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Tetrahedron
Tetrahedron 63 (2007) 9997–10002

Synthesis of substituted salicylamines and dihydro-2*H*-1,3-benzoxazines

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Received 20 April 2007; revised 4 July 2007; accepted 19 July 2007
Available online 26 July 2007

Abstract—Phenols were converted to their magnesium salts with the $MgCl_2$–Et_3N base system and subsequently reacted with Eschenmoser's salt, affording *N*,*N*-dimethyl substituted benzylamines in high to excellent yields. A series of mono *N*-substituted benzylamines were prepared in one-pot syntheses by *ortho*-formylation of phenols to corresponding salicylaldehydes, which in turn reacted with amines to imines. The imines were subsequently reduced to mono *N*-substituted benzylamines. Some of these benzylamines were further converted, without work-up, to mono *N*-substituted dihydro-2*H*-1,3-benzoxazines.

1. Introduction

Salicylamines and their derivatives are useful intermediates for the synthesis of heterocyclic and biologically active compounds.[1] Aminomethylation of phenols is traditionally achieved with formaldehyde and amines under acidic conditions using the Mannich reaction,[2,3] which occurs readily in *ortho*- and *para*-positions affording polysubstituted phenols.[4] The position and nature of the substituents as well as the reaction conditions play an important role on the orientation of the Mannich reaction.

Pochini et al. reported that phenols reacted with Eschenmoser's salt in the presence of potassium carbonate affording exclusively *ortho*-substituted products in variable yields.[5] Recently Ley and co-workers reported one example of a carbonate exchange resin catalyzed reaction between 2-allyl phenol and Eschenmoser's salt to yield 2-allyl-6-((dimethylamino)-methyl)phenol in excellent yield.[6]

We have recently reported a regioselective *ortho*-formylation of substituted phenols using the $MgCl_2$–Et_3N base system and paraformaldehyde to afford salicylaldehydes in excellent yields.[7] The salicylaldehydes obtained by this method can, without isolation, be converted to salen ligands,[8] catechols,[9] and *ortho*-hydroxycinnamate esters[10] in one-pot procedures. With the complete regioselectivity observed in the aforementioned *ortho*-formylation method of phenols, a similar protocol seemed feasible also for a regioselective Mannich reaction.

2. Results and discussion

To a dichloromethane suspension of anhydrous $MgCl_2$–Et_3N and 2-bromophenol, *N*,*N*-dimethylmethylene iminium iodide (Eschenmoser's salt) was added. After stirring for 3 h at ambient temperature, complete conversion of the phenol was observed, and only one regioisomer of the *N*,*N*-dimethylamino Mannich base **1** was isolated in 83% yield (Scheme 1). Subjecting several other 2-substituted phenols to the same conditions, the corresponding Mannich bases **2–6** were obtained in 66–82% yields. A quantitative yield of the product **7** was observed when β-napthol was subjected to these reaction conditions. According to the ^1H NMR spectra of the crude reaction mixtures, complete regioselectivity was observed in all cases. The products were identified by physical and spectral data. Mannich bases are versatile intermediates for the synthesis of a wide range of biologically active compounds, and our protocol compares favorable with others when considering yields, regioselectivity, and simplicity.

Since few other methods for the synthesis of salicylamines have been reported,[11] efforts to develop facile and efficient procedures for the synthesis of mono *N*-substituted salicylamines are still desirable. Hence, we turned our attention to the facile imine formation of salicylaldehydes for the synthesis of this class of amines.[8,12] Moreover, preparative procedures in which two or more transformations carried out as

