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C–H Oxygenation and *N*-Trifluoroacylation of Arylamines Under Metal-Free Conditions: A Convenient Approach to 2-Aminophenols and *N*-Trifluoroacyl-*ortho*-aminophenols

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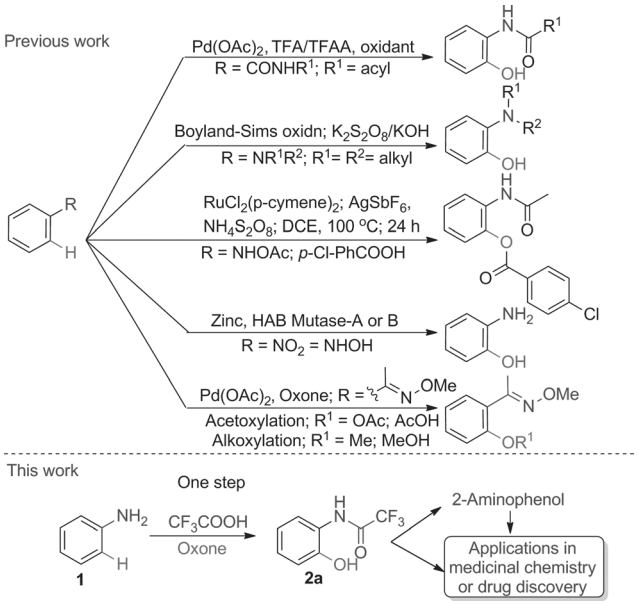
Abstract: Direct *ortho*-hydroxylation through C–H oxygenation and *N*-trifluoroacylation of anilines was achieved in a single step under metal-free conditions by using a combination of TFA and oxone. The method allowed the formation of functionalised amino phenolic compounds such as *ortho*-hydroxy-*N*-trifluoroacetanilides in good yields with broad substrate scope.

N-Acetyl-*p*-aminophenols are widely used as "aniline analgesics"[1,2] and serve as anti-inflammatory drugs and cyclooxygenase (COX) inhibitors, which are of great interest to medicinal chemists. Even though, several acetaminophen analogues have been reported, identifying new synthetic routes to this unique class of molecule is still an important goal. Although, there are several reports on direct hydroxylation of aryl or non-aryl substrates,[3,4] aryl substrates bearing amino groups have been less explored for direct hydroxylation.

Traditional approaches toward *ortho*- or *para*-aminophenols involve nitration of phenols followed by reduction of the nitro group. There are very few reports of *ortho*-directed hydroxylation of amines and many of them are metal catalysed, as shown in Scheme 1. Methods such as *ortho*-acetoxylation or alkoxylation on various acetanilides using oxone and $K_2S_2O_8$ have been reported.[5] Recently, Wang et al. reported direct acetoxylation of anilides through palladium-catalysed C–H activation, and Rao et al. reported direct hydroxylation on arylamines using palladium and ruthenium catalyst, also ruthenium-catalysed oxidative *ortho*-benzoxylation of acetanilides with aromatic acids is reported by Jeganmohan et al.[6] Some reports are available on the formation of 2-aminophenols using microbial transformations or enzymes.[7] Spain et al.[8] reported a metal and biocatalyst mediated formation of 2-aminophenols, in which nitroaromatic compounds were reduced to hydroxylamines by zinc and then to corresponding *ortho*-aminophenols, using hydroxylaminobenzene (HAB) mutase A and B from *Pseudomonas pseudoalcaligenes*. This report included the synthesis of a novel analogue of chloramphenicol. The Boyland–Sims persulfate mediated oxidation reaction is very well known to give a mixture of *ortho*- and *para*-aminophenols.[9] As there are limited methods for this transformation, further methods for the direct hydroxylation of arylamine substrates are required.



Scheme 1. Various methods reported for hydroxylation reaction of arylamines and present approach for direct *ortho*-hydroxylation.

There are no reports on the direct formation of 2-hydroxy-*N*-trifluoroacetanilides as such, which could otherwise be obtained by following a synthetic route using selective *N*-trifluroacylation of aminophenols by using a protection/deprotection strategy. These compounds could be of interest from a medicinal chemistry and drug discovery perspective as important precursors or intermediates. Furthermore, mostly in various drug discovery programs, at lead optimisation stage, introducing $-CF_3$ group in a compounds is often preferred because it plays an important role to sort out the issues related to bioavailability or lipophilicity and physicochemical properties.[10] The pres-

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ent method can be applied on biologically active small molecules and natural products as well.

