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Synthesis of α-chloroamides in water

Andrew J. Harte and Thorfinnur Gunnlaugsson*

School of Chemistry, Centre for Synthesis and Chemical Biology, Trinity College Dublin, Dublin 2, Ireland

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Abstract—The reaction between chloroacetyl chloride and mono- or bis-aliphatic or aromatic amines in water under basic or neutral conditions gives rise to the formation of a variety of functionalized α-chloroamides. The resulting products were obtained as solids in moderate to good yields, upon precipitation and isolation by filtration.

Amides are important building blocks in both Nature and in chemical synthesis.[1] For the latter, such reactions are conducted in organic solutions or in a mixture of organic and aqueous solutions (Schotten–Baumann conditions) where the organic reagents are generally dissolved in the organic solution and treated with aqueous base.[1] The development of alternative methods for achieving amide synthesis in high yield and/or in a stereospecific manner is of great current interest. Over the last few years several new methods such as the use of the CuI catalyzed transformation of alkynes, biocatalysts and PEG supported pyridylthioesters have been employed for amide synthesis.[2] Such synthesis is also of significant industrial importance, for example, for the synthesis of polypeptides and amide based drugs. Recently, Bode et al. have developed a novel method for peptide coupling using decarboxylative condensation of α-ketoacids and *N*-alkylhydroxylamines in organic or mixed aqueous solutions.[3] An important family of amides are the α-chloroamides, which have been used as alkylating agents in a range of organic syntheses, for instance, in the synthesis of lactams and α,β-unsaturated amides.[4] Importantly, these are also valuable synthons for the development of stable lanthanide-based macrocycles for biological applications.[5,6] We have used varieties of α-chloroamides in the synthesis of such macrocyclic cyclen complexes, where the amides function as pendent arms, coordinating to lanthanide ions giving rise to octa-coordinated supramolecular lanthanide complexes.[5] These can be used as potential MRI contrast agents, as luminescent probes and as ribonuclease mimics.[5–10] For all of these compounds the starting point is the synthesis of the desired pendant arms, or spacer moieties in the case of the dinuclear complexes, which are introduced by alkylation with α-chloroamides. During the development of macrocyclic systems such as **1**, **2** and **3** as MRI contrast agents,[11] Figure 1, we discovered that the classical reaction between the corresponding amine and chloroacetyl chloride (2 equiv) in dry THF (or CH_2Cl_2) at −10 °C in the presence of freshly distilled Et_3N, gave very low yields of the desired α-chloroamides. Furthermore, changing to solvents such as DMF, CH_2Cl_2, $CHCl_3$ or Et_2O did not increase significantly the yield of the products, and the reaction only proceeded in EtOAc, but in low yields. For the aromatic bis-amine **4**, the reaction was even more problematic. Hence, we turned our focus towards alternative synthetic methods and found that the amide coupling could be conducted in water in the presence of medium or strong bases such as Et_3N, $KHCO_3$, K_2CO_3 or NaOH, where the desired products were formed as solids in

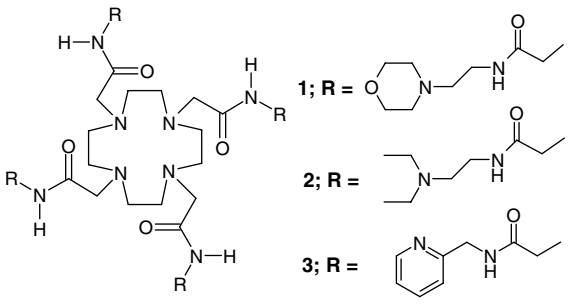

Figure 1. Macrocyclic ligands for MRI contrast agents.