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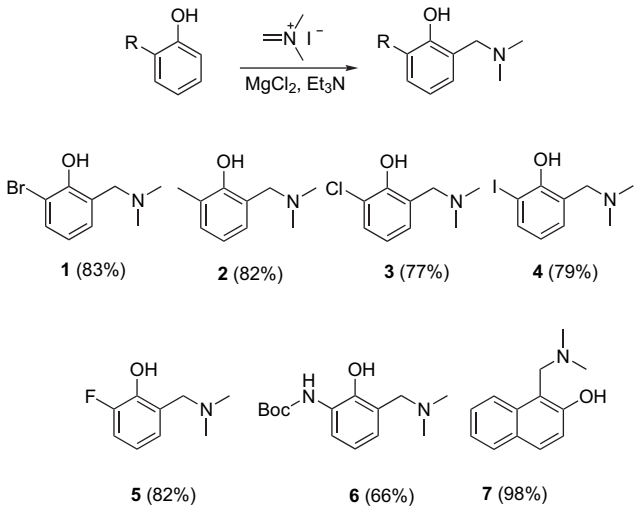
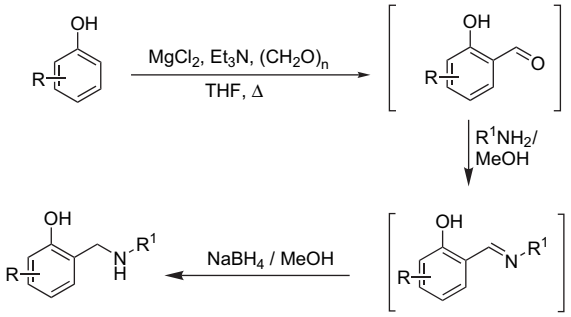
doi:10.1016/j.tet.2007.07.064



Scheme 1.

a one-pot process offer a number of advantages. In particular, they result in a reduced number of operations giving time–cost benefits by allowing direct transformation of intermediates to desired products by avoiding isolation, handling, and chromatography.

To the THF solution of the appropriate salicylaldehyde prepared as previously described,[7] the amine was added followed by the addition of $NaBH_4$. After heating to reflux for 30 min and further stirring the reaction mixture for another 2–10 h at room temperature, the reaction mixture was worked up in the usual manner. The products were purified by column chromatography and characterized by physical and spectral data (Table 1). This one-pot procedure was carried out with both alkyl and halogen substituted phenols as starting materials, and the overall yields ranged from 51% to 74% and were not optimized (Scheme 2).



Scheme 2.

This facile experimental protocol was investigated further when the solution of mono *N*-substituted benzylamine was treated with additional 2 equiv of paraformaldehyde. This gave, after purification by column chromatography, substituted dihydro-2*H*-1,3-benzoxazines in 38–53% isolated yields (Scheme 3). Benzoxazines have previously been reported to exhibit a wide range of interesting biological activities.[13] The operational simplicity of this method makes it attractive for preparative applications as well as for the synthesis of screening libraries for drug discovery.

Table 1

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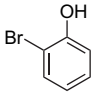
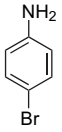
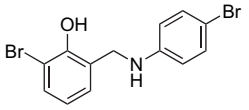
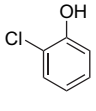
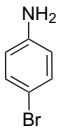
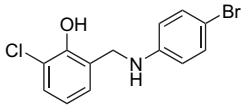
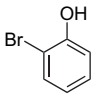
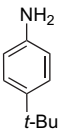
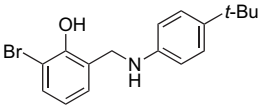
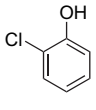
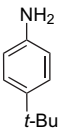
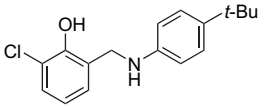
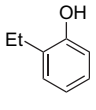
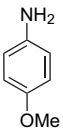
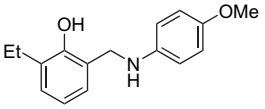
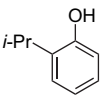
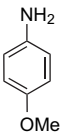
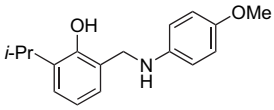
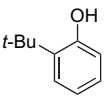
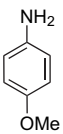
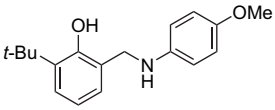
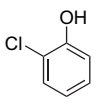
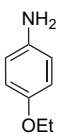
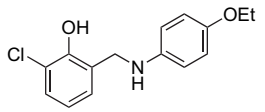
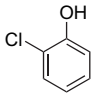
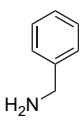
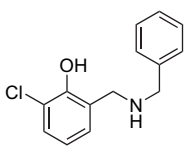
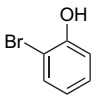
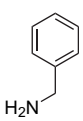
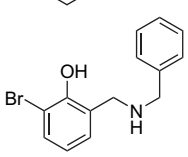
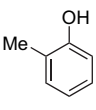
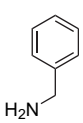
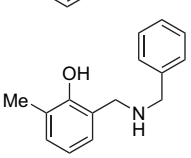
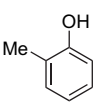
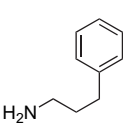
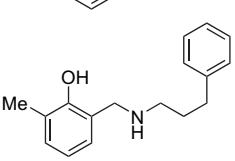
8				56
9				51
10				57
11				58
12				61
13				55
14				68
15				56
16				61
17				51
18				64
19				63

