2-Aminophenols Containing Electron-Withdrawing Groups from *N*-Aryl Hydroxylamines

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Abstract: Reaction of substituted *N*-aryl hydroxylamines with methanesulfonyl chloride, *p*-toluenesulfonyl chloride, or trifluoromethanesulfonic anhydride under basic conditions leads to the rearranged 2-aminophenols (45–94%). The overall reaction sequence can be performed using polymer-supported sulfonyl chloride resin allowing for the effective conversion of *N*-aryl hydroxylamines to the 2-aminophenols without the need for chromatography.

Key words: rearrangement, hydroxylamine, solid-phase synthesis, 2-aminophenol

2-Aminophenols are valuable precursors in the preparation of heterocycles such as benzoxazoles,[1] benzoxazolones,[2] indoles,[3] benzoxathiazole-2,2-dioxides,[4] and benzoxazepines[5] amongst others, highlighting their importance in synthesis. As a consequence, simple and effective methods for their preparation are of great use in the preparation of pharmaceutically relevant compounds.

We recently described methods to prepare 2-aminophenols[6] and 2-aminoanilines[7] through rearrangement of *N*-aryl hydroxylamine derivatives which were readily accessible from either aryl halides[8] or nitroarenes.[9] Throughout these investigations a specific challenge that emerged was the rearrangement of electron-deficient *N*-aryl hydroxylamines **1**, such that we were unable to prepare 2-aminophenols (or their derivatives) through this strategy where the aromatic ring contained an electron-withdrawing group (Figure 1). Within this report we describe a method to overcome these problems and have found suitably protected electron-deficient *N*-aryl-*O*-sulfonyl hydroxylamines effectively undergo rearrangement to give protected 2-aminophenol products.

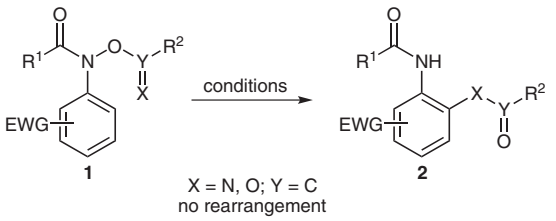

Figure 1

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In previous investigations a specific trend that emerged in the rearrangement of O-functionalised *N*-aryl hydroxylamines was increasing the electron-withdrawing nature of the oxygen-substituent (i.e., R^2 in compound **1**), increased the propensity of rearrangement. Further work showed that for a series of oxygen-substituents, the sulfonyl group allowed for the most facile rearrangement. For example, for the substrates **3**, **4**, and **5** (Figure 2) rearrangement occurred at 160 °C, 140 °C, and r.t.,[2,6] respectively. With regards the aromatic portion of the substrate, mechanistic studies by Gassman have shown the dramatic effect of reducing electron density on the aromatic ring on decreasing the rate of rearrangement for a series of hydroxamic acid derivatives.[10] Combination of these two factors suggested that use of the sulfonyl group for the rearrangement of electron-deficient substrates would provide the best opportunity for success in the overall strategy.

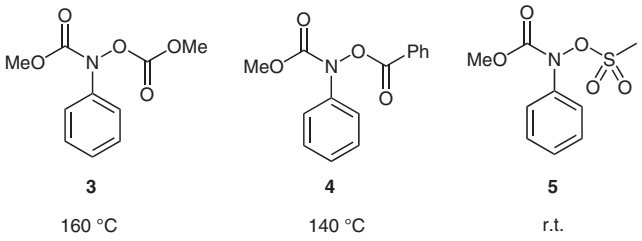
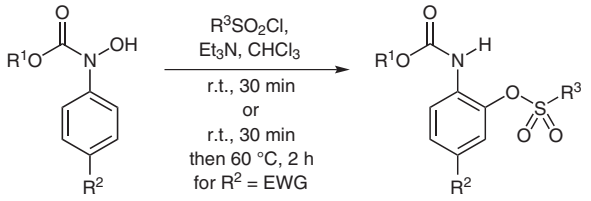