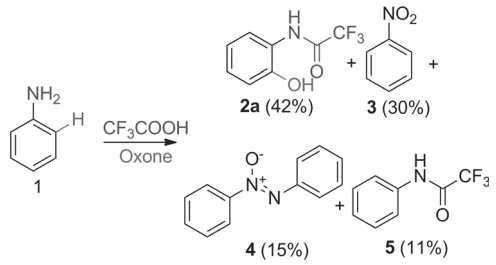
In our initial study, we examined the possibility of hydroxylation of aniline **1**, using various oxidants (Table 1) in the presence of TFA. The reactions with reagents such as oxone, *m*-CPBA, H_2O_2, and $K_2S_2O_8$ led to interesting observations, and

Table 1. Screening of various oxidants for formation of **2a**.[a]

Entry	Oxidant	Yield [%][b]
1	oxone	42
2	TBHP	0
3	Fe_2O_3	0
4	*m*-CPBA	25
5	DDQ	0
6	$K_2S_2O_8$	30
7	H_2O_2	25

[a] All reactions carried out in dioxane at reflux. [b] Yields are based on GC-MS analysis.

we could detect the selective formation of *ortho*-hydroxylated trifluoroacetanilide **2a** as the major product along with side products nitrobenzene (**3**), 1,2-diphenyldiazene oxide (**4**), and *N*-trifluoroacylated product **5** (Scheme 2). In case of Fe_2O_3, *tert*-butylhydroperoxide (TBHP), and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) no product formation was observed. Initially, we carried out all reactions using dioxane at reflux conditions.



Scheme 2. Reaction of aniline with TFA and oxone.

Considering the importance of *ortho*-hydroxy amino group bearing class of pharmacologically active compounds,[11] and our chance encounter of the potential of "greener"[12] oxone in this important transformation, we decided to explore this reaction and its application in more detail (Scheme 2). For optimisation of reactions we conducted the solvent screening using various solvents and dried dioxane was found to give the best results (Table 2). All future reactions were carried in anhydrous dioxane under inert conditions.

Based on this early interesting observation and encouraging results, we intended to improve the yields of 2-hydroxy-*N*-trifluoroacetamide **2a**. In this direction, we planned for conducting the temperature dependent reactions. The reactions at various temperatures gave varying yields. Amongst all, the reaction conducted at 90 °C for 1.5 h gave maximum yield of **2a** (Table 3), there was no increase in yields even after the reaction was continued till 12 h at this temperature. The equivalence study for oxone and trifluoroacetic acid (TFA) was carried out, wherein the reaction with 1.2 equivalents of oxone and 2.4 equivalents of TFA gave maximum yields.

Table 2. Screening of solvents for formation of **2a**.[a]

Entry	Solvent	*T* [°C]	Yield [%][b]
1	dioxane	101	42
2	THF	66	0
3	DMF	152	0
4	MeCN	82	25
5	MeCN/H_2O (1:1)	reflux	0
6	DMSO	189	30
7	MeOH	65	25

[a] All reactions were performed by using oxone as the oxidant and a reaction time of 12 h. [b] Yields are based on GC-MS analysis.

Table 3. Yields of product **2a** at various temperatures.[a]

Entry	*T* [°C]	Yield [%][b]	Side products		
			3	**4**	**5**
1	101	42	30	15	11
2	90	64	11	16	1.2
3	70	35	10	30	2
4	50	25	5	40	5
5	25	18	5	68	5

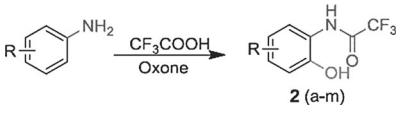
[a] All reactions performed by using oxone as the oxidant, dioxane as the reaction solvent, and a reaction time of 12 h. [b] Yields are based on GC-MS analysis.

The acidic nature of TFA was explored on the basis that its role may be important in hydroxylation. We carried out experiments with various acids. The reaction with TFA without oxone gave only *N*-acylated product **5** and reaction with HCl, H_2SO_4, and methanesulfonic acid using oxone, led to formation of nitrobenzene (**3**) exclusively. However, acetic acid gave 1,2-diphenyldiazene (**9**) as a major product.

