Pergamon

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Tetrahedron Letters 44 (2003) 4399–4402

TETRAHEDRON LETTERS

Synthesis and *N*-methylation of tetrabutylammonium isocyanurate

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Received 21 November 2002; revised 31 March 2003; accepted 4 April 2003

Abstract—A simple and efficient method for the synthesis of ammonium salt of isocyanuric acid is set out. This process is based on the direct addition of the corresponding hydroxide to isocyanuric acid. This salt exhibits several interesting properties. Its alkylation by iodomethane in various solvents is demonstrated and leads to various substituted isocyanurate derivatives.

1. Introduction

The value of isocyanuric acid (ICA) lies mostly in its high thermal resistance which is due to its cyclic triamide structure. But the product itself offers little chemical interest. Moreover, the restricted solubility of the acid in most standard solvents limits its use. However, isocyanuric derivatives present characteristics of the greatest significance and consequently offer some economic interest. Most isocyanuric products are trisubstituted triazines that present the same three groups in their structure. But those isocyanuric compounds that possess a lesser degree of substitution are of interest to the polymer industry—which is a considerable consumer of additives—or to the pharmaceutical chemistry—which uses a sizeable amount of heteroatomic cyclic compounds.

There are two ways of synthesizing a mono- or a disubstituted isocyanuric product. Firstly, by producing a complete triazinic ring with the right function groups in place and secondly, by adding an appropriate reagent on the isocyanuric acid ring. Concerning the latter approach, different reactions are possible.

Some typical reactions such as Michael reactions,[1] elimination reactions from trisubstituted products[2,3] or Mannich reactions[4] can be used to obtain either mono- or disubstituted isocyanuric derivatives. Condensation of aziridine on ICA is also very typical and leads, for instance, to the production of monoaminoethyl isocyanurate with a 62% yield.[5] The action of formaldehyde onto the acid in pyridine allows monohydroxymethyl isocyanurate to be obtained with a 75–95% yield, depending on the experimental conditions.[6]

The most common way of synthesizing these substituted derivatives is obviously through nucleophilic substitution. But the reaction does not allow to obtain only mono- or diisocyanurate. The required selectivity cannot be reached. For example, addition of monosodium isocyanurate to alkyl halogen nearly always produces a major amount of trialkyl isocyanurate or a mix of the various substituted derivatives. Indeed, the *N*-alkylation reaction of ICA presents a fundamental problem related to the nature of the intermediate salt, i.e. its nucleophilicity and its basicity. Through a set of reactions, the basic effects lead to the polysubstitution on the heterocyclic compound, which explains why the synthesis has no selectivity.

Literature shows that ICA alkali salts in aqueous media have been most studied. But these intermediates are not suitable for an *N*-alkylation. The only disubstituted derivative obtained with a satisfactory yield (55%) through a nucleophilic substitution in aqueous phase is diallyl isocyanurate.[7] Isocyanuric acid in a basic medium reacts with allyl chloride in the presence of copper(I) chloride.

ICA alkali salts have recently been studied for *N*-alkylation in organic solvents.[8] Several monosubstituted

Keywords: ammonium isocyanurate; isocyanurate derivatives; solvent effect.

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0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00892-X

isocyanurates have been synthesized with a good yield from ICA lithium salt or from ICA with lithium hydroxide in formamide. For example, monohexyl isocyanurate has been produced with a 60% yield. Nevertheless, literature quite frequently relates such disadvantages of alkali isocyanuric acid salts as their being difficult to use in experiments or their lack of reactivity in an organic medium.

Very few ICA organic salts have been described[9,10] and none seem to have been used to enhance the value of the acid. This study aimed at an *N*-methylation of isocyanuric acid through the synthesis of a new intermediate, i.e. an organic salt which can present a higher solubility in an organic phase. Moreover, the organic salt is expected to be more reactive than, for instance, the lithium one mentioned above because the ammonium cation makes the cyanurate anion more easily available kinetically. The nature of the salt allows different reactivities to be obtained depending on the solvent used and consequently different ratios of substituted isocyanuric products.