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Table 1. (*continued*)

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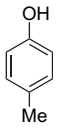
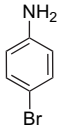
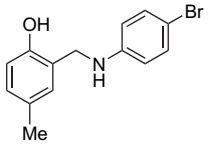
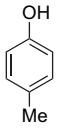
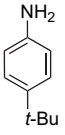
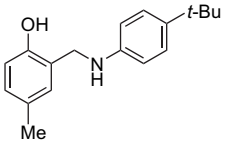
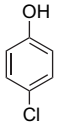
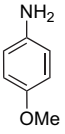
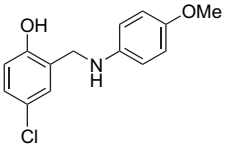
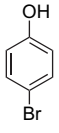
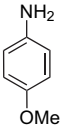
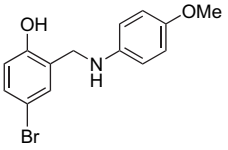
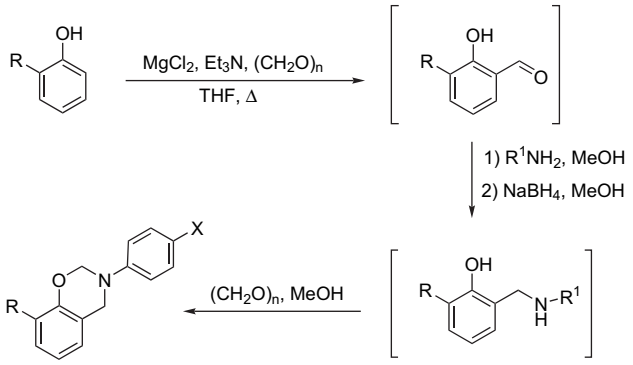
20				74
21				73
22				66
23				69



24: R = *t*-Bu and X = OMe (53%)
25: R = Br and X = OMe (49%)
26: R = Cl and X = Br (38%)
27: R = Cl and X = OMe (51%)

Scheme 3.

3. Conclusion

In conclusion, using the $MgCl_2$–Et_3N base system, substituted salicylamines are available from the corresponding phenols in good to excellent overall yields. This one-pot methodology can be further extended to the preparation of benzoxazines in good overall yields, considering the four reaction steps.

4. Experimental

4.1. General

All reagents and solvents were used as purchased without further purification. Melting points are uncorrected. Analytical TLC was performed using silica gel 60 F_{254} glass plates (Merck). Flash column chromatography was performed on silica gel 60 Geduran (35–75 μm, EM Science). NMR spectra were recorded on a Bruker Avance DPX-300 MHz spectrometer for ^{1}H NMR and 75 MHz for ^{13}C NMR. Coupling constants (*J*) are reported in Hertz, and chemical shifts are reported in parts per million (δ) relative to $CHCl_3$ (7.24 ppm for ^{1}H and 77.2 ppm for ^{13}C) and DMSO-d_6 (2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C). Mass spectra were recorded at 70 eV with Fission's VG Pro spectrometer.