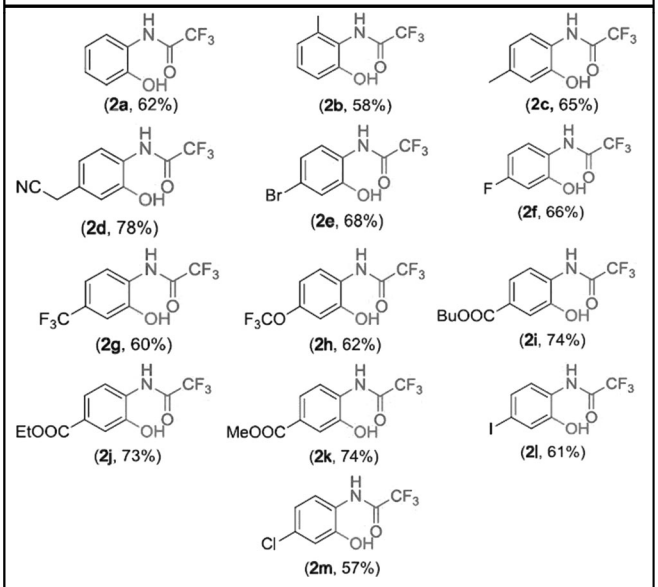
With these optimised conditions, the present reaction offers wide substrate scope and applicability. To demonstrate this, several electron-withdrawing as well as electron-donating substrates were explored. In this context, varieties of substrate were reacted in presence of oxone and TFA and all gave the *ortho*-hydroxyl-*N*-trifluoroacylated aryamine products in good yields (Tables 4 and 5). However, comparatively low yields were obtained for substrates bearing electron-donating groups. In case of 2,6-dimethylaniline, the required transformation was not observed, which indicates the specificity of the substrates. However, in case of *meta*-substituted aryl amines, two products were observed and *ortho*-hydroxylation towards the sterically hindered side was found to be very low or negligible. The examples of *meta*-substituted substrates are presented separately in Table 5.

Furthermore, to see the substrate specificity of the present reaction, we explored the possibility of *ortho*-hydroxylations on different arylamines (Table 6). The reaction of *N*-arylsulfonamide under optimised condition could go easily offering the desired product **2a** (Table 6, entry 1) in good yields. 2-Hydroxy-

Table 4. Formation of *N*-trifluoroacyl-2-hydroxy arylamine products under optimised conditions.[a]

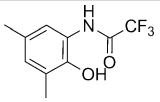
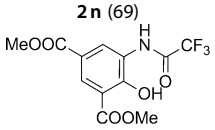
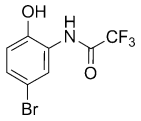
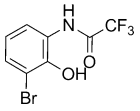
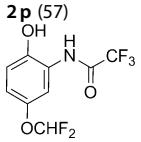
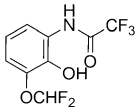
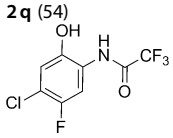
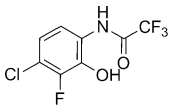
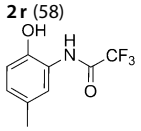
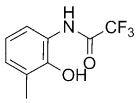


2 (a-m)



[a] Yields after purification by column chromatography.

Table 5. Formation of *N*-trifluoroacyl-2-hydroxy arylamine products with *meta*-substituted substrates under optimised conditions.

Entry	Substrate	Products (Yield [%])[a]	
1	3,5-Me		
		2n (69)	
2	3,5-COOMe		
		2o (74)	
3	3-Br		
		2p (57)	**2p′** (3)
4	3-$OCHF_2$		
		2q (54)	**2q′** (trace)
5	3-F,4-Cl		
		2r (58)	**2r′** (trace)
6	3-Me		
		2s (64)	**2s′** (trace)

[a] Yields after purification by column chromatography.

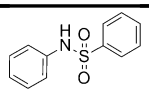
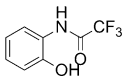
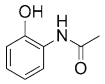
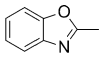
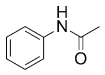
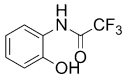
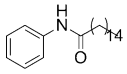
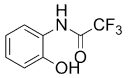
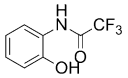
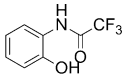
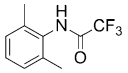
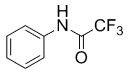
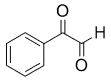
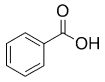
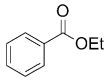
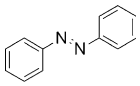
N-acetylarylamine gave 2-methyl benzoxazole exclusively (Table 6, entry 2). However, in case of small and long *N*-acyl chain bearing groups (Table 6, entries 3 and 4) the reaction went smoothly to give the expected transacylated and hydroxylated product; particularly, in case of *N*-acetyl and *N*-palmitoylated substrate formation of **2a** was observed. Curiously, the reaction of 2-hydroxyaniline did not undergo the required conversion and gave only acylated product, expected 2,6-dihydroxylated product was not observed (Table 6, entry 5).

