Convenient preparation of trifluoroacetyl Meldrum's acid and its use as a building block for trifluoromethyl-containing compounds

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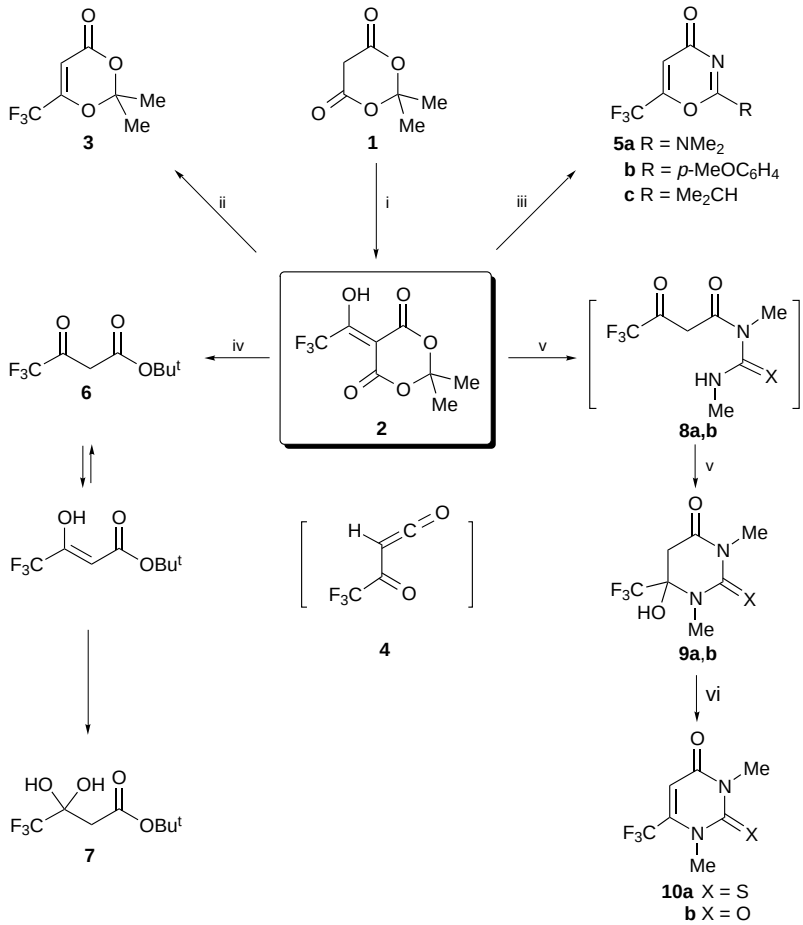
Trifluoroacetyl Meldrum's acid is conveniently prepared and applied to the synthesis of trifluoromethyl-containing compounds.

Building block approaches are currently of major interest for the construction of biologically significant trifluoromethyl-containing organic compounds.[1] Additionally, acylketenes are reactive intermediates that have been widely used in organic synthesis.[2] In this context, trifluoroacetylketene will serve as one of the most useful building blocks. However, only a few publications have appeared concerning trifluoromethyl-containing acyl ketenes, which are generated *in situ* by the thermolysis of 4*H*-1,3-dioxin-4-one[3] or by the trifluoroacetylation of ketene.[4] Acyl Meldrum's acids[5] (5-acyl-2,2-dimethyl-1,3-dioxane-4,6-dione) also behave as a precursor of acylketene. Here we describe our preliminary findings on the simple preparation of trifluoroacetyl Meldrum′s acid and its successful application to the preparation of trifluoromethyl-containing compounds such as 6-trifluoromethyl-2*H*,4*H*-1,3-dioxin-4-one, *tert*-butyl trifluoroacetoacetate, 6-trifluoromethyl-4*H*-1,3-oxazin-4-ones and 6-trifluoromethyl (thio)uracil derivatives.†

Existing methods for the preparation of acyl Meldrum's acid include the reaction of Meldrum's acid **1** with acyl chloride[6] in the presence of a tertiary amine, the reaction of **1** with a carboxylic acid[7] in the presence of a dehydrating agent and the reaction with an *in situ* generated acyl imidazolide.[8] It may be possible to carry out the acylation reaction with commercially available trifluoroacetyl chloride. However, this reagent is rather expensive and somewhat difficult to handle (bp −27 °C). Thus, we employed the imidazolide method for the preparation of trifluoroacetyl Meldrum's acid **2**. The reaction of isolated *N*-trifluoroacetylimidazole[9] with **1** in the presence of imidazole at room temperature afforded **2** in 71% yield.‡ Attempts to generate the acyl imidazolide *in situ*, however, were un-



Scheme 1 *Reagents and conditions*: i, *N*-trifluoroacetylimidazole (1.1 equiv.), imidazole (1 equiv.); ii, acetone; iii, nitrile–solvent (benzene or toluene) or neat; iv, Bu^{t}OH (1.1 equiv.); v, *N*,*N*′- dimethyl(thio)urea; vi, cat. *p*-TsOH

successful. Treatment of trifluoroacetic acid with carbonyldiimidazole, followed by the reaction with **1**, gave none of the desired compound and recovery of a small amount of **1**.

