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New Access to Fluorinated Glycolic Acid Derivatives fromTrifluoropyruvamides

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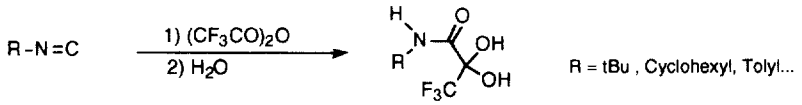
Abstract: Trifluoropyruvamide in their hydrates forms participate in various Friedel-Crafts type reactions with electron rich aromatic compounds. Good diastereoisomeric excess have been obtained starting from the chiral isobornylamine derivative.

Since the discovery of the therapeutic effects displayed by 5-Fluorouracil derivatives[1] and fluorosteroids[2] in the 1950's, the demand for new methods for the preparation of fluoro compounds with potential biological activities has not ceased. In this context fluorocarbonyl compounds have been recognised as valuable targets and intermediates in synthetic work[3]. We reported recently that electrophilic addition of trifluoroacetic anhydride to isocyanides followed by hydrolysis produces trifluoropyruvamides (**1**) in high yields (Scheme 1)[4].



Scheme 1 **1**

The easy access to such poorly studied compounds prompted us to investigate their potential in organic synthesis. Carbonyl function bearing fluorine containing electron withdrawing groups are known to be highly reactive towards nucleophiles[5a]; in our case it would be interesting to test nucleophilic additions directly on the hydrate, thus avoiding the troublesome preparation of the free ketone.

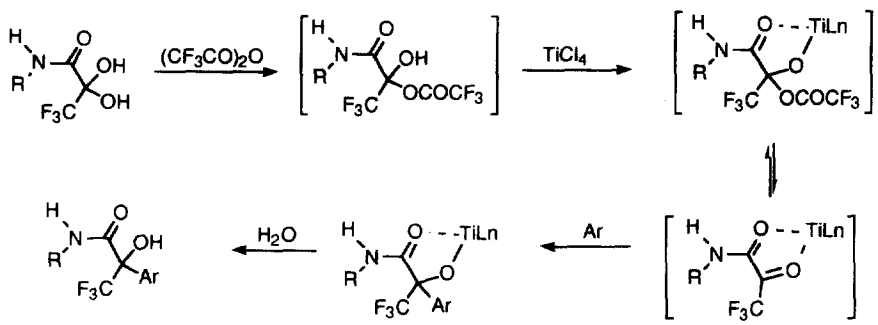
We found indeed that pyruvamides (**1a**), (**1b**), (**1c**) cleanly add to various heterocycles by a Friedel-Crafts type reaction. In the case of indole, adducts (**2a**), (**2b**) were obtained in quantitative yield by simply heating the two compounds in toluene. Pyrrole and furan required activation by TsOH for the reaction to proceed to substituted pyrrole (**2c**) and furan (**2d**) at the 2 position (see table 1). The less reactive thiophene gave addition compound (**2e**) when it was used as solvent under acidic activation.

These conditions were not suitable for benzene derivatives, and activation by a stronger Lewis acid was necessary. Thus *m*-Xylene reacted at the 4 position only when two equivalents of titanium tetrachloride were

added to a solution of pyruvamide (**1a**) in this solvent. Glycol (**2f**) was then obtained in a fair 78% yield after two hours at room temperature. Toluene under the same conditions was unreactive.

A more efficient activation was gained when two equivalents of trifluoroacetic anhydride were added to the solution prior to the addition of $TiCl_4$. The adduct (**2g**) could then be obtained in a 90% yield after one hour at room temperature. The same method gave a 97% yield of the addition compound (**2h**) starting with the pyruvamide (**1b**). Switching from toluene to benzene did not alter the course of the reaction whereas chlorobenzene was unreactive even under reflux. This makes chlorobenzene an attractive solvent for reaction with aromatic compounds sensitive to $TiCl_4$ or trifluoroacetic anhydride; (**2j**) was thus obtained by letting trifluoropyruvamide (**1b**) react with $(CF_3CO)_2O$ and $TiCl_4$ in chlorobenzene followed by addition of N-N-dimethylaniline.

In these reactions, trifluoroacetic anhydride probably promotes dehydration leading to the formation of the hemiacetal in situ . The latter when submitted to $TiCl_4$ activation is highly reactive in Friedel-Crafts type reaction (Scheme 2).

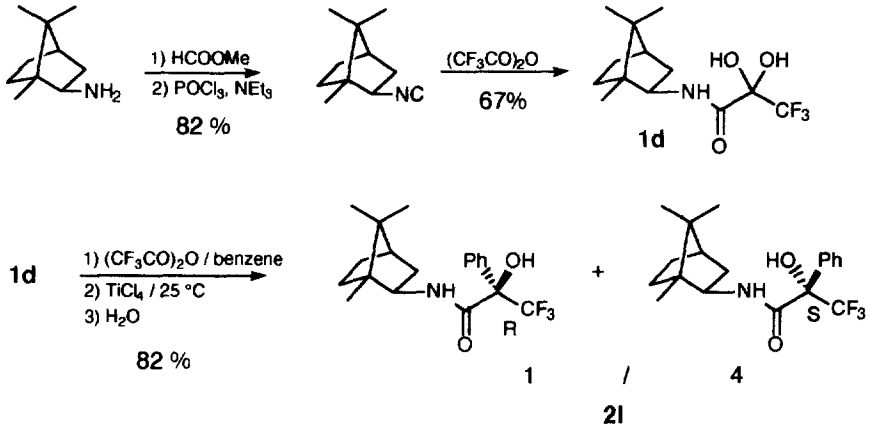


Scheme 2

Though all these amides are new compounds, alternatives routes are available for their synthesis. They all involve the intermediate preparation of the related ester or acid which can be obtained through cyanhydrin formation and hydrolysis[6] or addition to trifluoromethylpuvate esters[5b].