4.2. General procedure for the Mannich reaction

N,*N*-Dimethylmethylene iminium iodide (0.93 g, 5 mmol) was added to a solution of the phenol (5 mmol), triethylamine (1.21 g, 12 mmol), and anhydrous magnesium chloride (0.95 g, 10 mmol) in dichloromethane (20 ml) or toluene (20 ml) for the synthesis of **2**. The reaction mixture was stirred at room temperature for 0.5–12 h and the reaction monitored by TLC (hexane–EtOAc=1:1). When necessary, the products were purified by column chromatography. Spectral and physical data of known compounds **2**, **3**, and **7** were in accord with previously published data.[5]

4.2.1. 2-Bromo-6-((dimethylamino)methyl)phenol (1). Pale yellow solid; mp 53–55 °C; ^{1}H NMR ($CDCl_3$): δ=2.33 (s, 6H), 3.64 (s, 2H), 6.63 (t, *J*=7.7 Hz, 1H), 6.88 (dt, *J*=7.7, 0.7 Hz, 1H), 7.40 (dd, *J*=7.7, 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=155.42, 132.45, 127.65, 123.37, 120.07, 110.95, 63.06, 44.68; HRMS calcd for (M^+): 229.0102, found: 229.0096.

4.2.2. 2-((Dimethylamino)methyl)-6-iodophenol (4). Yellow solid; mp 64–66 °C; ^{1}H NMR ($CDCl_3$): δ=2.30 (s, 6H), 3.60 (s, 2H), 6.51 (t, *J*=7.4 Hz, 1H), 6.91 (dt, *J*=7.4, 0.7 Hz, 1H), 7.61 (dd, *J*=7.4, 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=157.82, 138.35, 128.70, 122.48, 120.89, 85.30, 63.09, 44.61; HRMS calcd for (M^+): 276.9964, found: 276.9974.

4.2.3. 2-((Dimethylamino)methyl)-6-fluorophenol (5). Pale yellow oil; ^{1}H NMR ($CDCl_3$): δ=2.32 (s, 6H), 3.66 (s, 2H), 6.65–6.72 (m, 2H), 6.92–7.24 (m, 1H), 10.47 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ=151.70 (d, *J*=717 Hz), 146.64 (d, *J*=48.9 Hz), 124.46 (d, *J*=12.9 Hz), 123.60 (d, *J*=12.9 Hz), 118.75 (d, *J*=28.2 Hz), 115.82 (d, *J*=72.0 Hz), 62.90 (d, *J*=9.6 Hz), 44.83; HRMS calcd for (M^+): 169.0903, found: 169.0909.

4.2.4. *tert*-Butyl-3-((dimethylamino)methyl)-2-hydroxyphenylcarbamate (6). Yellow liquid; ^{1}H NMR ($CDCl_3$): δ=1.50 (s, 9H), 2.31 (s, 6H), 3.62 (s, 2H), 6.59–6.76 (m, 2H), 7.06 (br s, 1H), 7.92 (d, *J*=7.9 Hz, 1H), 9.85 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ=153.38, 146.53, 127.40, 121.95, 121.06, 119.37, 117.73, 80.40, 62.96, 44.75, 28.78; HRMS calcd for (M^+): 266.1630, found: 266.1626.

