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Synthesis of Tertiary Amides from Anionically Activated Aromatic Trifluoromethyl Groups

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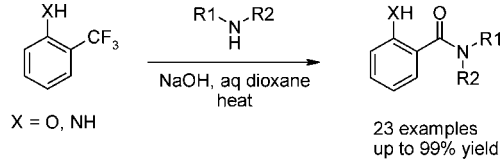
ABSTRACT



In this paper, a novel synthesis of tertiary amides from anionically activated aromatic trifluoromethyl groups is presented. Anionically activated trifluoromethyl groups react with secondary amines under aqueous conditions to afford tertiary amides. The mechanism involves initial elimination of hydrogen fluoride by an E1cB mechanism to afford an electrophilic quinone methide- or azafulvene-type intermediate that reacts with secondary amines under aqueous conditions to afford the tertiary amide in good yield (up to 99%).

Aromatic trifluoromethyl groups are widely encountered in medicinal chemistry.[1−3] They are often employed as isosteric replacements for methyl groups and are generally considered chemically inert. However, under some circumstances, aromatic trifluoromethyl groups exhibit a range of reactivities that have been the subject of a number of review papers.[4−6]

It has long been known that 2-[7] and 4-(trifluoromethyl)-phenols[8] are hydrolyzed under basic aqueous conditions to afford the corresponding 2- and 4-hydroxybenzoic acids, respectively. The mechanism involves initial elimination of HF (via an E1cB mechanism) to give a key electrophilic quinone methide intermediate, which can be attacked by a range of nucleophiles, such as hydroxide.[6,9] Similar reactivity of 2- and 4-(difluoromethyl)phenols, formed by in situ enzymatic cleavage of 2- and 4-(difluoromethyl)phenyl-β-D-glucosides, has been exploited in the design of enzyme-activated irreversible inhibitors of almond β-glucosidase.[10] Similarly, 2-(difluoromethylphenyl) phosphate esters have been used as suicide substrates to identify catalytic antibodies with phosphate monoesterase activity.[11]

2-[12] and 4(5)-(Trifluoromethyl)imidazoles[13−17] are also hydrolyzed to the corresponding carboxylic acids by heating

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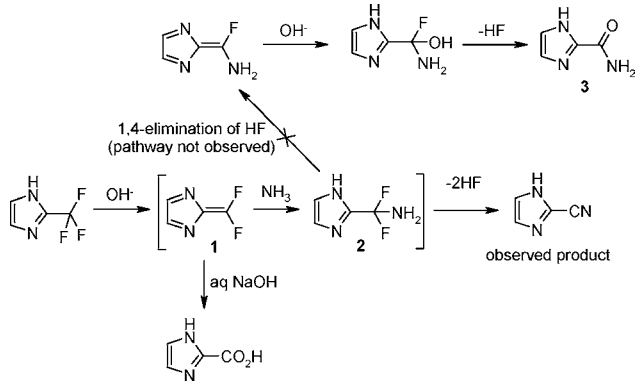
in aqueous sodium hydroxide. However, reaction with 5% ammonium hydroxide affords exclusively the corresponding 2-[18] and 4(5)-cyanoimidazoles.[19] Both the hydrolysis and ammonolysis reactions proceed via an electrophilic azafulvene intermediate (e.g., **1**, Scheme 1). Interestingly, in the

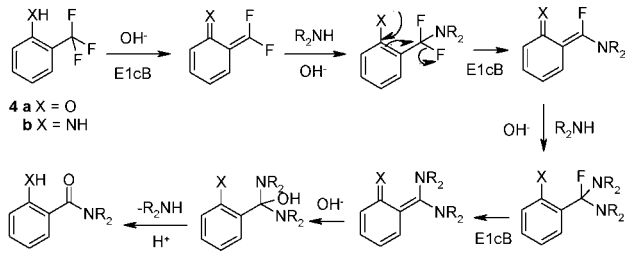
Scheme 1. Ammonolysis of 2-Trifluoromethyl Imidazole



ammonolysis reactions, none of the primary amide **3** was formed, despite the aqueous conditions and low concentrations of ammonia used. It could be envisaged that trapping of a difluoroamino intermediate **2** by hydroxide or water could lead to formation of the primary amide. However, 1,2-elimination of HF from **2** predominates and 2-cyanoimidazole is the only observed product.

It was predicted that the reaction of such anionically activated trifluoromethyl groups with secondary amines would furnish the corresponding tertiary amides, as 1,2-elimination of HF from a difluoromethylamino intermediate of type **2** would not be possible, thereby forcing elimination of HF across the ring in a 1,4-fashion, leading to the tertiary amide (Scheme 2). In this paper, we present a novel method

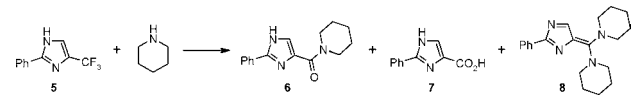
Scheme 2. Proposed Mechanism for Formation of Tertiary Amides from Anionically-Activated Trifluoromethyl Compounds



for the synthesis of tertiary amides from anionically activated trifluoromethyl groups under aqueous conditions and without the use of coupling reagents.

