Trifluoromethyl Substituted 4-Pyrones *via* Self-condensation of Trifluoroacetoacetates

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When 3-(acetoxy)-4,4,4-trifluoro-2-butenoates **7** and **8** are heated at 100°, in the presence of catalytic amounts of zinc chloride, they undergo self-condensation to yield 2,6-bis(trifluoromethyl)-4-pyrones **1** and **2** respectively. Compounds **1** and **2** were further converted to the corresponding pyridine derivatives **3** and **4** *via* ammoniolysis.

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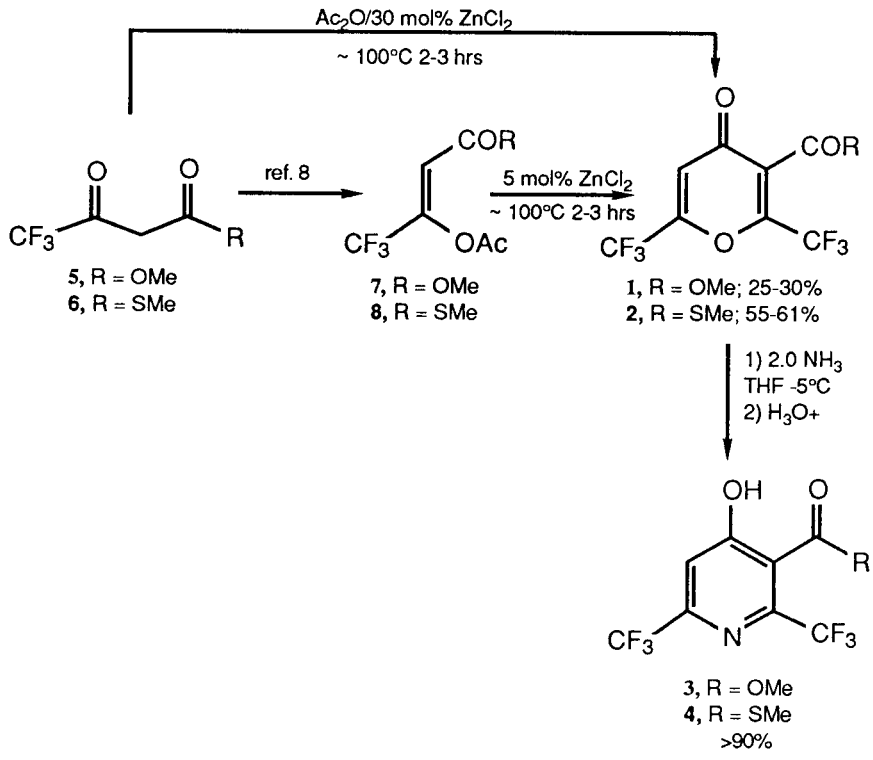
Introduction.

In many instances, pyrones, serve as key precursors to a variety of biologically active pyridine derivatives [1]. Herein, we wish to report a novel, one-pot synthesis of 2,6-bis(trifluoromethyl)-4-pyrones (Scheme 1, **1** and **2**) through a Lewis acid catalyzed self-condensation of 3-(acetoxy)-4,4,4-trifluoro-2-butenoates. These pyrone intermediates have been further converted to known, agrochemically important pyridine derivatives (Scheme 1, **3** and **4**) [2]. Our methodology provides a facile route to these particular 4-pyrones and related pyridines **3** and **4**, and has distinct advantages over the conventional multistep approach that was previously employed in the preparation of these compounds [2].

Results and Discussion.

The primary objective of this study was to develop an efficient synthesis of 2,6-bis(trifluoromethyl)-4-pyrones and the corresponding pyridine derivatives, **1-4**, from trifluoroacetoacetates **5** and **6**. A survey of the literature indicated numerous methods for effective condensation of non-fluorinated β-keto esters (*eg.*, methyl acetoacetate) to analogous 4-pyrones and pyridines (Scheme 1) [1,3,4]. However, applying those conditions to convert methyl 4,4,4-trifluoroacetoacetate (**5**) or methylthio 4,4,4-trifluoroacetoacetate (**6**) [5], to the desired 4-pyrones **1** and **2** or the corresponding pyridines **3** and **4** yielded disappointing results. In all cases, the reactions gave either unreacted starting material or an intractable mixture of products. Further

