Tetrahydropyranyl protecting group. I. Tetrahydropyran-2-yl isocyanate

D. E. HORNING AND J. M. MUCHOWSKI

Bristol Laboratories of Canada, Candiac, Quebec

Received April 10, 1968

It is shown that monoalkyl and unsymmetrical dialkyl ureas, and alkyl carbamates, are preparable *via* a two-step sequence involving tetrahydropyran-2-yl isocyanate, and a primary or secondary amine, or an alcohol, respectively.

Canadian Journal of Chemistry, 46, 2617 (1968)

The synthesis of monoalkyl and/or unsymmetrical dialkyl ureas is usually accomplished¹ by the alkylamination of isocyanic acid, the amination of alkyl isocyanates and carbamyl chlorides, and by amine exchange with urea. Each method has specific advantages, but none is generally applicable.

The decomposition of nitrourea (into nitramide and isocyanic acid) in the presence of a suitable amine is reported (3) to be an excellent route to both mono and unsymmetrical dialkyl ureas, but this attractive method has not enjoyed widespread application.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by CONCORDIA UNIV on 07/10/13 For personal use only.

In connection with another problem, we required a method whereby medium quantities of high molecular weight ureas (of the type discussed above) could be obtained routinely and efficiently. The solution, in our estimation, was essentially one of equipping isocyanic acid with a "handle" whose removal could be easily accomplished subsequent to urea formation. The results presented below show that the tetrahydropyranyl group adequately fulfilled the stipulated requirements.

Tetrahydropyran-2-yl isocyanate, which has recently been described in the patent literature (see Experimental), is a stable liquid conveniently prepared in the laboratory from 2-chlorotetrahydropyran and silver cyanate. It reacted with primary and secondary amines to give excellent yields of 1-alkyl-3-tetrahydropyran-2-yl and 1,1dialkyl-3-tetrahydropyran-2-yl ureas (see Table I). Their structures were substantiated by a nitrogen analysis, by infrared absorptions at 3435 ± 20 , 3355 ± 25 , 1665 ± 15 , and 1550 ± 15 cm⁻¹ for the 1,3-disubstituted members,² and at 3468, 1652, and 1514 cm⁻¹ for the trisubstituted compound, and lastly, and most significantly, by the conversion to the known ureas (Table II) in satisfactory overall yield.

$$RR_{1}NH + (\bigcirc NCO \rightarrow RR_{1}NCONH \rightarrow RR_{1}NCONH_{2}$$

The removal of the tetrahydropyranyl group was effected with 1% hydrochloric acid (ca. 0.1 N) in refluxing 10% aqueous methanol (1 h).³ For preparative purposes, the high yields obtained in the initial condensation, make the purification of the intermediate unnecessary; it is sufficient to evaporate the solvent *in vacuo*, and then to proceed directly with the cleavage of the tetrahydropyranyl group.

Tetrahydropyranyl isocyanate can also be used to synthesize alkyl carbamates, as is exemplified by the preparation of benzyl carbamate in 82% overall yield from the corresponding alcohol.

¹For brief compilations of the methods used to synthesize these compounds see refs. 1 and 2, and the papers cited therein.

²A series of eight 1,3-disubstituted ureas had strong absorption bands which occurred within the four specified regions. An absorption at 1670 cm⁻¹ has been tentatively assigned to the carbonyl stretching frequency of ureas (4). ³These conditions are somewhat more vigorous than necessary since 1-benzyl-3-tetrahydropyran-2-yl urea was

³These conditions are somewhat more vigorous than necessary since 1-benzyl-3-tetrahydropyran-2-yl urea was completely converted to benzyl urea in 2.5 h at room temperature, or in less than 5 min at reflux temperature. (The progress of the reaction was followed by thin-layer chromatography on alumina.)

The protected urea was recovered unchanged after 1 h at reflux temperature in benzene-containing acetic acid and a trace of *p*-toluenesulfonic acid.

CANADIAN JOURNAL OF CHEMISTRY. VOL. 46, 1968

TABLE I

1-Substituted-3-tetrahydropyran-2-yl ureas*

| | | | Melting point | % N | | Crystallization [†] |
|---|-------------------------|------------------------|--|-----------------------------------|----------------------------------|------------------------------|
| R | R ₁ | Yield (%)† | (°C)† | Calculated | Found | solvent |
| n-Butyl n-Propyl Benzy! Phenyl | H n-propyl H H | 86 100§ 95 93 | 79–81 60–64 118–120 181.5–183 | 13.99 11.38§ 11.96 12.72 | 13.88 11.56 12.08 12.81 | A A B C |

*The preparation sequence can be represented as:

$RR_1NH +$ $-NCO \rightarrow RR_1NCONH$

[†]The yields and melting points refer to once crystallized products. Unless otherwise stated, the analytical specimens had the tabulated melting points. [‡]A, cyclohexane – petroleum ether (b,p. 35–60°); B, benzene-cyclohexane; C, benzene. [§]100% Yield of the cyclohexane solvate, $C_{12}H_{24}N_{20}$:1/6 C_6H_{12} . The presence of cyclohexane was corroborated by a strongly ringing peak of the correct intensity at 61.40 in the n.m.r. spectrum. No other solvent absorptions were detectable. [¶]The analytical specimen had m.p. 185–186°.

