Novel and Convenient Aldolization of Methyl 3,3,3-Trifluoropyruvate Using Enamines Instead of Ketones

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Abstract: Piperidine enamines derived from acetone, acetophenone, cyclopentanone and cyclohexanone react easily in minutes with methyl 3,3,3-trifluoropyruvate (1) to afford products of the aldol condensation in high yields at room temperature, which is in contrast to the direct aldolization of 1 with the ketones.

Key words: piperidines, nucleophilic additions, ketones, ene reactions, aldol reactions

Esters of 3,3,3-trifluoropyruvic acid have become valuable building blocks in organic chemistry.1 The aldols of methyl trifluoropyruvate2 (MeTFP, 1) can be employed in a stereoselective synthesis of analogues of the alkaloid peganine.1d,3 Some of the aldols of trifluoropyruvate have been reported4 to be prepared by a direct aldol condensation. The reactions took place within 1–2 weeks at room temperature or several hours at 100 °C. We report in this paper a novel method by which the desired aldols 7–10 can easily be prepared by the reaction of 1 with piperidine enamines of ketones.

Enamines are usually prepared by an acid catalysed reaction of aldehydes or ketones with secondary amines.5 p-Toluenesulfonic acid5,6 or titanium tetrachloride5,7 have frequently been used as catalysts. In particular cases, the formation of enamines took place in the absence of a catalyst.8 For the preparation of piperidine enamines we applied a modified methodology previously reported7a using titanium tetrachloride5 as a catalyst. Cyclopentanone, cyclohexanone and acetophenone afforded the corresponding enamines 2–4 in 78–84% yield (Scheme 1). The enamine formation from acetone was not successful using this method. Therefore we applied a two-step synthesis according to the literature.9

The reactions of enamines with non-halogenated aldehydes and ketones are usually promoted by Lewis acid-type catalysts.10 The corresponding aldol intermediates formed in these reactions could not be isolated and sometimes dehydration occurred to afford alkyldiene ketones.10 The use of piperidine enamines gave much lower yields than the use of morpholine enamines, while pyrrolidine enamines failed to react.10

With respect to the above observations,10 we applied easy accessible and medium reactive10 piperidine enamines to test their reactivity towards methyl 3,3,3-trifluoropyruvate (1). We have found that the reactions proceeded very easily at room temperatures under an inert atmosphere without a catalyst. The reactions were usually finished in several minutes as checked by 19F NMR. Subsequent stirring of the reaction mixtures did not result in any changes (check by 19F NMR). Pure aldols 7–10 were obtained by column chromatography in yields of 76–89% (Scheme 2) (Table 1), which are higher yields than those obtained by 7 or 14 day reactions.4,11 The stereoselectivity of the formation of aldols 7 and 8 measured as the ratio of diastereoisomers has been better for our method than previously reported4,11 for the direct aldolization. Unfortunately, we were not successful in determining the relative configurations by NMR methods or by the transformation of the major diastereoisomer of the product 7 to the corresponding 3,5-dinitrobenzoate (11), which appeared to be a non-crystalline compound.

The hydrate of methyl 3,3,3-trifluoropyruvate (12) is easily formed by the reaction of trifluoropyruvate 1 with moisture. It is a very stable compound resistant to complete dehydration even using phosphorus pentoxide.2 Therefore it could be expected to exhibit low reactivity.
in the aldol condensation. We observed that the hydrate 12 did not react with cyclohexanone or acetone under the conditions previously applied.4,11 Surprisingly, the hydrate reacted with acetone enamine 6 to afford the aldol 10. This result is of practical importance because trifluoropyruvate 1 usually contains 2–5% of the hydrate 12, which can be now involved in the aldol reaction as well.

The temperature data were not corrected. Distillations of high boiling compounds were carried out on a Vacuubrand RCS high vacuum oil pump. Column chromatography: column 50 cm; d, 2.5 cm. NMR spectra were recorded on a Bruker 400 AM (FT, 19F at 376.6 MHz), Varian Gemini 300 HC (FT, 1H at 300.07 MHz, 13C at 75.46 MHz) instruments: TMS and CFCl3 as the internal standards, chemical shifts in ppm (s singlet, d doublet, t triplet, q quadruplet, m multiplet), coupling constants J in Hz, solvent CDCl3 and DMSO-d6. MS spectra were scanned on a Hewlett–Packard MSD 5971A instrument (1989, EI 70 eV).

Chemicals used were as follows. Methyl 3,3,3-trifluoropyruvate (1) was prepared from hexafluoropropene-1,2-oxide according to our procedure.2,3,11 Silica gel (60–100 μm, Merck); cyclopentanone, cyclohexanone, acetonophenone, piperidine, DMAP and acetone cyanohydrin (all from Aldrich); acetone, titanium(IV) chloride, 3,5-dinitrobenzoyl chloride (Lachema Brno). Reagents were prepared as follows: t-BuOK (prepared by dissolving potassium in anhyd t-BuOH, removing the alcohol and drying at r.t./0.2 mmHg), benzene (distilled over Na, bp 80 °C), pentane (distilled over Na, bp 35–36 °C), CHCl3 (distilled over P 2O5, bp 61 °C), hexane (distilled over CaCl2, bp 69 °C), CH2Cl2 (distilled, bp 42 °C) (Lachema Brno).

