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A New and Efficient Synthesis of Trifluoroalkyl Aldehydes or Ketones from the Same Starting Material

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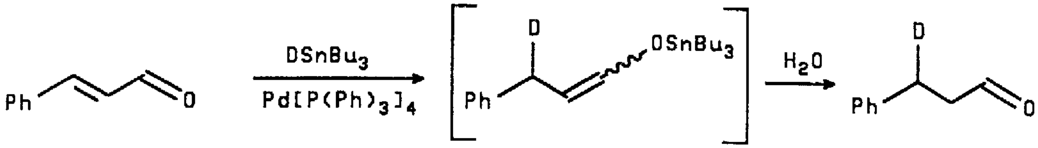
Abstracts : 4,4,4-Trifluoroacroleines **2** have been converted specifically by tributyl tin hydride to aldehydes **3** or ketones **4**, according to the catalyst and conditions employed.

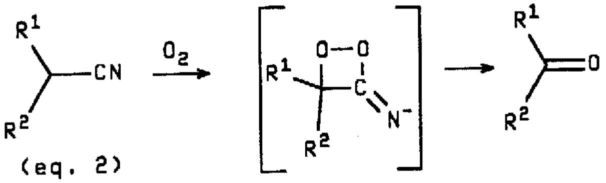
Several synthetic reactions are known for the preparation of 1,1,1-trifluoromethylketones **1**.[1] On the other hand, compounds **3** and **4** with one or two methylene or methine groups built in between the trifluoromethyl and the carbonyl groups are not easy to prepare.[2] These compounds are of biological interest, as the trifluoromethyl group increases extensively their lipophilicity without disturbing the biological and chemical reactivity since it is far enough from the functional group. In the present study, we want to describe the synthesis of trifluoromethyl aldehydes **3** and ketones **4** from the same starting material **2** easily obtained through a Vilsmeier's reaction with trifluoromethylketones **1a,b**[5] (scheme).

Guibé[7] and Keinan[8] have found that tributyl tin hydride serves as an efficient hydride donor to π-allyl palladium complexes. They suggested that an analogous transfer of hydride to activated olefin-palladium complexes followed by concomitant protonation, should result in net conjugate reduction of Michael acceptors (eq. 1).

