Tetrahedron Letters 50 (2009) 4903–4905

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Methyl 2-methoxytetrafluoropropionate as a synthetic equivalent of methyl trifluoropyruvate in the Claisen condensation. The first synthesis of 2-(trifluoroacetyl)chromones and 5-aryl-2-hydroxy-2-(trifluoromethyl)furan-3(2*H*)-ones

Roman A. Irgashev [a], Vyacheslav Ya. Sosnovskikh [a,*], Nataliya Kalinovich [b], Olesya Kazakova [b], Gerd-Volker Röschenthaler [b]

[a] *Department of Chemistry, Ural State University, pr. Lenina 51, 620083 Ekaterinburg, Russian Federation*
[b] *Institute of Inorganic and Physical Chemistry, University of Bremen, 28334 Bremen, Germany*

ARTICLE INFO

Article history:
Received 17 April 2009
Revised 22 May 2009
Accepted 12 June 2009
Available online 16 June 2009

Keywords:
Methyl 2-methoxytetrafluoropropionate
Acetophenones
Claisen condensation
Deprotection
Trifluoromethyl 1,2,4-triketones

ABSTRACT

2-(Trifluoroacetyl)chromones and 5-aryl-2-hydroxy-2-(trifluoromethyl)furan-3(2*H*)-ones were obtained in good yields via the Claisen condensation of acetophenones with methyl 2-methoxytetrafluoropropionate, followed by sulfuric acid-mediated deprotection of the reaction products.

Trifluoromethylated heterocycles continue to be of great academic and industrial interests. Replacement of hydrogen with fluorine sometimes can lead to dramatic changes in the physical properties, chemical reactivity, and biological activity of compounds, as a result of the high electronegativity of fluorine and the high C–F bond energy.[1] In connection with this, the development of new methods for incorporation of the CF_3 group into organic compounds remains an important area of research. In view of the unique biological properties displayed by many fluorinated heterocyclic compounds,[2] and as an extension of our continuing synthetic studies in the field of 3-(trifluoroacetyl)chromones **1**,[3] we have focussed our attention on 2-(trifluoroacetyl)chromones **2** as a new class of polydentate electrophilic substrates (Fig. 1). These compounds, despite their potential interest as building blocks in organic synthesis for the construction of more complex trifluoromethylated heterocycles, have received little attention. In contrast to the well-known 2-acetylchromones,[4] no data on the preparation and chemical properties of 2-(trifluoroacetyl)chromones **2** have been documented, probably owing to the lack of general methods for their synthesis.

The importance of highly reactive substrates **2** prompted us to develop a general and efficient method for their preparation as useful precursors of a wide variety of heterocycles containing a CF_3 group. Our approach to these compounds follows the same design as many earlier methods for the preparation of 2-substituted chromones and includes a Claisen condensation of an appropriately substituted acetophenone with methyl 2-methoxytetrafluoropropionate.

Esters of trifluoropyruvic acid are used as trifluoromethylated building blocks in organic chemistry. However, it is well known that the reaction of methyl trifluoropyruvate **3** with methyl ketones occurs only at the carbonyl adjacent to the CF_3 group to give the corresponding β-ketols **4** (aldol condensation),[5] and not the triketones **5** (Claisen condensation). On the other hand, the starting material for the preparation of **3**, methyl 2-methoxytetrafluoropropionate **6**, was found to be a very stable compound, especially

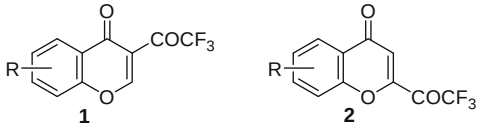


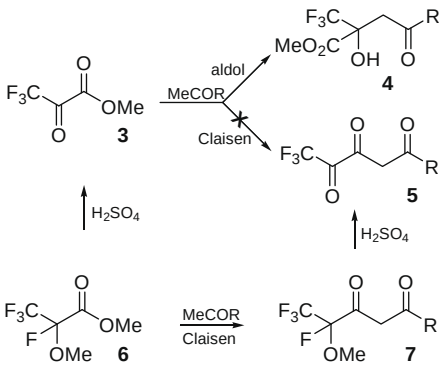
Figure 1.