Initial investigations were performed using 2-phenyl-4-trifluoromethylimidazole **5**,[20] piperidine, and 1 M aqueous sodium hydroxide at 160 °C for 1 min using microwave irradiation (Table 1). Gratifyingly, the desired tertiary amide was obtained.

Table 1. Tertiary Amide Formation in Microwave at 160 °C[a]



entry	equiv piperidine	equiv 1 M aq NaOH	solvent	ratio **5**:**6**:**7**:**8** (%)[b]
1	1	4	water	0:70:30:0
2	1	4	dioxane	0:73:27:0
3	1	3	dioxane	0:87:13:0
4	1	2	dioxane	9:66:0:25
5	1	1	dioxane	25:33:0:42
6	4	0	water	0:30:0:70

[a] 1 equiv **5**, 160 °C, 1 min, μW. [b] Determined by LCMS at pH 3.

Complete conversion of **5** into a mixture of amide **6** and acid **7** was obtained with 1 equiv piperidine and 3 equiv NaOH in water (Table 1, entry 1). The addition of dioxane (entry 2) improved the ease of operation. Formation of significant amounts of acid byproduct **7** was observed when the reaction was performed at 160 °C due to competing basic hydrolysis of **5**. Reducing the amount of NaOH (entries 3−5) led to reduced acid formation, but also to lower yields of the amide, as water alone appeared to be insufficiently nucleophilic to completely convert the diazafulvene to the desired product. If NaOH was omitted and an excess of secondary amine was used as base (entry 6), complete conversion to a 3:7 mixture of amide **6** and diazafulvene **8**, respectively, was observed, with no acid formation (entry 6). Subsequent addition of extra sodium hydroxide followed by heating led to complete hydrolysis of the diazafulvene to the desired tertiary amide with no acid formation. The use of such a two-step protocol minimized the amount of the acid byproduct formed, but a one-step protocol that maximized the yield of the tertiary amide while minimizing byproduct formation was considered preferable. Direct observation of base-sensitive diazafulvene **8** by LCMS indicates that the proposed mechanism (Scheme 2) for the transformation is indeed in operation.

Further experimentation on the commercially available 2-(trifluoromethyl)phenol **4a** showed that acid formation was dependent on reaction temperature. Acid formation could be minimized (or eliminated in many cases) by performing the reaction with conventional heating at lower temperatures (e.g., 75 °C for **4a**, Table 2). This procedure was then applied to the synthesis of a number of salicylamides.

A total of 19 secondary amines were reacted with **4a**. Yields generally reflected the nucleophilicity of the secondary

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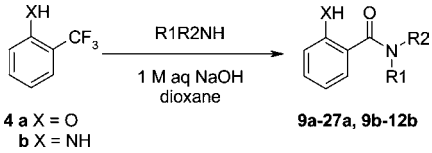
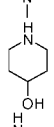
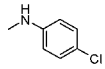
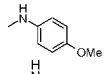
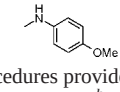
Table 2. Synthesis of Tertiary Amides Using 2-(Trifluoromethyl)phenol **4a** and 2-(Trifluoromethyl)aniline **4b**[a]



4 a X = O
b X = NH

9a-27a, 9b-12b

entry	product	R1R2NH	time (h)	yield (%)[b]
1	**9a**		3.5	89
2	**10a**		5.0	64
3	**11a**		18.5	96
4	**12a**		1.2	99
5	**13a**		2.5	68
6	**14a**		20.0	50
7	**15a**		20.0	69
8	**16a**		20.5	70
9	**17a**		20.5	75
10	**18a**		4.0	75
11	**19a**		20.5	6
12	**20a**		0.5	81
13	**21a**		5.0	52
14	**22a**		6.0	67
15	**23a**		3.5	96
16	**24a**		5.0	60
17	**25a**		2.5	18
18	**26a**		48.0	12
19	**27a**		N/A	0
20	**9b**		6.0[c]	69
21	**10b**		6.0[c]	52
22	**11b**		6.0[d]	14
23	**12b**		6.0[d]	30

[a] Full experimental procedures provided in Supporting Information. For X = O, reactions performed at 75 °C. [b] Isolated yields. [c] Performed at 200 °C. [d] Performed at 195 °C.