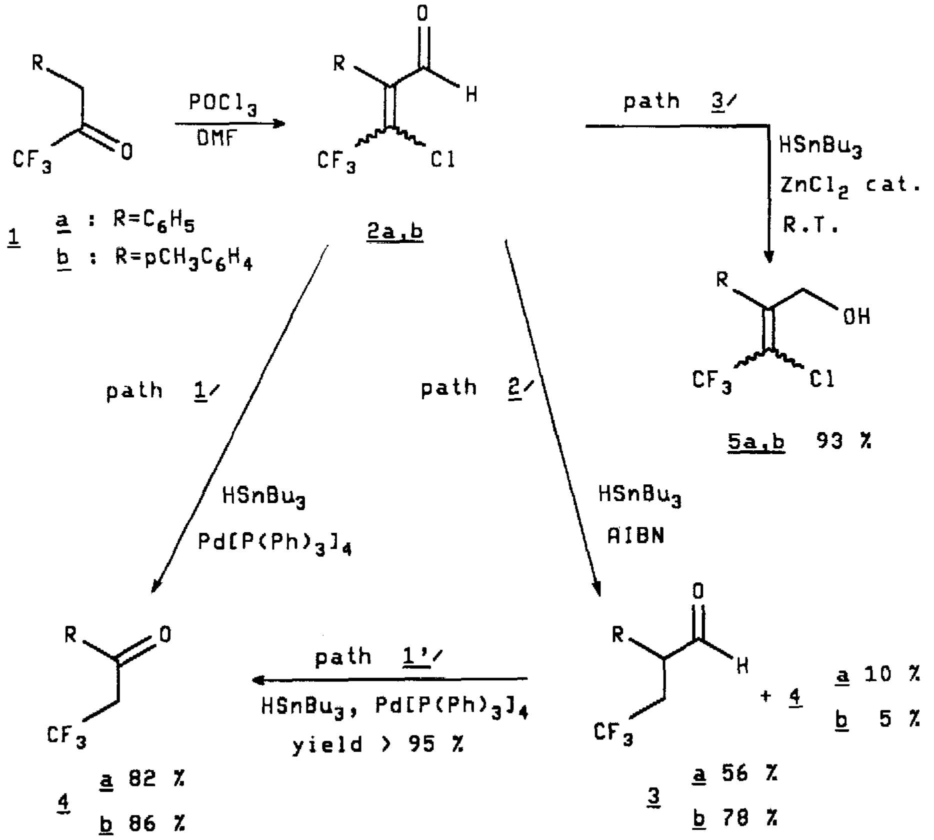


(eq. 1)

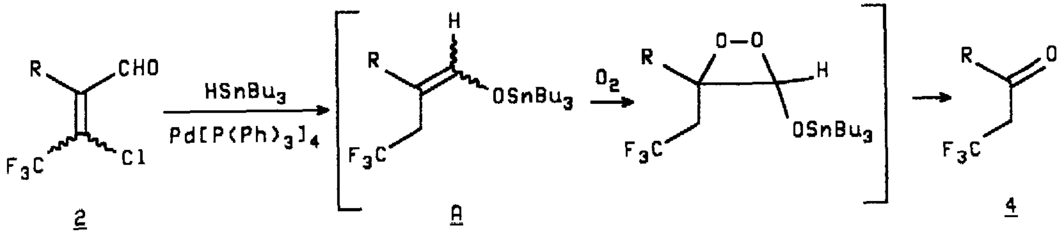
On the other hand Donetti *et al.*[9] have shown that α,α-disubstituted nitriles can be transformed to ketones in basic medium by oxidative decyanation (eq. 2).



(eq. 2)

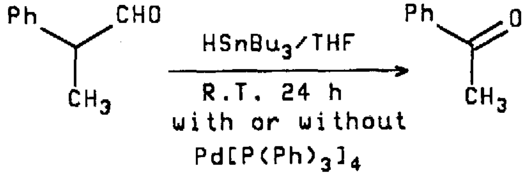


So, it should be possible to transform aldehydes **2** to ketones **4** in a one-pot reaction by treating **2** with tributyl tin hydride in the presence of palladium and oxygen (eq. 3).



(eq. 3)

To test the possibility of oxidizing stannyl enolate intermediate **A** with air oxygen, we have made the reaction of hydratropic aldehyde **6** with tributyl tin hydride (in the presence as well as in the absence of palladium) and air.[10] In these conditions, aldehyde **6** was quantitatively transformed to acetophenone (eq. 4).

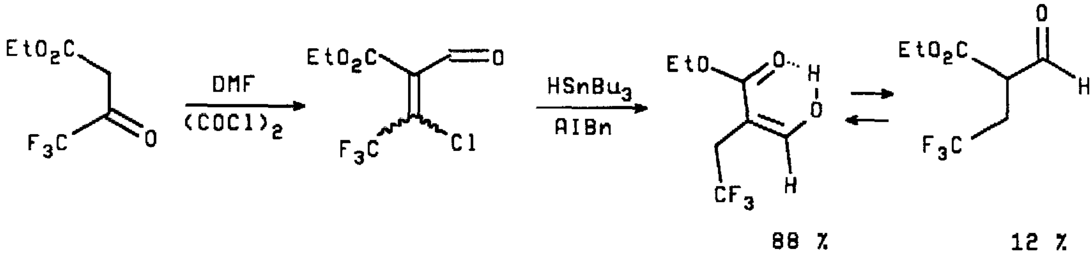


(eq. 4) 6

Aldehydes **2a,b** (scheme) were treated with tributyl tin hydride in the presence of $Pd[P(Ph)_3]_4$ under Guibé[7] or Keinan's[8] conditions, but the reaction was carried out in the presence of air and with continuous stirring for 24 h.[10] Under these conditions, aldehydes **2a,b** were converted into ketones **4a,b** in more than 80 % yield of isolated product.[11] So, it is possible to transform trifluoromethylketones **1a,b** in their regioisomers **4a,b** in a two-step reaction.

