

## 206. Steric Carbonyl Protection Metalation and Cleavage of Highly Hindered Ureas

Preliminary communication

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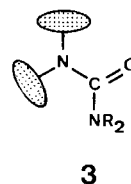
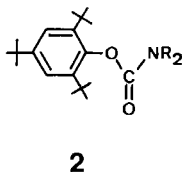
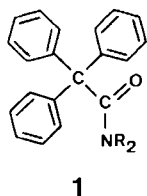
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### Summary

Ureas of type **3** with sterically protected carbonyl groups such as **4a-7a** are prepared by successively adding 2 equivalents of a highly substituted sec. amine and an excess of dimethylamine to benzene or toluene solutions of phosgene. The piperidine derivatives **6a** and **7a** are metalated in high yields to **6b** and **7b**, respectively, with *sec.*-butyllithium/TMEDA in THF at 0° [see derivatives **6**, **7** (c-i) in *Table 1*]. Methods of cleaving urethanes **2** (see **8** → **9**) and ureas **3** are described, among which the *retro-Mannich* reaction, removing the piperidine ring from **7** under acidic hydrolysis conditions, appears to be promising also for other applications of sterically blocked carbonyl compounds in organic synthesis.

In previous papers we have shown that imides [1] and amides with sterically protected but electronically effective carbonyl groups such as triphenyl-acetamides (**1**) [2] or tris(*t*-butyl)phenoxy-derivatives (**2**) [3] can be metalated at the *α*-N-CH-

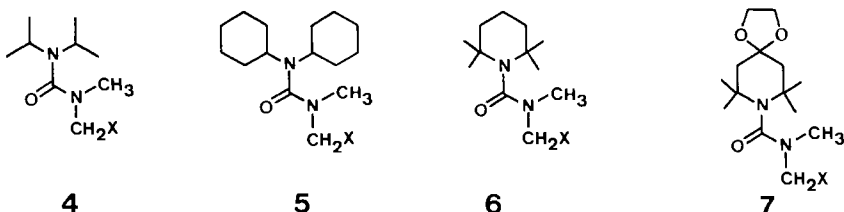


<sup>1)</sup> Part of the planned dissertation of *T.H.*, Universität Giessen.

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position *and* cleaved to amines under appropriate conditions. We then turned our attention to ureas **3** with bulky substitution at one of the nitrogen atoms.

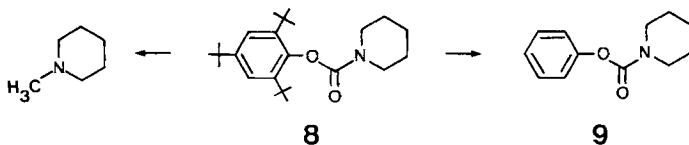
Following a procedure described for the preparation of **4a** [4] [5], we obtained the ureas **4a-7a** from phosgene and the corresponding amines<sup>3)</sup> in yields ranging from 65 to 85% (calc. from  $\text{COCl}_2$ ), see *Table 1*. Treatment of the urea solutions in THF with *sec*-butyllithium/TMEDA (1.1 equiv.) for 6 hours at  $-80^\circ$  in the case



- |   |  |   |  |
|---|--|---|--|
| a | X=H  | f | X=C(OH)(CH <sub>3</sub> ) <sub>2</sub> |
| b | X=Li   | g | X=CH <sub>3</sub>                      |
| c | X=C(OH)(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> | h | X=C <sub>8</sub> H <sub>17</sub>       |
| d | X=CH(OH)(C <sub>6</sub> H <sub>5</sub> )             | i | X=C <sub>10</sub> H <sub>21</sub>      |
| e | X=CH(OH)( <i>n</i> -C <sub>5</sub> H <sub>11</sub> ) |   |  |

of **4a** and **5a** and for 1.5 hours at  $0^\circ$  with **6a** and **7a** produced the lithio derivatives **4b**, **5b**, **6b**, and **7b** in yields of 23 (reaction with benzophenone), 60 ( $\text{CH}_3\text{I}$ -quenching), >95 ( $\text{CH}_3\text{I}$ -quenching), and 80% (trapping with benzaldehyde), respectively<sup>4)</sup>. The alkylations and hydroxyalkylations of these novel nucleophiles furnished ureas **4-7** (c-i) of higher methyl alkyl amines, see *Table 1*. Evidently, the lithio derivatives **6b** and **7b** would be effective aminomethylating reagents if the products could be cleaved under mild conditions.

Of course, the cleavage of amides and ureas with sterically effective carbonyl protection poses problems. The most obvious approach is to strip off the bulky groups which prevent the carbonyl carbon atoms from being attacked by nucleophiles, rather than using forcing conditions. For example, it takes treatment with



LAH in refluxing dioxane to convert **8** into *N*-methyl piperidine [3]. In contrast, the removal of the *t*-butyl groups in a *Friedel-Crafts* transalkylation (toluene/ $\text{AlCl}_3$ , *cf.* [8]) to give **9**, and subsequent alkaline hydrolysis [9] is a much milder procedure, compatible with a variety of functional groups.

A similar situation is encountered in the case of the ureas **4-7** without and with "Achilles' heel". The dicyclohexyl urea **5c** could be cleaved only with LAH in

<sup>3)</sup> The non-commercially available acetal amine in **7** was prepared following [6].

<sup>4)</sup> For unsuccessful attempts of metalating tetramethyl urea see [7].