* Corresponding author. Fax: +7 343 261 59 78.
E-mail address: vyacheslav.sosnovskikh@usu.ru (V.Ya. Sosnovskikh).

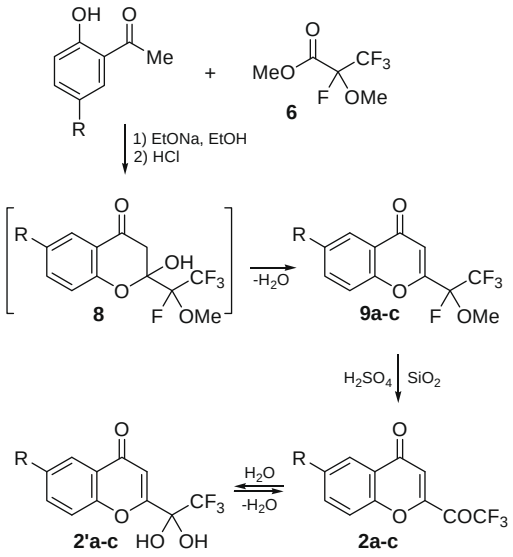
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.067

against alkaline hydrolysis.[6] Moreover, very recently[7] this ester was used as a carbonyl component in the condensation with cyclohexanone. Bearing these facts in mind, we envisaged that the reaction of ester **6** with methyl ketones would produce the corresponding triketones **7** with one protected carbonyl group, which could be converted into the trifluoromethyl 1,2,4-triketones **5** (Scheme 1).

As the Claisen reaction usually affords β-dicarbonyls, in the case of 2-hydroxyacetophenones, we would expect the formation of chromanones **8**, whose acid-catalyzed dehydration would result in chromones **9** with a masked trifluoroacetyl substituent at the 2-position. Indeed, we found that methyl 2-methoxytetrafluoropropionate **6**, easily prepared from hexafluoropropene epoxide and methanol,[6,8] reacted with 2-hydroxyacetophenones under Claisen reaction conditions (refluxing ethanol and NaOEt as catalyst or refluxing THF and LiH as catalyst) affording, after hydrochloric acid hydrolysis, chromones **9a–c** in 57–87% yields.[9] It should be noted that the intermediates **8** could not be isolated and underwent spontaneous dehydration to **9a–c**. Deprotection of chromones **9a–c** was carried out using 96% H_2SO_4 and SiO_2, as previously reported for the preparation of ester **3** from **6**,[8] to afford 2-(trifluoroacetyl)chromones **2a–c** in 76–88% yields[10] (Scheme 2).



Scheme 1.



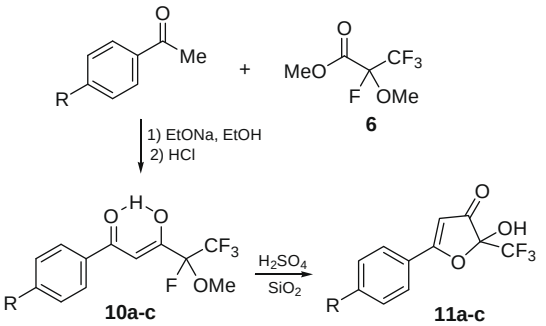
R = H (**a**), Me (**b**), Cl (**c**)

Scheme 2.