Scheme 1



pursuit of new methods for the synthesis of 4-pyrones **1** and **2** from these starting materials, eventually led to the discovery of an efficient route. It was found that heating the enol acetate **8** at 100° for 2.5 hours, in the presence of 5% anhydrous zinc chloride, led to the formation of pyrone **2** in 55-61% yield (Scheme 1). With the exception of methylthio acetate (an inevitable by-product of this reaction), gc, ^1H and ^{19}F nmr spectral analysis indicated very few side-products in the crude reaction mixture. On the other hand, subjecting **6** to similar reaction conditions led to the recovery of significant amounts of unreacted starting material. However, the self-condensation of **6** can be facilitated by adding one equivalent of acetic anhydride (needed to generate the enol acetate *in-situ*), but the desired product is formed in only 25-30% yield, and is accompanied by significant amounts of by-products.

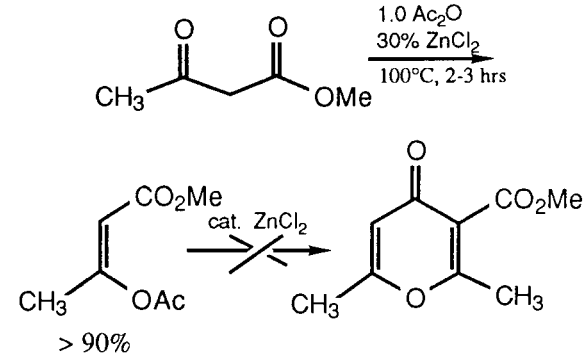
In order to expand the scope of this new synthesis, various enol substrates of **6** were submitted to zinc chloride treatment. Surprisingly, in all these cases very little conversion to be desired product was observed. In fact, decomposition of substrate to **6** seems to be the preferred reaction pathway. The reason for the anomalous behaviour of acetyl enol substrates in this reaction is not yet fully understood.

Other Lewis acid catalysts such as zinc bromide, zinc chloride, titantium tetrachloride and magnesium chloride also proved effective for converting **8** to **2**, but in lower yields compared to zinc chloride. After screening several reaction parameters, it became apparent that self-condensation proceeds best at 100°, with neat enol acetate as substrate and anhydrous 5% zinc chlorde as catalyst.

We further expanded the scope of this reaction to oxy-esters by submitting **7** to catalytic zinc chloride treatment. The desired pyrone **1** was indeed the major product, but the crude reaction mixture (unlike the thioester) contained ~40-50% of tarry by-products. The differences between methylthio and methoxyl groups in the leaving ability could account for the relative substrate reactivity. As is the case with **6**, direct self-condensation of **5** to **1** could also be accomplished by using one equivalent of acetic anhydride and catalytic zinc chloride. However, in this case the isolated yields of **1** (~25-30%) were comparable under both preformed and *in-situ* generated enol acetate conditions. The isolated pyrones **1** and **2** have been converted to the corresponding pyridines **3** and **4** in high yields *via* ammoniolysis (Scheme 1). Compound **3** has been previously prepared and identified as a chemical hybridization agent for wheat [6].

Interestingly, when methyl acetoacetate was treated with acetic anhydride and zinc chloride at 100°, the reaction stopped at the enol acetate stage and failed to proceed any further to form the desired pyrone even under forcing conditions (equation 1).

Equation 1



This difference in reactivity between fluorinated and non-fluorinated methyl acetoacetates further illustrates the unique properties associated with fluorinated keto-esters [7]. Efforts to understand the mechanism and the limitations of this unique self-condensation reaction are currently underway and the details of this study will be published later.

In conclusion, this novel procedure provides a unique method by which 2,6-bis(trifluoromethyl)-4-pyrones, and ultimately their pyridine analogs can be prepared. This synthesis represents a significant improvement over existing chemistry in overall yield, number of steps and ease of operation. It has proven to be cost-effective and easily amenable to large scale preparations.

EXPERIMENTAL

All ^1H and ^{13}C nmr spectra were recorded either on a Varian 400 or 300 MHz spectrometer. ^{19}F nmr spectra were recorded either on an EM-360 or an IBM-300 NMR spectrometer. The analyses were carried out using a Varian 3700 gas chromatograph equipped with a DB-1701 micro-capillary column. Anhydrous zinc chloride (98%, Mallinckrodt) was used directly as obtained.

