Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 600

www.rsc.org/obc

PAPER

Synthesis of trifluoromethyl cyclohexyl, cyclohexenyl and aryl compounds *via* stepwise Robinson annulation†‡

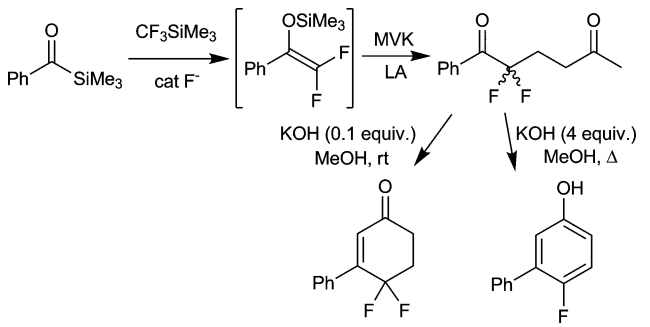
Fabien Massicot,[a] Alex Mor Iriarte,[a] Thierry Brigaud,[b] Aurélien Lebrun[a] and Charles Portella*[a]

Received 30th July 2010, Accepted 22nd September 2010
DOI: 10.1039/c0ob00518e

The diketone 2-fluoro-2-(trifluoromethyl)-1-phenylhexane-1,5-dione **3** was synthesized by a Mukaiyama Michael type reaction from the corresponding tetrafluoroenol silyl ether prepared from pentafluoropropiophenone. This diketone was treated under basic conditions and was converted, depending on the stoichiometry of the base, into the surprisingly stable ketol 4-fluoro-4-(trifluoromethyl)-3-hydroxy-3-phenylcyclohexanone **4** as a single diastereomer (catalytic KOH) or to the biphenylol 6-(trifluoromethyl)biphenyl-3-ol (excess KOH, THF) **5**. Solvolysis of the trifluoromethyl group (anionic activation) occurred using excess KOH in alcohol. The corresponding cyclohexenone derivative **7**, the usual product of Robinson annulation, might be prepared in good yield *via* mesylation of the ketol. Thus various unprecedented fluorinated cyclohexane and aromatic derivatives were achieved in a few steps from the commercially available pentafluoropropiophenone.

Introduction

Several years ago we reported the regioselective synthesis of fluorocyclohexenones and fluorophenols by a process beginning by Mukaiyama Michael reaction from difluoroenol silyl ether (Scheme 1).[1] The latter was generated *in situ* from acylsilane and trifluoromethyl(trimethyl)silane;[2] basic treatment of the intermediate 1,5-diketone yielded either of the cyclic products depending on the base concentration. Another feature of that work was the control of the regioselectivity, in case of aliphatic derivatives, by the effect of fluorine which activate enolate formation in its vicinity.[1] We considered that a similar methodology could apply to the trifluoromethyl (TFM) series, and would lead to substituted trifluoromethyl phenols as final products. To the best of our knowledge, 1,5-diketones have not been used so far as possible building blocks for their preparation.[3] TFM phenols and their derivatives are compounds of interest both as bioactive species and as synthetic intermediates. The emblematic compound containing a TFM phenoxy moiety is the well known antidepressant drug fluoxetine (Prozac®).[4] On the other hand, a TFM group in *ortho* or *para* position of phenols allows carboxylic functionalization through quinone methides, according to the anionically activation methodology.[5]



Scheme 1 Reported procedure for the synthesis of difluorocyclohexenones and fluorophenols.[1]

Results and discussion

Our attempt to prepare the requisite tetrafluoroenol silyl ether **2** from benzoylsilane and C_2F_5TMS, according to our method,[2] failed. Then we have applied the Mg-promoted reductive defluorinative-silylation of pentafluoropropiophenone **1** proposed by Uneyama.[6] Perfluoroalkyl phenones may be prepared using condensation of an organometallic reagent on a perfluorocarboxylic acid derivative.[7] The condensation of pentafluoroethyl lithium with an alkyl benzoate[8] was also reported to prepare phenone **1**. Inspired by the method consisting of addition of CF_3TMS onto an ester to prepare TFM ketones proposed by Prakash then Shreeve,[9] we have adapted the latter to prepare