4.3. General procedure for the preparation of salicylamines 8–24

To a dry THF solution (30 ml) of the phenol (5 mmol), anhydrous magnesium chloride (0.95 g, 10 mmol) and

triethylamine (1.01 g, 10 mmol), paraformaldehyde (0.45 g, 15 mmol) was added. The reaction mixture was heated to reflux under an argon atmosphere for 2–4 h and the reaction was monitored by TLC (hexane–EtOAc=9:1). After complete consumption of the phenol, a solution of the amine (5 mmol) in MeOH (5 ml) was added dropwise. The reaction mixture was heated to reflux for 30 min and further stirred for an additional 2–10 h. After complete consumption of the salicylaldehyde, a solution of $NaBH_4$ (0.38 g, 10 mmol) in MeOH (10 ml) was added dropwise over 15–30 min. The reaction mixture was stirred at ambient temperature for 2–10 h and the reaction monitored by TLC (hexane–EtOAc=8:2). After complete reduction of the imines, pH was adjusted to 8 by addition of HCl (1 N) and the reaction mixture extracted with Et_2O (2×30 ml). The organic layer was washed with brine (20 ml), dried ($MgSO_4$), and the product purified by column chromatography using a gradient of hexane–EtOAc (9:1–7:3).

4.3.1. 2-Bromo-6-((4-bromophenylamino)methyl)-phenol (8). White solid; mp 98–99 °C; ^{1}H NMR (DMSO-d_6): δ=4.24 (s, 2H), 6.47–6.52 (m, 2H), 6.74 (t, J=7.7 Hz, 1H), 7.11–7.20 (m, 3H), 7.36–7.39 (m, 1H), 9.22 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=152.14, 148.58, 132.25, 131.88, 129.64, 128.25, 121.93, 115.08, 112.10, 107.46, 43.00; HRMS calcd for (M^+): 354.9207, found: 354.9192.

4.3.2. 2-(2-((4-Bromophenylamino)methyl))-6-chlorophenol (9). Pale yellow solid; mp 121–122 °C; ^{1}H NMR (DMSO-d_6): δ=4.24 (s, 2H), 6.50–6.53 (m, 2H), 6.80 (t, J=7.7 Hz, 1H), 7.11–7.25 (m, 4H), 9.40 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ=151.19, 148.60, 132.24, 129.52, 128.76, 127.61, 121.52, 121.16, 115.04, 107.40, 42.68; HRMS calcd for (M^+): 310.9712, found: 310.9722.

4.3.3. 2-Bromo-6-((4-*tert*-butylphenylamino)methyl)-phenol (10). Pale yellow solid; mp 84–86 °C; ^{1}H NMR ($CDCl_3$): δ=1.20 (s, 9H), 4.24 (s, 2H), 5.9 (br s, 1H), 6.50 (d, J=8.6 Hz, 2H), 6.73 (t, J=7.7 Hz, 1H), 7.06 (d, J=8.6 Hz, 2H), 7.19 (m, 1H), 7.35 (m, 1H), 9.3 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ=152.26, 146.76, 139.41, 131.67, 130.10, 128.37, 126.34, 121.85, 113.18, 111.84, 43.75, 34.31, 32.30; HRMS calcd for (M^+): 333.0728, found: 333.0717.

4.3.4. ((4-*tert*-Butylphenylamino)methyl)-6-chlorophenol (11). Yellow solid; mp 82–84 °C; ^{1}H NMR ($CDCl_3$): δ=1.30 (s, 9H), 4.43 (s, 2H), 6.77–6.85 (m, 3H), 7.30–7.26 (m, 1H), 7.11 (m, 3H); ^{13}C NMR ($CDCl_3$): δ=152.19, 144.55, 143.97, 129.36, 127.62, 126.59, 125.43, 121.41, 120.83, 115.83, 48.32, 34.47, 31.86; HRMS calcd for (M^+): 289.1233, found: 289.1230.

4.3.5. 2-Ethyl-6-((4-methoxyphenylamino)methyl)-phenol (12). White solid; mp 65–66 °C; ^{1}H NMR (DMSO-d_6): δ=1.13 (t, J=7.5 Hz, 3H), 2.58 (q, J=7.5 Hz, 2H), 3.63 (s, 3H), 4.21 (d, J=5.5 Hz, 2H), 5.66 (br t, J=5.5 Hz, 1H), 6.61 (m, 2H), 6.7 (m, 3H), 6.75–7.05 (m, 2H), 8.78 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ=153.74, 152.25, 143.51, 131.33, 128.16, 126.69, 120.12, 115.79, 115.36, 115.15, 56.13, 45.32, 23.47, 15.24; HRMS calcd for (M^+): 257.1416, found: 257.1412.

