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Oxidative carbonylation of benzotrifluoride to form trifluoromethylbenzoic acid

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ABSTRACT

The oxidative carbonylation of benzotrifluoride to form trifluoromethylbenzoic acid (TFMBA) has been catalyzed using either Rh(III) or a Pd(II) cation in combination with a carboxylic acid and its anhydride, ammonium metavanadate, CO, and O_2. The influence of metal cation and vanadate concentrations, temperature, time, acid composition, and gas pressures, were explored. The accumulated data suggest that oxidative carbonylation of benzotrifluoride proceeds via an electrophilic mechanism. Rh-catalyzed reactions exhibited higher activity (~70 turnovers in 4 h at 353 K) and trifluoromethylbenzoic acid selectivity (~92–95%) than Pd-catalyzed reactions (~6 turnovers in 4 h at 353 K and a trifluoromethylbenzoic acid selectivity of 80%). Formation of the principle reaction byproducts, benzoyl fluoride and benzoic acid, was highly dependant on the V(V) concentration and the acid composition. Reactions conducted in the presence of CF_3COOH yielded the highest catalytic activity, but reactions conducted in CCl_3COOH resulted in the highest trifluoromethylbenzoic acid selectivity. A possible mechanism for the reaction has been proposed.

1. Introduction

Trifluoromethylbenzoic acid has attracted considerable interest as a precursor for a wide range of pharmaceuticals [1]. For example, it can be used as a synthon for products that act as an inhibitor of interluken-1β, which plays a pathogenic role in atherosclerosis, sepsis syndrome, inflammatory bowel syndrome, and periodontal disease [2]. Trifluoromethylbenzoic acid can also be used as an analogue of α-galactosylceramide and other derivatives, which possess anti-tumor activity [3,4], and as a precursor to Luotonin A derivates, which serve as anti-leukemia agents [5]. Trifluoromethylbenzoic acid has been demonstrated to be effective in drugs for the treatment of strokes [6], whereas the coupling of trifluoromethylbenzoic acid with amino acids and peptides [7,8], or its electrophilic aromatic aroylation [9], can be used to produce products that are useful as antibiotics or precursors to anti-malarial drugs [9]. Finally, trifluoromethylbenzoic acid can be converted to oxazoles [10] and 2-hydroxy-4-trifluormethylbenzoic acid (HTB) [11], which can be used as an anti-inflammatory drug.

A number of approaches have been investigated for synthesizing trifluoromethylbenzoic acid from benzotrifluoride or related compounds. These included lithiation of the benzene ring of benzotrifluoride and subsequent reaction of the lithium with CO_2 and HCl [12]. Alternatively, trifluoromethylbenzoic acid can be formed by reacting (trifluoromethyl)phenyl iodide with CO in the presence of Pd and aqueous sodium or potassium hydroxide [13]. The oxidation of compounds, such as trifluoromethylbenzaldehye [14,15] or the corresponding alcohol [16], and the saponification and hydrolysis of the methyl and ethyl esters of trifluoromethylbenzoic acid [17,18] have also been shown to be effective routes to trifluoromethylbenzoic acid. The decarboxylation of mandelic acid derivates represents yet another approach for the synthesis of trifluoromethylbenzoic acid [19–21]. Recently, it has been shown that the carboxylation of alkenylboronic esters can be used to synthesize trifluoromethylbenzoic acid, a process which proceeds with high yields [22]. Since most of the previously mentioned methods involve multiple steps or the utilization of compounds inherently more complex than trifluoromethylbenzoic acid, the development of a direct method for converting benzotrifluoride to trifluoromethylbenzoic would be attractive.

The aim of the present work is to show that trifluoromethylbenzoic acid can be synthesized by the oxidative carbonylation of benzotrifluoride. This effort is based on recent studies of the oxidative carbonylation of aromatic hydrocarbons to form aromatic acids using a Rh(III) or Pd(II) precursor in combination with a mixture of trifluoroacetic acid, its anhydride [23–27], and ammonium metavanadate [26,27]. Our work suggests that in a low dielectric medium such a toluene, the metal cations form cation–anion pairs with trifluoroacetate anions serving as the ligands [27]. During the course of the reaction, the metal cations undergo a two-electron reduction and are re-oxidized by the metavanadate cations present in solution. The reduced metavanadate cations are then re-oxidized by molecular oxygen.

