Reactivity of Carbamoyl Radicals. A New, General, Convenient Free-Radical Synthesis of Isocyanates from Monoamides of Oxalic Acid†

Francesco Minisci,* Francesca Fontana, Fausta Coppa, and Yong Ming Yan

Dipartimento di Chimica del Politecnico, via Mancinelli, 7, I-20131 Milano, Italy

Received January 23, 1995®

A new, general, simple synthesis of isocyanates was developed by oxidation of monoamides of oxalic acid with peroxydisulfate catalyzed by Ag and Cu salts. The reaction was carried out in a two-phase system (water and an organic solvent), and it is suitable also for practical applications, due to the simple experimental conditions and the inexpensive as well as nontoxic reagents. The first example of homolytic intramolecular aromatic carbamoylation is also reported.

Introduction

Isocyanates are an important class of organic compounds, that have found wide ranging applications in polymer chemistry (polyurethanes) and for fine chemicals (herbicides, pharmaceutical products, crop-protecting agents etc.).[1]

Industrially the phosgenation of amines[1] is by far the most widely utilized procedure, due to the low cost of phosgene. This latter compound, however, is volatile and highly toxic, so that its use requires particularly expensive safety apparatus; therefore, it can be compatible with large plants and productions, but it is much less suitable for the smaller productions of fine chemicals.

In this paper we report the first free-radical synthesis of isocyanates; due to the cheap and nontoxic reagents, the general character, and the simple experimental conditions, the procedure is also suitable for practical applications.[2]

Results and Discussion

The new synthesis of isocyanates is based on the oxidation of monoamides of oxalic acid by persulfate, catalyzed by metal salts. The stoichiometry of the reaction is shown in eq 1.

$$\text{R-NH-CO-COOH} + S_2O_8^{=} \longrightarrow \text{R-N=C=O} + CO_2 + 2\,HSO_4^{-} \quad (1)$$

The simplest, general laboratory procedure for the synthesis of the monoamides of oxalic acid involves the reaction of the commercial methyl ester of oxalyl monochloride with amines (eq 2), followed by the selective basic hydrolysis of the ester (eq 3).

$$CH_3OCO\text{-}COCl + \text{R-}NH_2 \longrightarrow CH_3OCO\text{-}CO\text{-}NHR + HCl \quad (2)$$

$$CH_3OCO\text{-}CONHR + NaOH \longrightarrow NaOCO\text{-}CONHR + CH_3OH \quad (3)$$

Cheaper sources of monoamides of oxalic acid are the direct reactions of the acid (eq 4) or the diester (eq 5) with amines, but they need to be optimized for each particular amine, to minimize the diamide formation, usually by using an excess of acid or ester, which for practical applications[2] must be recovered and recycled.

$$HOCO\text{-}COOH + \text{R-}NH_2 \longrightarrow HOCO\text{-}CO\text{-}NHR + H_2O \quad (4)$$

$$CH_3OCO\text{-}COCH_3 + \text{R-}NH_2 \longrightarrow CH_3OCO\text{-}CO\text{-}NHR + CH_3OH \quad (5)$$

The isocyanates readily react with water, giving the amine (eq 6), which adds rapidly to the isocyanate to form urea derivatives (eq 7)

$$\text{R-N=C=O} + H_2O \longrightarrow \text{R-}NH_2 + CO_2 \quad (6)$$

$$\text{R-}NH_2 + \text{R-N=C=O} \longrightarrow \text{R-NH-CO-NH-R} \quad (7)$$

The synthesis of isocyanates is generally carried out in nonaqueous medium, which is not suitable for the use of persulfate. We have overcome this difficulty by using a two-phase system. The isocyanate must be very soluble in the organic solvent: this way, the oxidation of the monoamide of oxalic acid takes place in the aqueous phase while the isocyanate is very rapidly extracted by the organic solvent, thus preventing its decomposition by water.