4.3.6. 2-Isopropyl-6-((4-methoxyphenylamino)methyl)-phenol (13). Yellow solid; mp 46–48 °C; ^{1}H NMR (DMSO-d_6): δ=1.15 (d, J=4.4 Hz, 6H), 3.30 (m, 1H), 3.63 (s, 3H), 4.21 (s, 2H), 5.70 (br s, 1H), 6.61–6.65 (m, 2H), 6.70–6.79 (m, 3H), 7.04 (dd, J=7.5, 1.7 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ=153.24, 152.43, 143.42, 135.89, 126.56, 126.46, 125.10, 120.25, 115.40, 56.12, 45.83, 26.77, 23.69; HRMS calcd for (M^+): 271.1572, found: 271.1578.

4.3.7. 2-*tert*-Butyl-6-((4-methoxyphenylamino)methyl)-phenol (14). White solid; mp 80–82 °C; ^{1}H NMR (DMSO-d_6): δ=1.34 (s, 9H), 3.64 (s, 3H), 4.25 (d, J=5.6 Hz, 2H), 5.81 (br t, J=5.6 Hz, 1H), 6.69–6.77 (m, 5H), 7.05–7.11 (m, 2H), 9.40 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ=155.69, 153.14, 142.93, 137.20, 127.11, 126.45, 125.86, 119.81, 116.50, 115.32, 56.10, 47.48, 35.21, 30.49; HRMS calcd for (M^+): 285.1729, found: 285.1726.

4.3.8. 2-Chloro-6-((4-ethoxyphenylamino)methyl)-phenol (15). White solid; mp 94–96 °C; ^{1}H NMR (DMSO-d_6): δ=1.23 (t, J=6.9 Hz, 3H), 3.86 (q, J=6.9 Hz, 2H), 4.21 (s, 2H), 5.70 (br s, 1H), 6.51 (d, J=8.8 Hz, 2H), 6.68 (d, J=8.8 Hz, 2H), 6.78 (t, J=7.7 Hz, 1H), 7.14–7.22 (m, 2H), 9.6 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ=151.45, 151.19, 143.30, 129.91, 128.58, 127.73, 121.30, 121.03, 116.18, 114.59, 64.13, 44.19, 15.71; HRMS calcd for (M^+): 277.0869, found: 277.0870.

4.3.9. 2-((Benzylamino)methyl)-6-chlorophenol (16). Yellow liquid; ^{1}H NMR ($CDCl_3$): 3.86 (s, 2H), 4.03 (s, 2H), 6.75 (t, J=7.7 Hz, 1H), 6.94 (d, J=7.3 Hz, 1H), 7.27–7.38 (m, 6H); ^{13}C NMR ($CDCl_3$): δ=154.21, 137.41, 129.77, 129.22, 129.02, 128.34, 127.58, 123.49, 121.70, 119.94, 52.67, 51.39; HRMS calcd for (M^+): 247.0764, found: 247.0753.

4.3.10. 2-((Benzylamino)methyl)-6-bromophenol (17). White solid; mp 48–50 °C; ^{1}H NMR (DMSO-d_6): δ=3.72 (s, 2H), 3.90 (s, 2H), 6.66 (t, J=7.1 Hz, 1H), 6.90 (br s, 1H), 7.01 (d, J=6.8 Hz, 1H), 7.28 (br s, 1H), 7.31–7.39 (m, 6H); ^{13}C NMR (DMSO-d_6): δ=156.09, 139.34, 132.01, 129.27, 129.14, 128.56, 128.04, 125.43, 120.27, 110.36, 52.11, 51.46; HRMS calcd for (M^+): 291.0259, found: 291.0251.

