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Articles

Urea as an Efficient Reagent for the Synthesis of 3-Ethyl-3-(hydroxymethyl)oxetane: A Novel Component in Cationic Ring-Opening Polymerisation

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Abstract:

Urea is a very attractive chemical raw material for large-scale production as it combines low cost with virtually unlimited supply and essentially no toxic effects. Here, we present a study on its use in the dehydration of trimethylolpropane with formation of 3-ethyl-3-(hydroxymethyl)oxetane. The reaction consists of carbonylation of trimethylolpropane and subsequent extrusion of carbon dioxide. The first step was run at a temperature of 120−160 °C at a pressure of approximately 300 mmHg for 1−5 h. Most likely, carbamates of TMP constitute the major product. In the latter step, the temperature was increased to 195−215 °C, the pressure was reduced to 10−50 mmHg, and the final product was isolated by distillation. A spiroorthocarbonate of TMP was formed as an unexpected by-product. The process has been demonstrated on a multikilogram scale. Toxicological screening revealed 3-ethyl-3-(hydroxymethyl)oxetane to be irritating to eye but not to skin.

Introduction

Although radiation-curable coating systems based on the acid-catalyzed ring opening of epoxides began to be marketed some two decades ago, they have been been slow to gain widespread acceptance.[2] Undoubtedly, the cationic cure of epoxides has some advantages over the free radical cure of, for example, acrylates. Two important advantages are that cure does not suffer from oxygen inhibition and minimal shrinkage occurs on cure. On the other hand, the number of components available to paint and ink formulators has been low, in contrast to the plethora of acrylates available. A greater number of components provides a greater freedom to compose systems optimised for specific applications. In recent years, the title compound, 3-ethyl-3-(hydroxymethyl)-oxetane (trimethylolpropane oxetane, TMPO) has appeared as a promising new compound for cationic photopolymerisation. Above all, TMPO confers increased cure speed, low viscosity, and low toxicity to formulations.[3]

Oxetanes have earlier been synthesised[4] from, for example, 1,3-carbonates,[5−7] by dehydrohalogenation of 1,3-halohydrins,[8] by ring-closure of 3-hydroxyalkyl sulphates,[9,10] or from alkenes and carbonyl compounds via the Paterno−Büchi reaction.[11] The route using 1,3-carbonates appeared the most interesting to us as it seemed fairly straightforward to scale up. Furthermore, when oxetanes are prepared from dialkyl carbonates (e.g, diethyl carbonate) and 1,3-diols, no corrosive chemicals are involved and no salt waste is generated, in contrast to routes based on phosgene. We were, however, concerned about the cost of the auxiliary carbonate and initiated a search for other raw materials. Urea appeared to be a most promising alternative.

Urea[12,13] was the first organic compound to be prepared in vitro by man. In 1828 Wöhler found that inorganic ammonium cyanate may be converted to organic urea. Urea is one of the principal nitrogenous excretion products of mammals. The human body produces 20−30 g of urea per day. Technically, urea is manufactured predominantly by dehydration of ammonium carbamate. The global installed capacity in 1993 was estimated to 43 Mton.[14] Urea is used for soil and leaf fertilisation (>90% of the total use), in the manufacture of urea−formaldehyde resins, in melamine production, for cattle feed production, and in various small applications (pharmaceutical, brewing, petroleum industry). As a typical bulk product, urea has a very low price.

As a carbonyl-transfer agent, urea may be evaluated in comparison with dimethyl carbonate and phosgene (Table

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[2] Davidson, S. *Exploring the Science, Technology and Applications of UV and EB Curing*; Sita Technology Limited: London, 1999.

[3] Conference proceedings: Carroy, A.; Chomienne, F.; Nebout, J. F. *RadTech Europe 99*; Berlin, Germany, November 8−10, 1999.

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[12] Meessen, J. H.; Petersen, H. *Ullman's Encyclopedia of Industrial Chemistry*; VCH Verlagsgesellschaft: Weinheim, 1996; Vol. *A27*, p 333.