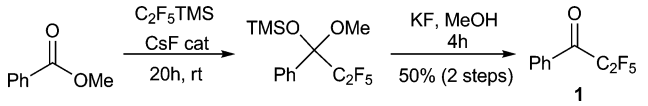
[a]*Université de Reims-Champagne-Ardenne, Institut de Chimie Moléculaire de Reims, UMR CNRS 6229, UFR Sciences, BP 1039, 51687, Reims cedex 2, France. E-mail: charles.portella@univ-reims.fr; Fax: +33 326 913166; Tel: +33 326 913234*

[b]*Current address: Université de Cergy-Pontoise, Laboratoire "Synthèse Organique Sélective et Chimie bioOrganique "(SOSCO), 5 Mail Gay-Lussac - Neuville sur Oise, 95031, Cergy-Pontoise cedex, France*

† This publication is part of the web themed issue on fluorine chemistry.

‡ Electronic supplementary information (ESI) available: ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra of **3**, **4**, **5** and **7**; HSQC ^{13}C-^1H, NOESY ^1H-^1H and HOESY ^{19}F-^1H NMR spectra of compound **4**. See DOI: 10.1039/c0ob00518e

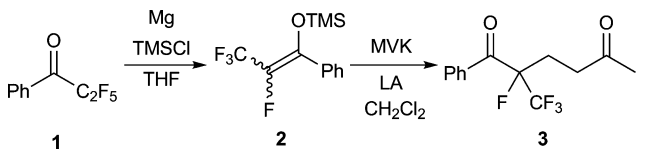
phenone **1**. We have found that it was possible to get **1** with a satisfactory overall yield from methyl benzoate and C_2F_5TMS by a solvent free procedure (addition step) and using potassium fluoride in methanol (desilylation step) (Scheme 2). In addition phenone **1** is also commercially available.



Scheme 2 Preparation of pentafluoropropiophenone **1**.

The procedure proposed by Uneyama gave quantitatively the desired tetrafluoroenol silyl ether **2**. Unfortunately the same procedure applied to an alkyl(pentafluoroethyl)ketone failed to give the corresponding enol silyl ether[10] so that the study was continued only with the phenone derivative.

Compound **2** was reacted with methyl(vinyl)ketone (MVK) under electrophilic activation (Scheme 3). Several conditions were tested, the results of which are reported in Table 1. Among the various Lewis acids considered, $BF_3{\cdot}OEt_2$ gave the diketone **3** with a satisfactory yield as long as an excess was used. Ytterbium triflate, which was a good catalyst for reaction with difuoroenol silyl ether,[1] gave poor results with the higher homologue. Trimethylsilyl triflate proved to be the best choice, since the highest yield of **3** was achieved using a catalytic amount.



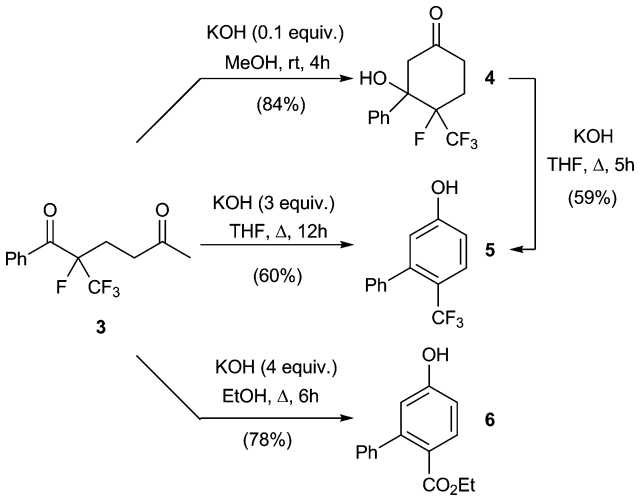
Scheme 3 Preparation of diketone **3**.