In marked contrast to the known 2-acetylchromones,[4] chromones **2a–c** obtained in this work were prone to easy and reversible covalent hydrate formation as observed from the ^{1}H NMR spectrum of **2a** in $CDCl_3$, which contained two sets of signals (**2a**:**2′a** = 83:17). The diagnostic signal for proton H-3 in chromone **2a**, which appeared at δ 7.18 ppm, was shifted upfield in its hydrate **2′a** (δ 6.84 ppm). In DMSO-d_6 solution, compounds **2** exist in the *gem*-diol form **2′**, exclusively (δ_{H3} = 6.60–6.66 ppm); the CF_3 group is bonded to the sp^3-hybridized carbon atom and occurs as a singlet at ca. 81 ppm (C_6F_6). The IR spectra (KBr) of **2** showed intense absorption bands in the ranges 3340–3290 cm^{-1} corresponding to the hydroxy groups, 1642–1636 cm^{-1} attributed to the chromone carbonyl group, and 1597–1584 cm^{-1} due to the C=C double bond. Therefore, in the solid state chromones **2** exist in the *gem*-diol form **2′**, as was observed in the case of 3-(trifluoroacetyl)chromones[3] and 3-(trifluoroacetyl)coumarins.[11]

Acetophenone and *p*-methyl- and *p*-chloroacetophenones were similarly reacted with methyl 2-methoxytetrafluoropropionate **6** under the same reaction conditions (refluxing ethanol and NaOEt as catalyst). The final products **10a–c**, which were fully enolic in $CDCl_3$ (δ_{OH} = 15.5–15.6 ppm), were produced in 60–79% yields after work-up. Treatment of **10a–c** with 96% H_2SO_4 in the presence of SiO_2 gave the corresponding triketones, which underwent spontaneous intramolecular cyclization at the $COCF_3$ group to yield furanones **11a–c** in 64–75% yields (Scheme 3). The structures of compounds **10** and **11** were confirmed by elemental analysis, ^{1}H, ^{19}F NMR, and IR spectroscopies, and mass spectrometry. This very practical and convenient approach has never been applied to the synthesis of CF_3-containing 1,2,4-triketones, despite the fact that methyl 2-methoxytetrafluoropropionate **6** is readily available.[6,8]

The synthesis of trifluoromethylated molecules is an ongoing area of research due to the unique physical and biological properties imparted by the CF_3 group.[1,2] We envisaged that the presence of a strongly electron-withdrawing CF_3 group would render the carbonyl moieties non-equivalent toward nucleophilic attack, leading to high regiochemical control when reacted with suitable nucleophiles. To demonstrate the ability of compounds **2** to undergo regioselective heterocyclization reactions, chromone **2a** was reacted with ethylenediamine (MeOH, AcOH, 48 h, ~20 °C) and *o*-phenylenediamine (AcOH, 8 h, reflux). Our preliminary results showed that **2a** behaves as a latent 1,2-diketone, having a masked aroyl fragment at the 3-position, and reacts with diamines to give compounds **12** and **13** in good yields (57% and 83%, respectively). In contrast with ethylenediamine, reaction of **2a** with *o*-phenylenediamine afforded a mixture of two tautomeric forms (**13A:13B** = 59:41) as was observed previously for 2-ketomethylquinolines.[12] These results clearly indicate that C-2 of chromones **2**, due to the electron-withdrawing effect of the CF_3CO group, is very susceptible to nucleophilic attack, which makes them useful



R = H (**a**), Me (**b**), Cl (**c**)

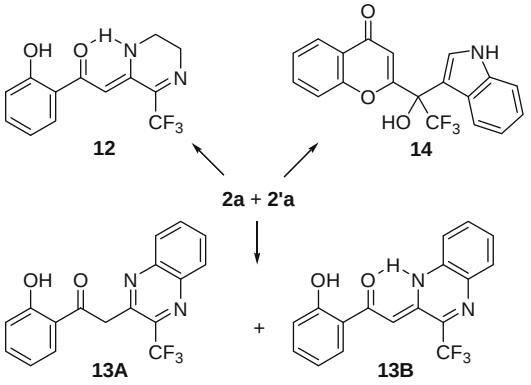
Scheme 3.

for constructing highly functionalized biologically and medicinally important products. In addition, chromone **2a** reacted smoothly with indole at 85 °C in 5 h to produce the expected adduct **14** in 75% yield (Scheme 4).

