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Graphical Abstract

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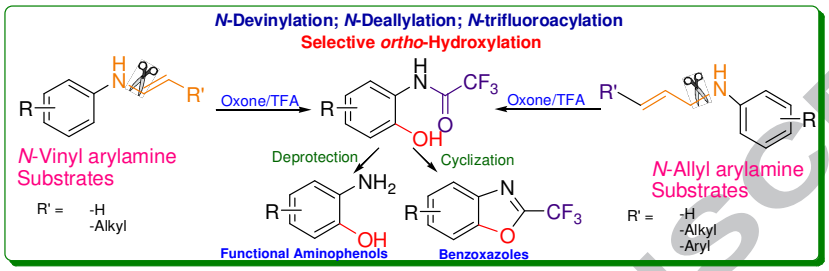
Shilpi Balgotra, Vunnam Venkateswarlu, Ram A. Vishwakarma, Sanghapal D. Sawant*



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Direct C–N bond cleavage of *N*-vinyl or *N*-allyl arylamines: A metal-free strategy for *N*-devinylation and *N*-deallylation

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ABSTRACT

A simple and convenient *N*-devinylation and *N*-deallylation strategy for *N*-vinyl and *N*-allyl arylamines in the presence of TFA/oxone is presented with the formation of selective *ortho*-hydroxylated and *N*-trifluoroacylated arylamine product in good yields. This method is important for protection/deprotection of arylamines in organic synthesis and useful as medicinal chemistry tool at late stage modifications in drug discovery programs.

Introduction

N-vinylation or *N*-allylation is normally used as a protection strategy in organic synthesis. Deprotection of these protecting groups is essential at certain stages and there are some methods reported for the removal of the functional groups. However, deprotection of *N*-vinyl is most uncommon, very few methods for *N*-vinyl deprotection are reported in literature such as oxidative method using $KMnO_4$,[1] another method using $Hg(OAc)_2$ and $NaBH_4$ mediated *N*-devinylation is reported by Trofimov *et. al* and Ganzalez *et. al*.[2] Apart from this, methods involving hydrolysis using acids[3] and ozonolysis[4] are also known. Although, there are some other methods related to *N*-devinylation of pyrroles, pyrazoles, or lactams, imidazoles, benzimidazoles, and porphyrins are reported, but to our knowledge there are no reports on direct *N*-devinylation of *N*-vinyl arylamines.[5]

N-allyl group is normally used in the protection of alcohols or phenols, carboxylic acids, phosphoric acids, amines or amides, as it sustains in acidic as well as basic conditions. In conventional deprotection methods of allyl groups, usually isomerization of allyl group to the 1-propenyl group and subsequent hydrolysis or oxidation is normally reported in literature.[6] More recently, some metal catalyzed methods including Rh-[7] and Ru-catalyst[8] are reported. It is desired to establish newer deprotection strategies for *N*-vinyl or *N*-allyl arylamine substrates.

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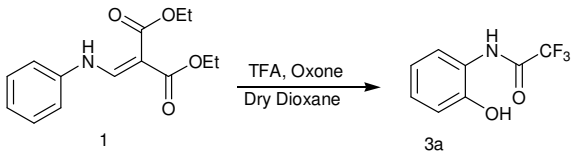
In our interest in the development of newer synthetic methods under metal-free conditions, we now report a very unique reaction in the context of deprotection of *N*-vinyl or *N*-allyl arylamine substrates.[9] This strategy is very simple and easy to implement and this is a first report for this kind of conversion. In this reaction, C–N bond cleavage of *N*-vinyl or *N*-allyl arylamine takes place, which subsequently *N*-trifluoroacylate the substrate with concomitant *ortho*-hydroxylation giving the desired product. Present method offers an advantage from the medicinal chemistry perspective; $–CF_3$ group, which has its own important role in alteration of physicochemical properties of the molecule.[10] This reaction goes in a tandem manner by deprotecting an allyl or vinyl group, along with introduction of –OH as well as trifluoroacyl group in the substrate in an easy way. There are several $–CF_3$ group bearing drugs available such as prozac or befloxatone (antidepressants), trifloxystrobin (fungicide), and efavirenz (anti-HIV drug), celecoxib, dutasteride, fluoxetine, and sitagliptin, as well as the agrochemicals beflubutamid, diflufenican, fusilade, and norfluazon.[11] Furthermore, the present reaction has potential in applications like the deprotection of *N*-trifluoroacyl group of resulting compounds can give the amino phenols directly, which gives functional anilines, useful starting materials for the synthesis of important bioactive heterocycles.[12] In many cases, functional groups, such as –OH, -SH, –COOH and also $-NH_2$ are to be selectively manipulated over an amine group. Moreover, as *N*-acetyl-*p*-aminophenol has got great potential as anti-inflammatory analgesic and it is reported for