[13] *Gmelins Handbuch der anorganischen Chemie, Kohlenstoff, Verbindungen*; Verlag Chemie GmbH: Weinheim/Bergstrasse 1971; Vol. *D1*, Chapter 45, p 389.

[14] Lauriente, D. H. Urea 758.00A. In *Chemical Economics Handbook*; SRI International, 1995.

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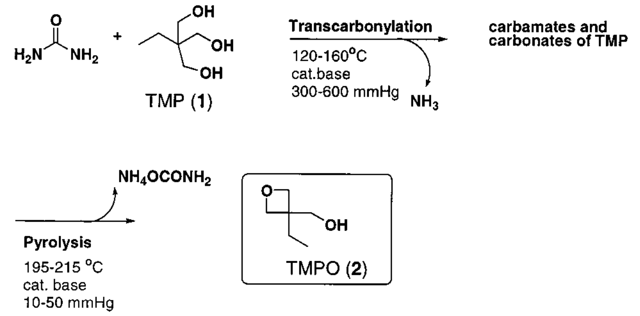
Table 1. **Properties of carbonyl sources**

carbonyl source	safety hazards	cost[a] (US \$/lb, \$/mol)	coproduct	reactivity
urea	none	0.07, 0.009	ammonia	low
dimethyl carbonate	highly flammable	1.4, 0.30	methanol	moderate
phosgene	very toxic	0.74, 0.16	hydrogen chloride	high

[a] *Chem. Mark. Rep.* **2000**, *257* (23), 26−33.

Scheme 1



1). There are numerous reports on the use of urea for preparing carbonates from alcohols. Some of those describe the synthesis of cyclic carbonates from 1,2- and 1,3-diols under the action of metal catalysts.[15] It is also known that cyclic and polymeric carbonates can be pyrolytically converted to oxetanes, and our objective was to link the urea-based carbonylation of trimethylolpropane with pyrolysis.[6,7] When we began the work presented here, only a very low-yielding urea-based process with respect to the monooxetane of pentaerythritol had been disclosed.[16]

Results and Discussion

We had had positive experience regarding preparations of hexyl carbamate/dihexyl carbonate and bis-(2-ethylhexyl) carbonate from urea, employing hexanol or 2-ethylhexanol, respectively, in the presence of zinc or tin catalysts. Thus, initially we chose $Zn(OAc)_2$ or $Bu_2Sn(OMe)_2$[17] for the carbonylation (140−195 °C, 10−760 mmHg, 3−5 h) of trimethylolpropane (**1**, TMP). However, the yield of TMPO (**2**) upon pyrolysis (195−210 °C, 10−760 mmHg, 2−4 h) never exceeded 10% based on urea. The same yield was reached even without added catalyst. Searles and co-workers[7] obtained oxetanes through pyrolyses of cyclic carbonates with basic/nucleophilic catalysts present. Accordingly, we also added small amounts of potassium or sodium hydroxide, which resulted in synthetically useful reactions (Scheme 1, Table 2). Later it turned out that zinc acetate could be omitted. The reaction time (1−5 h) and the temperature (120−160 °C) during the first stage of the reaction, the transcarbonylation, was not crucial to the yield of TMPO, as confirmed by analysis of data obtained from a series of factorially designed experiments.

Table 2. **Formation of oxetane 2 from triol 1 and urea**[a]

TMP (**1**)/urea (molar ratio)	catalyst[b]	recovered (%)[c] **1**	yield (%)[c]		
			2[d]	**3**	**4**
1:1	$Zn(OAc)_2$/KOH	*e*	(54)	*e*	*e*
1.2:1	$Zn(OAc)_2$/KOH	37	42 (51)	*e*	18
2:1	$Zn(OAc)_2$/KOH	70	30 (60)	*e*	*e*
4:1	KOH	70−79[f]	17−20[f] (67−80[f])	0−2[f]	0−1[f]

[a] TMP (**1**), urea (20−25 g), and catalysts were kept at 140 °C (ca. 300 mmHg) for 1−5 h. The pyrolysis was performed at 195−215 °C (10−50 mmHg) for 2−4 h. [b] 1.5−2 mol % of each relative to total amount of components. [c] Relative to starting amount of TMP (**1**). Determined by ^1H NMR unless otherwise stated. [d] Figures in parentheses are relative to starting amount of urea. [e] Not determined. [f] Determined by GC (hexadecane as internal standard).