**Enamines 2–4 and 6; General Procedure for 2–4**

The reactions were carried out under argon. A three-necked flask containing a magnetic spinbar was charged with anhyd pentane, ketone and piperidine. The mixture was stirred at r.t. for 1 h, then was cooled to 0 °C and a solution of titanium tetrachloride in pentane was added dropwise over 30 min. The mixture was stirred for 1 h, then allowed to warm to r.t. and stirred for another 5 h. The liquid part of the mixture was filtered off by an immersion-type glass filter under argon. Solvent and volatile components were removed by distillation. Pure enamines 2–4 were obtained by distillations of the crude products under vacuum. The enamine of acetone 6 was not formed by this procedure.

1-(Cyclopent-1-en-1-yl)piperidine (2)

Enamine 2 was formed from cyclopentanone (3 g, 35.7 mmol), piperidine (9.11 g, 107 mmol), TiCl4 (3.38 g, 17.8 mmol), and pentane (150 mL).

Yield: 4.51 g (83.6%); bp 58–59 °C/1 mmHg (Lit.12 41 °C/0.7 mmHg; Lit.13 58–59 °C/0.9 mmHg).

1H NMR (CDCl3): \(\delta = 1.52–1.62 (m, 6 H, CH2), 1.79–1.86 (m, 2 H, CH2), 2.26–2.42 (m, 4 H, CH2), 2.81–2.89 (m, 4 H, CH2), 4.32 (s, 1 H, CH).

13C NMR (CDCl3): \(\delta = 22.5 (CH2), 24.2 (CH2), 25.6 (2 CH2), 30.4 (CH2), 32.0 (CH2), 49.6 (2 CH2), 96.9 (CH), 151.9 (CN).

1-(Cyclohex-1-en-1-yl)piperidine (3)

Enamine 3 was formed from cyclohexanone (3 g, 30.6 mmol), piperidine (7.81 g, 91.7 mmol), TiCl4 (2.9 g, 15.3 mmol), and pentane (150 mL).

Yield: 4.25 g (84.2%); bp 90–92 °C/1 mmHg (Lit.14 92 °C/1 mmHg; Lit.15 71–73 °C/0.9 mmHg).

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Table 1 Preparation of Aldols 7–10 from Enamines 2–4, 6 and MeTFP (1)

<table>
<thead>
<tr>
<th>Starting enamine</th>
<th>Aldols 7–10</th>
<th>Yield (%)</th>
<th>dr</th>
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<tr>
<td>2 CH3CH2CH2</td>
<td>7</td>
<td>81, 77:23</td>
<td>ab</td>
</tr>
<tr>
<td>3 CH3CH2CH2CH3</td>
<td>8</td>
<td>82, 74:26</td>
<td>c</td>
</tr>
<tr>
<td>4 H, Ph</td>
<td>9</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>6 H, Me</td>
<td>10</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

*Ref.4 ratio 64:36.

*Ref.11 ratio 70:30.

*Ref.4 ratio 62:28.

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1H NMR (CDCl3): δ = 1.41–1.72 (m, 10 H, CH2), 1.96–2.11 (m, 4 H, CH2), 2.68–2.79 (m, 4 H, CH2), 4.64 (t, 1 H, JHH = 3.3 Hz, CH). 13C NMR (CDCl3): δ = 22.9 (CH2), 23.5 (2 CH2), 24.6 (2 CH2), 26.0 (CH2), 27.7 (CH2), 49.0 (2 CH2), 100.0 (CH), 146.1 (CN). 1-1(Phenylethenyl-1-yl)piperidine (4) Enamine 4 was formed from acetophenone (3 g, 24.9 mmol), piperidine (6.38 g, 74.9 mmol), TiCl4 (2.37 g, 12.5 mmol), pentane 150 mL.

Yield: 3.67 g (78.5%); bp 96–99 °C/0.6–0.8 mmHg; Lit.9b 93–94 °C/14 mmHg).

Methyl 2-Hydroxy-2-(2-oxocyclohexyl)-3,3-trifluoro propanoate (8) Product 8 was formed from enamine 3 (0.68 g, 4.11 mmol), MeTFP (I) (0.64 g, 4.11 mmol), and CH2Cl2 (60 mL), and purified by column chromatography (silica gel, 50 g).

Yield: 0.86 g (82.3%); diastereoisomeric ratio 74:26; mp 57–59 °C (Lit.3 mp 57–59 °C).

