Tetrahedron Letters 49 (2008) 4443–4445

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A one-pot synthesis of substituted salicylnitriles

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ARTICLE INFO

Article history:
Received 7 April 2008
Revised 24 April 2008
Accepted 1 May 2008
Available online 6 May 2008

Keywords:
Phenols
ortho-Formylation
IBX
Salicylnitriles

ABSTRACT

Phenols were converted to salicylaldehydes with paraformaldehyde, $MgCl_2$–Et_3N in THF, and subsequent treatment with aqueous ammonia gave the corresponding imines which were oxidized with IBX to the desired salicylnitriles. The sequence of reactions was conveniently carried out as a one-pot procedure under mild conditions.

Aromatic nitriles can be prepared by metal-mediated displacement of aromatic halides by the cyanide ion, that is, the Rosemund–von Braun reaction[1,2] and are versatile starting materials and intermediates for the synthesis of heterocyclic and biologically active compounds.[3] Stoichiometric quantities of toxic cyanide salts and high temperatures (>150–160 °C) are commonly employed for this reaction.[4] Not many examples of the preparation of substituted salicylnitriles have been reported using the Rosemund–von Braun reaction.[5] Since few substituted salicylnitriles are commercially available, efforts towards developing mild and reliable methods are of interest to the synthetic community. Herein we describe an efficient one-pot method for the conversion of phenols to substituted salicylnitriles.

The recently reported regioselective *ortho*-formylation of substituted phenols using the $MgCl_2$–Et_3N base system and paraformaldehyde affords salicylaldehydes in excellent yields.[6] The salicylaldehydes obtained by this method have been converted, without isolation and in one-pot procedures, to useful products and intermediates.[7] With complete regioselectivity observed in the aforementioned formylation of phenols, it seemed feasible to apply this method for the regioselective introduction of a nitrile group via oxidation of an imine intermediate to give salicylnitriles.

There are several oxidative methods available for the preparation of nitriles from amines, but few methods exist for the synthesis of salicylnitriles.[8]

Recently, hypervalent iodine reagents such as *ortho*-iodoxybenzoic acid (IBX) and Dess–Martin periodinane have attracted interest as oxidants for synthetic transformations.[9] The oxidation of amines to nitriles using IBX in aqueous ammonia, recently reported by Akamanchi and co-workers,[10] inspired us to develop a one-pot procedure for the synthesis of substituted salicylnitriles. Preparative procedures in which two or more transformations can be carried out as a one-pot process offer a number of advantages, that is, the time-cost benefits gained by avoiding isolation, handling and chromatography of intermediates.

The *ortho*-formylation of 2-chlorophenol afforded 3-chlorosalicylaldehyde which was treated, without isolation, with aqueous ammonia to give the corresponding 3-chlorosalicylimine in the same pot. The imine was oxidized with a slight excess of IBX to 3-chlorosalicylnitrile in 70% overall yield after purification by chromatography. Several 2-substituted phenols were subjected to the same one-pot procedure, affording the corresponding salicylnitriles in 48–71% isolated yields over three steps.[11] As expected, 4-substituted phenols afforded the 5-substituted salicylnitriles in comparable yields (Table 1). 2,3-(Methylenedioxy)-phenol, a structural entity found in some highly oxygenated natural products such as narciclasine and pancratistatin,[12] was also converted cleanly to the desired nitrile in 58% overall yield (entry 12). Complete regioselectivity was observed in all cases and the products were identified by physical and spectral data. IBX afforded higher yields compared to the Dess–Martin reagent under these conditions. New compounds were characterized on the basis of physical and spectral data.[11]

In conclusion, we have reported the transformation of phenols into salicylnitriles in good overall yields by a simple, regioselective and one-pot experimental procedure. Since substituted phenols are readily available, the present method appears to be a mild and convenient procedure for preparing salicylnitriles (see Scheme 1).