Use of excess of TMP resulted in very clean reactions, as demonstrated in the case of TMP/urea 2:1. After TMPO (**2**) had been distilled off, the remaining polyol was mixed with fresh urea, and the process was repeated with results essentially identical to those of the first cycle. This indicates that using an excess of TMP does not represent a loss of material.

The transcarbonylation was usually run at reduced pressure (300 mmHg) to remove ammonia. During this period, the urea lost about 50% of its nitrogen as ammonia, which was collected in a cooling trap (N_2(l)). These measurements were made in experiments on a laboratory scale. The remaining fragments of urea, most probably, existed as carbamates/carbonates of TMP, not exceeding 250 ("peak M_w") in molecular weight as determined by size-exclusion chromatography. This suggested that polymeric carbonates were not produced.[18] No evidence for the presence of carbonate **5** was found.[19] At the end of the transcarbonylation, the ^1H NMR spectrum of the reaction mixture showed two or more groups of signals between 4.0 and 4.5 ppm (CH_2O_2C), as well as a strong, broad signal around 6.5 ppm (NH_2/OH). The IR spectrum revealed a strong carbonyl signal centered at 1730 cm^{-1}.

Urea is known to decompose to biuret, triuret, and cyanuric acid around and above its melting point (132.6 °C).[20] Analysing samples withdrawn from a transcarbonylation mixture (130 °C, 760 mmHg, 10−60 min) indicated

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(15) See, for example: (a) Doya, M.; Ohkawa, T.; Kanbara, Y.; Okamoto, A.; Kimizuka, K. (Mitsubishi). EP 581131, 1994; *Chem. Abstr.* **1994**, *120*, 245070. (b) Doya, M.; Kimizuka, K.; Kanbara, Y. (Mitsubishi). EP 638541, 1998; *Chem. Abstr.* **1995**, *122*, 264907. (c) Mathys, G. M. K.; Saleh, R. Y.; Michaelson, R. C. (Exxon). GB 2280672, 1995; *Chem. Abstr.* **1995**, *123*, 2340. (d) Su, W.-Y.; Speranza, G. P. (Texaco Chemical Company). U.S. Patent 5,003,084, 1991; *Chem. Abstr.* **1991**, *114*, 247258.

(16) Watabe, Y.; Suzuki, T. (Mitsui Toatsu Chemicals). JP 07076541, 1995; *Chem. Abstr.* **1995**, *123*, 33860.

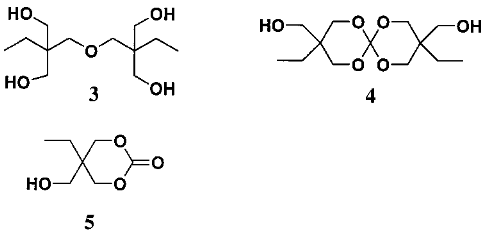
(17) This compound is very efficient in catalysing formation of bis-(2-ethylhexyl) carbonate from methyl carbamate; Suciu, E. N.; Kuhlmann, B.; Knudsen, G. A.; Michaelson, R. C. *J. Organomet. Chem.* **1998**, *556*, 41.

(18) The interconversion of cyclic and polycarbonates, and their decomposition to oxetanes has been studied, see ref 7 and references therein.

(19) ^1H NMR, the indicative signals, δ 4.33, 4.16 (each d, 2 H, $J = 11$ Hz, $OCOOCH_2$), were not found.

