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Trifluoropyruvamides from Isocyanides and Trifluoroacetic Anhydride

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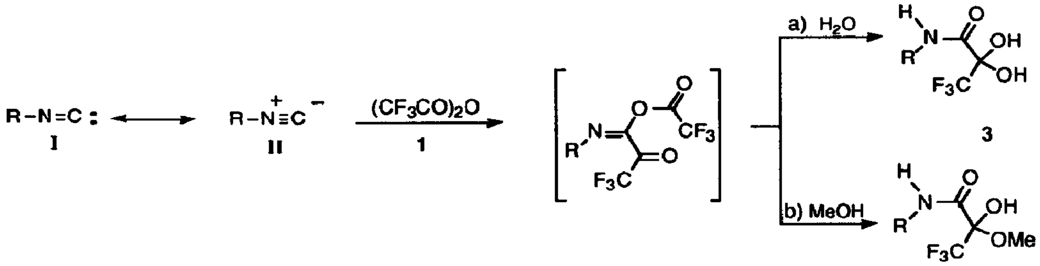
Abstract: Addition of trifluoroacetic anhydride to isocyanides proceeds smoothly to give after treatment trifluoropyruvamide derivatives in high yield.

We reported a few years ago that electrophilic addition of trifluoroacetic anhydride (**1**) to ketenes followed by hydrolysis produces trifluoromethyl ketones in good yield.[1] Interest in new fluoro derivatives is such that we looked for other potentiel carbon nucleophiles to react with (1).



Scheme 1

Isocyanides can be viewed as a hybrid of two limiting forms: a carbene structure (I) and a charge separated form (II) (Scheme 1), the latter consistent with nucleophilic activity at the terminal carbon atom. Their reaction with various electrophiles is well documented,[2] giving in the first place an imine α adduct which eventually evolves to an amide. We expected a similar formation of an imine α adduct on exposure to the highly electrophilic anhydride (1) leading after workup to fluoro-pyruvamides (3) (Scheme 1).

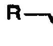
Upon addition of (1) to a cold solution of isocyanide (2a) in dry dichloromethane under nitrogen, the fluoroderivative (3a) was indeed isolated in good yield after hydrolysis of the mixture. A number of other isocyanides behaved similarly, as shown by the results collected in Table 1. As observed for trifluoropyruvate esters,[3] the hydrate form of the trifluoropyruvamides thus prepared is greatly stabilized by the presence of two electron withdrawing groups.

Water can be advantageously replaced by methanol for the preparation of hemiketal derivatives (Scheme 1-path b-). The fluorocompounds (3b) and (3c) were thus obtained in quantitative yield from the respective isocyanides. As demonstrated by the last two example switching from primary to tertiary isocyanides does not alter the outcome of the reaction.

Aromatic isocyanides (e.g. **2d**) are also good starting materials for this addition. Compound (3d) was obtained in 86% yield after methanolysis of the reaction mixture followed by chromatography on a silica gel which caused hydrolysis of the expected hemiacetal. Sulphone (2e) was quite unreactive, giving the expected product (3e) only after several hours at room temperature.

Starting material	Reaction temp./°C	Reaction time/min	Treatment	Product (yield)
(2a)	- 60	120	H_2O	(3a) (63 %)
(2b)	- 80	60	MeOH	(3b) (quant.)
(2c)	- 70	180	MeOH	(3c) (quant.)
(2d)	- 10	15	MeOH	(3d) (86 %)
(2e)	r.t.	600	H_2O	(3e) (quant.)
(2f)	- 80	90	H_2O	(3f) (83 %)
(2g)	- 60	120	H_2O	(3g) (quant.)

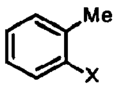
Table 1 : Reaction of $(CF_3CO)_2O$ with isocyanides



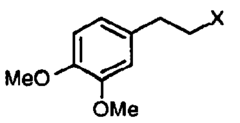
(2a) R = 4-chloro-phenyl ; X = NC
(3a) R = 4-chloro-phenyl ; X = $NHCOC(OH)_2CF_3$
(2e) R = Tosyl ; X = NC
(3e) R = Tosyl ; X = $NHCOC(OH)_2CF_3$

R—X

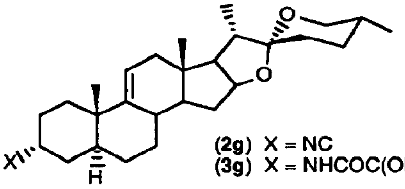
(2b) R = tBu ; X = NC
(3b) R = tBu ; X = $NHCOC(OH)(OMe)CF_3$
(2c) R = cyclohexyl ; X = NC
(3c) R = cyclohexyl ; X = $NHCOC(OH)(OMe)CF_3$



(2d) X = NC
(3d) X = $NHCOC(OH)_2CF_3$



(2f) X = NC
(3f) X = $NHCOC(OH)_2CF_3$



(2g) X = NC
(3g) X = $NHCOC(OH)_2CF_3$

This new reaction is of synthetic value for the preparation of compounds related to ethyl trifluoropyruvate. In spite of their uneasy preparation trifluoropyruvic esters have been extensively used for the synthesis of various fluorinated compounds.[4] In comparison with esters the related trifluoropyruvamides have been poorly studied, being mainly described with simple amines (diethylamine,[5] ammonia[6]); high electrophilicity of the carbonyl next to the trifluoromethyl group probably hamper the preparation of higher pyruvamides.[7] Apart from their interest as synthetic intermediates the trifluoropyruvamides obtained by our procedure may find interesting application as transition state analog inhibitors.[8] Isocyanides are easy to prepare from amine by the carbylamine reaction under phase transfer catalysis[9] or by dehydratation of the related formamide.[10] The reaction proceeds smoothly and can be performed on complex isocyanides with sensitive functions (the ketal in (2g) is not affected during the reaction). The scope and various mechanistic aspects of this addition are currently under study.

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