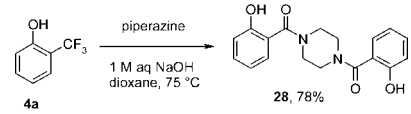
amine. Unhindered cyclic and acyclic aliphatic amines gave the desired tertiary amides in moderate to excellent yields (Table 1, entries 1, 3−5, 11). Branched cyclic and acyclic aliphatic amines (entries 7−9) gave moderate yields, while very sterically hindered amines such as diisopropylamine (entry 11) gave a low yield (6%) of the product as expected. A free alcohol was tolerated (entries 6, 10), as was a tertiary amine (entry 5). Both electron-rich (entry 15) and electron-poor (entry 14) aromatic amines gave good yields of the desired amide. Aminopyridines gave only low yields or none of the desired product (entries 17−19). In most cases, low yields of the desired product were accompanied by conversion of the remaining trifluoromethylphenol into salicylic acid. Attempts to perform the reaction with Boc-protected primary amines or secondary sulfonamides failed, with exclusive hydrolysis of **4a** to salicylic acid being observed, which is most likely due to insufficient nucleophilicity of the carbamate or sulfonamide. Primary amines afforded the symmetrical amidine as the major product, as the diazafulvene/quinone methide intermediate in such cases is a tautomer of the corresponding amidine.

Neither 3-(trifluoromethyl)phenol nor 1-methoxy-2-trifluoromethylbenzene reacted with piperidine under these conditions, with the starting materials remaining unchanged. This provides additional evidence (along with direct observation by LCMS of the quinone methide intermediates) that the proposed mechanism (Scheme 2) is in operation.

2-(Trifluoromethyl)aniline **4b** did not react under the conditions (75 °C, conventional heating) employed for reactions with the phenol **4a**, with only starting material being recovered. However, heating to 195 to 200 °C using microwave irradiation led to conversion to the desired tertiary amide products. This lower reactivity may be attributed to the lower acidity of the aniline **4b** compared to the phenol **4a**, thus leading to a reduced rate for the initial E1cB elimination of HF. Aliphatic amines gave good yields of the desired tertiary amides (Table 1, entries 20 and 21). The relatively poor nucleophile aniline gave a low yield (entry 22), while a more nucleophilic, electron-rich aromatic amine gave a slightly better yield (entry 23).

Piperazine reacted with two equivalents of phenol **4a** to give the diamide **28** in 78% isolated yield (Scheme 3).

Scheme 3. Preparation of Diamide **28**

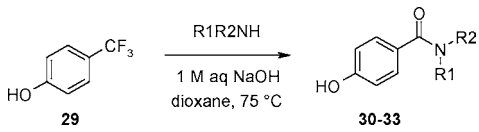


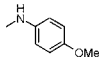
4a **28**, 78%

4-(Trifluoromethyl)phenol **29** reacted, under identical conditions, in a similar fashion to the *ortho* isomer **4a** (Table 3), affording the desired tertiary amides. The yields were comparable to those obtained with **4a**, although the reaction times were somewhat longer for the aliphatic amines.

Tertiary imidazole-4(5)-carboxamides have found a range of applications in drug discovery, for example, as cholecys-

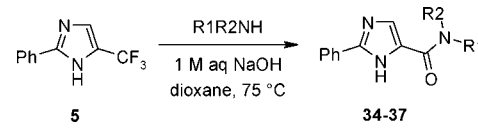
Table 3. Synthesis of Tertiary Amides from Secondary Amines and 4-(Trifluoromethyl)phenol **29**[a]

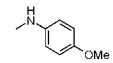


product	R1R2NH	time (h)	yield (%)[b]
30		48	88
31		16	87
32		1	80
33		1	83

[a] Full experimental procedures provided in Supporting Information. [b] Isolated yield.

Table 4. Formation of Tertiary Amides from 2-Phenyl-4(5)-trifluoromethyl Imidazole[a]



compound	R1R2NH	time (h)	yield (%)[b]
34		8	91
35		1	85
36		1	89
37		3	92

[a] Full experimental procedures provided in Supporting Information. [b] Isolated yield.

tokinin 1 receptor[21,22] and cannabinoid receptor 1 agonists,[23] as protease inhibitors,[24] carbonic anhydrase inhibitors,[25] potassium channel inhibitors,[26] and as histamine H3 receptor modulators.[27] Their precursor carboxylic acids are somewhat difficult to isolate due to their zwitterionic nature. Therefore, the amidation conditions used in the synthesis of the amides from phenols **4a** and **29** were then also applied to the 4(5)-(trifluoromethyl)imidazole **5**, with the desired tertiary amides being obtained in excellent yield, thus, avoiding the use of the carboxylic acids (Table 4).

In conclusion, we have developed a novel method for the synthesis of tertiary amides from secondary amines and anionically activated aromatic trifluoromethyl groups that can be performed under aqueous conditions and that does not require any hazardous coupling reagents beyond aqueous sodium hydroxide. Previous syntheses of the amides of hydroxy- and amino-benzoic acids have often required protection of the hydroxy or amino moieties or the use of alternative acid activation procedures.[28] This method affords a one-pot preparation of the tertiary amides of such acids without the need for protecting groups. In addition, a novel method for the synthesis of the pharmaceutically important tertiary imidazole carboxamides that avoids the troublesome isolation of the precursor carboxylic acids has been developed.

Acknowledgment. A.K.P. thanks AstraZeneca for financial support.

Supporting Information Available: Experimental procedures and characterization data for compounds **5**, **9a**−**27a**, **9b**−**12b**, **28**, and **30**−**37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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