(20) See refs 12, p 334, and ref 13, p 412.

Scheme 2



declining levels of TMP and urea. The level of biuret during the sampling period was very low (<1%). Triuret could not be analysed, and cyanuric acid was not detected.

In the subsequent step, the pyrolysis (195−215 °C, 10−50 mmHg), crude TMPO was collected continuously by distillation from heavier constituents. Running the pyrolysis at temperatures above ca. 220 °C should be avoided due to possible decomposition of the components in the reaction mixture.[21]

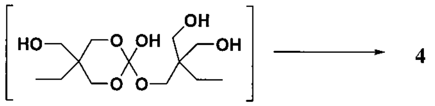
Some white solid always deposited in the cooler, but most of this material was found in the cooling traps. When running the process in the pilot plant, steam was flushed through the column and cooler at intervals to prevent clogging. The solid was shown to be ammonium carbamate (IR). Ammonium cyanate,[20] which was suspected to be present, could not be detected. The solid lost carbon dioxide and ammonia on heating (TGA-IR). In neither case was any cyanate signal found. The amount of this solid material corresponded to 40−50% of the nitrogen content of urea.

The same yields and selectivities as those given in Table 2 were found on a 6-fold scale-up (120 g of urea). However, in the pilot plant (ca. 50 kg of urea, TMP/urea = 1.47) the yield of TMPO declined (32% based on urea).

Besides TMP (**1**), the residue after separation of TMPO (**2**) contained spiroorthocarbonate **4** and small amounts of di-TMP (**3**).[22] Data from lab-scale experiments suggested formation of **4** to be promoted at a lower TMP/urea ratio. Its presence was indicated by TLC and ^{1}H NMR even after transcarbonylation at low temperature (120 °C, 14 h). According to size-exclusion chromatography, there was no build-up of polymeric species during pyrolysis either ("peak M_w" $\leq$ 250). The intermediacy of carbonate **5** remains uncertain (Scheme 2).

The spiroorthocarbonate **4** deserves further comments, since it could constitute a valuable by-product. Spiroorthocarbonates are known to polymerise with low volume reduction, which may have profound influence on adhesion and other properties of coatings.[23] Ring-opening polymerisations of such compounds can even occur with expansion in volume.[23a] Compared to previously published methods of preparation, which often rely on the use of toxic or corrosive chemicals,[23,24] spiroorthocarbonate **4** is formed here from environmentally benign raw materials. It may arise from an open carbonate of TMP, via a monocyclic intermediate (Scheme 3), which under the highly polar conditions might lose its center carbon hydroxyl in an S_N1-type process. A stabilised cation would result, and on ring-closure, spiroorthocarbonate **4** is formed.

Scheme 3



Toxicological Characterisation. The primary skin irritation effect of TMPO was investigated according to the method recommended by OECD.[25] Rabbits were exposed to the article at two skin sites on their back. After 4 h of exposure the test article was removed and the skin examined from 1 to 72 h after termination of exposure. No or very slight skin reactions were observed in all animals during the examination period. According to the directive of the Commission 93/21/EEC (April 27, 1993), TMPO should not be classified as a skin irritant. Also, the eye irritant effect of TMPO was investigated according to official recommendations.[26] One albino rabbit was exposed to 0.1 mL of the test article in the left eye. The eye was examined from 1 h to 14 days after dosing. Marked signs of corneal and conjunctival irritation were observed on early observations. On day 14, no abnormalities were observed in the rabbit. According to the same directive as above, TMPO should be classified as eye irritating.

Conclusions

This report summarises a novel route to 3-ethyl-3-(hydroxymethyl)oxetane. The approach uses inexpensive, widely available starting materials, urea and trimethylolpropane, and provides some mechanistic insights. This chemistry can be performed on a multikilogram scale and avoids use of environmentally malign chemicals. Toxicological screening revealed 3-ethyl-3-(hydroxymethyl)oxetane to be irritating to eye but not to skin.