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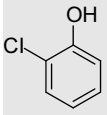
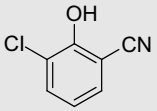
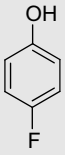
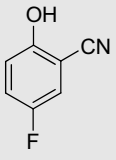
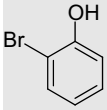
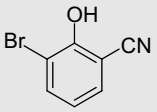
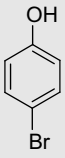
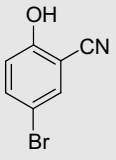
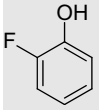
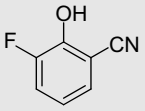
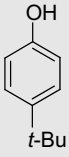
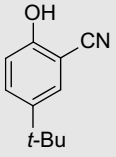
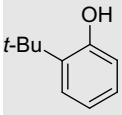
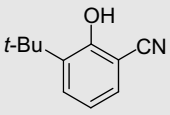
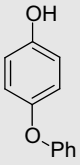
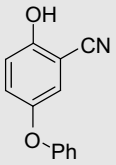
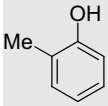
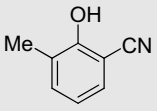
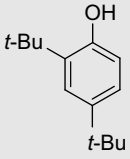
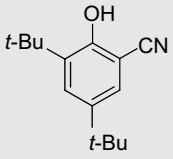
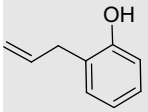
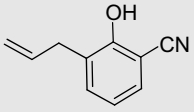
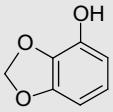
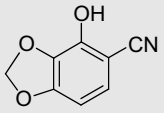
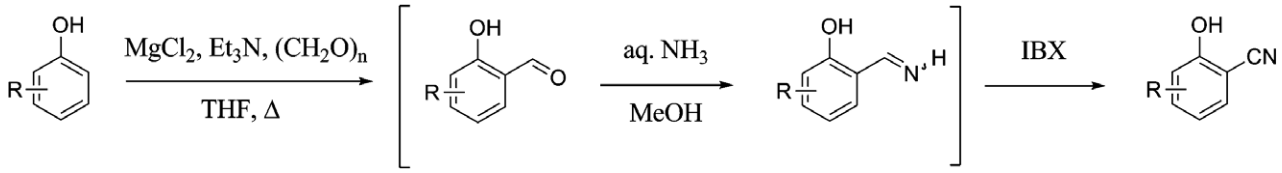
doi:10.1016/j.tetlet.2008.05.006

Table 1
One-pot synthesis of substituted salicylnitriles

Phenol	Product	Yield %	Phenol	Product	Yield %
	 **1**	70		 **7**	67
	 **2**	55		 **8**	70
	 **3**	48		 **9**	67
	 **4**	71		 **10**	54
	 **5**	62		 **11**	56
	 **6**	53		 **12**	58



Scheme 1.