* Corresponding author. Tel.: +353 1 608 3459; fax: +353 1 671 2826; e-mail: gunnlaut@tcd.ie

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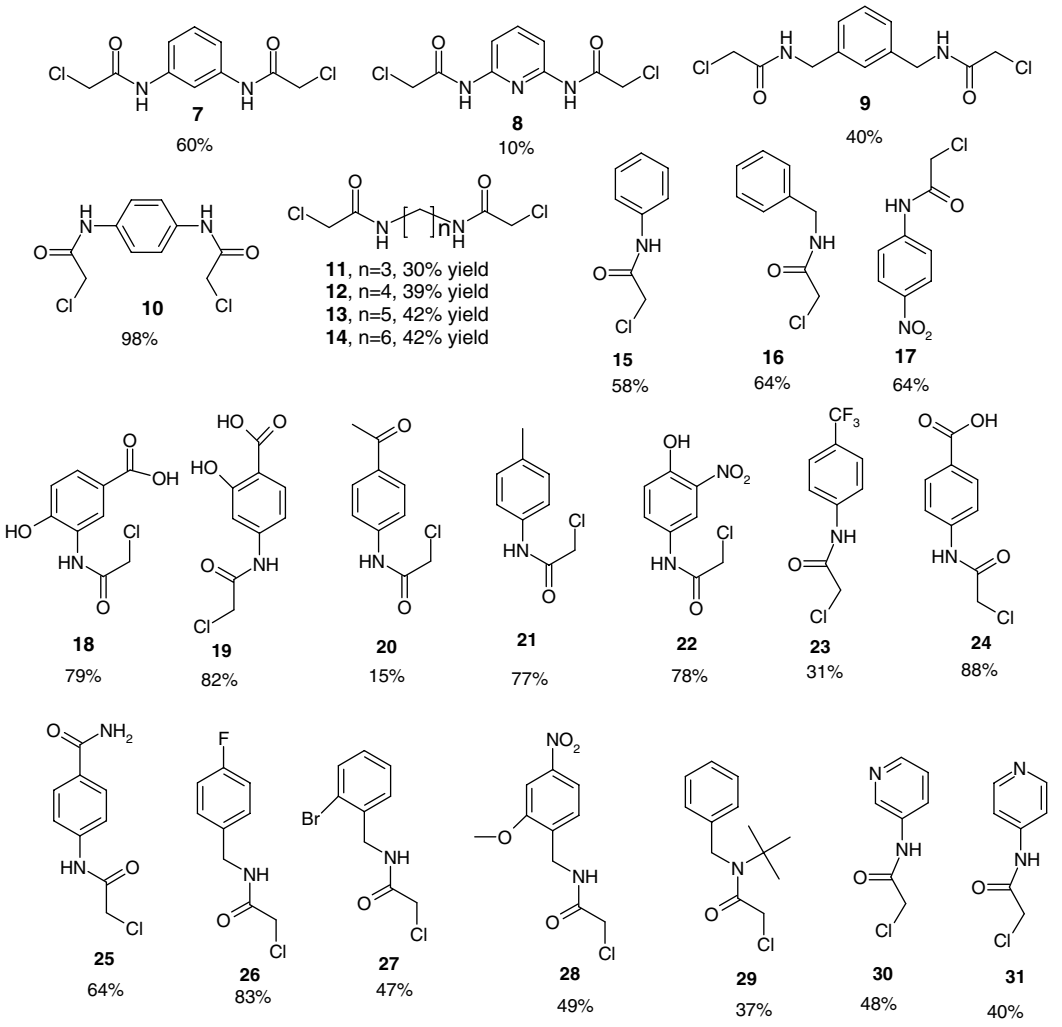
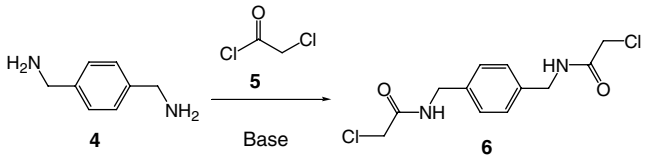


acceptable yields, under ambient conditions. Here, we give a preliminary account of our investigation into the use of this simple synthetic method for the generation of a number of α-chloroamides, which have significant value in general organic synthesis and in developing macrocyclic ligands for targeting lanthanide ion complexes.[5–13] These ligands and the synthetic method in general, is highly applicable to industry as potential green chemistry.