The silver salt catalysis is necessary to obtain the isocyanate, as it determines the decarboxylation of the monoamide of oxalic acid (eqs 8–10), generating the corresponding carbamoyl radical.

$$S_2O_8^{=} + Ag(I) \longrightarrow SO_4^{2-} + SO_4^{\cdot-} + Ag(II) \quad (8)$$

$$SO_4^{\cdot-} + Ag(I) \longrightarrow SO_4^{2-} + Ag(II) \quad (9)$$

$$\text{R-NH-CO-COOH} + Ag(II) \rightleftharpoons \text{R-NH-CO-COO-}Ag(II) + H^{+} \longrightarrow$$
$$\longrightarrow \text{R-NH-CO} + CO_2 + Ag(I) \quad (10)$$

The conditions, much milder compared to the decarboxylation of primary carboxylic acids by the same catalytic system,[3] suggest that the oxidation might take place through an "inner-sphere" (eq 10) rather than through an "outer-sphere" (eq 11) electron-transfer mechanism.

$$\text{R-NH-CO-COOH} + Ag(II) \longrightarrow \text{R-NH-CO-COO}^{\cdot} + Ag(I) + H^{+} \longrightarrow$$
$$\longrightarrow \text{R-NH-CO} + CO_2 \quad (11)$$

† Dedicated to Professor Glen A. Russell on the occasion of his 70th birthday.

® Abstract published in *Advance ACS Abstracts,* July 1, 1995.

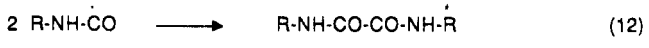
(1) Richter, R.; Ulrich, H. *The Chemistry of Cyanates and their Thio Derivatives*; Patai, S., Ed.; Wiley: New York, 1977; p 619.

(2) Minisci, F.; Fontana, F.; Coppa, F. *Ital.* Pat. MI93A002277, 1993.

(3) Fontana, F.; Minisci, F.; Nogueira Barbosa, M. C.; Vismara, E. *Tetrahedron* **1990**, *46*, 2525 and references cited therein.

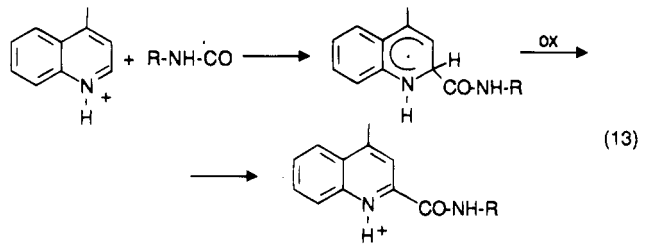
0022-3263/95/1960-5430$09.00/0

The presence of silver salt is necessary but not sufficient to obtain a selective reaction because, in addition to the isocyanate, the diamide of oxalic acid is also formed in substantial amount; these results represent strong evidence that carbamoyl radical intermediates are involved in the reaction. The oxidation of the carbamoyl radical to the isocyanate must not be particularly fast under these conditions, so that it can attain a steady state concentration suitable for competitive homocoupling (eq 12).



(12)

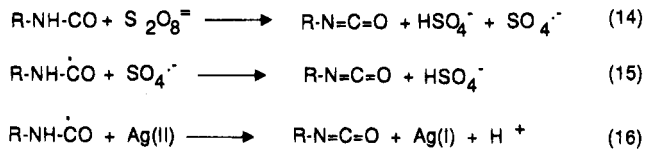
Further evidence of the intermediate formation of the carbamoyl radical and of its relatively slow oxidation to isocyanate was obtained in the presence of protonated lepidine under the same conditions. No isocyanate and no diamide were formed; the only reaction was the selective substitution of lepidine by the carbamoyl radical (eq 13).



(13)

We have previously shown that carbamoyl radicals have a clear-cut nucleophilic character and react selectively with protonated heteroaromatic bases.[4]

The oxidation of carbamoyl radicals to isocyanates can be determined in principle by the three oxidizing species present in the reaction medium, namely $S_2O_8^{2-}$, $SO_4^{\bullet-}$, and Ag(II) (eqs 14–16).



(14)
(15)
(16)

We believe that reactions 15 and 16 should be very fast, but their involvement would be limited by the low steady state concentrations of highly reactive species such as $SO_4^{\bullet-}$ and Ag(II); thus, reaction 14 would be mainly responsible for the oxidation of the carbamoyl radical. It appears to be a relatively slow reaction, as the coupling of the carbamoyl radical (eq 12) is a competitive process. Reaction 14 is, in any case, significantly slower than the addition of the carbamoyl radical to the protonated heteroaromatic bases, while it is much faster than the oxidation of the alkyl radicals generated by decarboxylation of carboxylic acids under the same conditions.[5] We explain the faster oxidation of the carbamoyl radicals compared to the alkyl radical by the relatively high acidity of the –NHCO group, due to the much lower energy of the –NH– bond in the radical compared to the energy of the same bond in the corresponding amides.