General Procedure for the Preparation for 2,6-Bis(trifluoromethyl)-4-pyrones **1** and **2**.

A mixture of the enol acetate **7**, [8] (2.12 g, 10 mmoles) and anhydrous zinc chloride (0.4 g, 30 mmoles) was heated at 100° under nitrogen for 2.5 hours. After cooling to room temperature, the crude reaction mixture was treated with water (150 ml) and extracted with methylene chloride (200 ml). The extracts were dried and concentrated to yield a dark-drown oil, which was then purified by flash chromatography using 4:1 hexanes/ethyl acetate solvent mixture. Compound **1** was isolated as a white solid in 26% (0.38 g) yield, mp 36-38°C; ^1H nmr (deuteriochloroform): δ 6.91 (s, 1H), 3.94 (s, 3H); ^{19}F nmr (deuteriochloroform): δ -69.32 (s, 3F), -72.35 (s, 3F); ^{13}C nmr (deuteriochloroform): δ 172.60, 159.87, 152.29 (q, J = 41.0 Hz), 129.16 (q, J = 274.3 Hz), 124.38, 117.38 (q, J = 274.2 Hz), 117.34 (q, J = 274.2 Hz), 115.95, 53.29.

Anal. Calcd. for $C_9H_4F_6O_4$: C, 37.24: H, 1.38. Found: C, 37.51; H, 1.43.

Compound **2** was prepared in a similar manner from **8** using 5

mol% anhydrous zinc chloride, yield, 61%, mp 83-85°; ^{1}H nmr (deuteriochloroform): δ 6.81 (s, 1H), 2.48 (s, 3H); ^{19}F nmr (deuteriochloroform): -68.09 (s, 3F), -73.10 (s, 3F); ^{13}C nmr (deuteriochloroform): δ 184.26; 172.24, 151.57 (q, J = 40.9 Hz), 148.27 (q, J = 40.9 Hz), 128.25, 116.57 (q, J = 274.5 Hz), 116.55 (q, J = 274.5 Hz), 76.14, 11.49.

Anal. Calcd. for $C_9H_4F_6O_3S$: C, 35.31; H, 1.31; S, 10.46. Found: C, 35.50; H, 1.41; S, 10.71.

Procedure for the Preparation of 2,6-Bis(trifluoromethyl)pyridines **3** and **4**.

Gaseous ammonia (0.9 g, 53.1 mmoles) was passed sub-surface into a solution of the pyrone, **1** (7.30 g, 25.2 mmoles), dissolved in 25 ml of THF kept at -5°. The addition was controlled in order to maintain the internal temperature at or below 3°. After the addition (2-3 hours), the crude reaction mixture was allowed to warm to room temperature and then stirred overnight. Dilute hydrochloric acid (~25 ml), followed by concentrated hydrochloric acid (10 ml) were added to the crude and stirring continued for another hour. The product was then extracted with methylene chloride (250 ml), dried and concentrated to yield **3** as a white solid, yield, 705 g, 92%, mp 89-92°; ^{1}H nmr (deuteriochloroform): δ 7.49 (s, 1H), 4.09 (s, 3H); ^{19}F nmr (deuteriochloroform): δ -67.65 (s, 3F), -71.08 (s, 3F); ^{13}C nmr (deuteriochloroform): δ 168.90, 167.71, 150.10 (q, J = 35.4 Hz), 148.81 (q, J = 36.9 Hz), 120.30 (q, J = 274.0 Hz), 120.15 (q, J = 272.0 Hz), 113.19, 112.11, 53.78.

The yield of **4** was 90%, mp 138-139°; ^{1}H nmr (methanol-d_4): δ 7.42 (s, 1H), 2.49 (s, 3H); ^{19}F nmr (methanol-d_4): -62.97 (s, 3F), -67.83 (s, 3F); ^{13}C nmr (methanol-d_4): 191.49, 165.87, 150.77 (q, J = 35.6 Hz), 147.56 (q, J = 36.2 Hz), 127.60, 122.04 (q, J = 273.8 Hz), 121.95 (q, J = 273.8 Hz), 112.37, 12.57.

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