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2. Results and discussion

Table 1 summarizes the results of scoping experiments in which some components of the reaction mixture were omitted in order to determine their importance. Entries 1 and 2 show standard reaction conditions for Rh- and Pd-catalyzed reactions, respectively. The observed products in all cases were 4-trifluoromethyl benzoic acid (4-TFMBA), 3-trifluoromethylbenzoic acid (3-TFMBA), 2-trifluoromethylbenzoic acid (2- TFMBA), benzoyl fluoride (BF) and benzoic acid (BA). The Rh-catalyzed reaction (entry 1) produces roughly equal quantities (~0.14 mmol) of trifluoromethylbenzoic acid, benzoyl fluoride, and benzoic acid, whereas the Pd-catalyzed reaction (entry 2) produces much more benzoyl fluoride and benzoic acid (~0.2 mmol) relative to trifluoromethylbenzoic acid (~0.05 mmol). 2-Trifluoromethylbenzoic acid was not formed using the Rh complex (entry 1) most likely as a consequence of steric inhibition by the CF_3 group on the benzene ring interacting with the bulky Rh complex. A small quantity of the 2-trifluoromethylbenzoic acid was observed using the Pd complex, with a typical 4/2 isomer ratio of approximately 3. In general, for all the reactions, the ratio of 4-trifluoromethylbenzoic acid to 3-trifluoromethylbenzoic acid was approximately 0.25 for the Rh-catalyzed system and 0.3 for the Pd-catalyzed system. Entries 3, 4, and 5 show the results of reactions carried out without CO. In each case, only benzoyl fluoride and benzoic acid were observed as products. Less benzoyl fluoride and benzoic acid were produced using the Rh complex (entry 3) than the Pd complex (entry 4). The absence of Rh or Pd (entry 5) resulted in the highest yields of benzoyl fluoride and benzoic acid. Further removal of the vanadate species (entry 6) resulted in only a small amount of benzoyl fluoride and benzoic acid and no trifluoromethylbenzoic acid. Entries 7 and 8 show the results of reactions without an oxidant present but in the presence of either the Rh or Pd complex. For these cases, a small amount of trifluoromethylbenzoic acid was observed, and the yields of benzoyl fluoride and benzoic acid were reduced significantly compared to what was observed under standard reaction conditions (entries 1 and 2). Substitution of NH_4VO_3 (entry 5) with $VO(acac)_2$ (entry 9) resulted in a significantly reduced yield of benzoyl fluoride and benzoic acid. Omission of the anhydride (entry 10) resulted in significantly reduced quantities of all products, and no products were observed when both the anhydride and acid were omitted (entries 11 and 12). These results indicate that the acid plays two roles. The first is as the source of ligands that coordinate with the Rh or Pd cations present in solution. These ligands withdraw electron density from the metal thereby enhancing the ability of the metal to coordinate benzotrifluoride and facilitate the abstraction of a proton from the coordinated molecule the C–H bond activation step [27]. The second role of the acid is to hydrogen bond with the fluorine atoms on the methyl group of the arene, a process that is unique to fluorine [28]. The interaction of the proton with the fluorine atoms facilitates the replacement of fluorine by oxygen from the vanadate species, leading to the formation of benzoyl fluoride.

Taken together, the results presented in Table 1 indicate that the catalyst (either Rh or Pd), carbon monoxide, and trifluoroacetic acid are indispensable for the oxidative carbonylation of benzotrifluoride to form trifluoromethylbenzoic acid. The presence of the anhydride is necessary to obtain high yields of product by maintaining an optimal water content as also observed during toluene oxidative carbonylation [27]. The product distribution, both of the desired trifluoromethylbenzoic acid isomers and the undesired benzoyl fluoride and benzoic acid, is influenced by whether Rh(III) or Pd(II) cations are used. The presence of an oxidant is important in the formation of the benzoyl fluoride and benzoic acid, although small quantities of these products are observed without the oxidant present. The observation of significantly more benzoyl fluoride and benzoic acid with vanadium in the 5+ oxidation state than the 4+

Table 1
Scoping experiments. Reaction conditions: benzotrifluoride (37.5 mmol); $T = 353$ K, $t = 4$ h.

	CF_3COOH (mmol)	$(CF_3CO)_2O$ (mmol)	$Rh(acac)_3$ (μmol)	$Pd(CF_3COO)_2$ (μmol)	NH_4VO_3 (mmol)	$VO(acac)_2$ (mmol)	O_2 (MPa)	CO (MPa)	4-TFMBA (mmol)	3-TFMBA (mmol)	2-TFMBA (mmol)	BF (mmol)	BA (mmol)
1	13.0	3.8	10	0	0.516	0.000	0.35	0.35	0.034	0.101	0.000	0.111	0.146
2	13.0	3.8	0	5	0.516	0.000	0.35	0.35	0.016	0.040	0.010	0.254	0.216
3	13.0	3.8	10	0	0.516	0.000	0.35	0.00	0.000	0.000	0.000	0.084	0.070
4	13.0	3.8	0	5	0.516	0.000	0.35	0.00	0.000	0.000	0.000	0.205	0.179
5	13.0	3.8	0	0	0.516	0.000	0.35	0.00	0.000	0.000	0.000	0.287	0.224
6	13.0	3.8	0	0	0.000	0.000	0.35	0.35	0.000	0.000	0.000	0.002	0.002
7	13.0	3.8	10	0	0.000	0.000	0.00	0.35	0.004	0.015	0.000	0.000	0.022
8	13.0	3.8	0	5	0.000	0.000	0.00	0.35	0.003	0.004	0.001	0.003	0.007
9	13.0	3.8	0	0	0.000	0.516	0.00	0.35	0.000	0.000	0.000	0.007	0.001
10	13.0	0.0	10	0	0.516	0.000	0.35	0.35	0.003	0.009	0.000	0.000	0.011
11	0.0	0.0	10	0	0.516	0.000	0.35	0.35	0.000	0.000	0.000	0.000	0.000
12	0.0	0.0	0	5	0.516	0.000	0.35	0.35	0.000	0.000	0.000	0.000	0.000