(4) Minisci, F., Porta, O. *Adv. Heterocycl. Chem.* **1974**, *16*, 166. (b) Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* **1985**, *41*, 4157. (c) Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *J. Chem. Soc., Chem. Commun.* **1983**, 916. (d) Coppa, F.; Fontana, F., Lazzarini, E.; Minisci, F. *Heterocycles* **1993**, *36*, 2687.

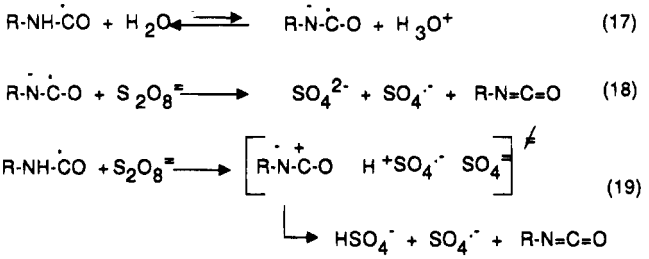
(5) Minisci, F.; Citterio, A. *Adv. Free-Radical Chem.* **1980**, *6*, 109.

Table 1. Synthesis of Isocyanates RN=C=O from RNHC(O)COOH

R	solvent	yield (%) isocyanate	yield (%) diamide
n-Pr	CH_2Cl_2	73	
n-Pr[a]	CH_2Cl_2	51	16
i-Pr	CH_2Cl_2	77	
n-Bu	CH_2Cl_2	72	
n-Bu[a]	CH_2Cl_2	49	22
n-Bu	hexane	83	
i-Bu	CH_2Cl_2	79	
i-Bu[a]	CH_2Cl_2	53	20
t-Bu	CH_2Cl_2	74	
t-Bu[a]	CH_2Cl_2	46	14
t-Bu	hexane	85	
cyclohexyl	hexane	78	
cyclohexyl[a]	hexane	52	24
cyclohexyl	1,2-dichloroethane	81	
cyclohexyl	CH_2Cl_2	87	
benzyl	CH_2Cl_2	84	
benzyl	hexane	76	
2-phenylethyl	hexane	84	
2-phenylethyl	1,2-dichloroethane	78	
2-phenylethyl	CH_2Cl_2	80	
2-phenylethyl[a]	CH_2Cl_2	58	18
phenyl	CH_2Cl_2	55	
p-chlorophenyl	CH_2Cl_2	46	
p-methylphenyl	CH_2Cl_2	45	

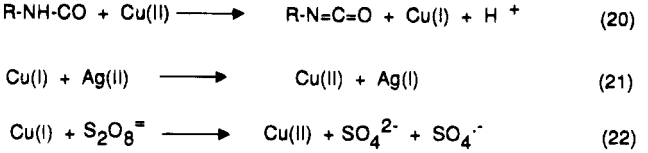
[a] In the absence of $Cu(OAc)_2$.

This relatively high acidity should be reflected either in an acid–base equilibrium (eq 17) and a faster oxidation of the corresponding anion (eq 18) or in a polar contribution to the transition state of the electron-transfer oxidation (eq 19).



(17)
(18)
(19)

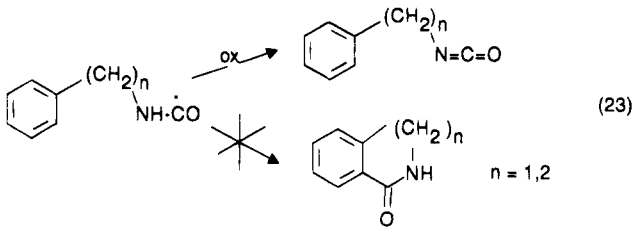
To eliminate the competitive formation of the diamide of oxalic acid (eq 12), we have utilized catalytic amounts of $Cu(OAc)_2$. This way, no diamide of oxalic acid is formed and the yields in isocyanate increase, as shown by the results in Table 1. The cupric salt selectively oxidizes the carbamoyl radicals (eq 20), and it is regenerated by oxidation of the cuprous salt (eqs 21 and 22).