Initially, the acylation of *p*-xylylenediamine **4**, to yield 1,4-bis-(2-chloro-acetylamino)-xylyene, **6** (Scheme 1) was conducted in $CHCl_3$ with freshly distilled Et_3N. However, this method gave a low yield of 11% of the desired product. Varying the reaction conditions such as solvent and base did not yield any improvement. The problem seemed to stem from the insolubility of **4**, which was only fully soluble in alcohols and water. Under Schotten–Baumann conditions, the formation of HCl is neutralized with NaOH by employing a two phase system consisting of water and CH_2Cl_2, or by using excess of the amine as a base. The solvents chosen are immiscible so that the amine and acid chloride remain in the lower CH_2Cl_2 layer, while NaOH remains in the upper aqueous layer.[12] However, due to the lack of solubility of **4** in organic solution, we decided to carry out a modification of this method using only water as the solvent. Moreover, instead of using an excess of the amine, we used 4 equiv of chloroacetyl chloride, which was added dropwise over 1 h to the aqueous amine solution. The solution was left to stir overnight and the desired product **6** was isolated as a precipitate in yields of 75% with no need for further purification. Hence, the two-phase procedure was *not* necessary and in fact this modification enabled the successful isolation of the desired product with minimal effort. Due to the success and simplicity of the above reaction, it was decided to investigate its range and suitability for other N-acylation type reactions, which would have significant synthetic value for developing targeting lanthanide-



Scheme 1. Acylation of *p*-xylylenediamine to yield 1,4–bis-(2–chloro-acetylamino)-xylylene (**6**).

Table 1. Effect of changing the base upon the yields of N-acylation

Compd	NaOH (%)	Et_3N (%)	$NaHCO_3$ (%)	No base (%)
14	**32**	27	7	13
16	64	69	**85**	74
8	8	**28**	14	0
6	**75**	39	17	9

based macrocycles.[†] Under the same conditions[‡] the α-chloroamides **7**–**10**, were synthesized from their corresponding aromatic diamines, while **11**–**14**, were synthesized from their corresponding aliphatic diamines. In all cases, the desired products precipitated out of solution and were collected by filtration. The versatility of this method was investigated further, by introducing more functional groups into the starting materials such as aryl acids, amides, halides, hydroxides and acids. Compounds **15**–**31** were synthesized from such functionalized aromatic amines, using the above procedure, and were generally obtained in good yields. As for **6**–**14**, the recorded yields are that of the products isolated by simple filtration, with no further need for purification (e.g., no recrystallization, extraction of aqueous layer, etc.). For those cases that gave low yields of the desired products, additional extraction of the aqueous layer using CH_2Cl_2 gave significantly increased yields. Moreover, in the case of **18**, **22**, **24**, **27** and **28**, which have additional functionalities, the yields were in the region of 50–90%, clearly demonstrating the versatility of this method. The reaction procedure was, however, not as successful when more extended ring systems such as anthracene, phenanthroline and methyl-quinoline were used.

A further investigation was conducted in order to determine whether the choice of base employed had an affect on the reaction. Four reactions from the above section, with a range of yields were chosen. From Table 1, it can clearly be seen that the choice of base did not have an impact upon the yield of the reaction. While no immediate trend was evident it is clear that the reaction yields are dependant upon the choice of base. It is noteworthy that in the case of **16** the reaction proceeded with good yield even in the absence of any base. Moreover, changing the temperature to lower temperatures generally gave rise to increased yields. The synthesis of simple alkyl based acetamides was also undertaken using these conditions, and found to be more successful for longer chain alkylamines than shorter chain alkylamines, for example, using *n*-butylamine gave rise to 45% yield of the desired product in comparison to only 5% yield when *N*,*N*-dimethylamine was used, which is typically formed using Schotten–Baumann conditions.[13]

In summary, we have synthesized a number of α-chloroamides by N-acylation of amines under purely aqueous conditions. Its usefulness stems from the fact that the solvent, H_2O, is environmentally friendly and as such, would be favoured by industry. The simplicity of the reaction as well as the ease of work-up are also major advantages. The reaction has been shown to be successful for a range of amines, both aromatic and aliphatic. Additional investigation within our laboratory has also shown that optimization of the above reaction can be achieved by tuning the temperature and the base employed. We are in the progress of exploring the scope of this method further.

[†] All compounds were fully characterized. See Supplementary data.

[‡] General experimental procedures for α-chloroamides discussed herein are given in Supplementary data.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.090.

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