The diketone **3** was then reacted with base in various conditions (Scheme 4). Under catalytic conditions similar to the one applied to the difluoroanalogue,[1] **3** was converted to the cyclic ketol **4**, isolated as a stable product and as a single diastereomer (vide infra). Potassium hydroxide (0.1 equiv.) in MeOH gave the best results. Using an excess of potassium hydroxide, an aldol condensation–elimination sequence led directly to an aromatic compound, the nature of which depends strongly on solvent and temperature. The trifluoromethyl biphenylol **5** was obtained in a satisfactory yield in refluxing THF. In refluxing ethanol, **5** was unstable and the reaction led to the ethyl ester **6**, *via* anionic activation.[5,11]

Table 1 Optimization of the preparation of diketone **3**

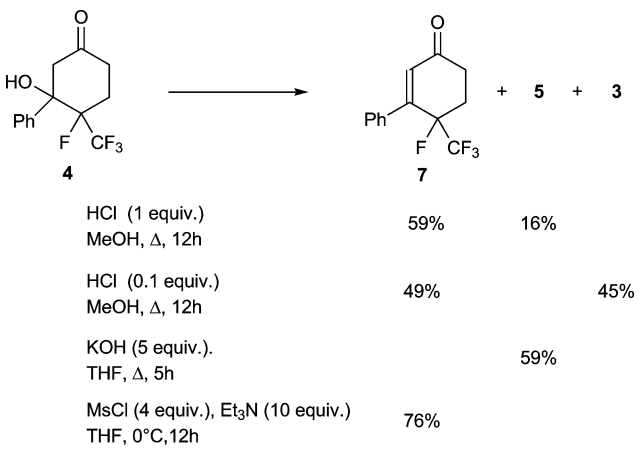
Lewis Acid	Equiv[a]	Temperature	Reaction time	Yield[b]
BF_3-Et_2O	2	–35 °C	12 h	60%
$Yb(OTf)_3$	0.5	rt	12 h	—
$TiCl_4$	1.8	–78 °C	7 h	29%
$BiCl_3$	0.5	rt	12 h	—
TMSOTf	1	0 °C	30 min	54%
TMSOTf	0.5	0 °C	30 min	71%
TMSOTf	0.2	0 °C	30 min	72%
TMSOTf	0.1	0 °C	60 min	61%

[a] Reactions realized with 2.5 mmol of **2** and 6 mmol of methylvinylketone in CH_2Cl_2. [b] Isolated yields.



Scheme 4 Reaction of diketone **2** with base.

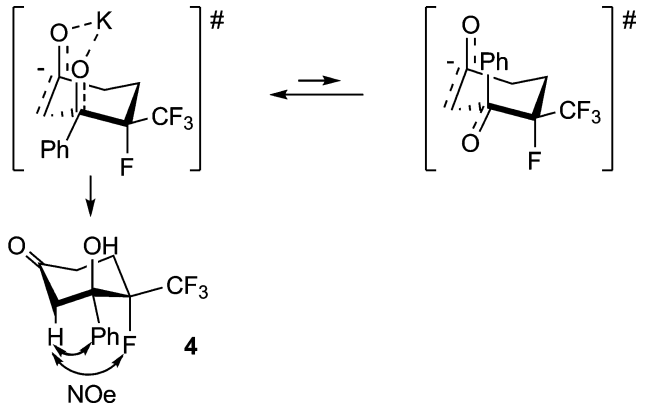
In contrast to the difluoroanalogue which under basic catalysis was directly converted to the cyclohexene derivative, the diketone **3** was converted into the stable ketol **4**. Several experiments were attempted to have access to the cyclohexene derivative **7** from **4** (Scheme 5).



Scheme 5 Reaction of the aldol **3** under various conditions.

Not surprisingly, treatment of **4** with excess potassium hydroxide in THF led to the phenol **5**. Dehydration was attempted under acidic conditions. Under catalytic conditions, the expected cyclohexenone **7** was obtained in 49% yield along with the precursory diketone **3** as a retroaldol product. Under stoichiometric conditions, the yield of **7** was improved (59%) but the reaction was difficult to stop at the cyclohexene stage. The best selectivity and yield (76%) were achieved using mesylation–elimination.

