Reactivity of Carbamoyl Radicals: the First General and Convenient Free-radical Synthesis of Isocyanates

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The first free-radical synthesis of isocyanates was performed by oxidation of oxalic acid monoamides by $S_2O_8^{2-}$, catalysed by silver(I) and copper(II) salts, in a two-phase system.

Isocyanates represent an important class of organic compounds, which have found wide-ranging applications in organic and polymer chemistry. Numerous methods are available for their synthesis,[1] but the phosgenation of amines is the most widely utilized, due to the low cost of the reagents. Phosgene, however, is volatile and very toxic and its use requires particularly expensive safety apparatus.

Here we report the first free-radical synthesis of isocyanates; this method, which for the low cost and toxicity of the reagents, the general character and the simple experimental conditions is suitable also for practical applications,[2] is based on the oxidation of the monoamides of oxalic acid in a two-phase system (water and an organic solvent such as CH_2Cl_2, $ClCH_2CH_2Cl$, hexane) by $S_2O_8^{2-}$, catalysed by Ag^I and Cu^{II} salts [eqn (1)].

$$\text{R-NH-COCO}_2\text{H} + \text{S}_2\text{O}_8^{2-} \xrightarrow[\text{Cu}^{\text{II}}]{\text{Ag}^{\text{I}}} \text{R-N=C=O} + \text{CO}_2 + 2\text{HSO}_4^- \qquad (1)$$

The two-phase system is of critical importance for the success of the synthesis because the oxidation takes place in the aqueous phase, while the isocyanate must be extracted by the organic solvent in order to avoid its decomposition by water. The monoamides of oxalic acid are very easily obtained by treating amines with oxalic acid, esters of oxalic acid or oxalyl monochloride, according to simple classical procedures. The results are reported in Table 1.

Table 1 Isocyanates (R–N=C=O)[a] from $RNHCOCO_2H$

R	Solvent	Yield (%)
Bu^n	CH_2Cl_2	72
Bu^n	Hexane	83
Bu^t	CH_2Cl_2	74
Bu^t	Hexane	85
Cyclohexyl	CH_2Cl_2	87
"	Hexane	78
"	1,2-Dichloroethane	81
Benzyl	CH_2Cl_2	84
"	Hexane	76
2-Phenylethyl	CH_2Cl_2	80
"	CH_2Cl_2	58[b]
"	Hexane	84
"	1,2-Dichloroethane	78
Ph	CH_2Cl_2	55
p-Chlorophenyl	CH_2Cl_2	46
p-Methylphenyl	CH_2Cl_2	45

[a] *Reagents and conditions*: Organic solvent (30 cm^3), water (30 cm^3), $RNHCOCO_2H$ (5 mmol), $(NH_4)_2S_2O_8$ (7.5 mmol), $AgNO_3$ (0.5 mmol), $CuSO_4$ (0.05 mmol), 40°C, 3 h. All the isocyanates were identified by comparison (NMR, IR, MS, GLC) with commercial (Aldrich) samples with the exception of $PhCH_2CH_2N{=}C{=}O$, identified by IR (2270 cm^{-1}), –N=C=O); NMR δ 2.85–2.95 (t, 2 H), 3.45–3.55 (t, 2 H), 7.2–7.4 (m, 5 H); MS m/z 147 (M^+), major peak 91 ($M^+ - CH_2 - NCO$), minor peaks 129 ($M^+ - H_2O$), 119 ($M^+ - CO$), 103 ($M^+ - CONH$). [b] Reaction in the absence of $CuSO_4$; 18% of the diamide $(PhCH_2CH_2NHCO)_2$ is also formed.

The mechanistic details will be discussed in a full paper, but the free-radical character of the reaction is well defined. The formation of alkyl[3] and acyl[4] radicals by silver-catalysed decarboxylation of carboxylic acids by $S_2O_8^{2-}$ is well established; moreover, when a protonated heteroaromatic base is present under the same conditions, no isocyanate is formed, while the carbamoyl radical is quantitatively trapped by the heteroaromatic base,[5] in agreement with the known[6–9] reactivity of the latter. No isocyanate is formed in the absence of silver salt, whereas its formation does occur if no Cu^{II} salt is added, though with low selectivity: in this case significant amounts of the dimer of the carbamoyl radicals, *i.e.* oxalic acid diamides, $(RNHCO)_2$ are formed, providing further evidence for a radical mechanism.

Yields are higher with aliphatic than with aromatic amides; in this latter case significant amounts of aniline oxidation products are formed, probably due either to competitive electron-transfer oxidation of the amidic nitrogen or to a partial decarbonylation of the carbamoyl radical determined by a higher stabilization of the *N*-arylamino radical compared to the *N*-alkylamino radical or to a faster decomposition of arylisocyanates by water. It is very likely that the yields reported in Table 1 can be improved by selecting the most suitable solvent for each substrate, because the solubilities of the monoamides and of the corresponding isocyanates in aqueous and organic phases play a fundamental role.

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