Experimental Section

Materials. Urea (Svenska Foder), trimethylolpropane (**1**), and ditrimethylolpropane (**3**) (Perstorp Specialty Chemicals), 5-ethyl-5-hydroxymethyl-1,3-dioxan-2-one (**5**) (Synthelec AB, S-223 70 Lund), 46% sodium hydroxide (Norsk Hydro), biuret and cyanuric acid (Fluka), and ammonium carbamate (Aldrich) were used as received. An analytical sample of 3,9-diethyl-3,9-dihydroxymethyl-1,5,7,11-tetraoxaspiro[5,5]-undecane (**4**) was obtained by chromatographic purification of pyrolysis residues.

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(22) Under similar conditions pentaerythritol and urea are claimed to yield some dipentaerythritol and bis-3,3-(hydroxymethyl)oxetane, see ref 16.

(23) (a) Bailey, W. J.; Sun, R. L.; Katsuki, H.; Endo, T.; Iwama, H.; Tsushima, R.; Saigou, K.; Bitritto, M. M. *ACS Symp. Series (Ring-Opening Polym.)* **1977**, *59*, 38, (b) Lam, P. W. K.; Piggott, M. R. *J. Mater. Sci.* **1989**, *24*, 4069, (c) Chappelow, C. C.; Eick, J. D.; Pinzino, C. S. U.S. Patent 5,808,-108, 1998; *Chem. Abstr.* **1998**, *129*, 246078.

(24) (a) DeWolfe, R. H. *Synthesis* **1974**, 153, (b) Kantlehner, W.; Funke, B.; Haug, E.; Speh, P.; Kienitz, L.; Maier, T. *Synthesis* **1977**, 73, (c) Mues, P.; Buysch, H.-J. *Synthesis* **1990**, 249.

(25) (a) Acute Dermal irritation/Corrosion. OECD Guidline No. 404, EEC, 1992. (b) Acute Toxicity (skin irritation). Guidline B.4, 29.12.1992, Scantox: Denmark, 1992.

(26) (a) Acute Eye Irritation/Corrosion. OECD Guideline No. 405, Feb. 1987. (b) Acute Toxicity (Eye irritation). EEC, No. L 383A/127:29.12.1992, B.5, Scantox: Denmark, 1992.

Analyses. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker DRX-400 instrument. Mass spectra were recorded on a JEOL SX 102 spectrometer. IR spectra were obtained using a Nicolet Protégé 460 FTIR. For analyses of thermal decomposition products we utilised a Polymer Labs TGA 1000 instrument, equipped with a BioRad heated cell and connected to a BioRad FTS-40 IR spectrometer. Measurements were made under a nitrogen stream (25−400 °C, 20 °C/min). Differential scanning calorimetry was run under nitrogen (50 bar) on a DSC Mettler TA 8000 instrument (50−300 °C, 5 °C/min). For analytical liquid chromatography a Varian instrument (9010 gradient pump, 9100 autosampler, and 9050 UV detector), equipped with a Genesis C18 column (150 mm × 4.6 mm, 4 μm), was used. Aqueous potassium dihydrogenphosphate buffer (0.1 M, pH 6.79) at 0.8 mL/min was used for elution. Size-exclusion chromatography (SEC) was performed with a system consisting of a Scantec 650 HPLC pump, a Spark Holland injector, a PLgel 5 μ column and a Varian RI-4 detector, using dimethylformamide as eluent. A sample of poly(ethylene glycol)s was used for calibration. Gas chromatographic analyses were made after silylation (BSTFA, pyridine) on a HP 6890 instrument equipped with a 30 m DB 5 capillary column, using hexadecane as internal standard. Potentiometric titrations were made with a Radiometer (Copenhagen) TitraLab 90. The identity of by-products was confirmed by comparison with authentic samples (see Materials).