TABLE II 1-Substituted ureas*

| R | | | Melting point (°C)† | | Crustallization |
|-----------------|----|------------|----------------------|----------------|-----------------|
| | R1 | Yield (%)† | Observed | Reported | solvent |
| <i>n</i> -Butyl | H | 46‡§ | 97–98 133 135 ¶** | 96¶ 136 ** | Benzene |
| Benzyl | H | 728 | 147–149 | 150†† | Ethyl acetate |
| Phenyl | Н | 76 | 147–148 | 147 | Water |

$$\operatorname{RR}_{1}\operatorname{NCONH}_{O} \rightarrow \operatorname{RR}_{1}\operatorname{NCONH}_{2}$$

The yields and melting points refer to once crystallized products. The yields are based on the starting amine. After chromatography on silica gel and crystallization. Without isolation of the intermediate tetrahydropyranyl urea. See ref. 3. Ilsolated as the picrate. **Melting point of the picrate. †See ref. 5.

RR₁

Experimental

The melting points were determined in a Gallenkamp melting point apparatus and are not corrected. The infrared (i.r.) spectra were measured in chloroform on a Perkin-Elmer 237-B grating spectrophotometer. The nuclear magnetic resonance (n.m.r.) spectrum was determined in deuteriochloroform at 60 Mc.p.s. on a Varian A-60A spectrometer, with tetramethylsilane as an internal standard.

Tetrahydropyran-2-yl Isocyanate

A 1 l, 3-necked flask, equipped with a calcium chloride tube, a thermometer, and a gas inlet tube, was charged with 800 ml of anhydrous benzene, and 35.0 g (0.29 mole) of 2-chlorotetrahydropyran (6). The magnetically stirred solution was cooled to 0°, and while the apparatus was flushed with purified dry nitrogen, 58.0 g (0.386 mole) of silver cyanate (7) was added all at once; a 6° temperature rise occurred. The cooling bath was removed and the mixture was stirred at room temperature for 2 h with protection from light. The solids were removed by filtration through Celite, the filter cake was washed with dry benzene, and the filtrate was flash distilled in vacuo

(ca. 15 mm) below 30°. The oil which remained was fractionally distilled *in vacuo*, and the fraction, 23.2 g, b.p. $61-62^{\circ}/16 \text{ mm}$, $u_{D}^{20} = 1.4519$, was collected. The flash distillate from above was evaporated in vacuo at 20° to give 2.1 g of an oily residue, which on fractionation in vacuo gave an additional 1.15 g of the isocyanate. The combined yield was 24.35 g (66.5).

Tetrahydropyranyl isocyanate had a strong i.r. absorption (liquid film) at 2257 cm⁻¹. The n.m.r. spectrum consisted of a singlet with fine structure at δ 5.07, a complex multiplet between δ 3.50 and 4.15, and a broad singlet at δ 1.68, with an integral ratio of 1:2:6 respectively.

This isocyanate has recently been prepared from isocyanic acid and tetrahydropyran (8), and from 2-chlorotetrahydropyran and alkali metal cyanates in mixed solvent systems (9). It is reported to have b.p. $51-52^{\circ}/7$ nim (8), and 47–48°/11 mm, and $n_D^{20} = 1.4500$ (9).

Preparation of Ureas

(a) 1-Substituted-3-tetrahydropyran-2-yl Ureas

A solution of 1.27 g (10 mmoles) of tetrahydropyran-2yl isocyanate in 30 ml of anhydrous benzene containing 10 mmoles of the amine, was heated at reflux temperature for 2 h. If the urea did not crystallize on cooling, the solvent was removed in vacuo, and the solid residue was crystallized from the solvent system indicated in Table I.

Alternatively, the crude residue could be used directly in the next step as described below.