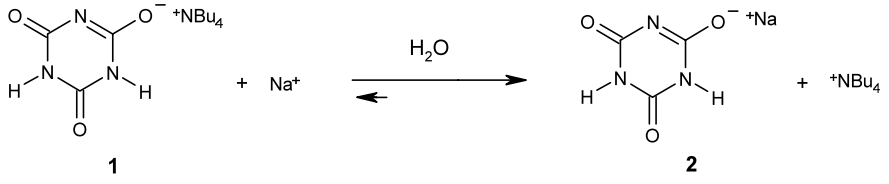
2. Synthesis of tetrabutylammonium isocyanurate

Experiments were carried out to try and synthesize tetrabutylammonium isocyanurate **1**. The required organic cyanurate could not be produced through the mixing of tetrabutylammonium sulphate hydrogen with sodium hydroxide on isocyanuric acid, whatever the experimental set-up was. From these experimental conditions, fundamental conclusions can be drawn. In fact, the sodium sulphate formed during the process plays a leading part in the orientation of the reaction. Sodium ions and ammonium ions are in competition; the sodium ones strongly displace the equilibrium towards the crystallization of sodium isocyanurate **2** (Scheme 1). The phase transfer catalysis process did not allow to extract the pseudo-alkali isocyanurate in the chlorinated phase. The exchange of the ammonium ion with the sodium one could not be avoided. The association of a cyanurate ion with a sodium ion makes up an intimate ion pair. So as to isolate the tetrabutylammonium isocyanurate, the sodium sulphate necessarily had to be eliminated.

Compound **1** can be synthesized in a more simple way from tetrabutylammonium hydroxide **4** (water or methanol solution). Isocyanuric acid **3** was added—at room temperature, in equimolar ratio (or with a slight excess of acid)—to the hydroxide solution, so as to produce the organic salt **1** that remained present in the mixture (Scheme 2). The synthesis process could be observed by means of a pH-meter apparatus. The pH evolution allowed the end of the reaction to be observed, which was accompanied at the same time by a diminution of solution opacity. Then, the solvent was removed so as to ensure the isolation of the tetrabutylammonium isocyanurate which was then dried. The reaction yield was 95%.

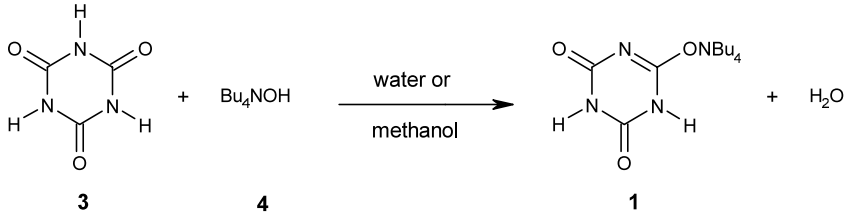
Characterizing an isocyanuric acid salt has often proved to be problematical. The best known example is that of disodium isocyanurate, the existence of which is still controversial. Eventually, compound **1** was fully characterized as a microanalysis (C, H, N, O), a pH metric titration (so as to find out the number of acidity functions and determine the molar mass), an NMR (^{1}H, ^{13}C) and a Karl Fischer analysis were carried out (most organic ICA salts are hydrate compounds). All results proved satisfactory and guarantee the existence of anhydrous tetrabutylammonium isocyanurate.

Isocyanurate **1** is a white, crystalline, odourless and slightly hygroscopic solid. It is a stable substance (no decomposition was observed after 90 days). Its melting point was determined at 204°C±1. The solubility of isocyanurate **1** was studied at room temperature: it is totally soluble in water, soluble in alcohol, DMF and formamide, slightly soluble in acetone, dichloromethane and chloroform—but totally soluble at 40°C—and insoluble in butanol and aprotic solvents.



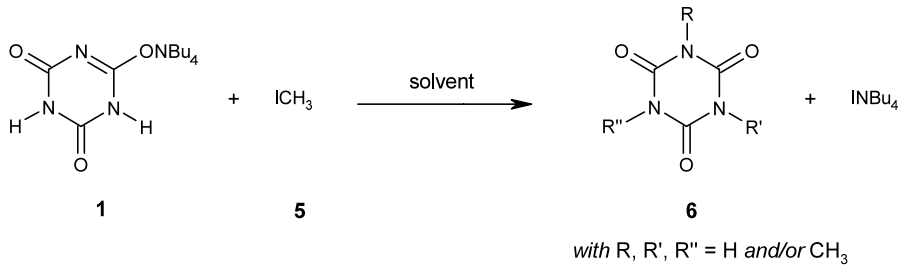
1 **2**

Scheme 1.



3 **4** **1**

Scheme 2.



Scheme 3.

Its solubility, either total or partial in an organic phase, makes it particularly interesting, moreover, the nature of the compound is particularly reactive. In fact, ammonium salts have a better reactivity than alkali ones, because the anion–cation distance is greater in the former and therefore the interaction energy between the charged entities is reduced.