Typical Synthesis of TMPO (2) in the Pilot Plant. To a 300 L reactor, equipped with column, condenser, and inlets for water vapour and nitrogen, were added trimethylolpropane (**1**, 150 kg, 1.12 kmol) and aqueous sodium hydroxide (46%, 2.30 kg, 26.4 mol). The contents were stirred and heated to approximately 100 °C, and the water was distilled off at 600 mmHg. Then urea (45.6 kg, 0.760 kmol) was charged, the temperature was raised to 140−150 °C, and the pressure was lowered to 600 mmHg. The mixture was agitated for 3 h, whereupon the temperature was slowly raised to 195 °C. Thereafter, the pressure was very slowly reduced to 45 mmHg. From time to time water vapour was injected at the top of the column to prevent clogging by ammonium carbamate. Crude TMPO distilled and was collected, 42 kg. According to GC, the purity was 67%, and the contained yield was 32% based on urea. Fractions from several batches were combined and re-distilled to a purity of 99%.

Relative to the starting amount of **1**, the reaction residue contained di(trimethylolpropane) **3** and spiroorthocarbonate **4** in 8 and 16% yields, respectively. No polymeric components were found in the reactor during the entire process (SEC, "peak M_w" $\leq$ 250).

TMPO (2). ^{1}H NMR ($CDCl_3$): in agreement with literature data.[27] ^{13}C NMR ($CDCl_3$): δ 78.46; 65.62; 44.70; 26.59; 8.58.

Spiroorthocarbonate 4. ^{1}H NMR (DMSO-d_6):[23c] δ 4.65 (t, 2H, *OH*); 3.65 (t, 4H); 3.60−3.50 (dd, 4H); 3.35 (d, 4H); 1.22 (q, 4H); 0.75 (t, 6H). ^{13}C NMR ($CDCl_3$): δ 115.0; 67.70; 67.24; 61.89; 37.02; 23.44; 7.55. HRMS ($CI-CH_4$): Calcd ($C_{13}H_{25}O_6$): 277.1651; found 277.1674. DSC: mp 83.5 °C; heat of decomposition 23.15 kJ/mol (150−293 °C, peak 268.5 °C).

Further Analyses Pertaining to Lab-Scale Experiments. Transcarbonylation (Table 2) was performed at 140 °C (300 mmHg). A cooling trap (liquid nitrogen) was connected between the reaction apparatus and the water jet pump. Before starting the pyrolytic step, the content of the cooling trap was taken up in water, and the aqueous solution allowed to reach room temperature. It was then weighed and submitted to potentiometric titration with 0.01 M HCl (aq); about 50% of the nitrogen of urea was trapped as ammonia. The remaining reaction mixtures were submitted to ^{1}H NMR and IR; apart from signals associated with the trimethylolpropane skeleton, signals between 4.0 and 4.5 ppm (CH_2O_2C), and at 6.5 ppm (NH_2/*OH*) were also observed, as well as a strong C═O signal at 1730 cm^{-1}. NMR indicated the absence of cyclic carbonate **5**, although spiroorthocarbonate **4** sometimes appeared to be present (NMR/TLC) even at this stage.

The apparatus was furnished with a clean cooling trap, and the process was continued at 195−215 °C (10−50 mmHg). When TMPO distillation ceased, the products (Table 2) were analysed by NMR, GC, and SEC. The solid in the condenser and cooling trap was shown to be ammonium carbamate (IR, TGA/IR). Its weight corresponded to 40−50% of the nitrogen of charged urea.

In a similar experiment (TMPO/urea/KOH 1:1:0.04, 760 mmHg, 130 °C) samples were withdrawn at intervals (10−60 min) and analysed for TMP (GC), TMPO (GC), urea (HPLC), biuret (HPLC), and cyanuric acid (GC). Analysis indicated declining levels of TMP and urea but only low levels of biuret (<1%) and TMPO (<1%). Triuret could not be analysed, and cyanuric acid was not detected.

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