COX inhibitory activity also. The resulting compounds obtained in present method are structural analogs of this important drug and they could also have great importance and interest to the medicinal chemists for finding such biologically active or potential molecules. Even though, several acetaminophen analogs have been reported, the interest and scope remains to be continued to find new molecules for this class of drugs.[13]



1 3a

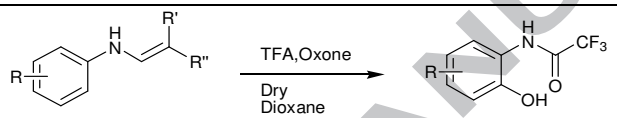
Scheme 1. Reaction of diethyl 2-((phenylamino)methylene)malonate for formation of 2,2,2-trifluoro-*N*-(2-hydroxyphenyl)acetamide

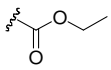
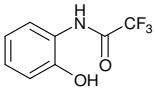
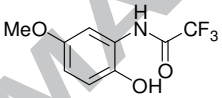
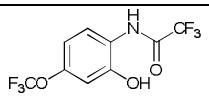
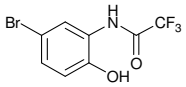
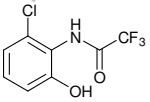
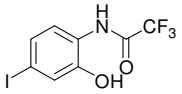
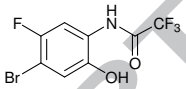
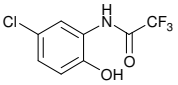
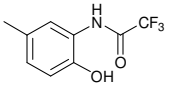
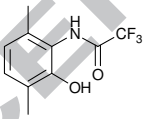
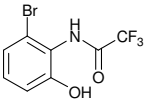
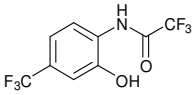
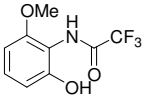
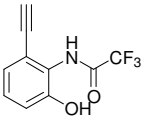
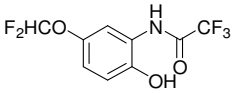
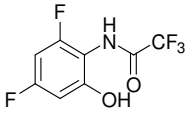
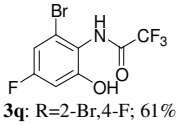
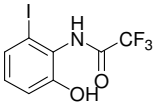
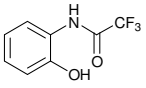
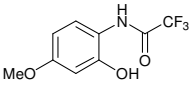
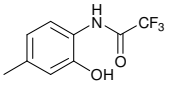
Apart from these advantages, as an application part, the obtained *N*-trifluoroacyl-*ortho*-aminophenols can also be converted to corresponding benzoxazoles, an important class of compounds by following a cyclization route.

Results and discussion

The work on optimization of present reaction was started based on our recent report[9] with the thought of expanding the method on some other substrates like *N*-allyl or *N*-vinyl arylamine. These substrates are typical and widely used as building blocks in organic synthesis. The newer methods for deprotection of vinyl or allyl groups are desirable and present method can stand as one of the helpful tool for removing these functional groups. The studies commenced with the optimization of reaction of *N*-vinylated aniline, typically the reaction with diethyl-2-((phenylamino)methylene)malonate **1**, by using previously reported oxone and TFA mixture gave the desired product 2,2,2-trifluoro-*N*-(2-hydroxyphenyl)acetamide **3a** in good yields (Scheme 1). We were pleased to observe the *N*-devinylated product by following the concomitant formation of *ortho*-hydroxy-*N*-trifluoroacetamide product. Being the present study is an extension of our earlier report,[9] the reaction conditions were implemented as such, except the equivalents of TFA/oxone was increased to double of its quantity reported earlier, in present reaction. Several examples for the *N*-vinylated arylamine substrates were generated by following this protocol.[15]