As mentionned above, the intramolecular aldol reaction was totally stereoselective. The structure of the ketol was tentatively deduced from NMR spectra analysis and correlation experiments (see Supplementary Information). According to this study, the reaction gave the diastereomer where the fluorine atom and the phenyl group are in *cis* relationship (Scheme 6). Such a stereochemistry is in accordance with a transition state where the trifluoromethyl and the phenyl groups are in equatorial position, minimizing the diaxial interactions. The unprecedented structure of compound **4** deserves a more detailed study of both structural



Scheme 6 Stereochemistry of ketol **4**.

and conformational aspects, in connection with its interesting NMR features (see ESI), which will be published shortly.

Conclusions

In summary, the three successive products of annulation may be prepared selectively from 2-fluoro-2-(trifluoromethyl)-1-phenylhexane-1,5-dione, applying well adapted reaction conditions. The very starting material of these transformations is pentafluoropropiophenone, converted quantitatively to the corresponding enol silyl ether. Thus fluorinated ketol **4**, bearing an uncommon geminal fluorine/trifluoromethyl motif, cyclohexenone **7** or the trifluoromethyl biphenylol **5** are prepared conveniently in a few steps from 1,1,1,2,2-pentafluoropropiophenone.

Experimental

1,1,1,2,2-Pentafluoropropiophenone (1)

To methyl benzoate (10 g, 73 mmol) were added under argon pentafluoroethyl trimethylsilane (14.4 g, 80.3 mmol, 1.1 equiv.) then caesium fluoride (661 mg, 4.38 mmol, 0.06 equiv.). After 12 h at rt, MeOH (50 mL) and potassium fluoride (8.47 g, 146 mmol, 2 equiv.) were added and the reaction mixture was stirred again during 4 h. The reaction was then concentrated under reduced pressure and the crude product was diluted in Et_2O. Mixture was washed with water and the combined aqueous layers extracted twice with Et_2O. Combined organic layers were finally washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by distillation (85 °C, 95 mBar) afforded **1** (8.2 g, 50%) as pale yellow oil which ^1H and ^{13}C NMR spectra were in agreement with litterature data.[8] δ_F (235.3 MHz; $CDCl_3$; $C(F)Cl_3$) 82.0 (3 F, s, CF_3), 115.9 (1 F, s, CF).

2-fluoro-2-(trifluoromethyl)-1-phenylhexane-1,5-dione (3)

To a solution of **2**[6] (1.39 g, 5 mmol) in CH_2Cl_2 (10 mL) was added, at 0 °C under argon, methylvinylketone (1 mL, 12 mmol, 2.4 equiv.) then trimethylsilyl trifluoromethanesulfonate (0.18 mL, 1 mmol, 0.2 equiv.). After 30 min. stirring, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by preparative centrifugal thin-layer chromatography (PE/EtOAc 95/5) afforded **3** (1.0 g, 72%) as pale yellow oil (Found: C, 56.6; H, 4.4. Calc. for $C_{13}H_{12}O_2F_4$: C, 56.5; H, 4.4%); δ_H (250 MHz; $CDCl_3$; Me_4Si) 2.1 (3 H, s, CH_3), 2.35–2.8 (4 H, m, 2 × CH_2), 7.5 (2 H, t, $^3J_{HH}$ 7.5, phenyl), 7.6 (1 H, t, $^3J_{HH}$ 7.25, phenyl), 8.0 (2 H, d, $^3J_{HH}$ 7.75, phenyl); δ_F (235.3 MHz; $CDCl_3$; $CFCl_3$) −76.9 (3 F, d, $^3J_{FF}$ 7, CF_3), −174.2 (1 F, m, CF); δ_C (62.9 MHz; $CDCl_3$; Me_4Si) 25.2 (d, $^2J_{CF}$ 20.6, CH_2), 28.7 (CH_3), 35.0 (d, $^3J_{CF}$ 2.6, CH_2), 98.1 (dq, $^1J_{CF}$ 203.6, $^2J_{CF}$ 29.7, CF), 120.8 (qd, $^1J_{CF}$ 286.1, $^2J_{CF}$ 28.5, CF_3), 127.6 (CH phenyl), 128.8 (2 x CH phenyl), 128.95 (2 x CH phenyl), 133.2 (C_{IV} phenyl), 192.4 (d, $^2J_{CF}$ 25.7, CO), 204.3 (CO).

