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ARYL TRIFLUOROMETHYL KETONE HYDRATES AS PRECURSORS OF CARBOXYLIC ACIDS AND ESTERS [1]

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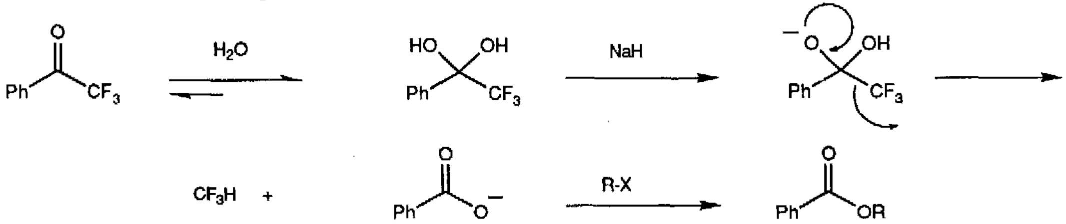
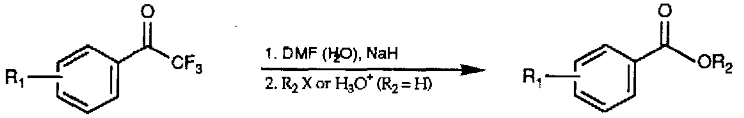
Summary: *A simple method for the preparation of aryl carboxylic acids and esters from aryl trifluoromethyl ketone hydrates is described.*

In the course of a recent synthesis, we attempted to convert an aryl trifluoromethyl ketone[2] into the corresponding carboxylic acid via basic hydrolysis (haloform-type conditions). In all attempts, the intermediate carboxylate salt decarboxylated—a well known complication.[3] Since formation of aryl carboxylate esters by nucleophilic displacement of aryl trifluoromethyl ketones had been reported to be ineffective,[4] we sought an alternative route from trifluoromethyl ketones to carboxylate derivatives. In this communication we report a general method utilizing aryl trifluoromethyl ketone hydrates as precursors of carboxylic acids and esters in the absence of nucleophiles.



Trifluoromethyl ketone hydrates are easily formed due to the strong electron withdrawing effect of the trifluoroacetyl group.[5] In our initial studies, treatment of α,α,α-trifluoroacetophenone hydrate with NaH in DMF readily afforded sodium benzoate, whose formation can be interpreted according to the scheme shown.[6] Subsequent treatment of the benzoate salt with alkyl halides gave a good yield of the corresponding esters, while aqueous acidic quenching afforded benzoic acid. By avoiding the use of nucleophilic reagents, this reaction sequence proved effective in the presence of alkoxycarbonyl, formyl or cyano functionalities in the molecule (Table 1, entries 1-12). Hydrate formation appeared unaffected by the presence of electron donating groups or steric hindrance around the trifluoroacetyl group, since the 2,4,6-trimethoxy derivative (entries 17-20, Table 1) showed a similar reactivity pattern.[7] Under the relatively mild temperatures required for the formation of aryl carboxylic acids, no decarboxylation products have been observed (Table 1, entries 1, 5, 9, 13, and 17). Finally, these conditions produced mixed esters without difficulty (Table 1, entries 2, 3, and 4).

TABLE 1. Aryl carboxylic esters and acids from aryl trifluoromethyl ketones.



Entry	R1	R2	yield(%)[a]	Entry	R1	R2	yield(%)
1	4-COOCH3	H	74	*11*	4-CN	iPr	73
2	4-COOCH3	Et	77	*12*	4-CN	Bn	76
3	4-COOCH3	iPr	79	*13*	H	H	70
4	4-COOCH3	Bn	86	*14*	H	Et	76
5	4-CHO	H	61	*15*	H	iPr	72
6	4-CHO	Et	65	*16*	H	Bn	69
7	4-CHO	iPr	62	*17*	2,4,6-(OCH3)3	H	62
8	4-CHO	Bn	67	*18*	2,4,6-(OCH3)3	Et	73
9	4-CN	H	71	*19*	2,4,6-(OCH3)3	iPr	75
10	4-CN	Et	74	*20*	2,4,6-(OCH3)3	Bn	65

a) Isolated yields. All compounds were characterized by IR, MS, GC, and ^{1}H NMR

Aryl carboxylic esters and acids from aryl trifluoromethyl ketone hydrates; general method: In a typical run, a solution of the starting aryl trifluoromethyl ketone (0.15 mmol) in 1 mL of wet DMF (0.1% v/v H_2O or dry DMF starting from the ketone hydrate) was added dropwise over a suspension of dry NaH (0.6 mmol) in DMF. The mixture was stirred at 60 °C for approximately 30 min until a thick precipitate of benzoate salt formed. The reaction mixture was then treated with a DMF solution of the corresponding alkyl halide (0.6 mmol) and stirred at 80 °C until completely solubilized (≈30 min). After cooling to 5 °C, excess NaH was quenched by careful addition of H_2O. Ether extractions yielded the corresponding esters (Table 1). Alternatively, treatment of the above benzoate salt with 5 mL of a 2N HCl solution, followed by Et_2O extractions, produced the corresponding carboxylic acids.

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References and notes

1. Presented at the 201 ACS Meeting, Atlanta, GA, (1991), Communication ORGN 45.
2. a) For the synthesis of aryl trifluoromethyl ketones, see Kerdesky, F. A. J; Basha, A., *Tetrahedron Lett.* **1991,** *32,* 2003-2004 and references therein. b) For a review on preparation of trifluoromethyl ketones, see Begue, J.P.; Bonnet-Delpon, D., *Tetrahedron,* **1991,** *47,* 3207-3258.
3. March, J. *Advanced Organic Chemistry;* John Wiley & Sons, p. 507 (1985).
4. Harbuck, J.W.; Rapoport, H., *J. Org. Chem.*, **1972,** *37,* 3618-3622.
5. a) Guthrie, J.P., *Can. J. Chem.*, **1975,** *53* , 898-906; b) Stewart, R.; Van Dyke, J.D., *Can. J. Chem.*, **1972,** *50* , 1992-1999.
6. Formation of sodium benzoate was confirmed by IR. Alternatively, when the reaction was monitored by ^{19}F NMR (TFA as external reference), resonances at 5.4 ppm ($C(O)C\underline{F}_3$) and -6.8 ppm ($C(OH)_2C\underline{F}_3$) were observed in ratios relative to the amount of water added to the sample. On addition of NaH, no ^{19}F resonances were observed.
7. Our results differ from those reported by Mackie *et al* . (*J. Fluorine Chem.*, **1977,** *10,* 437-445) concerning the outcome of the haloform reaction from the 2,4,6-trimethoxy derivative.

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