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From isocyanides to trichloropyruvamides: application to a new preparation of oxamide derivatives

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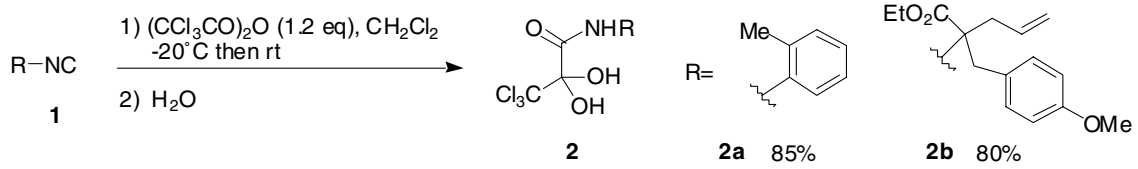
Abstract—Isocyanides react readily with trichloroacetic acid anhydride forming stable hydrates of trichloropyruvamides. These compounds are valuable intermediates for obtaining oxamides by reaction with $TMSCl/NEt_3$ followed by addition of an amine.

Since the discovery of the haloform reaction,[1] the trihalomethyl group has been recognized as a potential leaving group in synthesis and its elimination is usually associated with the development of a negative charge at a β-position. This is the case with the formation of isocyanates after basic treatment of *N*-monoalkyltrichloroacetamides[2] or in the addition–elimination process between amines and trichloromethylketones.[3] Following our studies on trifluoropyruvamides,[4] we wished to prepare the analogous chloro derivatives by a similar addition of isocyanides to trichloroacetic acid anhydride. As these pyruvamides had never been prepared before, we were prompted to examine the behaviour of these compounds towards various nucleophiles.

When trichloroacetic anhydride was added to *o*-tolylisocyanide **1a** in dichloromethane and the mixture left at room temperature, the new pyruvamide **2a** was obtained in a 85% isolated yield. The more complex **1b** behaved similarly (Scheme 1). As observed with the hydrates of trifluoropyruvamides, the chloro analogues were highly soluble in hot toluene and almost insoluble at room temperature, indicating a potential equilibrium between the free ketone and its hydrate.

The highly electrophilic carbonyl function of chloropyruvamides should promote easy additions of nucleophiles, and the stabilization of the tetrahedral adducts should enhance, under basic conditions, the removal of the trichloromethyl group.

The pharmacological interest in oxamides made us first test the behaviour of these pyruvamides with amines. Indeed, heating morpholine **3a** and **2a** in toluene brought about the expected elimination of the trichloromethyl group, but oxamide **4a** was only formed in traces, the acid **5** being obtained almost quantitatively. The starting hydrate appears to be sensitive to the basic medium leading to direct removal of CCl_3 and formation of acid **5** (Scheme 2). A two-step procedure using silylation was then adopted in order to suppress the acid formation: TMSCl (2 equiv) and triethylamine (2 equiv) were added



Scheme 1.

Keywords: Trichloromethyl; Amide; Pyruvamide; Isocyanides.
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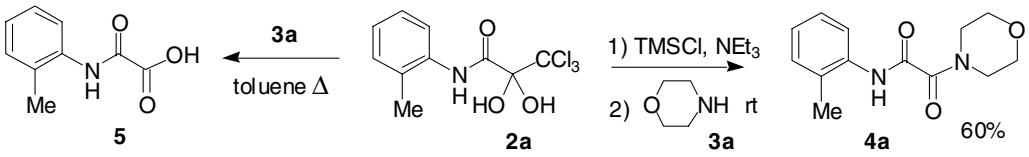
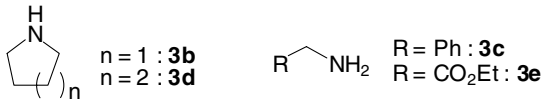


Scheme 2.

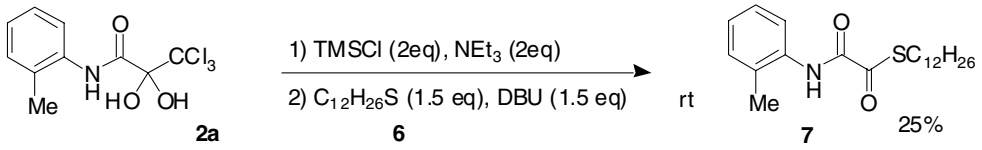
Table 1.



Starting **2**[a]	Amine **3**	Product[b]	Time (h)	Yield (%)
2a	**3a**	**4a**	3	60
2a	**3b**	**4b**	2	95
2a	**3c**	**4c**	22	100
2a	**3d**	**4d**	2	75
2a	**3e**	**4e**	72	66
2b	**3b**	**4f**	15	68
2b	**3e**	**4g**	72	72

[a] To a 0.3 M solution of trichloroacetic anhydride (1.2 equiv) in dry dichloromethane was added **1** at −20 °C and the mixture stirred at rt for 16 h before adding water and aqueous $NaHCO_3$. The crude mixture was purified by column chromatography on silica gel.

[b] To a 0.25 M solution of **2** in dry THF was added TMSCl (2 equiv) and NEt_3 (2 equiv). The resulting mixture was stirred for 2 h at rt before adding the amine. Stirring was continued at rt for the time given in the table.



Scheme 3.

to pyruvamide **2a** before adding the amine. The overall process, conducted in THF at room temperature, leads now to the formation of the expected oxamide in a 60% isolated yield (Scheme 2).

Several secondary and primary amines behaved similarly as shown by the results compiled in Table 1. Most noteworthy is the quantitative formation of oxamide **4b** and **4c** with pyrrolidine and benzylamine as well as the successful addition of aminoester **3e** to pyruvamides **2a** and **2b**.

Oxamides derivatives have already been prepared by several routes. The most efficient involves addition of amines to oxalyl chloride monoesters.[5] Besides its interest as an alternative procedure for the synthesis of unsymmetrical oxamides, this new synthetic strategy could be applied to additions of other nucleophiles such as thiols; the new thioester **7** was thus obtained in a 25% isolated yield from pyruvamide **2a** and dodecanethiol **6**. The scope of these nucleophilic additions as well as the mechanism involved are currently under study (Scheme 3).

References and notes

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