(20)
(21)
(22)

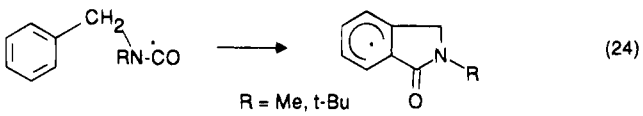
N-Benzyl and *N*-(2-phenylethyl) amides of oxalic acid give high yields of isocyanate (Table 1) and no cyclization products, indicating that the oxidation of the carbamoyl radical is prevailing over the intramolecular addition to the benzene ring (eq 23).

Carbamoyl radicals of dialkylamines cannot give isocyanates; the oxidation of the corresponding carbamoyl radicals is, however, slower compared to the carbamoyl radicals of primary alkylamines, thus supporting the importance of the acidity of the –NHCO– group in

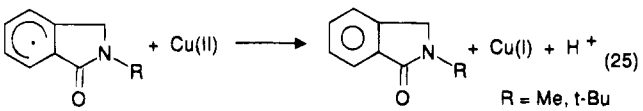


(23)

determining the oxidation rate. Thus, *N*-methyl-*N*-benzyl- and *N*-*tert*-butyl-*N*-benzylcarbamoyl radicals give the diamide of oxalic acid and the intramolecular cyclization (eqs 24 and 25) under the same conditions in which the *N*-benzylcarbamoyl radical gives the isocyanate without formation of the carbamoyl radical dimer (eq 12).



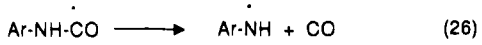
(24)



(25)

This represents the first example of intramolecular homolytic aromatic carbamoylation. The intermolecular free-radical carbamoylation of the benzene ring has never been reported, while the corresponding reaction with protonated heteroaromatic bases is an important substitution in the heterocyclic series.[4]

Yields of isocyanates are generally higher with aliphatic than with aromatic amides (Table 1); in this latter case, significant amounts of aniline oxidation products are formed, probably due to a partial decarbonylation of the carbamoyl radical (eq 26), determined by the higher stabilization of the *N*-arylamino radicals or to a faster decomposition of aryl isocyanates by water (eq 6).



(26)

A detailed investigation has been carried out for the synthesis of 2,6-diisopropylphenyl isocyanate, due to the commercial interest of the product. The results under various conditions are reported in Table 2.

The choice of the organic solvent in the two-phase system plays a fundamental role, as it affects the distribution of the monoamides of oxalic acid and of the isocyanates between the aqueous and organic solvents. The solubility of water in the organic solvent must be the lowest possible to minimize the decomposition of the isocyanates (eq 6).

A successful attempt has been carried out to directly obtain carbamates from the monoamides of oxalic acid by working in a homogeneous alcoholic medium with $(n\text{-}Bu_4N^+)_2S_2O_8^{2-}$; in this case the initially formed isocyanate reacts with the solvent, leading to the corresponding carbamate (eq 27).

(27)

However, the disadvantages of utilizing $(n\text{-}Bu_4N^+)_2S_2O_8^{2-}$ in anhydrous alcohol overcome the advantage of minimizing the decomposition of the isocyanate by water. The carbamates can be simply obtained in the two-phase system by separating the organic solvent and by adding the suitable alcohol.

Table 2. 2,6-Diisopropylphenyl Isocyanate from 1 mmol of the Oxalic Monoamide, 1 mmol of $(NH_4)_2S_2O_8$, 0.1 mmol of $AgNO_3$, and 0.01 mmol of $Cu(OAc)_2$

solvent	*T* (°C)	*t* (h)	yield (%)
toluene	50	4	27
ethyl acetate	50	4	19
hexane	50	4	60
CH_2Cl_2	40	4	73
$C_2H_4Cl_2$	50	4	37
$C_2H_4Cl_2$	83	0.5	62
$C_2H_4Cl_2$	83	4	53
CH_2Cl_2	40	0.5	49
CH_2Cl_2	40	1	65
CH_2Cl_2	40	2	77
CH_2Cl_2	40	4.5	72
hexane	69	0.25	59
hexane	69	0.5	73
hexane	69	5	71
hexane	rt	7	23

