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New access to fluorinated ketoglycolic acid derivatives from trifluoropyruvamides

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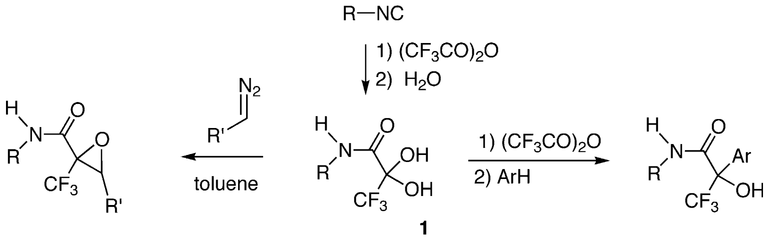
Abstract—Hydrates of trifluoropyruvamides are readily obtained from isocyanides and trifluoroacetic anhydride. Under catalysis with secondary amines, these hydrates were successfully reacted with various methylketones to form fluorinated aldol type compounds. The effect of the amine is discussed as well as Henry type additions with nitromethane.

The growing pharmaceutical and agrochemical interest for fluorinated compounds has focused the attention of organic chemists on the synthesis of new highly functionalized fluorine containing structures from readily available precursors.[1]

We reported a few years ago a high yielding formation of trifluoropyruvamides **1** by electrophilic addition of trifluoroacetic anhydride to isocyanides.[2] These pyruvamides were obtained as stable hydrates and all attempts to access the free ketone failed. Nevertheless, we have shown that these hydrates could be used in various Friedel–Crafts type reactions[3] as well as in reactions with diazo compounds to form epoxides[4] (Scheme 1). We have now further investigated the electrophilic behaviour of these hydrates **1** towards ketones.

When a solution of piperidine, acetone and pyruvamide **1a** in toluene was heated for 12 h at 80 °C, the new trifluoromethyl hydroxyketone **3a** was obtained in a 69% isolated yield. Several ketones behaved similarly when added to trifluoropyruvamides **1a** and **1b** (Table 1). A much higher reactivity was observed with methylketones: 3-pentanone **2d** reacted sluggishly with **1a** forming **3c** in 6% isolated yield after 10 h heating. Cyclic ketones (cyclohexanone, cyclopentanone) were highly reactive but the expected product could be only isolated in low yield from a complex mixture.

These experimental conditions and results suggest the intermediate formation of enamines as the reactive species in the medium. Among secondary amines, pyrrolidine has been recognized to induce easy enamine



Scheme 1.

Keywords: Trifluoromethyl group; Pyruvamide; Isocyanide; Enamines.

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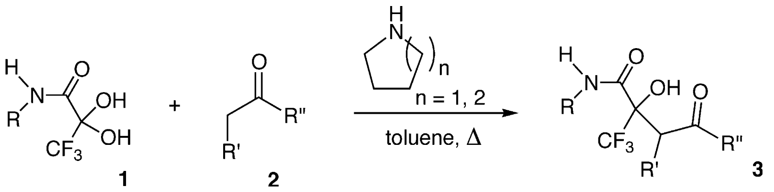
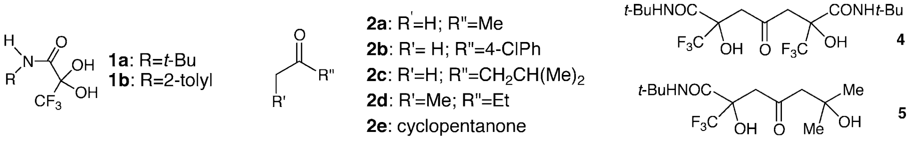
Table 1

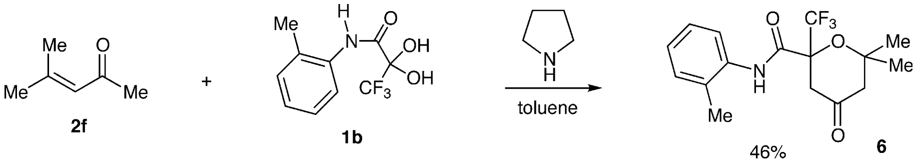


Starting **1**	Ketone **2**	Product[a]	Time for $n = 2$ ($n = 1$)	Yield (%) for $n = 2$ ($n = 1$)
1a	**2a**	**3a**	12 h (3 h)	69 (0)[b]
1a	**2b**	**3b**	8 h	75
1a	**2d**	**3c**	10 h (5 h)	6 (48)
1a	**2e**	**3d**	3 h	15
1b	**2b**	**3e**	7 h	80
1b	**2c**	**3f**	16 h (3 h)	34 (53)
1b	**2d**	**3g**	$$	6

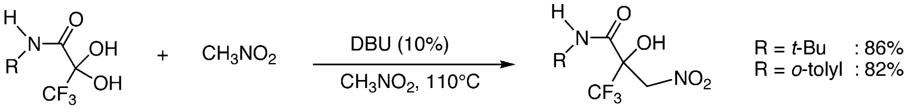
[a] To a 0.2 M suspension of pyruvamide **1** in toluene was added ketone **2** (2 equiv) and the amine (1 equiv). The mixture was heated 1 h at 80 °C then refluxed for the time given in the table. After evaporation in vacuo, the crude residue was purified by flash chromatography on silica gel.

[b] With pyrrolidine, mixtures of double addition compounds **4** and **5** could only be obtained.





Scheme 2.



Scheme 3.

formation as well as the higher reactivity of the latter.[5] When using this amine, rate enhancement and higher yields were effectively obtained for several ketones and pyruvamides. Pyruvamide **1b** and ketone **2c** gave **3f** in a 53% isolated yield within 3 h (34%, 16 h with piperidine), whereas **3c** was obtained in 48% yield (as a single diastereomer). The higher reactivity of pyrrolidine was however troublesome with acetone as the addition product corresponding to **3** reacts further either with acetone or with the starting pyruvamide to give double addition compounds **4** and **5**. More interestingly, mesityl oxide **2f** gave the new tetrahydropyranone **6** in a 46% isolated yield (Scheme 2).

These results open the way for a broader use of trifluoropyruvamides as substitutes for trifluoropyruvic esters.[6] Although the latter can be prepared in the free ketone form, the preparation from simple fluorinated synthons requires some difficult experimental procedures with the handling of reactive gaseous compounds.[7] In our case, the hydrate is probably involved in an equilibrium with the free ketone in hot toluene making possible the use of moderately basic nucleophiles in efficient couplings. Indeed, Henry type addition compounds were obtained in high yield in nitromethane as solvent under DBU catalysis (Scheme 3).

From these nitro adducts or ketones **3**, one can easily devise synthesis for various trifluoromethylated heterocyclic structures through functional group modifications. These possibilities as well as the use of chiral amines to induce asymmetric couplings are currently under study.

References and notes

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