Table 1. *N*-devinylation followed by *N*-trifluoroacylation and *ortho*-hydroxylation of different *N*-vinylated arylamines



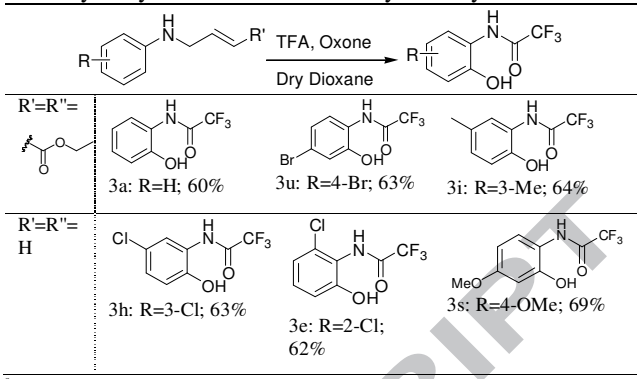
R'=R"= 	 **3a**: R=H; 60%	 **3b**: R=3-OMe; 59%	 **3c**: R=4-OCF_3; 62%
	 **3d**: R=3-Br; 55%	 **3e**: R=2-Cl; 59%	 **3f**: R=4-I; 65%
	 **3g**: R=4-Br,3-F; 63%	 **3h**: R=3-Cl; 60%	 **3i**: R=3-Me; 70%
	 **3j**: R=2,5-Dimethyl; 62%	 **3k**: R=2-Br; 68%	 **3l**: R=4-CF3; 65%
	 **3m**: R=2-OMe; 59%	 **3n**: R=2-ethynyl; 61%	 **3o**: R=3-OCHF2; 64%
	 **3p**: R=2,4-Difluoro; 62%	 **3q**: R=2-Br,4-F; 61%	 **3r**: R=2-I; 58%
R'=R"= H	 **3a**: R=H; 59%	 **3s**: R=4-OMe; 68%	 **3t**: R=4-Me; 58%

[a]The yields are after column chromatography

As shown in Table 1, the substrates bearing different substitutions were converted to corresponding *ortho*-hydroxy-*N*-trifluoroacetamide products with the yields in the range of 58% to 70%. Two different kind of *N*-vinylic group bearing anilines viz. simple *N*-vinyl and 2,2-bis(ethoxycarbonyl)-*N*-vinyl (BECV), were either prepared or procured from commercial sources and subjected for this reaction. All kind of substitutions like electron donating or withdrawing groups were accommodated on the arylamine substrates and the reactions went smoothly. The examples for this reaction are shown in Table 1.

Further to expand the scope of present reaction, this reaction was applied on the *N*-allyl bearing aniline substrates and as expected the desired products were obtained with good yields, in the range of 60 to 70%. The examples of *N*-allylated arylamine substrates are presented in Table 2. However, in case of aryl substituted substrates at R′ position, it gave cinnamyl alcohols as side products, seen in mass spectra.

Table 2. *N*-deallylation followed by *N*-trifluoroacylation and *ortho*-hydroxylation of different *N*-allylated arylamines