(b) 1-Substituted Ureas

The urea, in a solution made up of 1 part of 10% hydrochloric acid and 9 parts of methanol (10 ml/mmole), was heated at reflux temperature for 1 h on a steam bath. Most of the solvent was removed in vacuo, the residue was diluted with water, and the urea was extracted into ethyl acetate. The dried (sodium sulfate) extract was evaporated in vacuo, and the residue was crystallized from the appropriate solvent (Table II), or it was taken up in ether and added to an excess of picric acid in the same solvent

Renzvl Carhamate

To a solution of the isocyanate (1.907 g, 15 mmoles) in 45 ml of dry benzene, was added 1.58 ml (1.65 g, 15.3 mmoles) of benzyl alcohol and 1 ml of anhydrous pyridine. After 24 h at reflux temperature (when 5 wt % of sodium hydride was utilized as a catalyst, the reaction was complete in 4 h), the solvent was removed in vacuo, the solid residue was taken up in hot cyclohexane (10 ml) diluted with 10 ml of petroleum ether (b.p. 30-65°), seeded, and left to cool. A beautifully crystalline solid, 3.19 g, m.p. 82-83° was obtained. Evaporation of the mother liquor and crystallization of the residue as above, gave an additional 0.06 g of the product, m.p. 81-82.5°. The combined yield was 3.25 g or 92.2% based on the isocyanate. For analysis, the solid was twice crystallized from the above solvent system, and then dried in vacuo over phosphorous

pentoxide at room temperature for 15 h. The melting point was not raised.

Anal. Calcd. for C13H17NO3: N, 5.95. Found: N, 6.07,

The tetrahydropyranyl group was removed in the same manner as described in the urea section. The yield of benzyl carbamate obtained upon crystallization of the crude product from 1:1 benzene-cyclohexane, was 89% or 82% based on the starting isocyanate. The product had m.p. 85-88°, undepressed on admixture with an authentic specimen of benzyl carbamate.

- 1. R. B. WAGNER and H. D. ZOOK. Synthetic organic chemistry. John Wiley and Sons, Inc., New York. 1961.p.645.
- P. A. S. SMITH. Open-chain nitrogen compounds. Vol. 1. W. A. Benjamin, Inc., New York. 1965. p. 275.
 T. L. DAVIS and R. C. BLANCHARD. J. Am. Chem.
- Soc. 51,1790 (1929).
 L. J. BELLAMY. The infrared spectra of complex molecules. 2nd ed. Methuen and Co. Ltd., London. 1958. p. 223.
- W. L. GARBRECHT and R. M. HERBST. J. Org. Chem. 5. 18, 1014 (1953).
- C. D. HURD and R. D. KIMBROUGH. J. Am. Chem. 6. Soc. 83, 236 (1961).
- 7. L. BIRCKENBACH and M. LINHARD. Ber. 62, 2261 (1929)
- J. L. HARPER. U.S. Patent No. 3, 168, 545 (1965);
 Chem. Abstr. 62, 11689 (1965).
 K. F. ZENNER, G. OERTEL, and H. HOLTSCHMIDT.
 Ger. Patent No. 1, 205, 087 (1965); Chem. Abstr. 64, 10420 9. 19413 (1966).

Oligomerization of isoprene

KYOICHI SUGA, SHOJI WATANABE, HIDEO KIKUCHI, AND TORU WATANABE Department of Applied Chemistry, Faculty of Engineering, Chiba University, Yayoicho, Chiba, Japan Received March 20, 1968

The oligomerization of isoprene with lithium naphthalene and the dimerization of isoprene with alkali dispersion are described. Isoprene dimer, prepared by the action of lithium naphthalene, is a mixture of 2,6-dimethyl-2,6-octadiene and 2,7-dimethyl-2,6-octadiene, but the trimer, tetramer, and hexamer are a mixture of 3,4-adducts of isoprene to the above mentioned isoprene dimer. The authors have found that alkali dispersion in the presence of a Lewis base is able to dimerize isoprene.

Canadian Journal of Chemistry, 46, 2619 (1968)

It is well known that alkali naphthalene and alkali dispersion are effective for the natural polymerization of conjugated dienes. The studies on the microstructure of polyisoprene and polybutadiene have been investigated by many workers (1). These studies have not, however, confirmed the production of oligomers of isoprene, such as monoterpene and sesquiterpene. The natural oligomerization of α -methylstyrene to the tetramer has recently been studied (2), but the oligomerization of isoprene has not been reported. It may be suspected that an oligomer of isoprene may be prepared from the monomer in the presence of excess lithium naphthalene. The authors prepared various isoprene oligomers by the action of lithium naphthalene and alkali dispersion in tetrahydrofuran solution.

Anionic oligomerization of isoprene, involving lithium naphthalene and proceeding in a tetrahydrofuran solution in the usual fashion (3), affords isoprene oligomers, and the typical results are presented in Table I. From these results, it can be said that the use of 1 mole of isoprene per mole of lithium gives mainly the