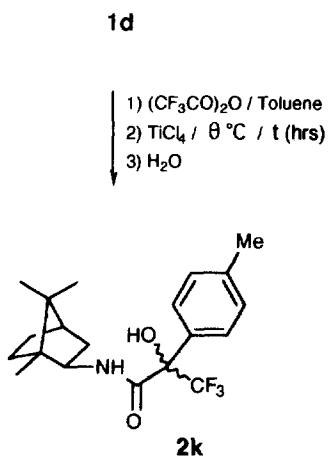
Starting from a chiral amine, an enantioselective version of this reaction can be easily devised. Formation of the isocyanide and its addition to trifluoroacetic anhydride would lead to a prochiral center next to the trifluoromethyl group. In the addition step, titanium tetrachloride complexation could then tighly constrict the transition state geometry thus inducing an efficient transfer of chirality.

We present here our preliminary results using R-(-)-isobornylamine, a chiral auxiliary easily prepared from (+)-camphor. The corresponding trifluoropyruvamide (**1d**) was obtained in a 55% non optimised overall yield starting from isobornylamine (scheme 3). The $(CF_3CO)_2O/TiCl_4$ induced addition to benzene gave a moderate 4/1 (d.e. 60%) ratio of the S/R diasteroisomers (**2l**). The absolute configuration of these compounds were obtained after methylation and comparaison with Mosher derivatives of isobornylamine by NMR ^1H and ^{19}F.



Scheme 3

Better results were obtained with toluene. Carried out at room temperature the reaction gave compounds (**2k**) with a 66% diastereoisomeric excess. At -15°C the diastereoisomeric excess raise to 80% without any decrease in yield (92%) (scheme 4).



θ °C	Yield	t	d.e
25 °C	91 %	6 hrs	66 %
- 15 °C	92 %	24 hrs	80 %

Scheme 4

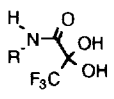
Starting Material	Reaction conditions	Treatment	Product (yield)
1a	toluene / Δ	solvent evapor.	**2a** (quant.)
1b	toluene / Δ	solvent evapor.	**2b** (quant.)
1b	toluene / TsOH cat. / Δ	Al_2O_3 filtration	**2c** (82%)
1b	toluene / TsOH cat. / Δ	Al_2O_3 filtration	**2d** (80 %)
1b	thiophene / TsOH cat. / Δ	Al_2O_3 filtration	**2e** (74 %)
1b	meta-xylene/ $TiCl_4$	H_2O / extrac.	**2f** (78 %)
1b	a	H_2O / extrac.	**2g** (90 %)
1c	a	H_2O / extrac.	**2h** (97 %)
1c	b	H_2O / extrac.	**2i** (85 %)
1c	c	H_2O / extrac.	**2j** (60 %)
1d	a	H_2O / extrac.	**2k** (91 %)
1d	b	H_2O / extrac.	**2l** (82 %)

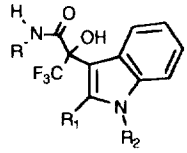
Table 1 : Reaction of trifluoro-pyruvamides with aromatic compounds

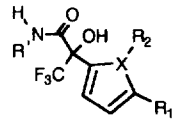
a: In a typical procedure: Trifluoroacetic anhydride (2 mmol) was added to a suspension of pyruvamide (1 mmol) in toluene (5 mL) under nitrogen. The suspension was stirred overnight at room temperature. To the resulting solution was added $TiCl_4$ (2 mmol) at - 5°C. The temperature was raised to room temperature and the red solution was hydrolysed after completion of the reaction as shown by TLC.

b: same procedure, solvent : benzene

c: same procedure, solvent : chlorobenzene. After addition of $TiCl_4$, N,N-dimethylaniline (3 mmol) was added at - 5°C; the resulting solution was warmed to room temperature and hydrolysed.



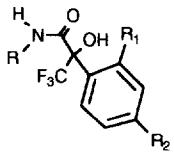




1a : R = 4-MePhSO$_2$CH$_2$
1b : R = tBu
1c : R = 4-ClPhCH$_2$
1d : R = isobornyl-

2a : R =Tosyl-CH$_2$; R_1 = Me ; R_2 = H
2b : R = tBu ; R_1 = H ; R_2 = Me

2c : R = tBu ; X = N ; R_1 = H ; R_2 = Me
2d : R = tBu ; X = O; R_1 = Me
2e : R = tBu ; X = S ; R_1 = H



2f : R = tBu ; R_1 = R_2 = Me
2g : R = tBu ; R_1 = H ; R_2 = Me
2h : R = 4-chlorobenzyl ; R_1 = H ; R_2 = Me
2i : R = 4-chlorobenzyl ; R_1 = H ; R_2 = H
2j : R = 4-chlorobenzyl ; R_1 = H ; R_2 = NMe$_2$
2k: R = isobornyl ; R_1 = H ; R_2 = Me
2l : R = isobornyl ; R_1 = H ; R_2 = H

= isobornyl

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