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Cyanuric chloride: an efficient reagent for the Lossen rearrangement

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ABSTRACT

An efficient method for the Lossen rearrangement that uses 2,4,6-trichloro-1,3,5-triazine (TCT) as a promoter is reported. This procedure allowed the preparation of various carbamates, thiocarbamates, and ureas in good yields directly from the corresponding hydroxamic acids.

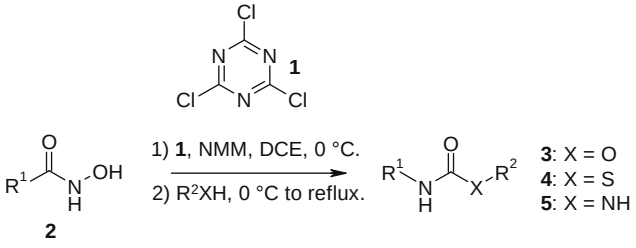
2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride, TCT) **1** (Scheme 1) is a very inexpensive commercially available reagent making its use extremely attractive in organic synthesis.[1] This compound was widely employed as a starting point for the preparation of 2,4,6-mono, di- or tri-substituted triazine derivatives. Recently, there has been a growth of interest in the use of cyanuric chloride in a wide range of functional group transformations. For instance, it has been shown that TCT can promote efficiently carboxylic acid activation,[2] Swern oxidation,[3] Friedel–Crafts acylation,[4] Beckman rearrangement,[5] or glycosyl chlorination.[6] Interestingly, in most of these cases the use of TCT presented advantages compared to other classical methods in terms of cost, yield, and mildness. Thus, in the light of these results, the discovery of new applications for TCT in organic synthesis is of interest.

The Lossen rearrangement is a useful chemical reaction in which O-activated hydroxamic acids can be converted into the corresponding isocyanates.[7] However, although the Lossen transformation has been known for more than one century,[8] it has received only little attention as a general synthetic method mainly due to complicated experimental procedure and formation of by-products.[9,10]

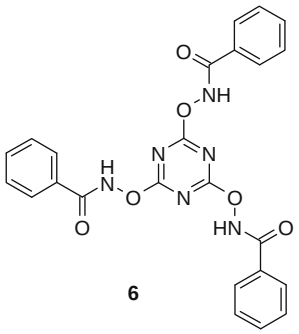
In this Letter, we report a new simple and efficient method for the Lossen rearrangement employing TCT as a promoter (Scheme 1).

Thus, we demonstrated that hydroxamic acids **2** can be O-activated with a sub-stoichiometric quantity of **1** and then transformed into the expected isocyanates which were subsequently trapped in situ by various nucleophiles (R^2XH) in the course of a one-pot procedure (Table 1).

Our initial efforts focused upon the preparation of the phenylcarbamic acid ethyl ester **3a** directly from the commercially available benzohydroxamic acid **2a**. Best results were obtained when **2a** reacted with 0.4 equiv of TCT **1** in the presence of an excess of *N*-methylmorpholine (NMM, 2 equiv) in dichloroethane (DCE) at



Scheme 1. Lossen rearrangement promoted by TCT.



Scheme 2. Proposed tri-substituted triazine intermediate.

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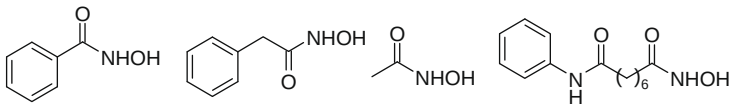
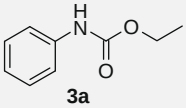
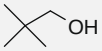
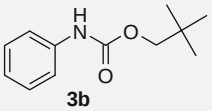
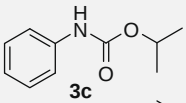
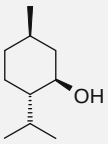
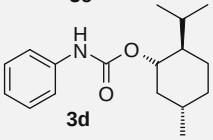
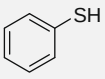
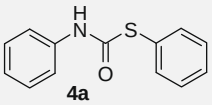
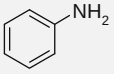
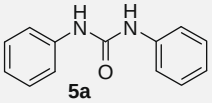
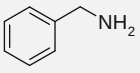
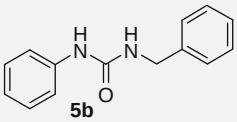
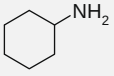
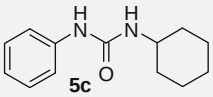
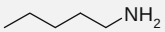
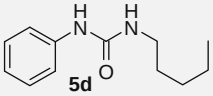
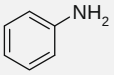
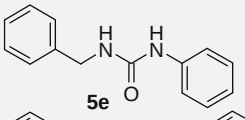
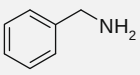
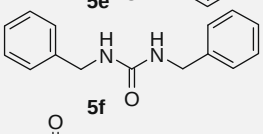
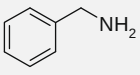
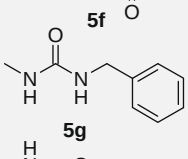
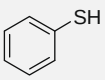
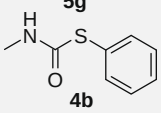
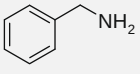
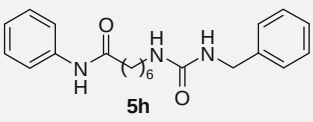
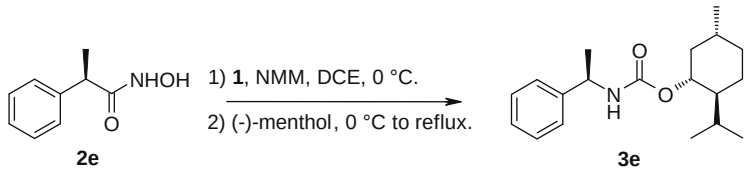
Table 1
Synthesis of carbamates, thiocarbamates and ureas from hydroxamic acids using TCT as a promoter