Figure 2 Effect of O-substitution on rearrangement temperature

Reassessment of the conditions reported for the rearrangement of *N*-aryl hydroxylamines[6] showed that, for unsubstituted aromatic rings, coupling/rearrangement occurred at room temperature for both methanesulfonyl and toluenesulfonyl chloride with the *N*-hydroxy carbamates examined giving the products in high yield (Table 1; entries 1–6; 78–94%). With electron-deficient substrates coupling with the sulfonyl chloride occurred at room temperature but, despite long reaction times, rearrangement did not take place. Pleasingly, warming the reaction mixture to 60 °C for two hours brought about rearrangement allowing the product to be isolated in excellent yield. This protocol was tolerant of a variety of functional groups including nitrile, ester, ketone, chloride, alkyne, and bromide with both Boc and methoxy carbamate nitrogen protecting groups (entries 7–15; 82–94%). This simple and highly effective strategy to access challenging tri- and tetrasubstituted aromatic compounds bearing electron-

withdrawing substituents significantly expands the scope of the transformation and suggests the 2-aminophenol of choice can be prepared through this methodology.

Table 1 Treatment of *N*-Aryl Hydroxylamines with Sulfonyl Chlorides[a]



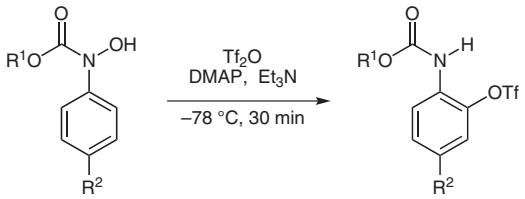
6 **7–21**

Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1[c]	Me	H	Me	**7**	78
2[c]	Me	H	Tol	**8**	86
3[c]	*t*-Bu	H	Me	**9**	88
4[c]	*t*-Bu	H	Tol	**10**	81
5[c]	Bn	H	Me	**11**	94
6[c]	Bn	H	Tol	**12**	89
7[d]	*t*-Bu	CN	Tol	**13**	88
8[d]	*t*-Bu	CO_2Et	Tol	**14**	85
9[d]	*t*-Bu	Ac	Tol	**15**	82
10[d]	*t*-Bu	Cl	Me	**16**	94
11[d]	Me	C_2H	Tol	**17**	91
12[d]	Me	Cl	Tol	**18**	85
13[d]	Me	Br	Tol	**19**	84
14[d]	Me	2-Me-4-Cl	Me	**20**	88
15[d]	Me	3-Br	Me	**21**	84[e]

[a] All reactions performed in $CHCl_3$ (0.25 M).
[b] Isolated yield.
[c] Reaction conducted at r.t. for 30 min.
[d] Reaction conducted at r.t. for 30 min then 60 °C for 2 h.
[e] Isolated as an inseparable mixture of isomers in a 30:70 ratio (1,2,6-isomer/1,2,4-isomer).

Along with providing access to N-protected 2-aminophenols as heterocyclic building blocks, the *O*-sulfonyl phenol products (e.g., **7**) represent potential partners for transition-metal-catalysed couplings.[11] Of the *O*-sulfonyl substrates reported to be effective in these reactions, the *O*-trifluoromethanesulfonate functionality readily undergoes oxidative addition and has the broadest applicability.[12] We therefore examined reaction of *N*-aryl hydroxylamines **6** with trifluoromethanesulfonic anhydride to determine if this would also undergo a similar rearrangement to that described above (Table 1). Reaction at room temperature (as above) or 0 °C proved difficult to control. However, addition of the anhydride to the hydroxylamine precursor **6** at –78 °C then allowing the solution to warm to room temperature gave the rearranged products in 45–74% yield (Table 2). Although isolated yields were lower than those with methanesulfonyl and toluenesulfonyl chloride (Table 1) the products could be isolated by chromatography and several of the challenging electron-deficient precursors were effective substrates within the reaction (entries 1–4).

Table 2 Formation of *O*-Trifluoromethane Sulfonate Products[a]



6 **22–25**

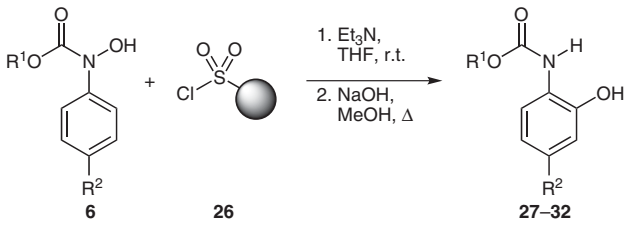
Entry	R^1	R^2	Product	Yield (%)[b]
1	Me	Cl	**22**	51
2	Me	Br	**23**	45
3	*t*-Bu	CO_2Et	**24**	55
4	*t*-Bu	CN	**25**	74

[a] All reactions performed in CH_2Cl_2 (0.18 M).
[b] Isolated yield.