[a]The yields are after column chromatography

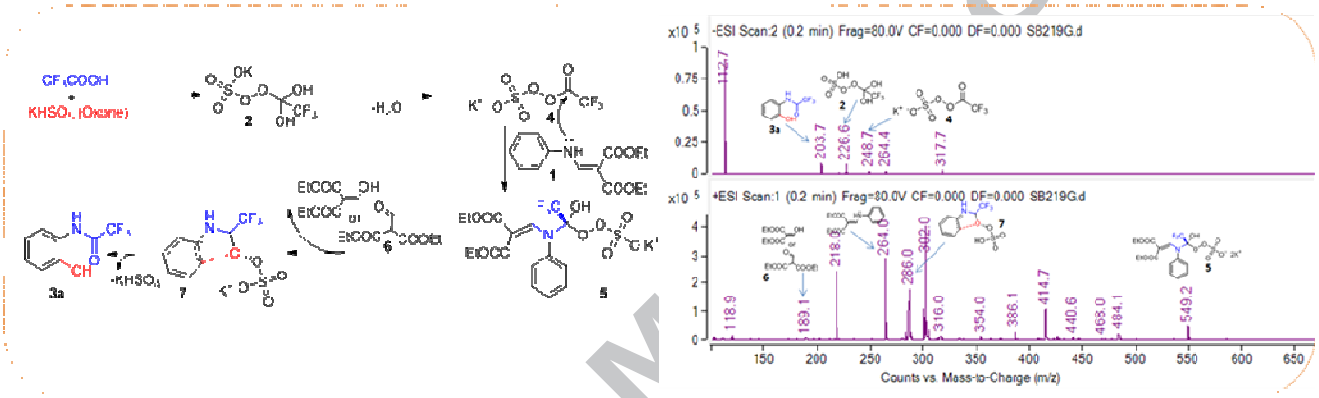


Figure 1. LC-MS based analysis of sample collected after 1 hr interval, the mechanistic hypothesis for the formation **3a** by deprotection of vinyl group followed by concomitant formation of *N*-trifluoroacyl-*ortho*-aminophenol is shown with the help of obtained mass peaks

In a mechanistic study, as reported in our earlier paper, we envision a similar pathway for this reaction as well.[9] To prove our hypothesis, the LC-MS based intermediate capture experiment was conducted, which revealed the expected mass peaks of the intermediates as shown in figure 1. With the support of mass peaks obtained in this experimental data, we strongly predict the route as shown in the figure 1. In this pathway there is a addition of arylamine to intermediate 4, which is formed from 2 and gives the adduct intermediate 5, further devinylation takes place at this stage with the release of corresponding vinyl aldehyde or in the form of alcohol as can be seen in a mass peak of 6. The intermediate 5, subsequently forms unstable intermediate 7 and in final step $KHSO_4$ is released, which forms the required product 3a.

In conclusion, we have developed a novel, simple and convenient protocol for the deprotection of *N*-vinyl or *N*-allyl arylamines offering the corresponding *N*-trifluoroacylated and selectively *ortho*-hydroxylated arylamine products with good yields. This method can be useful in organic synthesis as protection/deprotection tool for respective *N*-protected arylamines. Further it can be used in direct preparation of aminophenols or $-CF_3$ bearing benzoxazoles and also in some other applications of organic synthesis as well.

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General Procedure for Synthesis of 2-hydroxy-N-trifluoroacetanilides from N-vinylaniline and N-allylaniline: In a typical procedure, *N*-vinylaniline (0.1g, 0.840 mmol) was dissolved in dry dioxane under inert atmosphere. To this was added trifluoroaceticacid (0.26 ml, 3.36 mmol) and oxone (0.515g, 1.68 mmol). The resulting mixture was heated to 90 ^{o}C under nitrogen atmosphere until starting material is consumed. During the progress of reaction, color of reaction mixture turned from light red to dark red. The mixture was then cooled to room temperature, washed with saturated solution of sodium bicarbonate. The mixture was extracted with EtOAc (20 mLx2). The combined organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure *in vaccuo*, the obtained residue was purified on silica-gel (100-200 mesh) column chromatography (Hexane: EtOAc = 9:1) to afford a light brown solid (60%) 2-hydroxy-*N*-trifluoroacetanilides, **3a**. ^{1}H NMR (400 MHz, MeOD): δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.84 – 6.70 (m, 2H); ^{13}C NMR (101 MHz, MeOD): δ 150.68, 128.45 , 124.75 , 124.36 , 120.61, 118.97 , 116.58 , 116.11; ^{19}F NMR (376.50 MHz, MeOD): δ -77.14 (s, 3F); IR($CHCl_3$) λ_{max}(cm^{-1}): 3389, 3248, 2923, 2851, 1690, 1597, 1562, 1465, 1194, 1159, 1101,1041, 851, 749 ; HRMS (ESI) calcd for $C_8H_5F_3NO_2$ ([M-H+]-) 204.0275, found 204.0273; Light brown solid; Mp: 155-156 ^{o}C.