Convenient Synthesis of Ethyl 4-Aryl-6-(trifluoromethyl)-2-oxo-2*H*-pyran-3-carboxylates and 4-Aryl-6-(trifluoromethyl)-2*H*pyran-2-ones: Novel Highly Reactive CF₃-Containing Building Blocks

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ABSTRACT



An expedient synthesis of a series of 2-pyrones, bearing a CF₃ group at the 6-position and aryl group at position 4, from readily available aryl-4,4,4-trifluorobutane-1,3-diones, PCl₅, and sodium diethyl malonate is described.

6-(Trifluoromethyl)-2*H*-pyran-2-ones, poorly explored heterocyclic compounds, have successfully been used as conjugated dienes in Diels—Alder reactions with several dienophiles for the synthesis of CF₃-anilines¹ and cage antiviral agents.² Only a few methods for preparing some of these compounds have been reported so far (Scheme 1).^{2–8}

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The methods A-H for the preparation of 6-CF₃-2*H*-pyran-2-ones of the general formula 1 often suffer from a narrow scope of substrates (A-E), long reaction time (A), tedious synthetic routes (A, D), drastic reaction conditions (E), low yields (A, B), as well as a very limited variety of substituents (A-E). Moreover, there are no approaches for the synthesis of 6-CF₃-2*H*-pyran-2-ones bearing an aryl group at the 4-position.

In this paper, we describe the preparation of new 2-pyrones substituted with CF_3 group at the 6-position, aryl group at the 4-position, and bearing an ethoxycarbonyl group or hydrogen at position 3. All of the starting products are commercially available or easily obtainable.⁹

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^{*a*}Reagents, conditions, and substituents: (i)³ maleic anhydride, 40 °C, 2 weeks, $R^1 = R^2 = Me$, $R^3 = CF_3$; (ii)² CF₃COMe, base, $R^1 = CO_2Et$, $R^2 = R^3 = H$; (iii)⁴ P₂O₅, Δ , $R^1 = COCF_3$, $R^2 = OH$, $R^3 = H$; (iv)⁵ mesitylene, reflux, $R^1 = R^3 = H$, $R^2 = CO_2Me$; (v)⁶ SF₄, HF, 120 °C, 4 h, $R^1 = R^2 = R^3 = H$; (vi)⁷ ArCH₂CO₂Et, $R^1 = Ar$, $R^2 = Alk$, $R^3 = H$, Me, CO₂H, CO₂Et; (vi)⁸ R¹CH₂CO₂Et, A² = NHCOAr, $R^2 = R^3 = H$; (vii)⁸ R¹CH₂CO₂A, $R^1 = NHCOAr$, $R^2 = H$, $R^3 = CO_2Et$ or COCF₃.

We discovered that treatment of 1-aryl-4,4,4-trifluorobutane-1,3-diones **2** with PCl₅ and then sodium diethyl malonate afforded ethyl 4-aryl-6-(trifluoromethyl)-2-oxo-2*H*-pyran-3carboxylates **3** in moderate yields (Table 1). The first stage is a slow reaction, while the second stage is fast.

The reaction of **2** with 1.1 equiv of PCl₅ (i.e., the first stage) leads to a mixture of products containing a major intermediate. Thus, four signals corresponding to the CF₃-bearing intermediates were observed in the ¹⁹F NMR spectra of the reaction mixture of **2a** and PCl₅ (C₆D₆): δ –79.8 (3%), δ < 2370.5 (8%), δ –70.0 (79%, major intermediate), δ –63.5 (3%). The reaction mass also contained 6% of the starting diketone **2a** (δ –77.4). The ¹⁹F NMR spectral data for the mixtures prepared from the other diketones and PCl₅ were similar to those observed for the mixture of **2a** and PCl₅.

Probably, the major intermediates with the signal at about δ -70.0 are responsible for the formation of the intermediate 4-aryl-1,1,1-trifluorobut-3-yn-2-ones A, which then react with sodium diethyl malonate to produce **3** through anions **B**.¹⁰ The reaction times for the first stage depend strongly on the nature of the aryl substituent. As can be seen in Table 1, an electron-withdrawing substituent (F, Cl, NO₂) at the para position of the aromatic ring retards the reaction, whereas an electron-donating aromatic group (p-tolyl, 2-naphthyl, 2-thienyl) greatly accelerates it (entries **b**-**d** versus entries e-g). The temperature level of the reactions should be as low as possible (25-35 °C). Prolonged heating at higher temperatures resulted in a more complex mixture of intermediates and decrease in the yields of 3. Nevertheless, in order to decrease the reaction time as much as possible, in the case of diketone 2d the reaction was carried out at 45-50°C to give pyrone **3d** in 18% yield.