4.3.11. 2-((Benzylamino)methyl)-6-methylphenol (18). Yellow liquid; ^{1}H NMR (DMSO-d_6): δ=2.17 (s, 3H), 3.71 (s, 2H), 3.85 (s, 2H), 6.63 (t, J=7.3 Hz, 1H), 6.83 (d, J=6.8 Hz, 1H), 6.83 (d, J=7.3 Hz, 1H), 7.32–7.37 (m, 5H); ^{13}C NMR (DMSO-d_6): δ=156.98, 139.75, 130.04, 129.20, 129.12, 127.91, 126.96, 124.68, 123.03, 118.93, 52.29, 51.51, 16.50; HRMS calcd for (M^+): 227.1310, found: 227.1308.

4.3.12. 2-Methyl-6-((3-phenylpropylamino)methyl)-phenol (19). Pale yellow liquid; ^{1}H NMR (DMSO-d_6): δ=1.88 (quintet, 2H), 2.26 (s, 3H), 2.69 (m, 4H), 3.96 (s, 2H), 6.70 (t, J=7.3 Hz, 1H), 6.84 (d, J=7.1 Hz, 1H), 7.06 (d, J=7.3 Hz, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR (DMSO-d_6): δ=152.06, 137.23, 125.55, 124.12, 124.04, 121.65, 121.56, 120.88, 117.52, 114.17, 48.41, 43.83, 29.07, 26.89, 11.38; HRMS calcd for (M^+): 255.1623, found: 255.1619.

4.3.13. 2-((4-Bromophenylamino)methyl)-4-methyl-phenol (20). Yellow solid; mp115–116 °C (lit.[14] mp 115.5 °C); ^{1}H NMR (DMSO-d_6): δ=2.28 (s, 3H), 4.30 (s, 2H), 5.75 (br s, 1H), 6.68 (d, J=8.8 Hz, 2H), 6.78 (d, J=8.1 Hz, 1H), 6.99 (m, 2H), 7.31 (d, J=8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ=149.50, 141.87, 127.79, 125.41, 125.17, 125.08, 118.01, 112.90, 112.00, 108.28, 43.80, 16.16; HRMS calcd for (M^+): 291.0259, found: 291.0259.

4.3.14. 2-((4-*tert*-Butylphenylamino)methyl)-4-methylphenol (21). Yellow solid; mp 78–80 °C; ^{1}H NMR (DMSO-d_6): δ=1.19 (s, 9H), 2.18 (s, 3H), 4.11 (s, 2H), 5.72 (br s, 1H), 6.51 (d, J=8.7 Hz, 2H), 6.62–6.70 (m, 1H), 6.80–6.84 (m, 1H), 7.00–7.08 (m, 3H), 9.30 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ=153.53, 147.38, 138.69, 129.51, 128.57, 127.87, 126.61, 126.24, 115.57, 112.77, 42.50, 34.27, 32.34, 21.20; HRMS calcd for (M^+): 269.1780, found: 269.1783.

4.3.15. 4-Chloro-2-((4-methoxyphenylamino)methyl)-phenol (22). Pale yellow solid; mp 117–118 °C (lit.[15] mp 119.2 °C); ^{1}H NMR (DMSO-d_6): δ=3.62 (s, 3H), 4.16 (d, J=5.2 Hz, 2H), 5.69 (br s, 1H), 6.50 (d, J=8.9 Hz, 2H), 6.69 (d, J=8.9 Hz, 2H), 6.82 (d, J=8.5 Hz, 1H), 6.82 (dd, J=8.5, 2.6 Hz, 1H), 7.17 (d, J=2.6 Hz, 1H), 9.82 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ=154.73, 151.67, 143.51, 129.47, 128.25, 127.74, 123.27, 117.20, 115.48, 114.06, 56.11, 42.54; HRMS calcd for (M^+): 263.0712, found: 263.0713.