Having established effective conditions for the preparation of electron-deficient N-protected 2-aminophenols, we sought to develop the work further by the use of a 'catch-and-release' strategy using a polymer-supported sulfonyl chloride resin. Standard conditions are outlined in Table 3. Treatment of N-protected *N*-aryl hydroxylamine **6** with commercially available sulfonyl chloride resin in THF at room temperature for 30 minutes followed by heating at 60 °C for two hours gave the polymer-supported rearranged product which could be thoroughly washed. Suspension of the residue in methanol and treatment with sodium hydroxide solution (2 M) at reflux for two hours gave the products **27**–**32** (44–56%; >82% purity LC-MS). This simple and standard protocol should have good applicability in the preparation of arrays of 2-aminophenols as key heterocyclic building blocks.

In summary, we have described a simple and effective method for the preparation of both electron-rich and electron-deficient 2-aminophenols by reaction of protected *N*-aryl hydroxylamines with sulfonyl chlorides. Use of polymer-supported sulfonyl chloride resin provides the specific advantage of giving the products through a standard protocol without the need for chromatography. Given the mild conditions required for rearrangement and the ready availability of *N*-aryl hydroxylamines we believe this strategy will have application in the preparation of a variety of biologically significant heterocycles in drug discovery campaigns.

Table 3 Catch-and-Release Strategy for Rearrangement



6 **26** **27–32**

Entry	R^1	R^2	Product	Yield (%)[a]	Purity (%)[b]
1	*t*-Bu	CN	**27**	47	82
2	*t*-Bu	CO_2Me	**28**	44[c]	87
3	*t*-Bu	Ac	**29**	52	88
4	*t*-Bu	Cl	**30**	48	91
5	*t*-Bu	Me	**31**	56	97
6	Me	Br	**32**	54	95

[a] Isolated yield.
[b] Determined by LC-MS.
[c] Conducting hydrolysis in EtOH gave the ethyl ester (35%).

Typical Experimental Procedures

Rearrangement of Methanesulfonates and Toluenesulfonates[13]
The N-protected *N*-phenyl hydroxylamine (1.0 mmol) was dissolved in $CHCl_3$ (4 mL) and Et_3N (0.28 mL, 2 mmol) was added followed by the addition of the sulfonyl chloride (1.1 mmol) at 0 °C. The ice bath was removed and the reaction mixture allowed to stir at r.t. If rearrangement precursor remained after 30 min the reaction was heated to 60 °C for 2 h. The crude mixture was directly subjected to column chromatography to obtain the rearrangement products.

Rearrangements of Trifluoromethanesulfonates[13]
The N-protected *N*-phenyl hydroxylamine (0.72 mmol) was dissolved in CH_2Cl_2 (4 mL), Et_3N (0.28 mL, 2 mmol), and a catalytic amount of DMAP were added followed by the slow addition of trifluoromethanesulfonic anhydride (0.17 mL, 1.0 mmol) at –78 °C. Stirring was continued at –78 °C for 30 min then the reaction mixture was allowed to warm to r.t. On completion, the mixture was diluted with CH_2Cl_2 (10 mL), washed with $NaHCO_3$ solution and brine (10 mL each). The solvent was evaporated and the crude product further purified by column chromatography on silica to give the rearrangement product.

Rearrangement Using Supported Sulfonyl Chloride
To a suspension of polymer-bound sulfonyl chloride (1 g, 1.5 mmol, Sigma Aldrich #498211) in THF (6 mL) was added Et_3N (0.23 mL, 2 mmol), followed by hydroxylamine (1 mmol) in THF (2 mL). The mixture was stirred for 30 min at r.t. and 2 h at 60 °C. The mixture was filtered and the residue washed with Et_2O. The residue was suspended in MeOH (8 mL) and NaOH (2 mL, 2 M) was added, and the mixture was heated to reflux for 2 h. The reaction mixture was filtered and washed with Et_2O. The filtrate was analysed by LC-MS. The organic layer was washed with H_2O and evaporated to give the 2-aminophenols in moderate yield.

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