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#### Trifluoromethyl Ketones from Enolizable Carboxylic Acids via Enediolate Trifluoroacetylation/Decarboxylation

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Primary and secondary (enolizable) carboxylic acids were converted in a single step to trifluoromethyl ketones. Treatment of the acid with 2.2 equiv of LDA generated an enediolate that was trifluoroacetylated with  $EtO_2CCF_3$ . Quenching the reaction mixture with aqueous HCl resulted in rapid decarboxylation and provided the trifluoromethyl ketone product in good yield. The process may be performed at -20 °C with a slight reduction in yield. The reaction was extended to the preparation of pentafluoroethyl and chlorodifluoromethyl ketones.

The trifluoromethyl group is an important structural motif in many active pharmaceutical ingredients.<sup>1</sup> Important precursors for introduction of trifluoromethyl groups are trifluoromethyl ketones.<sup>2</sup> Several methods are available for the synthesis of trifluoromethyl ketones, but many require multiple steps and/

SCHEME 1. Pfeffer and Silbert's Conversion of Carboxylic Acids to Aldehydes

$$R \xrightarrow{O} OH \xrightarrow{2 \text{ equiv LDA}}_{HCO_2Et} \left[ R \xrightarrow{O}_{CHO} OLi \right] \xrightarrow{HCI}_{-CO_2} R \xrightarrow{O}_{H}$$

or expensive reagents.<sup>3</sup> To support drug development activities, we required a scalable synthesis of trifluoromethyl ketones which would ideally employ starting substrates of the carboxylic acid oxidation level. The two-step sequence of base-promoted Claisen condensation of esters with ethyl trifluoroacetate and subsequent acidic hydrolysis and decarboxylation to trifluoromethyl ketones has been known for over 50 years.<sup>4</sup> Yields for the Claisen condensation, however, are low with alkoxide bases, and while higher yields are obtained with NaH or Na metal in refluxing solvents, these conditions were undesirable for scaleup. Olah and Prakash reported a one-step conversion of methyl esters to trifluoromethyl ketones using TMSCF<sub>3</sub> and catalytic TBAF.<sup>5</sup> Although this direct conversion is attractive, the high cost of TMSCF<sub>3</sub> and the requirement for anhydrous TBAF are serious limitations to large-scale application. In addition, in our hands this reaction was difficult to drive to completion, and the unreacted starting ester proved impossible to separate from the trifluoromethyl ketone product by nonchromatographic means. The method of Zard and co-workers, in which a primary acid chloride is treated with trifluoroacetic anhydride (TFAA) and pyridine in CH<sub>2</sub>Cl<sub>2</sub> followed by hydrolysis/decarboxylation on addition of water, is attractive due to the low cost of reagents.<sup>6</sup> Recently, we reported a variation on Zard's method which allowed for direct conversion of primary and secondary carboxylic acids to trifluoromethyl ketones using TFAA/pyridine in toluene at 60-100 °C for 6-48 h followed by hydrolysis/ decarboxylation on addition of water.<sup>7</sup> While this procedure expanded the scope of amenable substrates, the long reaction times, requirement for a large excess (4.5-6.0 equiv) of TFAA, and modest yields obtained with secondary carboxylic acids provided the impetus to search for a more general alternative preparation.

In 1970, Pfeffer and Silbert reported a one-step synthesis of aldehydes from carboxylic acids by treating the dianion of the acid (from 2 equiv of LDA) with ethyl formate.<sup>8</sup> The intermediate  $\alpha$ -formylcarboxylate was not isolated but underwent spontaneous decarboxylation on neutralization (Scheme 1). The

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procedure was also applied to the synthesis of nitro compounds by quenching with *n*-propylnitrate. We postulated the analogous trapping of a carboxylic acid dianion with ethyl trifluoroacetate would give an intermediate  $\alpha$ -trifluoroacetyl carboxylate that would readily decarboxylate on acidification to give a trifluoromethyl ketone.<sup>9</sup> This proved to be the case, and herein we present the scope of this reaction.

Exploratory experiments were performed on adamantane-1acetic acid 1 (Scheme 2). Enediolate formation was best effected by addition of LDA (1.5 M in cyclohexane) to a -20 °C solution of 1 in THF, warming to 20 °C, and aging for 4 h.<sup>10</sup> The reaction mixture was then cooled to -65 °C and treated with EtO<sub>2</sub>CCF<sub>3</sub> (1.5 equiv). On quenching the reaction mixture with aqueous HCl, an immediate evolution of gas was observed. Extractive workup and chromatographic purification of the crude product gave the desired trifluoromethyl ketone 2 in 68% yield.<sup>7</sup> The majority of the mass balance was the starting acid 1 (22%) recovery). None of the intermediate  $\alpha$ - trifluoroacetyl acid was detected, indicating decarboxylation of this species is facile. Increasing the time for enolization did not increase the yield, while decreasing the enolization period to 1 h gave a 59% yield of 2. When an inverse quenching protocol was employed, i.e. the enediolate solution was added dropwise to a -65 °C solution of  $EtO_2CCF_3$  (3.0 equiv) in THF, the yield of 2 increased to 75%. The inverse quench protocol was preferred not only for the increased yield, but also for the greater control it imparts over the exothermicity of the enediolate trifluoroacetylation, particularly in large-scale reactions. In addition, the EtO<sub>2</sub>CCF<sub>3</sub> quench could be performed at -20 °C instead of -65 °C with only a slightly lower yield (65%).