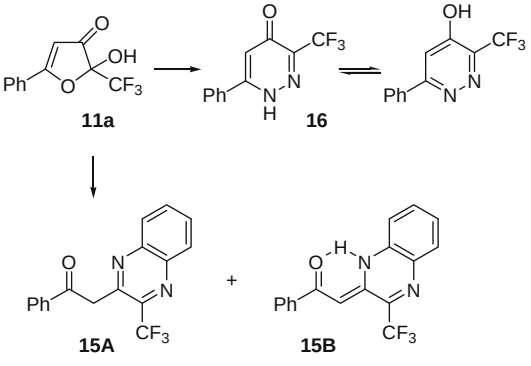
Reaction of furanone **11a** with *o*-phenylenediamine also occurred in refluxing AcOH to give a 55:45 mixture of tautomers **15A** and **15B** in 68% yield. Treatment of **11a** in refluxing AcOH with $N_2H_4{\cdot}2HCl$ (2 equiv) resulted in the formation of 6-phenyl-3-(trifluoromethyl)pyridazin-4(1*H*)-one **16**[13] (yield 60%) which exists as a mixture of two tautomeric forms (95:5) in DMSO-d_6 solution (Scheme 5). It should be noted that isomeric 6-phenyl-4-(trifluoromethyl)pyridazin-3(2*H*)-one can be prepared from acetophenone, methyl trifluoropyruvate, and hydrazine hydrate.[5d]

The structures of **12**–**16** were confirmed with the aid of spectral and analytical data. For example, in the ^{19}F NMR spectra of **13** and **15**, the CF_3 group of tautomer **A** appeared as a triplet ($^5J_{F,H}$ = 1.3–1.6 Hz) at 98.8 ppm and the CF_3 group of **B** appeared as a doublet ($^5J_{F,H}$ = 1.8–1.9 Hz) at 96.1–96.8 ppm (C_6F_6).

In summary, we have developed a simple and convenient two-step synthesis of 2-(trifluoroacetyl)chromones and 5-aryl-2-hydroxy-2-(trifluoromethyl)furan-3(2*H*)-ones starting from commercially available acetophenones and hexafluoropropene epoxide via introduction of a CF_3COCO group into methylketones. Hexafluoropropene epoxide is advantageous as a starting material in that it is stable, readily available, comparatively inexpensive, and environmentally safe. The compounds obtained are of interest as precursors for the synthesis of other useful organic materials. Further studies on the synthetic application of this methodology and on the reactivity of the described chromones and furanones are in progress.



Scheme 4.



Scheme 5.

Acknowledgment

This work was financially supported by a DFG (Grant No. 436 RUS 113/901/0-1).