Table 1. Preparation of Ethyl 4-Aryl-6-(trifluoromethyl)-2-oxo-2H-pyran-3-carboxylates 3



		Conditions (fir			
		Temperature	Time	Yield	Мр
Entry	Ar	(°C)	(h)	(%)	(°C)
a	\bigcirc -	25-30	30	24	90
b	F-	30-35	36	39	121-123
c	ci-	30-35	24	29	78
d	02N-	45-50	48	18	134-136
e	Me	25-30	7	39	60
f	())	25-30	6	45	108-110
g	res	25-30	0.5	22	112-113

The reaction mass was then treated with sodium diethyl malonate at -50 to 0 °C within 1 h (the second stage). After several trials, we were pleased to find that the use of 4.5 equiv of sodium diethyl malonate relative to starting **2a**, the maximum yield of the sequential reaction product **3a** was reached (Table 1, entry **a**). In the other cases (entries **b**-**g**, Table 1), 4.5 equiv of sodium diethyl malonate was also found to be sufficient. No pyrone **3a** was obtained, when the same reaction was conducted using 1.1 or 9.5 equiv of sodium diethyl malonate.

The structure of the synthesized 6-CF₃-2*H*-pyran-2-ones **3a**-**g** was confirmed by NMR, EI-MS, HRMS, IR spectra, and elemental analysis. The proton H-5 appeared as a singlet at about δ 6.8. In the ¹⁹F NMR, the signal at about δ -77.0 corresponding to the trifluoromethyl group was observed. In the ¹³C NMR spectra of compound **3a**, the characteristic quartets of C-6 at δ 148.00 (²*J*_{C,F} = 39.7 Hz) and C-5 at δ 107.09 (⁴*J*_{C,F} = 3.6 Hz) were observed. In the EI-MS spectra, characteristic fragmentation of **3** was presented by intense ion peaks [M]⁺, [M - 28]⁺, [M - 45]⁺, [M - 28 - 69]⁺, and by ion peak [CF₃]⁺ (~30%).

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We have found that ethyl 4-aryl-6-(trifluoromethyl)-2-oxo-2*H*-pyran-3-carboxylates **3** can be decarbethoxylated in high yields to 6-(trifluoromethyl)-4-aryl-2*H*-pyran-2-ones **4** by refluxing in aqueous acetic acid with H_2SO_4 (Table 2). The

Table 2. Preparation of 4-Aryl-6-(trifluoromethyl)-2H-pyran-2-ones 4 by Decarbethoxylation of 3

$F_{3}C$ O O O 3	H ₂ O, DEt <u>r</u>	AcOH, H ₂ SO ₄ reflux, 4 h 64-90%	Ar F ₃ C 0 0 4
Entry	Ar	Yield (%)	Mp (°C)
a	\frown	83	60
b	F	87	106-107
c	ci-	90	101-102
d	0 ₂ N-	69	178-180
e	Me	74	114-115
f		70	147-148
g	s	64	141-143

structure of pyrones 4a-g was confirmed by conventional spectroscopic methods.

To demonstrate the principal possibility of the application of pyrones 3 in organic synthesis, we examined reactivity of 3a under nucleophilic and electrophilic conditions: ammonolysis with excess of NH₄OAc, reaction with 2,3dihydrofuran, and treatment with H₂SO₄ (Scheme 2). Thus, the reaction of **3a** with NH₄OAc in refluxing aqueous DMF, involving loss of the ethoxycarbonyl group at the 3-position, afforded the pyridinol derivative 5 in 69% yield. The solventfree inverse electron-demand Diels-Alder reaction of 3a with 2,3-dihydrofuran gave bicyclic lactone 6 in 61% yield. The characteristic coupling constant J 7.8 Hz for the vicinal protons H^a-H^b confirms the *endo*-configuration of **6**.^{11a} Very high regio- and stereoselectivity of the cycloaddition reaction is in agreement with previous observations for the transformation of structurally related pyrones into the corresponding bicyclic lactones.¹¹ Remarkably, treatment of **3a** with H₂SO₄ at 125 °C for 10 min afforded the intramolecular Friedel-Crafts reaction product 7 in 41% yield. 3-(Trifluoromethyl)indeno[2,1-c]pyran-1,9-dione 7, the first representative of a novel polynuclear fused heterocyclic system, due to the



presence of antiaromatic cyclopentadienone fragment, showed high reactivity relative to weak nucleophiles such as water. Thus, usual recrystallization of **7** from aqueous ethanol led to the formation of (*E*)-3-(3,3,3-trifluoro-2-oxopropylidene)indan-1-one **8** in 33% yield. In the ¹H NMR spectrum of **8**, chemical shift of the proton H-4 at the benzene ring (doublet at δ 8.0, J = 7.8 Hz) confirms its *E*-isomer structure.¹² A possible mechanism of the transformation of **7** into **8** includes attack by a molecule of water on the pyrone ring leading to the formation of the intermediate β -ketoacid **C**, which easily decarboxylates to indanone **8**.

In summary, we have demonstrated a new and efficient approach to $6\text{-}CF_3\text{-}2H\text{-}pyran\text{-}2\text{-}one$ derivatives via readily available 1-aryl-4,4,4-trifluorobutane-1,3-diones, PCl₅, and diethyl malonate. The synthesized $6\text{-}CF_3\text{-}2H\text{-}pyran\text{-}2\text{-}ones$ **3** and **4** can be used as essential building blocks for the construction of trifluoromethylated heterocycles and bicyclic systems.

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Supporting Information Available: Experimental procedures, spectral data, and elemental analysis for **3a**, **4a**, and **5–8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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