Compound **2** was found to be labile even at room temperature. Thus, upon standing in chloroform at room temperature for 2 days or refluxing in CH_2Cl_2 for 1.5 h in the presence of acetone, 6-trifluoromethyl-2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-one **3**,[4]§ was obtained in moderate yield. The conversion of **2** to **3** is rationalized in terms of generation of trifluoroacetylketene **4** followed by cycloaddition across the carbon–oxygen double bond of acetone.[10]

The hetero-Diels–Alder reaction of acylketene with a variety of dienophiles is one of the most useful methods for the synthesis of heterocyclic compounds.[2b] Treatment of **2** with dimethylcyanamide in benzene under reflux (1 h) gave 2-dimethylamino-6-trifluoromethyl-4*H*-1,3-oxazin-4-one **5a** in 46% yield. Similarly, **5b** was obtained by the reaction of **2** with anisonitrile (toluene, reflux, 1 h, 60%). Treatment of **2** with a large excess of isobutyronitrile (40 equiv.) under reflux (1 h) gave **5c** in 71% yield. However, the cycloaddition reaction of acylketene with carbon–nitrogen triple bonds is limited to substituted acylketenes. Thus, the reaction of an unsubstituted acylketene such as benzoylketene with an aromatic nitrile gives only dimerized or polymerized products of acylketene and none of the cycloaddition product with nitrile was obtained.[11] The first example of a cycloaddition reaction of an unsubstituted acylketene with a simple nitrile was achieved with the trifluoroacetylketene **4**. These 1,3-oxazin-4-ones would also be useful building blocks for the synthesis of trifluoromethyl-containing nitrogen heterocycles *via* ring transformations.[12]

Reactions of **2** with nucleophiles such as *tert*-butyl alcohol, dimethylthiourea and dimethylurea were examined. Treatment of **2** with 1.1 equiv. of *tert*-butyl alcohol in chloroform at room temperature for 3 days, followed by vacuum distillation, afforded the previously unknown *tert*-butyl trifluoroacetoacetate **6** (80%). When **6** was left without protection from atmospheric moisture, solid **7** was formed. On the basis of the spectral and analytical characteristics, **7** was assigned the structure of the hydrated product of **6**. The hydration of compounds containing the trifluoromethylcarbonyl moiety is a well known phenomenon.[13] However, to the best of our knowledge, this is the first example of the isolation of the hydrated form of a trifluoromethylated β-keto ester.

The reaction with 1,3-dimethylthiourea (THF, room temperature, 24 h) gave the dihydrouracil derivative **9a** (90%) *via* trifluoroacetoacetyl derivative **8a**. Subsequent dehydration of **9a** in toluene under reflux with a catalytic amount of toluene-*p*-sulfonic acid afforded 6-trifluoromethyluracil **10a** (80%). Similarly, 2-oxo analogue **9b** (THF, room temperature, 24 h, 45%) and **10b** (91%) were obtained.

Further investigation of the application of **2** as a convenient method for the synthesis of biologically important heterocycles is in progress.

Footnotes

† All new compounds gave satisfactory analytical and spectral data.

‡ The procedure for the preparation of **2** is as follows: to a solution of **1** (10 mmol) and imidazole (10 mmol) in 20 ml of $CHCl_3$ was added a solution of *N*-trifluroacetylimidazole (11 mmol) in 20 ml of $CHCl_3$ over a period of 30 min at room temperature. After stirring for an additional 5 min the solution was washed with 10% HCl (10 ml × 3), dried ($MgSO_4$) and the solvent evaporated while maintaining the temperature below 20 °C. Washing the resulting colourless solid with small amount of cold diethyl ether gave analytically pure **2**.

§ Preparation of compound **3** by trifluoroacetylation of *in situ* generated ketene with trifluoroacetic anhydride is reported by Boivin *et al.*,[4] but the reported yield is 8%. Iwaoka *et al.*[3] reported the preparation of 6-trifluoromethyl-4-oxo-4*H*-1,3-dioxine-2-spirocyclohexane from 4,4,4-trifluoro-3-oxobutanoic acid, cyclohexanone and acetic anhydride in the presence of a catalytic amount of sulfuric acid.

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