2a **2b** **2c** **2d (SAHA)**

Entry	$R^1CONHOH$	R^2XH	$R^1NHCOXR^2$	Yield (%)
1	**2a**		 **3a**	87
2	**2a**		 **3b**	84
3	**2a**		 **3c**	81
4	**2a**		 **3d**	77
5	**2a**		 **4a**	73
6	**2a**		 **5a**	99
7	**2a**		 **5b**	90
8	**2a**		 **5c**	87
9	**2a**		 **5d**	88
10	**2b**		 **5e**	80
11	**2b**		 **5f**	77
12	**2c**		 **5g**	76
13	**2c**		 **4b**	67
14	**2d**		 **5h**	73



Scheme 3. Stereospecific Lossen rearrangement.

0 °C. After 90 min under such conditions TLC analysis indicated total consumption of the starting hydroxamic acid together with the clean formation of one less polar product. Since **1** has been introduced in only sub-stoichiometric amounts, the structure of this intermediate could be attributed to the tri-substituted triazine **6** (Scheme 2). Similar tri-substituted intermediates have been postulated by some authors in the course of carboxylic acid's activation by TCT.[2a,b] However, it is worth mentioning here that the di-substituted triazine intermediate could also be formed in the reaction media. Two equivalents of EtOH were then added at 0 °C and the reaction mixture was refluxed overnight to afford carbamate **3a** in 87% yield (entry 1).

It is worth mentioning here that other attempts with higher quantities of TCT gave lower yields. Moreover, the addition of EtOH at the beginning of the reaction or before the total consumption of **2a** resulted in a complex mixture.

At this stage, we decided to pursue our investigations with other nucleophiles including alcohols, thiols, and amines (Table 1). In the course of these experiments, we obtained the corresponding carbamates **3b**–**d** (entries 2–4), thiocarbamate **4a** (entry 5), and ureas **5a**–**d** (entries 6–9), respectively, in good to excellent yields (73–99%) after purification by flash column chromatography.

We examined next the Lossen rearrangement under the same reaction conditions with the two commercially available hydroxamic acids **2b** and **2c** as well as with the well known HDAC inhibitor SAHA **2d**.[11] In all cases, the reaction provided the expected product **4** or **5** resulting from the trapping in situ of the corresponding isocyanate by the nucleophile indicated in Table 1 (entries 10–14). Interestingly, since our reaction conditions appeared to be compatible with the presence of SAHA, this procedure may open a new door for the synthesis of new analogues of this bioactive compound.

Finally, we investigated the stereo-chemical aspects of this reaction. Indeed, previous studies showed that the Lossen rearrangement proceeds in a stereospecific manner with retention of configuration of the migrating group.[12] For this purpose, we first prepared the novel hydroxamic acid **2e** from the corresponding chiral methyl ester in the presence of hydroxylamine (Scheme 3).[13] When **2e** was placed under the reaction conditions described above, carbamate **3e** was produced as a single diastereoisomer without any detectable racemization of the stereogenic center at the benzylic position hence demonstrating the stereospecificity of this reaction.[14] In this case, **3e** was isolated in 40% yield after purification by flash column chromatography.

In summary, we developed a simple and efficient method for the Lossen rearrangement that uses the 2,4,6-trichloro-1,3,5-triazine as a promoter. This procedure appeared to be general and appropriate to the one-pot synthesis of a wide range of carbamates, thiocarbamates, and ureas directly from the corresponding hydroxamic acids. Additionally, this procedure could be useful in order to avoid the problems of phosgene-based approaches for the preparation of isocyanates. Thus, it seems that this methodology could be used as a valuable alternative to other known procedures for the Lossen transformation.

General procedure: To a solution of hydroxamic acid (1 mmol) in dichloroethane (3 mL) at 0 °C under nitrogen atmosphere, *N*-methylmorpholine (2 mmol) then TCT (0.4 mmol) were added and the mixture was stirred during 90 min at 0 °C. The amine, alcohol, or thiol (2 mmol) was then added and the reaction mixture was stirred during 15 h at 84 °C. The crude mixture was acidified with HCl (0.1 N) and the solution was extracted with CH_2Cl_2 (twice) and EtOAc. The organic layers were then combined, dried with $MgSO_4$, and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel (230–400 mesh) using petroleum ether and ethyl acetate as eluent.

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14. Composition of the crude product was analyzed by HPLC. Pure samples of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*R*)-1-phenylethylcarbamate 3e and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-1-phenylethylcarbamate were prepared by coupling either (*R*)-(+)- or (*S*)-(−)-alpha-methylbenzylamine with (−)-(1*R*)-menthylchloroformate according to literature procedure and used as references.[15] Analytical HPLC was carried out using a Waters 2695 System with UV variable wavelength detector. Analyses were performed on a reverse phase column chromatography (SunFire™, C18, 5 μm, 1 × 150 mm) using a mobile phase (0.5 mL/min) of CH_3CN/H_2O 7/3 (+0.1% HCOOH). Retention times is for **3e** and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-1-phenylethylcarbamate were 6.18 and 5.83 min, respectively.
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