The scope of the reaction was explored as depicted in Table 1. Both primary (entries 1–7) and secondary (entries 8–13) carboxylic acids give consistently good yields of trifluoromethyl ketones. Conveniently, carboxylate salts may be used, allowing the LDA charge to be reduced to 1.1 equiv (entry 2). Silyl ether (entry 6) and  $\alpha$ -phenylthio (entry 7) substituents were tolerated. Key advantages of this procedure over the TFAA/pyridine protocol are the consistently good yields for both primary and secondary carboxylic acids, even highly hindered substrates, and the uniform reaction times for all substrates.

The reaction was successfully extended to the synthesis of pentafluoroethyl ketone **15** and chlorodifluoromethyl ketone **16** 

 
 TABLE 1.
 One-Step Synthesis of Trifluoromethyl Ketones from Enolizable Carboxylic Acids



<sup>*a*</sup> Isolated yields after chromatography on SiO<sub>2</sub>. <sup>*b*</sup> Lithium 4-cyclohexylbutyrate used as starting material with 1.1 equiv of LDA.

(Table 2).<sup>15,17</sup> In these cases, the reaction was conducted by using the same procedure developed for trifluoromethyl ketones, except that ethyl pentafluoropropionate and ethyl chlorodifluoroacetate were used for the quench. As with the trifluoromethyl ketone substrates, decarboxylation was spontaneous on acidification of the quenched reaction mixture, and good yields of the products were obtained. This procedure offers a direct and

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## TABLE 2.Extension to Pentafluoroethyl andChlorodifluoromethyl Ketones



<sup>a</sup> Isolated yields after chromatography on SiO<sub>2</sub>.

efficient entry to higher perfluoroalkyl ketones from carboxylic acids and commercially available perfluoroalkyl esters.

In conclusion, an efficient and general one-step conversion of primary and secondary carboxylic acids to trifluoromethyl ketones has been reported. The method employs cheap, commercially available reagents and the procedure is operationally simple. While optimal yields are obtained by quenching with EtO<sub>2</sub>CCF<sub>3</sub> at low temperature (-65 °C), the quench may be performed at -20 °C with only a slight decrease in yield. The method is equally well suited to the preparation of pentafluoroethyl and chlorodifluoromethyl ketones. This procedure should prove to be a method of choice for the preparation of primary and secondary trifluoromethyl ketones.

#### **Experimental Section**

General Procedure: 2,2,2-Trifluoro-1-indan-2-yl-ethanone (11). To a solution of indane-2-carboxylic acid (1.62 g, 10.0 mmol) in THF (20 mL) at -20 °C was added dropwise LDA (14.7 mL, 22.0 mmol, 1.5 M in cyclohexane) over 10 min. The temperature of the reaction mixture was allowed to rise to 10 °C during the addition of LDA. The reaction mixture was then aged at 20 °C for 4 h. In a separate flask, a solution of ethyl trifluoroacetate (3.6 mL, 30.0 mmol) and THF (10 mL) was cooled to -65 °C. The enediolate solution was added dropwise via cannula to the ethyl trifluoroacetate solution. Upon completion of the addition, the reaction mixture was aged for 15 min at -65 °C and then quenched with 6 N HCl (20 mL) [Caution: CO<sub>2</sub> is evolved during the quench]. The reaction mixture is diluted with EtOAc (10 mL), the layers are separated, and the organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated. Column chromatography on SiO<sub>2</sub> (hexanes) gave 11 (1.48 g, 69% yield) as a colorless oil. IR (neat) 3028, 2955. 2859, 1755, 1486, 1450, 1205, 1115 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.24–7.14 (m, 4 H), 3.80 (p, J = 8.7 Hz, 1 H), 3.34–3.23 (m, 4 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  192.7 (q, J = 34 Hz), 140.2, 126.9, 124.3, 115.9 (q, J = 290 Hz), 45.5, 34.9. Anal. Calcd for C<sub>11</sub>H<sub>9</sub>F<sub>3</sub>O: C, 61.68; H, 4.24. Found: C, 61.39; H, 4.13.

**Supporting Information Available:** Characterization data for **6**, **7**, **10**, and **11** and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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