4-fluoro-4-(trifluoromethyl)-3-hydroxy-3-phenylcyclohexanone (4)

To a solution of **3** (828 mg, 3 mmol) in methanol (20 mL) was added, under argon, potassium hydroxide (17 mg, 0.3 mmol, 0.1 equiv.). After 2 h at rt, the reaction was concentrated under reduced pressure and the crude product was diluted in AcOEt. Mixture was washed with a saturated aqueous solution of NH_4Cl and the combined aqueous layers extracted twice with AcOEt. Combined organic layers were finally washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by preparative centrifugal thin-layer chromatography (PE/EtOAc 94/6) and crystallization from AcOEt-PE afforded **4** (695 mg, 84%) as white crystals mp 110–111 °C (from EP/EtOAc); (Found: C, 56.7; H, 4.7. Calc. for $C_{13}H_{12}O_2F_4$: C, 56.5; H, 4.4%); δ_H (250 MHz; $CDCl_3$; Me_4Si) 2.4–2.8 (5 H, m, $CH_2CH_2C(O)CH_aH_b$), 3.5 (1 H, dd, $^2J_{HH}$ 14.8, $^4J_{HF}$ 3.6, C(O)CH_aH_b), 3.7 (1 H, br s, OH), 7.3–7.4 (3 H, m, phenyl), 7.5–7.55 (2 H, m, phenyl); δ_F (235.3 MHz; $CDCl_3$; $CFCl_3$) −74.3 (3 F, d, $^3J_{FF}$ 7, CF_3), −177.6 (1 F, dm, $^3J_{HF}$ 42.6, CF); δ_C (62.9 MHz; $CDCl_3$; Me_4Si) 26.6 (dq, $^2J_{CF}$ 20.2, $^3J_{CF}$ 1.4, CFCH_2), 34.8 (d, $^3J_{CF}$ 2.4, COCH_2), 51.9 (d, $^3J_{CF}$ 2.2, C(OH)CH_2), 77.9 (d, $^2J_{CF}$ 24.4, C(OH)), 94.5 (dq, $^1J_{CF}$ 190.5, $^2J_{CF}$ 28.9, CF), 123.0 (qd, $^1J_{CF}$ 286.6, $^2J_{CF}$ 28.9, CF_3), 125.3 (2 x CH phenyl), 125.4 (2 x CH phenyl), 128.3 (CH phenyl), 140.2 (C_{IV} phenyl), 207.9 (CO).

6-(trifluoromethyl)biphenyl-3-ol (5)

Method A. To a solution of **4** (276 mg, 1 mmol) in THF (10 mL) was added potassium hydroxyde (280 mg, 5 mmol, 5 equiv.). After 5 h at reflux, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted twice with AcOEt. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by preparative centrifugal thin-layer chromatography (PE/EtOAc 90/10) afforded **5** (140 mg, 59%) as a pale yellow oil.

Method B. To a solution of **3** (276 mg, 1 mmol) in THF (10 mL) was added potassium hydroxyde (168 mg, 3 mmol, 3 equiv.). After 12 h at reflux, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted twice with AcOEt. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by preparative centrifugal thin-layer chromatography (PE/EtOAc 90/10) afforded **5** (142 mg, 60%) as a pale yellow oil. δ_H (250 MHz; $CDCl_3$; Me_4Si) 5.6 (1 H, br s, OH), 6.75 (1 H, m, phenyl), 6.85–6.9 (1 H, m, phenyl), 7.3–7.4 (2 H, m, phenyl), 7.6 (1 H, m, phenyl); δ_F (235.3 MHz; $CDCl_3$; $CFCl_3$) −56.0 (3 F, s, CF_3); δ_C (62.9 MHz; $CDCl_3$; Me_4Si) 113.9 (CH phenyl),