Azidobenzene was converted to **2a** with high yields (Table 6, entry 6). 2,6-Dimethylaniline has not given the required product as expected, no hydroxylation was observed at any position, only *N*-trifluoroacyl product along with benzoquinone was formed (Table 6, entry 7), which indicates the specificity of the substrate for this reaction. Also interestingly, when *N*-trifluoroacylated substrate was kept for the reaction, it did not give the expected product (Table 6, entry 8) in TFA/oxone mixture or in oxone alone, indicating a very interesting mechanism. The reason could be because of exchanging an acyl group is difficult due to the presence of $-CF_3$ group, as fluorine atoms are electron withdrawing in nature. Subsequently, the reaction conditions were applied to other substrates, including the substrates like acetophenone, phenylglyoxal, benzoic acid, ethylbenzoate, and nitrobenzene were also explored for this reaction; no product formation was observed in any of these cases (Table 6, entries 9–13). To know the specificity and requirement of TFA reagent in this transformation, the reaction of aniline **1** with trichloroacetic acid (TCA) instead of TFA was carried out under optimised conditions, the desired product was not formed, it led to the formation of 1,2-diphenyldiazine compound **9**.

Based on these findings, investigations were performed to gain an insight into the reaction mechanism. Here, we envision that the reaction might be going through the mechanistic path as shown in Figure 1 a.

As soon as oxone and TFA are mixed, potassium trifluoromethtylsulfoperoxoate **10** is formed immediately, which is converted to **11** by removal of water. Subsequently, aniline **1** reacts with this intermediate **11** to form the zwiterionic intermediate **12**, which leads to *ortho*-hydroxylated product **2a**. Here, we propose that the oxygen was provided by oxone and not from TFA or air. To confirm our hypothesis, we carried out the intermediate capture experiment during the progress of reaction at different time intervals, in which the trapped intermediate **10**, **11**, and **12** could be observed by mass spectrometry (Figure 1 b), confirming our mechanistic hypothesis. The mass was acquired for aliquots directly without workup. Further, we moved our attention to find the source of oxygen, in this direction; we planned the experiments to establish the source of oxygen, and also to understand the role of TFA in this oxygenation. A reaction with deuterated-TFA was followed by NMR spectroscopy and mass analysis; the mass (Figure S2

Table 6. Screening of various substrates for exploring scope of reaction and substrate specificity.

Entry	Substrate	Products		Yield [%][a]
1			**2a**	30
2			**7**	94
3			**2a**	63
4			**2a**	61
5			**2a**	79
6			**2a**	79
7			**8**	75
8		no reaction		–
9		no reaction		–
10		no reaction		–
11		no reaction		–
12		no reaction		–
13		no reaction		–
14			**9**	75
	reaction in TCA			

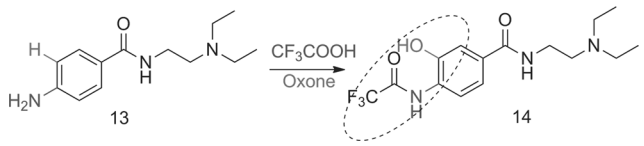
[a] Yields after purification by column chromatography.

in the Supporting Information), and ^{1}H NMR (Figure S3 in the Supporting Information), of aliquots (to avoid possibility of exchange of proton in aqueous workup) was acquired. There was no change observed in mass peak and the ^{1}H NMR showed usual hydroxyl proton peak (Figure S4 in the Supporting Information). This experiment rules out the possibility of involvement of TFA as source of oxygen. Furthermore, the possibility of air oxidation is also ruled out, as the reactions are carried out under inert conditions and only works under this conditions using dry dioxane. Therefore, as per our hypothesis the only source for oxygen remains is oxone. As proposed, this ionic mechanism was further supported by evidence that the reaction in presence of a free radical scavenger TEMPO went smoothly, giving the desired product, confirming that a radical mechanism was not involved in this reaction (TEMPO = 2,2,6,6-tetramethylpiperidinyloxy).