4.3.16. 4-Bromo-2-((4-methoxyphenylamino)methyl)-phenol (23). Pale yellow solid; mp 114–115 °C; ^{1}H NMR ($CDCl_3$): δ=3.78 (s, 3H), 4.34 (s, 2H), 6.40 (br s, 1H), 6.77–6.83 (m, 5H), 7.25–7.32 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=156.78, 155.32, 140.16, 132.19, 131.44, 125.13, 118.87, 118.52, 115.24, 111.93, 56.03, 50.34; HRMS calcd for (M^+): 307.0198, found: 307.0208.

4.4. General procedure for the preparation of dihydro-2*H*-1,3-benzoxazines 24–27

A mixture of paraformaldehyde (0.30 g, 10 mmol) and methanol (5 ml) was added to the salicylamines obtained as described above, and the reaction mixture was refluxed for 5–10 h. After complete conversion of the salicylamines, the reaction mixture was extracted with Et_2O (2×30 ml). The organic layer was washed with brine (20 ml), dried ($MgSO_4$), and the product purified by column chromatography using hexane–EtOAc (9:1).

4.4.1. 8-*tert*-Butyl-3-(4-methoxyphenyl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (24). Pale yellow liquid; ^{1}H NMR (DMSO-d_6): δ=1.30 (s, 9H), 3.65 (s, 3H), 3.55 (s, 2H), 5.67 (s, 2H), 6.75–6.87 (m, 4H), 7.00–7.09 (m, 3H); ^{13}C NMR (DMSO-d_6): δ=154.66, 153.50, 142.67, 137.37, 125.92, 125.27, 121.87, 120.51, 120.06, 115.17, 79.69, 56.02, 51.58, 35.11, 30.37; HRMS calcd for (M^+): 297.1729, found: 279.1722.

4.4.2. 8-Bromo-3-(4-methoxyphenyl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (25). Pale yellow solid; mp 99–100 °C; ^{1}H NMR (DMSO-d_6): δ=3.66 (s, 3H), 4.59 (s, 2H), 5.48 (s, 2H), 6.77–6.83 (m, 3H), 7.03–7.07 (m, 2H), 7.11 (dd, J=7.5, 2.0 Hz, 1H), 7.37 (dd, J=7.9, 1.4 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ=154.98, 151.38, 141.98, 131.81, 127.45, 124.21, 122.18, 120.39, 115.29, 110.31, 81.89, 56.04, 50.25; HRMS calcd for (M^+): 319.0208, found: 319.0211.

4.4.3. 3-(4-Bromophenyl)-8-chloro-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (26). White solid; mp 139–140 °C; ^{1}H NMR (DMSO-d_6): δ=4.70 (s, 2H), 5.58 (s, 2H), 6.88 (t, J=7.78 Hz, 1H), 7.10–7.13 (m, 3H), 7.25 (dd, J=7.8, 1.5 Hz, 1H), 7.39–7.42 (m, 2H); ^{13}C NMR (DMSO-d_6): δ=150.34, 147.55, 132.69, 128.99, 126.92, 123.92, 121.75, 120.75, 120.36, 113.21, 80.24, 49.35; HRMS calcd for (M^+): 322.9712, found: 322.9711.

4.4.4. 8-Chloro-3-(4-methoxyphenyl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (27). White solid; mp110–111 °C; ^{1}H NMR (DMSO-d_6): δ=3.66 (s, 3H), 4.59 (s, 2H), 5.48 (s, 2H), 6.80–6.86 (m, 3H), 7.03–7.10 (m, 3H), 7.32 (dd, J=7.9, 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ=154.97, 150.50, 141.99, 128.84, 126.81, 124.10, 121.49, 120.60, 120.39, 115.29, 81.73, 56.04, 50.17; HRMS calcd for (M^+): 275.0713, found: 275.0710.

Acknowledgements

Financial support to H.F.A. from the University of Oslo (The Quota Scheme) is gratefully acknowledged.

References and notes

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