ORGANIC LETTERS

2008
Vol. 10, No. 13
2857−2859

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 CF_3-Containing Building Blocks

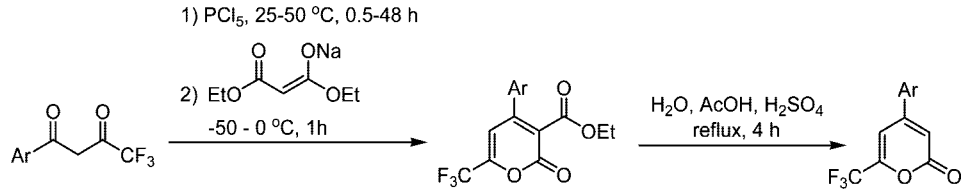
Boris I. Usachev,*,† Dmitrii L. Obydennov,† Gerd-Volker Röschenthaler,‡ and Vyacheslav Ya. Sosnovskikh†

Department of Chemistry, Ural State University, 620083 Ekaterinburg, Russia, and Institute of Inorganic & Physical Chemistry, University of Bremen, 28334 Bremen, Germany

boris.usachev@mail.ru

Received April 30, 2008

ABSTRACT



An expedient synthesis of a series of 2-pyrones, bearing a CF_3 group at the 6-position and aryl group at position 4, from readily available aryl-4,4,4-trifluorobutane-1,3-diones, PCl_5, 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 CF_3-anilines[1] and cage antiviral agents.[2] Only a few methods for preparing some of these compounds have been reported so far (Scheme 1).[2−8]

The methods **A**−**H** for the preparation of 6-CF_3-2*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-CF_3-2*H*-pyran-2-ones bearing an aryl group at the 4-position.

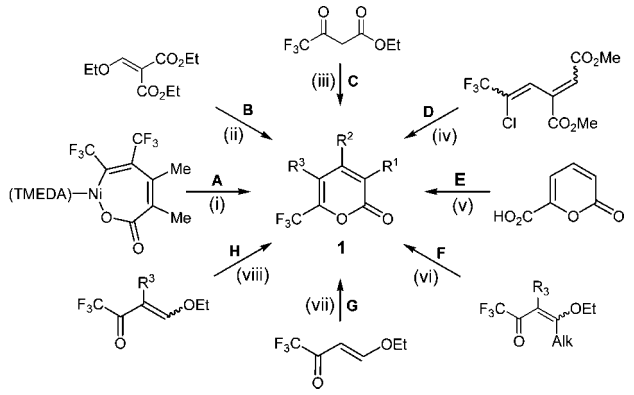
In this paper, we describe the preparation of new 2-pyrones substituted with CF_3 group at the 6-position, aryl group at the 4-position, and bearing an ethoxycarbonyl group or hydrogen at position 3. All of the starting products are commercially available or easily obtainable.[9]

† Ural State University.
‡ University of Bremen.

(1) Tolmachova,; N, A.; Gerus, I. I.; Vdovenko, S. I.; Essers, M.; Fröhlich, R.; Haufe, G. *Eur. J. Org. Chem.* **2006**, 4704–4709.
(2) Whitney, J. G.; Gregory, W. A.; Kauer, J. C.; Roland, J. R.; Snyder, J. A.; Benson, R. E.; Hermann, E. C. *J. Med. Chem.* **1970**, *13*, 254–260.
(3) Hoberg, H.; Schaefer, D. *J. Organomet. Chem.* **1982**, *238*, 383–387.
(4) German, L. S.; Sterlin, S. R.; Cherstkov, V. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1982, 1657−1659; *Chem. Abstr.* 1982, *97*, 162758.
(5) (a) Martin, P.; Streith, J.; Rihs, G.; Winkler, T.; Belluš, D. *Tetrahedron Lett.* **1985**, *26*, 3947–3950. (b) Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Belluš, D. *Tetrahedron* **1985**, *41*, 4057–4078.
(6) Boulanger, W. A.; Katzenellenbogen, J. A. *J. Med. Chem.* **1986**, *29*, 1159–1163.
(7) Yamaguchi, M.; Ito, Y.; Shubayama, A.; Yamaji, Y.; Hanai, R.; Uotsu, S.; Sadohara, H. PCT Int. Appl. WO 9728127, 1997; *Chem. Abstr.* 1997, *127*, 190757
(8) Gerus, I. I.; Tolmachova, N. A.; Vdovenko, S. I.; Fröhlich, R.; Haufe, G. *Synthesis* **2005**, 1269–1278.