3. Alkylation of tetrabutylammonium isocyanurate

The aim is to improve the nucleophilic power and to reduce the basic effect by using different solvent natures in order to get the best selectivity, i.e. to obtain the maximum amount of mono (or di-) substituted product from the organic salt.

Preliminary experiments were made with monosodium or monopotassium cyanurate (1 equiv.) with methyl iodide (1.2 equiv.) in DMF, acetonitrile and dichloromethane, at 25°C, for 24 h. No isocyanurate was synthesized except in acetonitrile where a few traces of an isocyanuric derivatives mix, for the two alkali salts, were obtained.

Concerning the synthesis of mono- or dihydroxymethyl isocyanurate in pyridine, mentioned above,[6] the authors show that no similar reaction happens in DMF or acetonitrile. This emphasises the extreme importance of the solvent nature.

The synthesis of isocyanurate derivatives **6** was carried out as shown in Scheme 3, at 35°C, for 36 h. Iodomethane **5** was chosen because this compound is highly reactive. Iodoethane and other halides had been tested but conversion rates into isocyanurates were of lesser importance (28% with iodoethane) than with iodomethane (33.5%). The alkyl halogen/salt molar ratio was 1.2. Three kinds of solvents were tested: protic solvents first, then polar and apolar aprotic ones. For each solvent test, the substituted triazines were monitored by HPLC. The results (chromatographic yields) are presented in Table 1. The other products present were essentially tetrabutylammonium isocyanurate which did not react and ICA which was formed by basic effects.

Regarding protic solvents, the dissociation and ionization of the ion pair proved to be important. The free ions are nucleophilic and basic in these media. The polysubstitution phenomena produced a high ratio of trimethyl isocyanurate. Concerning aprotic solvents, which are either slightly polar (dichloromethane) or apolar (hexane), the conversion rate was less important. In dichloromethane, the salt was soluble and slightly dissociated, thus yielding an appreciable ratio of monomethyl isocyanurate. The salt was totally insoluble in hexane but reacted on iodomethane. The heterogeneous phase allowed a good selectivity of the reaction.

The best solvent for the synthesis of monomethyl isocyanurate is DMF, an aprotic polar solvent. DMF is a dissociating and ionizing solvent that effectively solvates the cations. Through this medium, the organic salt is almost completely dissociated, the nucleophilic reactivity of the cyanurate is enhanced, thus ensuring the favourable development of an *N*-alkylation. The basic effects seem to have been annihilated. Compound **1** is less soluble in acetonitrile than in DMF. The monosubstituted product that formed is insoluble in the solvent and reacts to the salt in acid–basic exchanges.

Many other solvents were tested leading to the same conclusions: compound **1** is quite nucleophilic, as well as basic. When sodium cyanurate forms an intimate (or contact) ion pair that is little reactive, whatever the media is (except in protic solvents), the ammonium cyanurate pair is very weak. Consequently, the organic salt proves to be nucleophilic and basic in the most solvents. The salt **1** is sensitive to the ionization and dissociation induced by the solubility effect, which results in the production of free ions.

Table 1. Yields reaction (Scheme 3) for different solvents

Solvent	Yield		
	Mono	Di	Tri
Water	10.5	14.0	14.2
Methanol	12.9	11.8	13.5
Ethanol	16.2	11.0	12.8
DMF	35.6	14.7	6.1
Acetonitrile	17.0	11.8	14.2
Dichloromethane	25.1	12.5	7.4
Hexane	21.8	11.9	3.4

4. Conclusion

This work is not only about the study of the *N*-methylation of tetrabutylammonium isocyanurate, it is also a study of the effect of the solvent onto the reaction. This compound offers a great reactivity, which is due its nature and the properties related to the alkali counterparts. Indeed, it is more soluble and more reactive than monosodium or monopotassium isocyanurate which can produce no substituted products in the same experimental conditions. It is a good nucleophilic compound but it has also high basic effects.

The alkylation of the salt may produce some substituted isocyanurates. Unfortunately, the reaction is not selective. The synthesis of heterogeneous trisalts (ammonium and alkali) of ICA could be a way to make selective alkylation and to avoid the production of a mix of substituted isocyanurates.

The method described here may result in the synthesis of an organic salt of the isocyanuric acid. Furthermore, ammonium salt is of much interest and its application has to be carried out.

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