References and notes

1. Hiyama, T. *Organofluorine Compounds. Chemistry and Application*; Springer-Verlag: Berlin, 2000.
2. (a) Dolbier, W. R., Jr. *J. Fluorine Chem.* **2005**, *126*, 157; (b) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992.
3. (a) Sosnovskikh, V. Y.; Irgashev, R. A.; Barabanov, M. A. *Synthesis* **2006**, 2707; (b) Sosnovskikh, V. Y.; Irgashev, R. A.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 2997; (c) Sosnovskikh, V. Y.; Moshkin, V. S.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 7877; (d) Sosnovskikh, V. Y.; Khalymbadzha, I. A.; Irgashev, R. A.; Slepukhin, P. A. *Tetrahedron* **2008**, *64*, 10172.
4. (a) Brown, R. C.; Cairns, H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1553; (b) Bevan, P. S.; Ellis, G. P.; Wilson, H. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2552.
5. (a) Golubev, A. S.; Galakhov, M. V.; Kolomiets, A. F.; Fokin, A. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 2127; (b) Paleček, J.; Paleta, O. *Synthesis* **2004**, 521; (c) Volochnyuk, D. M.; Kostyuk, A. N.; Sibgatulin, D. A.; Petrenko, A. E. *Synthesis* **2004**, 2545; (d) Sibgatulin, D. A.; Volochnyuk, D. M.; Kostyuk, A. N. *Synlett* **2005**, 1907.
6. Sianesi, D.; Pasetti, A.; Tarli, F. *J. Org. Chem.* **1966**, *31*, 2312.
7. Sevenard, D. V.; Khomutov, O. G.; Boltachova, N. S.; Filyakova, V. I.; Vogel, V.; Lork, E.; Sosnovskikh, V. Ya.; Iaroshenko, V. O.; Roschenthaler, G.-V. Z. *Naturforsch.* **2009**, *64b*, 541.
8. Dolenský, B.; Kvíčala, J.; Paleček, J.; Paleta, O. *J. Fluorine Chem.* **2002**, *115*, 67.
9. *2-(1,2,2,2-Tetrafluoro-1-methoxyethyl)chromone* (**9a**): A mixture of methyl 2-methoxytetrafluoropropionate **6** (25.0 g, 0.132 mol) and 2-hydroxyacetophenone (17.4 g, 0.128 mol) was added dropwise to an alcoholic solution of NaOEt obtained by dissolution of sodium (8.6 g, 0.374 mol) in anhydrous EtOH (150 mL). The resulting reaction mixture was refluxed with stirring for 5 h. Concentrated HCl (65 mL) was added to the disodium salt, and the mixture was refluxed with stirring for 1 h. The cooled mixture was quenched by addition of water (200 mL) and the solvent was concentrated under reduced pressure. The organic product thus obtained was extracted with ether (3 × 100 mL) and the combined extracts were washed with 5% KOH (60 mL) and water (60 mL), dried over anhydrous $MgSO_4$, and evaporated to afford a colorless solid. The solid was recrystallized from hexane–ether (10:1) to give **9a** in 57% yield (20.0 g), mp 95–96 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (d, 3H, MeO, $^4J_{H,F}$ = 0.8 Hz), 6.77 (d, 1H, H-3, $^4J_{H,F}$ = 1.8 Hz), 7.49 (ddd, 1H, H-6, *J* = 8.0, 7.2, 1.0 Hz), 7.56 (dd, 1H, H-8, *J* = 8.5, 1.0 Hz), 7.76 (ddd, 1H, H-7, *J* = 8.5, 7.2, 1.7 Hz), 8.23 (dd, 1H, H-5, *J* = 8.0, 1.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 25.05 (m, F), 79.94 (d, CF_3, $^3J_{F,F}$ = 4.0 Hz); MS (EI), *m/z* (%) 276 $[M]^+$ (100), 207 $[M-CF_3]^+$ (100). Anal. Calcd for $C_{12}H_8F_4O_3$: C, 52.19; H, 2.92. Found: C, 52.16; H, 3.30.