118.8 (*C*H phenyl), 121.25 (q, $^{2}J_{CF}$ 30, *C*CF_3), 124.4 (q, $^{1}J_{CF}$ 272, *C*F_3), 127.6 (*C*H phenyl), 127.8 (*C*H phenyl), 128.2 (q, $^{3}J_{CF}$ 5.4, C(CF_3)*C*H), 128.8 (*C*H phenyl), 139.5 (C_{IV} phenyl), 143.6 (q, $^{3}J_{CF}$ 1.6, *C*(Ph)C(CF_3)), 157.5 (*C*(OH)); HRMS (ESI-) Calcd for $[C_{13}H_9F_3O - H]^-$: 237.0527; found: 237.0535.

4-fluoro-4-(trifluoromethyl)-3-phenylcyclohex-2-enone (7)

Method A. To a solution of **4** (276 mg, 1 mmol) in THF (10 mL) was added, at 0 °C under argon triethylamine (1.01 g, 10 mmol, 10 equiv.) then methanesulfonyl chloride (572 mg, 5 mmol, 5 equiv.). After 12 h the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted twice with AcOEt. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by preparative centrifugal thin-layer chromatography (PE/EtOAc 95/5) afforded **7** (196 mg, 76%) as a pale yellow oil.

Method B. To methanol (20 mL) cooled down to 0 °C under argon was added slowly acetyl chloride (80 mg, 1 mmol). The mixture was warmed up to rt, **4** (276 mg, 1 mmol, 1 equiv.) in methanol (5 mL) was added and the mixture was heated 12 h at reflux. The reaction was then concentrated under reduced pressure and the residue diluted in AcOEt. Mixture was washed with a saturated aqueous solution of Na_2CO_3 and the combined aqueous layers extracted twice with AcOEt. Combined organic layers were finally washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by preparative centrifugal thin-layer chromatography (PE/EtOAc 95/5) afford **7** (152 mg, 59%) and **5** (38 mg, 16%) as two pales yellow oils. δ_H (250 MHz; $CDCl_3$; Me_4Si) 2.55–2.7 (4 H, m, 2 × CH_2), 6.2 (1 H, s, C*H*), 7.3 (5 H, m, phenyl); δ_F (235.3 MHz; $CDCl_3$; $CFCl_3$) −76.5 (3 F, d, $^{3}J_{FF}$ 10, C*F*$_3$), −163.8 (1 F, m, C*F*); δ_C (62.9 MHz; $CDCl_3$; Me_4Si) 29.2 (d, $^{2}J_{CF}$ 22.5, CF*C*H_2), 32.5 (d, $^{3}J_{CF}$ 9.1, CFCH$_2$*C*H_2), 91.4 (dq, $^{1}J_{CF}$ 188.6, $^{2}J_{CF}$ 31.8, *C*F), 122.9 (qd, $^{1}J_{CF}$ 286.8, $^{2}J_{CF}$ 31.0, *C*F_3), 128.3 (*C*H phenyl), 128.4 (d, $^{4}J_{CF}$ 3.0, *C*H phenyl), 129.7 (*C*H phenyl), 134.1 (d, $^{3}J_{CF}$ = 5.7 Hz, *C*H), 135.1 (C_{IV} phenyl), 151.5 (d, $^{2}J_{CF}$ = 18.5 Hz, *C*(Ph)), 195.5 (d, $^{4}J_{CF}$ = 2.7 Hz, *C*O); HRMS (EI+) Calcd for $[C_{13}H_{10}F_4O]^+$: 258.0668; found: 258.0652.

Acknowledgements

We are grateful to CNRS, Université de Reims Champagne-Ardenne and Erasmus programme (AMI) for supporting this research. We also thank Dominique Harakat for Mass Spectrometry analysis and Sylvie Lanthony for elemental analyses.

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