Acknowledgement

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

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11. *Typical experimental procedure for the synthesis of salicylnitriles:* To a dry THF solution (30 ml) of the phenol (2 mmol), anhydrous magnesium chloride (0.38 g, 4 mmol) and triethylamine (0.40 g, 4 mmol) paraformaldehyde (0.18 g, 6 mmol) were added. The reaction mixture was heated to reflux under an argon atmosphere for 2–4 h, and monitored by TLC (hexane–ethyl acetate = 9:1). After complete consumption of the phenol, the reaction mixture was cooled, and aqueous ammonia (10 ml of a 25% solution) and methanol (3 ml) were added. After stirring for 30 min IBX (45 wt. %, 1.20 g) was added, and the yellow coloured solution was stirred for an additional 2–10 h. The reaction mixture was diluted with water and extracted with ethyl acetate (2×15 ml), the combined organic layers were washed successively with water (2×15 ml) and a solution of $Na_2S_2O_5$ (2×15 ml), and then dried ($MgSO_4$). The product was purified by column chromatography using a gradient of hexane–ethyl acetate (95:5–70:30). Spectral and physical data of products: 3-Chloro-2-hydroxybenzonitrile (**1**): Orange solid; mp 113–114 °C (lit.[13] mp 114–115 °C); IR (KBr, cm^{-1}) ν: 3414, 2245, 1641; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.56 (dd, J = 8.0, 1.5 Hz, 1H), 7.48 (dd, J = 7.8, 1.5 Hz, 1H), 6.96 (t, J = 7.9 Hz, 1H), 6.29 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 154.22, 134.17, 132.47, 121.94, 121.56, 115.47, 101.62; LC/MS: m/z 154.0 ($M+H^+$, 100%), 156.0 ($M+2+H^+$, 36%). 3-Bromo-2-hydroxybenzonitrile (**2**): yellow solid; mp 116–117 °C (lit.[13] mp 116 °C); IR (KBr, cm^{-1}) ν: 3278, 2242, 1591; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.70 (dd, J = 8.1, 1.5 Hz, 1H), 7.52 (dd, J = 7.7, 1.5 Hz, 1H), 6.91 (t, J = 7.9 Hz, 1H), 6.22 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 154.54, 136.78, 132.84, 121.93, 115.07, 110.98, 100.95; LC/MS: m/z 197.9 ($M+H^+$, 75%), 199.8 ($M+2+H^+$, 100%). 3-Fluoro-2-hydroxybenzonitrile (**3**): yellow solid; mp 115–117 °C; IR (KBr, cm^{-1}) ν: 3417, 2240, 1643; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.29–7.35 (m, 2H), 6.94–6.98 (m, 1H), 6.10 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm):δ = 151.24 (d, J = 237.0 Hz), 147.16 (d, J = 16.0 Hz), 128.95 (d, J = 3.9 Hz), 121.49 (d, J = 7.0 Hz), 120.76 (d, J = 17.0 Hz), 115.20, 102.30 (d, J = 3.3 Hz); LC/MS: m/z 138.2 ($M+H^+$, 100%); HRMS calcd for C_7H_4FNO: 137.0277, found: 137.0273. 3-*tert*-Butyl-2-hydroxybenzonitrile (**4**): white solid; mp 131–132 °C; IR (KBr, cm^{-1}) ν: 3298, 2234, 1580; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.50 (dd, J = 7.9, 1.3 Hz, 1H), 7.34 (dd, J = 7.7, 1.6 Hz, 1H), 6.93 (t, J = 7.8 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 157.08, 137.82, 132.25, 129.78, 120.88, 116.77, 100.17, 34.98, 29.29; LC/MS: m/z 176.0 ($M+H^+$, 100%); HRMS calcd for $C_{11}H_{13}NO$: 175.0997, found: 175.1002. 2-Hydroxy-3-methylbenzonitrile (**5**): yellow solid; mp 87–88 °C (lit.[5d] mp 89–91 °C); IR (KBr, cm^{-1}) ν: 3306, 2233, 1590; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.33–7.35 (m, 2H), 6.90 (t, J = 7.7 Hz, 1H), 5.75 (br s, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 156.43, 135.87, 129.95, 125.72, 120.93, 116.45, 99.00, 15.75; LC/MS: m/z 134.0 ($M+H^+$, 100%). 3-Allyl-2-hydroxybenzonitrile (**6**): pale yellow solid; mp 34–37 °C (lit.[14] mp 38–39 °C); IR (KBr, cm^{-1}) ν: 3328, 2231, 1590; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.40 (dd, J = 7.8, 1.8 Hz, 1H); 7.33–7.36 (m, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.06 (br s, 1H), 5.91–6.04 (m, 1H), 5.13–5.21 (m, 2H), 3.43 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 156.59, 135.20, 134.99, 130.83, 127.16, 121.06, 117.45, 116.36, 99.81, 34.59; LC/MS: m/z 160.0 ($M+H^+$, 100%). 5-Fluoro-2-hydroxybenzonitrile (**7**): white solid; mp 120–121 °C; IR (KBr, cm^{-1}) ν: 3269, 2236, 1508; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.21–7.28 (m, 2H), 6.96–7.02 (m, 1H), 6.11 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 156.01 (d, J = 240.0 Hz), 154.87 (d, J = 2.2 Hz), 122.42 (d, J = 23.3 Hz), 118.42 (d, J = 25.7 Hz), 118.10 (d, J = 7.9 Hz), 115.13, 99.90 (d, J = 9.4 Hz); LC/MS: m/z 138.1 ($M+H^+$, 100%); HRMS calcd for C_7H_4FNO: 137.0277, found: 137.0272. 5-Bromo-2-hydroxybenzonitrile (**8**): pale yellow solid; mp 155–156 °C (lit.[15] mp 157–158 °C); IR (KBr, cm^{-1}) ν: 3427, 2227, 1644; ^1H NMR (300 MHz, DMSO-d_6, ppm): δ = 10.45 (br s, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.35 (dd, J = 8.9, 2.4 Hz, 1H), 6.83 (d, J = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 159.14, 136.41, 134.31, 117.79, 115.23, 109.76, 101.03; LC/MS: m/z 198.1 ($M+H^+$, 77%), 199.8 ($M+2+H^+$, 100%). 5-*tert*-Butyl-2-hydroxybenzonitrile (**9**): white solid; mp 130–131 °C; IR (KBr, cm^{-1}) ν: 3432, 2230, 1641; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.52–7.47 (m, 2H), 6.92 (dd, J = 8.5, 0.6 Hz, 1H), 5.90 (br s, 1H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 155.90, 144.16, 132.11, 129.07, 116.57, 116.12, 98.75, 34.13, 31.05; LC/MS: m/z 175.9 ($M+H^+$, 100%); HRMS calcd for $C_{11}H_{13}NO$: 175.0997, found: 175.0990. 2-Hydroxy-5-phenoxybenzonitrile (**10**): white solid; mp 114–115 °C; IR (KBr, cm^{-1}) ν: 3291, 2238, 1594, ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.31–7.38 (m, 2H), 7.10–7.20 (m, 3H), 6.93–6.98 (m, 3H), 6.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 157.42, 155.34, 150.76, 130.41, 126.91, 124.15, 122.66, 118.81, 118.51, 116.29, 100.14; LC/MS: m/z 211.9 ($M+H^+$, 100%); HRMS calcd for $C_{13}H_9NO_2$: 211.0633, found: 211.0633. 3,5-Di-*tert*-butyl-2-hydroxybenzonitrile (**11**): white solid; mp 135–136 °C (lit.[16] mp 135–136 °C); IR (KBr, cm^{-1}) ν: 3401, 2230, 1638; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.52 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 5.70 (br s, 1H), 1.41 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 154.68, 143.65, 136.96, 129.76, 125.96, 117.15, 99.53, 35.13, 34.42, 31.22, 29.34; LC/MS: m/z 232.2 ($M+H^+$, 100%). 2-Hydroxy-3,4-(methylenedioxy)benzonitrile (**12**): white solid; mp 180–181 °C; IR (KBr, cm^{-1}) ν: 3185, 2233, 1635; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.10 (d, J = 8.3 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 6.08 (s, 2H), 5.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 153.15, 142.36, 135.01, 128.38, 116.37, 103.35, 103.07, 95.61; LC/MS: m/z 163.9 ($M+H^+$, 100%); HRMS calcd for $C_8H_5NO_3$: 163.0269, found: 163.0264.
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