To prove the formation of stannyl intermediate **A**, aldehydes **2a,b** were treated with tributyl tin hydride, in the presence of AIBN ; and indeed aldehydes **3a,b** were isolated in, respectively, 56 % and 78 %[12] yields of purified product. Treating aldehydes **3a,b** with tributyl tin hydride in the presence of $Pd[P(Ph)_3]_4$ formed quantitatively ketones **4a,b**[13] (yield > 95 % of purified product).

When the aldehyde **2c**, obtained from ethyl 4,4,4-trifluoroacetoacetate,[6] was treated by tributyl tin hydride, in the presence of AIBN,[12] saturated aldehyde **3c** was obtained in a 91 % yield.[14] **3c** exists mainly as the enolic form (88 %). As in the ^1H NMR spectrum there is coupling between the vinylic proton and the enolic proton, it is assumed that the enolic form of compound **3c** exists in the *cis*-configuration, stabilized by intramolecular hydrogen bonding (eq. 5).



(eq. 5) 2c

3c 91 %

It is known[15] that the formation of tin alkoxides, from ketones or aldehydes, by a radical mechanism is rather sluggish, whereas their preparation by a polar mechanism can efficiently by carried out by Lewis acid catalysts.[7] Effectively, in THF solution containing a catalytic amount of $ZnCl_2$, tributyl tin hydride reduces **2a,b** to the allylic alcohol **5a,b** in a nearly quantitative yield.[16] No reduction of the double bond and no elimination of the chlorine is observed. The 1,2 addition is specifically observed (scheme, path 3/).

So from the same starting material, aldehyde **2** and tributyl tin hydride, it is possible to realize regioselectively a 1,2 or a 1,4 addition (path 2/ or 3/) or the transformation of **2** in the ketones **4** (path 1/).

REFERENCES AND NOTES

1 J.P. Bégué and D. Bonnet-Delpon, Tetrahedron, 1991, **47**, 3207.

2 For example, recently **4a** was described by Hojo[3] and Shono.[4]

3 Y. Kamitori, M. Hojo, R. Masuda, S. Ohara, Y. Kawamura and T. Ebisu, Synthesis, 1989, 43.

4 T. Shono, N. Kise and H. Oka, Tetrahedron Lett., 1991, **32**, 6567.

5 Ketone **1b** was obtained by the reaction $CH_3C_6H_4CH_2MgBr$ with CF_3CO_2Et at -70°. Distil. at 50°C/0.4 torr and recryst. from light petroleum. Yield 23 %, m.p. 48-49°C. IR : 1780 $\nu_{C=O}$. ^1H NMR : $\delta_{CH3}=2.35$, $\delta_{CH2}=3.93$, $\delta_{C6H4}=7.13$, $\phi=-79{,}0$. **2a,b** experimental procedure : $POCl_3$ (155 mmol), DMF (284 mmol) **1a,b** (53 mmol) stirring 3 h at 65°C ; work up with water and AcONa. **2a**, ref[6]. **2b** (81 %) Distil. at 68°/0.4 torr ; Z/E = 55/45 ; IR (Z/E) : 1695 $\nu_{C=O}$. ^1H NMR **2bZ** : $\delta_{CHO}=10.50$, $\delta_{CH3}=2.40$; $\phi=-62.0$, $J_{F,CHO}=0$. ^{13}C NMR : $\delta_{CHO}=189.9$, $J_{F,CHO}=0$. MS m/z : 248 (100 %). **2bE** ^1H NMR : $\delta_{CHO}=10.30$, $\delta_{CH3}=2.40$; $\phi=-58.0$, $J_{FCHO}=2$ Hz. ^{13}C NMR : $\delta_{CHO}=187.04$, $J_{F,CHO}=4$ Hz. MS m/z : 248 (100 %).