1H NMR (CDCl3): diastereoisomer A, δ = 1.56–2.48 (m, 8 H, CH2CH2CH2CH2), 3.25 (dd, 1 H, JHH = 6.1, JHH = 12.4 Hz, CH), 3.76 (s, 3 H, COOCH3), 4.02 (s, 1 H, OH); diastereoisomer B, δ = 1.56–2.48 (m, 8 H, CH2CH2CH2CH2), 3.02 (dd, 1 H, JHH = 6.1, JHH = 12.4 Hz, CH), 3.98 (s, 3 H, COOCH3), 5.11 (s, 1 H, OH).

13C NMR (CDCl3): diastereoisomer A, δ = 22.9 (CH2), 26.1 (CH2), 26.1 (2 CH2), 48.2 (CH2), 56.3 (CCN), 120.3 (CCN). 1-Propene-2-yl)piperidine (6) Under argon, a flask (250 mL) with magnetic spinbar was charged with piperidine (11.2 g, 91.6 mmol) and the mixture was stirred at r.t. for 30 min. The flask was then equipped with a Dimroth reflux condenser and the mixture was refluxed for 14 h. The liquid part of the mixture was filtered off by an immersion chromatography (silica gel 1:60/100, CHCl3) and finally by crystallization (hexane).
Yield: 1.17 g (76.1%); mp 61–63 °C (Lit.411 mp 61–63 °C).

1H NMR (CDCl3): δ = 2.17 (3, s, 3 H, CH2), 3.11 (d, 1 H, 1JHH = 17.6 Hz, CH3), 3.21 (d, 1 H, 1JHH = 17.6 Hz, CH3), 3.88 (s, 3 H, COOCH3), 4.11 (s, 1 H, OH).

13C NMR (CDCl3): δ = 30.3 (CH3), 44.8 (CH3), 54.0 (COOCH3), 78.9 (q, 1JCF = 30.3 Hz, CF3), 122.9 (q, 1JCF = 285.5 Hz, CF3), 169.1 (COOCH3), 203.51 (C=O).

19F NMR (CDCl3): δ = –79.7 (s, CF3).

Methyl 2-(3,5-Dinitrobenzoyloxy)-2-(2-oxocyclopentyl)-3,3,3-trifluoropropanoate (11) (11)
A mixture of aldol 7 (0.38 g, 1.5 mmol), 3,5-dinitrobenzoyl chloride (1.04 g, 4.5 mmol), pyridine (0.35 g, 4.5 mmol), DMAP (0.18 g, 1.5 mmol) and 1,2-dichlorethane (50 mL) was refluxed overnight (check by 19F NMR). Column chromatography of the crude product (silica gel, 50 g; CH2Cl2) afforded a fraction of waxy pure major diastereoisomer 11a of the product 11 (70 mg, 10.4%). Several attempts to obtain crystalline 11a using various solvents were unsuccessful.

Diastereoisomer 11a
1H NMR (CDCl3): δ = 2.75 (m, 3 H, CH2CH2CH2), 3.04 (m, 3 H, CH2CH2CH2), 3.57 (s, 3 H, COOCH3), 6.65 (m, 1 H, CH), 9.18 (d, JHH = 17.6 Hz, CH3), 9.73 (d, JHH = 17.6 Hz, CH3), 12.87 (s, 1 H, OH).

13C NMR (CDCl3): δ = 27.3 (CH3), 123.1 (CH), 129.7 (Ph), 132.5 (Ph), 137.1 (Ph), 148.8 (Ph), 159.9 (OCOPh), 163.9 (COOCH3), 214.7 (C=O) (the signal of CF3 was not observed in the spectrum).

19F NMR (CDCl3): δ = –60.0 (s, CF3).

MS (EI): m/z (%) = 416 (4) [M+ – 59], 385 (5), 359 (4), 281 (4), 235 (9), 221 (23), 205 (32), 195 (100), 199 (25), 179 (9), 165 (62), 149 (34), 133 (9), 103 (21), 91 (12), 75 (25), 63 (22).

Calcd for C16H12F3NO6: C: 44.24, H: 3.02, N: 6.45. Found: C: 44.89, H: 3.12, N: 6.97.

Minor Diastereoisomer 11b
19F NMR (376.6 MHz, CDCl3): δ = –59.5 (s, CF3).

Methyl 3,3,3-Trifluoro-2,2-dihydroxypropanoate (12)
Under argon, a dry flask (100 mL) equipped with septum and magnetic spinbar was charged with CH2Cl2 (50 mL), MeTFP (1) (0.78 g, 5.01 mmol) and subsequently a solution of H2O (0.09 g, 5.01 mmol) in CH2Cl2 (50 mL) was added dropwise at r.t. while stirring. The reaction was finished immediately after the addition of H2O (check by 19F NMR). The solvent was removed on a rotary evaporator and the crude aldol 10 was purified first by column chromatography (silica gel, 50 g) and finally by crystallization (hexane).

Yield: 0.69 g (64.2%); mp 61–63 °C (Lit.411 mp 61–63 °C).

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References