10.1021/ol800992z CCC: $40.75
Published on Web 06/07/2008

Scheme 1[a]



[a]Reagents, conditions, and substituents: (i)[3] maleic anhydride, 40 °C, 2 weeks, $R^1 = R^2 = Me$, $R^3 = CF_3$; (ii)[2] CF_3COMe, base, $R^1 = CO_2Et$, $R^2 = R^3 = H$; (iii)[4] P_2O_5, 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] SF_4, HF, 120 °C, 4 h, $R^1 = R^2 = R^3 = H$; (vi)[7] $ArCH_2CO_2Et$, $R^1 = Ar$, $R^2 = Alk$, $R^3 = H$, Me, CO_2H, CO_2Et; (vii)[8] $R^1CH_2CO_2H$, Ac_2O, $R^1 = NHCOAr$, $R^2 = R^3 = H$; (viii)[8] $R^1CH_2CO_2H$, Ac_2O, Δ, $R^1 = NHCOAr$, $R^2 = H$, $R^3 = CO_2Et$ or $COCF_3$.

We discovered that treatment of 1-aryl-4,4,4-trifluorobutane-1,3-diones **2** with PCl_5 and then sodium diethyl malonate afforded ethyl 4-aryl-6-(trifluoromethyl)-2-oxo-2*H*-pyran-3-carboxylates **3** in moderate yields (Table 1). The first stage is a slow reaction, while the second stage is fast.

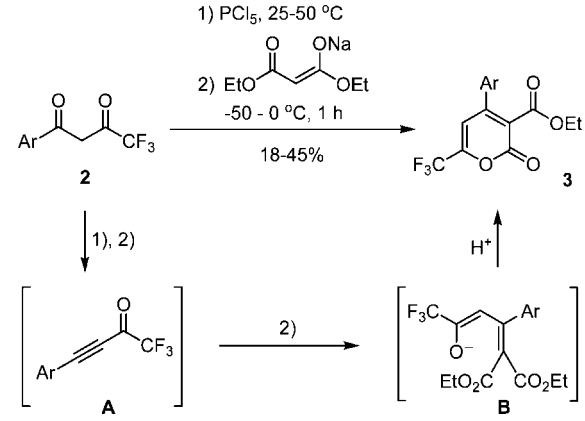
The reaction of **2** with 1.1 equiv of PCl_5 (i.e., the first stage) leads to a mixture of products containing a major intermediate. Thus, four signals corresponding to the CF_3-bearing intermediates were observed in the ^{19}F NMR spectra of the reaction mixture of **2a** and PCl_5 (C_6D_6): δ −79.8 (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 ^{19}F NMR spectral data for the mixtures prepared from the other diketones and PCl_5 were similar to those observed for the mixture of **2a** and PCl_5.

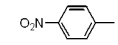
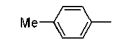
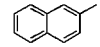
Probably, the major intermediates with the signal at about δ −70.0 are responsible for the formation of the intermediate 4-aryl-1,1,1-trifluorobut-3-yn-2-ones **A**, which then react with sodium diethyl malonate to produce **3** through anions **B**.[10] The reaction times for the first stage depend strongly on the nature of the aryl substituent. As can be seen in Table 1, an electron-withdrawing substituent (F, Cl, NO_2) 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.

(9) (a) Reid, J. C.; Calvin, M. *J. Am. Chem. Soc.* **1950**, *72*, 2948–2952. (b) Barkley, L. B.; Levine, R. *J. Am. Chem. Soc.* **1951**, *73*, 4625–4627.

(10) Korshunov, S. P.; Vereshyagin, L. I.; Bugerova, G. S.; Okhapkina, L. L. *Zh. Org. Khim. SSSR* **1965**, *1*, 2212–2214.