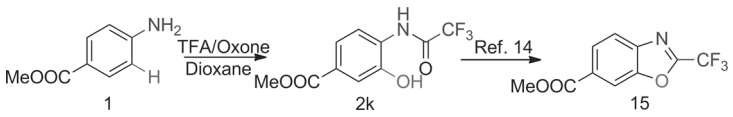
Further investigations were performed to understand the scope by extending the applicability of the method on biologically important drug candidates using the late stage modification approach. Procainamide (**13**),[13] is an antiarythmic drug, it could be converted to the oxygenated and trifluoroacyl group containing analogue by using present method. 2-Hydroxy-*N*-trifluoroacyl bearing procainamide structural analogue **14**, was prepared (Scheme 3) in a single step that could be of some biological importance.

In addition, this reaction was also applied for synthesis of $-CF_3$ analogues of benzoxazoles that are important precursors for the synthesis of various drug intermediates or inherent part of many important bioactive molecules or natural products. In this endeavour, $-CF_3$ group bearing benzoxazole was prepared to show the utility and scope of this reaction. In a representative example, **2k** was prepared and further cyclised by conventional method to obtain methyl-2-(trifluoromethyl)benzo[*d*]oxazole-6-carboxylate (**15**; Scheme 4).[14]

In conclusion, we have discovered a new method for the direct *N*-trifluoroacylation and *ortho*-hydroxylation of anilines under metal-free conditions. The procedure delivers 2-hydroxy-*N*-trifluoroacyl arylamine products in good yields by using a combination of trifluoroacetic acid and oxone. The method has wide applicability and can be proved as an important tool for bringing functional moieties to fine-tune the physicochemical properties of the molecule. Further expansion of the scope of the reaction and substrates as well biological investigations of the products are underway.



Scheme 3. Functional oxygen bearing modified analogue of procainamide with *N*-trifluoroacyl group.



Scheme 4. Synthesis of $-CF_3$ bearing benzoxazole analogue.

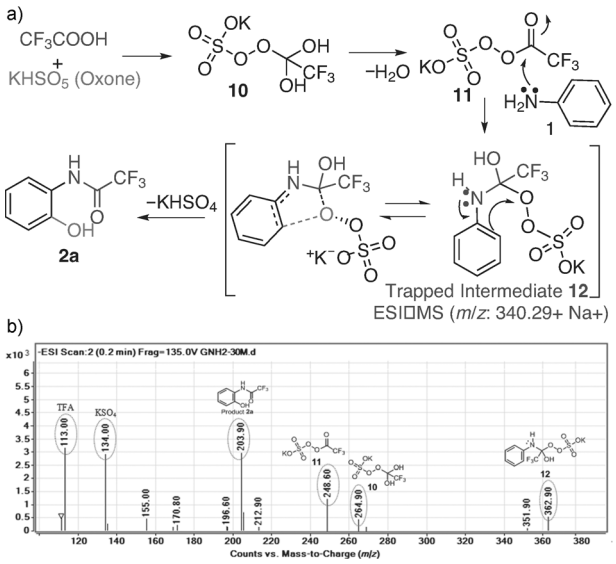


Figure 1. a) Plausible mechanism for the formation of **2a**; b) ESI–MS for crude reaction mass at 30 min: MS peaks of intermediate at *m/z* 264.90 (**10**), 248.60 (**11**), 362.90 (**12**) and product **2a** (203.90).

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Keywords: arylamines · C–H oxygenation · hydroxylation · oxone · *N*-trifluoroacylation

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Synthetic Methods

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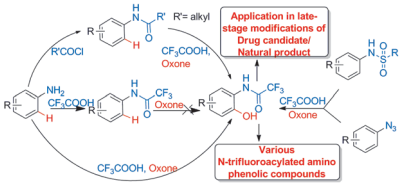
C–H Oxygenation and *N*-Trifluoroacylation of Arylamines Under Metal-Free Conditions: A Convenient Approach to2-Aminophenols and *N*-Trifluoroacyl-*ortho*-aminophenols



Direct *ortho*-hydroxylation through C–H oxygenation and *N*-trifluoroacylation of anilines was achieved in a single step under metal-free conditions by using a combination of TFA and oxone (see figure). The method has a broad substrate scope and allowed the formation of functionalised amino phenolic compounds such as *ortho*-hydroxy-*N*-trifluoroacetanilides in good yields.