Experimental Section

General Procedure for the Synthesis of Monoamides of Oxalic Acid. The monoamides of oxalic acid were prepared by slight modifications of the known procedure:[6] 50 mmol of ClC(O)C(O)OMe (Fluka) and 65 mmol of pyridine were dissolved in 70 mL of CH_2Cl_2 at 0 °C; then 55 mmol of the amine was added dropwise at 0 °C; after 1 h the mixture was allowed to reach room temperature; the precipitated pyridine hydrochloride was filtered and the CH_2Cl_2 solution was washed twice with 5% aqueous H_2SO_4 and then with water. The solvent was removed under vacuum, and the residue was substantially pure monoamide of oxalic acid methyl ester (>98% by GLC). The product was dissolved in 60 mL of CH_3OH, and a solution of 55 mmol of KOH in 50 mL of CH_3OH was added by dropping at 15 °C. The precipitated RNHC(O)C(O)OK was filtered and washed with CH_3OH and Et_2O. Yields were in all cases >80%.

The diamides of oxalic acid were prepared from the corresponding amines and oxalyl chloride according to the known procedure.[7]

General Procedure for the Synthesis of Isocyanates. (A) A mixture of 30 mL of water, 30 mL of organic solvent, 5 mmol of the monoamide of oxalic acid, 7.5 mmol of $(NH_4)_2S_2O_8$, 0.5 mmol of $AgNO_3$, and 0.05 mmol of $Cu(OAc)_2$ was warmed to 40 °C for 3 h. The organic phase was separated and analyzed by GLC. All the isocyanates were identified by comparison with commercial samples (NMR, IR, MS, GLC) with the exception of $PhCH_2CH_2NCO$, which was identified by IR (2270 cm^{-1}, $-N=C=O$) and NMR.

(B) The same procedure as in A, but in the absence of $Cu(OAc)_2$, was used. The results are reported in Table 1. Table 2 reports the results obtained with 2,6-diisopropylaniline under various conditions. Characterization of 2,6-diisopropylphenyl isocyanate by IR (2280 cm^{-1}, $-N=C=O$) and NMR.

Synthesis of 1a and 1b. A mixture of 30 mL of water, 30 mL of CH_2Cl_2, 5 mmol of *N*-benzyl-*N*-methyl(or *tert*-butyl)-monoamide of oxalic acid, 7.5 mmol of $(NH_4)_2S_2O_8$, 0.5 mmol of $AgNO_3$, and 0.05 mmol of $Cu(OAc)_2$ was refluxed for 3 h. The organic phase was separated and the aqueous phase further extracted with CH_2Cl_2. The CH_2Cl_2 solution was analyzed by GLC. **1a** and **1b** and the corresponding oxalic diamides were obtained in 27%, 53%, 30%, and 8% yields, respectively; **1a** and **1b** were separated by flash chromatography on silica gel (hexane:ethyl acetate 7:3) and analyzed by NMR, MS, and IR.

The *N*-benzyl-*N*-methyl- and *N*-benzyl-*N*-*tert*-butyldiamides of oxalic acid were identified by comparison with authentic samples obtained from oxalyl dichloride and the corresponding amines.

(6) Henry, L. *Chem. Ber.* **1871**, *4*, 598.
(7) Armbrecht, B. H.; Rice, L. M.; Grogan, C. H.; Reid, E. E. *J. Am. Chem. Soc.* **1953**, *75*, 4829.

Reaction in the Presence of Lepidine. The procedure B was utilized with the *N*-cyclohexylamide of oxalic acid in the presence of 5 mmol of lepidine and 5 mmol of H_2SO_4. No isocyanate or oxalic diamide was formed, but 2-(*N*-cyclohexylcarbamoyl)-4-methylquinoline was obtained in 87% yield.

Synthesis of Ethyl *N*-Cyclohexylcarbamate. A solution of *N*-cyclohexylmonoamide of oxalic acid (5 mmol), $(n\text{-}Bu_4N)_2S_2O_8$ (7.5 mmol), 0.5 mmol of $AgNO_3$, and 0.05 mmol of $Cu(OAc)_2$ in 40 mL of ethanol was refluxed for 3 h. The solvent was removed under vacuum, and the residue was extracted by CH_2Cl_2. GLC revealed the formation of the ethyl *N*-cyclohexylcarbamate in 55% yield; the compound was identified by comparison with an authentic sample obtained from cyclohexyl isocyanate and ethanol.

JO950131W