6 G. Alvernhe, B. Langlois, A. Laurent, I. Le Dréan, A. Selmi and M. Weissenfels, Tetrahedron Lett., 1991, **32**, 643.

7 P. Four and F. Guibé, Tetrahedron Lett., 1982, **23**, 1825.
Y. Ting Xian, P. Four, F. Guibé and G. Balavoine, Nouveau Journal de Chimie, 1984, **8**, 611.

8 E. Keinan and P. Gleize, Tetrahedron Lett., 1982, **23**, 477.

9 A. Donetti, O. Boniardi and A. Ezhaya, Synthesis, 1980, **12**, 1009.

10 To the solution of 1 mmol of **2** or **6**, in 5 ml of THF containing 0.03 mmol $Pd[P(Ph)_3]_4$, 4 mmol of $HSnBu_3$ was added in one portion. The mixture was stirred for 24 h at a room temperature. The solvent removed on vacuum and the residue was filtrated through silica. Eluation with light petroleum allows to isolate the majority of tin derivatives. Carbonyl compounds were eluated with mixture light petroleum-ethyl ether 8:2. These compounds were purified by Kügelrohr distillation.

11 **4a** (82 % isolated compound) previously described in ref.[3] **4b** (86 % isolated compound). Kügelrohr distillation under 110°/4 torr and recristal. from light petroleum. M.p. 48-48.5°. IR : 1690 $\nu_{C=O}$, 1130 ν_{CF3}. ^1H NMR : $\delta=2.40$ (s, 3H) ; 3.73 (q, $^3J_{HF}=11$ Hz, 2H) ; 7.20-7.46 (m, 2H) ; 7.74-8.0 (m, 2H) ; $\phi=-62.7$ ($^3J_{HF}=11$ Hz). ^{13}C NMR : $\delta=21.69$ (s, $\underline{C}H_3$) ; 42.06 (q, $^2J_{CF}=28.2$ Hz, $\underline{C}H_2$) ; 124.16 (q, $^1J_{CF}=276.9$ Hz, $\underline{C}F_3$) ; 128.58 and 129.67 (s, Co,m) ;133.56 and 145.34 (s, 2Cq) ; 189.28 (q, $^3J_{CF}=2.4$ Hz, $\underline{C}O$). MS m/z : 202, 119 (100 %), 91, 65, 63, 51, 39.

12 To 1 mmol of **2** in 5 ml of benzene, containing catalytic amount of AIBN, 4 mmol of $HSnBu_3$ was added. Refluxed for 0.5 h, the same work-up as in ref.[10] **3a** (56 % isolated compound) Kügelrohr distillation under 78°/4 torr. IR : 1725 $\nu_{C=O}$; 1260, 1135 ν_{CF3}. ^1H NMR : $\delta=2.26$-2.53 (m, 1H) ; 2.99-3.25 (m, 1H) ; 3.90 (t, l, J=6.5 Hz, 1H) ; 7.15-7.44 (m, 5H) ; 9.59 (d, J=0.5 Hz, 1H) ; $\phi=-65.3$ ($J_{HF}=12$ Hz). ^{13}C NMR : $\delta=33.60$ (q, $^2J_{CF}=29$ Hz, $\underline{C}H_2$) ; 52.70 (q, $^3J_{CF}=2.2$ Hz, $\underline{C}H$) ; 126.45 (q, $^1J_{CF}=276.7$ Hz, $\underline{C}F_3$) ; 128.49 (s, Cq) ; 128.91 and 129.56 (s, Co,m) ; 133.99 (s, Cq) ; 196.35 (s, $\underline{C}O$). MS m/z : 202, 174, 173, 151, 133, 109, 86, 84, 77, 63, 61, 57, 52, 51, 50, 49 (100 %), 47, 45, 44, 43, 42. **3b** (78 % isolated compound) Kügelrohr distillation under 120°/4 torr and TLC purification. IR : 1720 $\nu_{C=O}$, 1250, 1140 ν_{CF3}. ^1H NMR : $\delta=2.29$-2.45 (m, 1H) ; 2.34 (s, 3H) ; 3.02-3.45 (m, 1H) ; 3.86 (t, l, J=6 Hz, 1H) ; 7.03-7.23 (m, 4H) ; 9.56 (s, 1H) ; $\phi=-65.0$ ($J_{HF}=11$ Hz). ^{13}C NMR : $\delta=21.08$ (s, $\underline{C}H_3$) ; 33.60 (q, $^2J_{CF}=28.9$ Hz, $\underline{C}H_2$) ; 52.33 (q, $^3J_{CF}=2.2$ Hz, $\underline{C}H$) ; 126.54 (q, $^1J_{CF}=276.7$ Hz, $\underline{C}F_3$) ; 128.80 and 130.28 (s, Co,m) ; 130.89 and 138.41 (s, 2Cq) ; 196.48 (s, $\underline{C}O$). MS m/z : 216, 188, 187, 123 (100 %), 117, 115, 105, 91, 77, 65, 63, 51, 39.