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



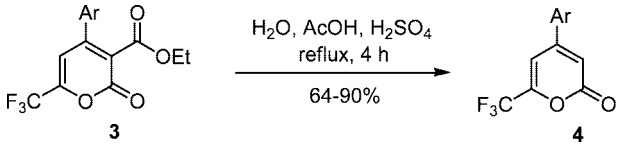
		Conditions (first stage)			
		Temperature	Time	Yield	Mp
Entry	Ar	(°C)	(h)	(%)	(°C)
a		25-30	30	24	90
b		30-35	36	39	121-123
c		30-35	24	29	78
d		45-50	48	18	134-136
e		25-30	7	39	60
f		25-30	6	45	108-110
g		25-30	0.5	22	112-113

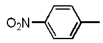
The reaction mass was then treated with sodium diethyl malonate at −50 to 0 °C within 1 h (the second stage). After several trials, we were pleased to find that the use of 4.5 equiv of sodium diethyl malonate relative to starting **2a**, the maximum yield of the sequential reaction product **3a** was 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-CF_3-2*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 ^{19}F NMR, the signal at about δ −77.0 corresponding to the trifluoromethyl group was observed. In the ^{13}C NMR spectra of compound **3a**, the characteristic quartets of C-6 at δ 148.00 ($^2J_{C,F}$ = 39.7 Hz) and C-5 at δ 107.09 ($^4J_{C,F}$ = 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 $[CF_3]^+$ (∼30%).

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)-2*H*-pyran-2-ones **4** by Decarbethoxylation of **3**

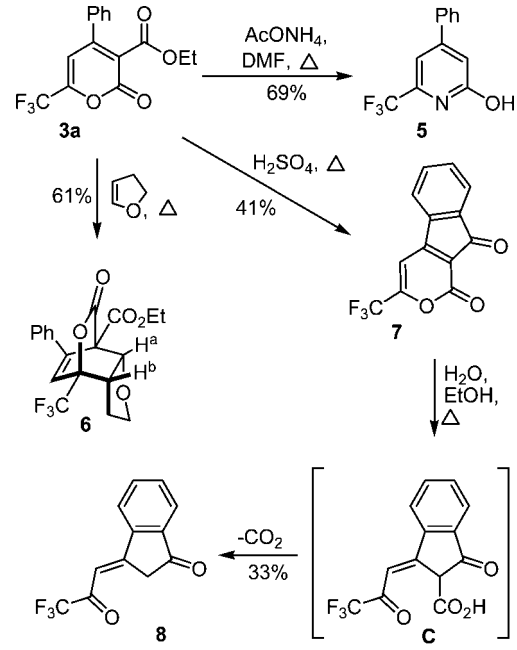


Entry	Ar	Yield (%)	Mp (°C)
a		83	60
b		87	106-107
c		90	101-102
d		69	178-180
e		74	114-115
f		70	147-148
g		64	141-143

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 NH_4OAc, reaction with 2,3-dihydrofuran, and treatment with H_2SO_4 (Scheme 2). Thus, the reaction of **3a** with NH_4OAc in refluxing aqueous DMF, involving loss of the ethoxycarbonyl group at the 3-position, afforded the pyridinol derivative **5** in 69% yield. The solvent-free 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 H_2SO_4 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

Scheme 2. Some Reactions of **3a**



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-CF_3-2*H*-pyran-2-one derivatives via readily available 1-aryl-4,4,4-trifluorobutane-1,3-diones, PCl_5, and diethyl malonate. The synthesized 6-CF_3-2*H*-pyran-2-ones **3** and **4** can be used as essential building blocks for the construction of trifluoromethylated heterocycles and bicyclic systems.

Acknowledgment. This research was supported by the Deutsche Forschungsgemeinschaft (Grant No. 436 RUS 113/901/0-1). We are very grateful to Dr. T. Dülcks, Institute of Organic Chemistry, University of Bremen (Germany), for recording the mass spectra.

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.

OL800992Z

(11) (a) Markü, I. E.; Evans, G. R.; Declercq, J.-P. *Tetrahedron* **1994**, *50*, 4557–4574. (b) Markü, I. E.; Evans, G. R. *Tetrahedron Lett.* **1993**, *34*, 7309–7312. (c) Markü, I. E.; Evans, G. R. *Tetrahedron Lett.* **1994**, *35*, 2767–2770. (d) Markü, I. E.; Evans, G. R. *Tetrahedron Lett.* **1994**, *35*, 2771–2774.

(12) Sevenard, D. V.; Sosnovskikh, V. Ya.; Schroeder, G.; Röschenthaler, G.-V. *Aust. J. Chem.* **2001**, *54*, 335–341.