Ar), 6.58 (d, 1H, *J* = 4 Hz, Ar), 6.68–6.78 (m, 4H, Ar). IR (KBr): 3384, 2876, 1610, 1506, 1240, 754 cm^{-1}. MS (*m/z*) 325 (M^+). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.84; H, 7.07; N, 4.30. Found: C, 73.80; H, 7.04; N, 4.24.

Compound (**3k**): Yellow liquid, ^{1}H NMR ($CDCl_3$, 200MHz): δ 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.98–2.04 (dt, 1H, H-6a, *J* = 11.2, 3.2 Hz), 3.72 (brs, 1H, NH), 3.74 (s, 3H, OMe), 3.98 (t, 1H, H-6, *J* = 11.4 Hz), 4.38–4.44 (dd, 1H, H-6, *J* = 2.8, 10.4 Hz), 4.56 (d, 1H, H-12a, *J* = 3.2 Hz), 6.38 (d, 1H, *J* =3.4 Hz, Ar), 6.60 (d, 1H, *J* = 4 Hz), 6.78 (s, 1H, Ar), 6.82–6.86 (m, 1H, Ar), 7.16 (d, 1H, *J* = 6 Hz, Ar), 7.26 (d, 1H, *J* = 4Hz, Ar). IR (KBr): 3350, 2892, 1600, 1500, 1240, 754 cm^{-1}. MS (*m/z*) 329. (M^+). Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.06; N, 4.24. Found: C, 69.12; H, 6.04; N, 4.19.

Compound (**4k**): Pale yellow solid, m.p. 110–112^0 C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.22 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.98–2.16 (td, 1H, *J* = 11.4, 3.4 Hz), 3.74 (brs, NH), 3.78 (s, 3H, OMe), 4.00 (t, 1H, H-6, *J* = 11.8 Hz), 4.38 (d, 1H, H-12a, *J* = 12 Hz), 4.58–4.64 (dd, 1H, H-6, *J* = 12.8, 3.2 Hz), 6.62 (s, 1H, Ar), 6.80–6.98 (m, 2H, Ar), 7.18–7.28 (m, 3H, Ar). IR (KBr): 3353, 2890, 1620, 1520, 1220, 760 cm^{-1}. MS (*m/z*) 329. (M^+). Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.06; N, 4.24. Found: C, 69.23; H, 6.12; N, 4.27.

Compound (**3l**): Yellow solid: m.p. 120–122^0 C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.98–2.06 (dt, 1H, H-6a, *J* = 11.4, 3.6 Hz), 2.22 (s, 3H, Me) 3.76 (brs, 1H, NH), 3.98 (t, 1H, H-6 *J* = 11.2 Hz), 4.40–4.48 (dd, 1H, H-6, *J* = 3.0,10.2 Hz), 4.58 (d, 1H, H-12a, *J* = 3.4 Hz), 6.36 (d, 1H, *J* = 3.6 Hz, Ar), 6.78–6.82 (m, 1H, Ar), 6.82–6.90 (m, 3H, Ar), 7.28 (d, 1H, *J* = 8 Hz, Ar). IR (KBr): 3370, 2880, 1620, 1215, 755 cm^{-1}. MS (*m/z*) 313. (M^+). Anal. Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.37; N, 4.46. Found: C, 72.79; H, 6.39; N, 4.38.

Compound (**4l**): Pale yellow solid: m.p. 140–142^0 C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.22 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.02–2.14 (td, 1H, H-6a, *J* = 10.8, 3.2 Hz), 2.24 (s, 3H, Me), 4.00 (t, 1H, H-6, *J* = 11.4 Hz), 4.38 (d, 1H, H-12a, *J* = 11.0 Hz), 4.62–4.68 (dd, 1H, H-6, *J* = 12.0, 3.4 Hz), 6.60 (d, 1H, *J* = 10 Hz, Ar), 6.82 (d, 1H, *J* = 6Hz, Ar), 6.92–6.96 (m, 1H, Ar), 7.08 (s, 1H, Ar), 7.22–7.28 (m, 2H, Ar). IR (KBr): 3376, 2860, 1640, 1200, 750 cm^{-1}. MS (*m/z*) 313. (M^+). Anal. Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.37; N, 4.46. Found: C, 72.67; H, 6.29; N, 4.40.

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