13 The same method as in the ref.[10], using only 2 mmol of $HSnBu_3$.

14 **3c** (91 % isolated compound) Kügelrohr distillation under 95°/10 torr. IR : 3300 ν_{OH}, 1700, 1660 $\nu_{C=O}$, 1615 $\nu_{C=C}$, 1210, 1140 ν_{CF3}. Enolic form : ^1H NMR : $\delta=1.32$ (t, J=7 Hz, 3H) ; 2.92 (q, J=10 Hz, 2H) ; 4.29 (q, J=7 Hz, 2H) ; 7.22 (d, l, J=13 Hz, 1H) ; 11.96 (d, l, J=13 Hz, 1H) ; $\phi=-68.3$ (t, $J_{HF}=$ 10 Hz). ^{13}C NMR : $\delta=14.16$ (s, CH_3) ; 31.69 (q, $^2J_{CF}=31.4$ Hz, $\underline{C}H_2$) ; 61.27 (s, $\underline{C}H_2$) ; 95.61 (q, $^3J_{CF}=3.2$ Hz, Cq) ; 125.88 (q, $^1J_{CF}=276.8$ Hz, CF_3) ; 165.53 (s, $\underline{C}H$). MS m/z : 198, 170, 153, 142, 132, 124, 105, 83, 69, 55, 45, 39, 29 (100 %), 27. Keto-form : ^1H NMR : $\delta_{C\underline{H}O}=9.80$. ^{13}C NMR : $\delta_{CHO}=192.76$.

15 W.P. Neumann, Synthesis, 1987, 665.

16 To the solution of 1 mmol of **2a,b** in 5 ml of THF, containing catalytic amount of $ZnCl_2$, 1.1 mmol of $HSnBu_3$ was added. Stirred for 10 min. Classical work-up and chromatographic purification, elution light petroleum-ethyl ether 95:5. Quantitative yield. **5a Z/E.** IR : 3350 ν_{OH}, 1630 $\nu_{C=C}$, 1180, 1140 ν_{CF3}. ^1H NMR : $\delta=2.03$ (s, l, 1H) ; 4.45 (m, 2H) ; 7.00-7.41 (m, 5H) ; $\phi=-59.5$ and -60.3. **5b Z/E.** IR : 3330 ν_{OH}, 1180, 1140 ν_{CF3}. ^1H NMR : $\delta=2.37$ (s, 3H) ; 2.43 (s, l, 1H) ; 4.50 (m, 2H) ; 7.00-7.36 (m, 4H) ; $\phi=-59.5$ and -60.6. MS m/z : 251, 250, 235, 215, 199, 197, 196, 195 (100 %), 184, 183, 182, 165, 164, 157, 147, 133, 123, 119, 115, 105, 92, 91, 77, 65, 63, 51, 39, 31.

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