10. *2-(Trifluoroacetyl)chromone* (**2a**) *and 2-(2,2,2-trifluoro-1,1-dihydroxyethyl) chromone* (**2′a**). To a suspension of SiO_2 (850 mg, 14 mmol) in concentrated sulfuric acid (22 mL) chromone **9a** (11.7 g, 42.4 mmol) was added in small portions with stirring. The resulting yellow solution was heated with stirring at 125–130 °C for 1 h. The cooled mixture was poured into water (300 mL) and extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed with water (3 × 50 mL) and evaporated under reduced pressure. The solid that formed was recrystallized from toluene–ethyl acetate (5:1) to give **2a** in 88% yield (9.0 g), mp 158 °C. IR (KBr) 3288, 1636, 1617, 1584, 1568, 1482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (**2a**, 83%) δ 7.18 (s, 1H, H-3), 7.52 (ddd, 1H, H-6, *J* = 8.0, 7.2, 1.0 Hz), 7.62 (dd, 1H, H-8, *J* = 8.6, 1.0 Hz), 7.81 (ddd, 1H, H-7, *J* = 8.6, 7.2, 1.7 Hz), 8.22 (dd, 1H, H-5, *J* = 8.0, 1.7 Hz); (**2′a**, 17%) δ 6.84 (s, 1H, H-3), 6.87 (s, 2H, 2OH), 7.45 (ddd, 1H, H-6, *J* = 8.0, 7.2, 1.0 Hz), 7.50 (d, 1H, H-8, *J* = 8.6 Hz), 7.71 (ddd, 1H, H-7, *J* = 8.6, 7.2, 1.7 Hz), 8.18 (dd, 1H, H-5, *J* = 8.0, 1.6 Hz); ^1H NMR (400 MHz, DMSO-d_6) (**2′a**, 100%) δ 6.64 (s, 1H, H-3), 7.54 (ddd, 1H, H-6, *J* = 8.0, 7.2, 1.0 Hz), 7.69 (dd, 1H, H-8, *J* = 8.5, 1.0 Hz), 7.86 (ddd, 1H, H-7, *J* = 8.5, 7.2, 1.7 Hz), 8.07 (dd, 1H, H-5, *J* = 8.0, 1.7 Hz), 8.37 (s, 2H, 2OH); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) (**2′a**, 100%) δ 80.84 (s, CF_3); MS (EI), *m/z* (%) 242 $[M]^+$ (100), 173 $[M-CF_3]^+$ (36), 145 $[M-COCF_3]^+$ (33), 101 (10), 92 (8), 89 (43), 69 $[CF_3]^+$ (8). Anal. Calcd for $C_{11}H_5F_3O_3{\cdot}H_2O$: C, 50.78; H, 2.71. Found: C, 50.76; H, 2.35.
11. Chizhov, D. L.; Sosnovskikh, V. Y.; Pryadeina, M. V.; Burgart, Y. V.; Saloutin, V. I.; Charushin, V. N. *Synlett* **2008**, 281.
12. (a) Greenhill, J. V.; Loghmani-Khouzani, H. *Tetrahedron* **1988**, *44*, 3319; (b) Greenhill, J. V.; Loghmani-Khouzani, H.; Maitland, D. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2831.
13. *6-Phenyl-3-(trifluoromethyl)pyridazin-4(1H)-one* (**16**): To a solution of furanone **11a** (350 mg, 1.43 mmol) in AcOH (5 mL) was added $N_2H_4{\cdot}2HCl$ (300 mg, 2.87 mmol). The reaction mixture was refluxed for 8 h, cooled, and diluted with water (15 mL). The solid was filtered, washed with water, and dried to give **16** in 81% yield (300 mg), mp 260–261 °C (sublimed). ^1H NMR (400 MHz, DMSO-d_6) (major tautomer, 95%) δ 6.96 (s, 1H, H-5), 7.57–7.66 (m, 3H, Ph), 7.78–7.84 (m, 2H, Ph), 14.07 (br s, 1H, NH); (minor tautomer, 5%) δ 7.08 (s, 1H, H-5), 7.43–7.55 (m, 3H, Ph), 7.87–7.90 (m, 2H, Ph), 14.48 (br s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) (major tautomer, 95%) δ 95.21 (s, CF_3), (minor tautomer, 5%) δ 97.30 (s, CF_3); ^{13}C NMR (100 MHz, DMSO-d_6) (major tautomer) δ 117.50, 121.09 (q, $^1J_{C,F}$ = 274.8 Hz), 127.45, 129.20, 130.20, 131.40, 142.72 (q, $^2J_{C,F}$ = 30.6 Hz), 152.42, 166.97.