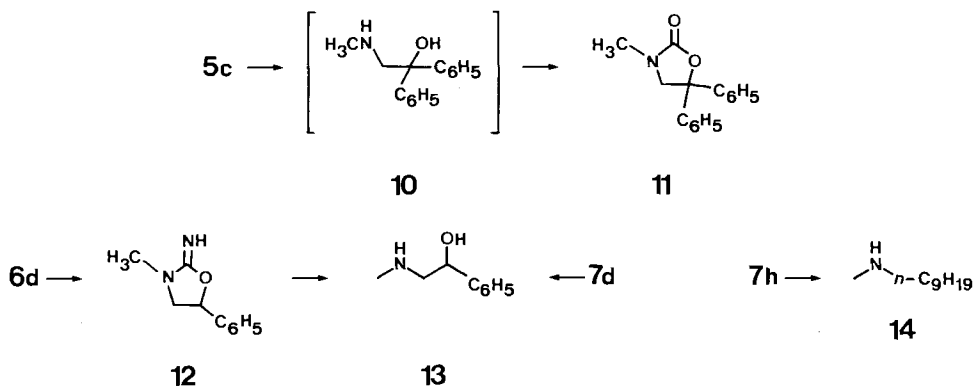
dioxane to give the aminoalcohol **10** (and dicyclohexylmethylamine); **10** was identified as the oxazolidone **11**. The tetramethylpiperidine derivative **6d** is completely stable towards LAH; it is however amenable to acid cleavage, since the nitrogen atom bears a tertiary carbon atom (*retro-Ritter*-type reaction); when refluxed in conc. hydrochloric acid, the iminoxazolidine **12** is formed and is readily hydrolyzed (KOH/C<sub>2</sub>H<sub>5</sub>OH/H<sub>2</sub>O) to ( $\pm$ )-halostahine (**13**). The highest degree of lability is already built into the acetals **7**, which under conditions of acidic hydrolysis undergo a *retro-Mannich*-reaction (*cf.* [10]). Thus, the ureas **7d** and **7h**, when treated

Table 1. Yields and some physical data of the compounds **4c-14**. The IR. absorptions of the CO groups in alkylated ureas **4-7** (a,g,h,i) are found around 1645 cm<sup>-1</sup> while the hydroxyalkyl derivatives **4-7** (c,d,e,f) absorb near 1610 cm<sup>-1</sup>, often the bands are broad or multiple. All ureas are exceedingly stable thermally, see b.p. The NMR. shifts are given in  $\delta$ -values [ppm] measured in CDCl<sub>3</sub> with TMS as internal standard. All yields are those of distilled or recrystallized, analytically pure samples.

Compound	Yield [%]	M.p. [°C] B.p. [°C/Torr]	<sup>1</sup> H-NMR.
<b>4c</b>	23	127	2.53 (s, N-CH <sub>3</sub> ); 4.10 (s, NCH <sub>2</sub> )
<b>5a</b>	84	66	2.73 (s, N(CH <sub>3</sub> ) <sub>2</sub> )
<b>5c</b>	43	141	2.48 (s, NCH <sub>3</sub> ); 4.00 (s, NCH <sub>2</sub> )
<b>6a</b>	76	69	1.20 (s, 2C(CH <sub>3</sub> ) <sub>2</sub> ); 3.02 (s, N(CH <sub>3</sub> ) <sub>2</sub> )
<b>6c</b>	81	127	1.0 and 1.33 (2s, 2C(CH <sub>3</sub> ) <sub>2</sub> ); 2.63 (s, NCH <sub>3</sub> ); 4.26 (s, NCH <sub>2</sub> )
<b>6d</b>	89	183/0.4	1.03, 1.06, 1.33 and 1.36 (4s, 2C(CH <sub>3</sub> ) <sub>2</sub> ); 3.10 (s, NCH <sub>3</sub> ); 3.23-3.96 (m, NCH <sub>2</sub> )
<b>6e</b>	75	127/5 · 10 <sup>-3</sup>	3.23 (s, NCH <sub>3</sub> )
<b>6f</b>	52	180/5 · 10 <sup>-3a</sup> )	1.16 and 1.36 (2s, 2C(CH <sub>3</sub> ) <sub>2</sub> ); 1.26 (s, C(OH)(CH <sub>3</sub> ) <sub>2</sub> ); 3.26 (s, NCH <sub>3</sub> ); 3.45 (s, NCH <sub>2</sub> )
<b>6g</b>	77.5	130/0.3 <sup>a</sup> )	1.16 (t, CH <sub>2</sub> CH <sub>3</sub> ); 1.16 and 1.26 (2s, 2C(CH <sub>3</sub> ) <sub>2</sub> ); 3.03 (s, NCH <sub>3</sub> ); 3.50 (qa, NCH <sub>2</sub> )
<b>6i</b>	68	124/0.3	3.12 (s, NCH <sub>3</sub> )
<b>7a</b>	80	93	1.33 (s, 2C(CH <sub>3</sub> ) <sub>2</sub> ); 1.73 (s, 2 pip-CH <sub>2</sub> ); 3.1 (s, N(CH <sub>3</sub> ) <sub>2</sub> ); 4.0 (s, O(CH <sub>2</sub> ) <sub>2</sub> O)
<b>7c</b>	70	177	1.03 and 1.43 (2s, 2C(CH <sub>3</sub> ) <sub>2</sub> ); 1.63 (doubletoid, 2 pip-CH <sub>2</sub> ); 2.70 (s, NCH <sub>3</sub> ); 3.77-4.13 (m, O(CH <sub>2</sub> ) <sub>2</sub> OH); 4.27 (s, NCH <sub>2</sub> )
<b>7d</b>	77.5	184/5 · 10 <sup>-3</sup>	1.13, 1.16, 1.43 and 1.46 (4s, 2C(CH <sub>3</sub> ) <sub>2</sub> ); 1.68 (s, 2 pip-CH <sub>2</sub> ); 3.07 (s, NCH <sub>3</sub> )
<b>7h</b>	72	160/5 · 10 <sup>-3</sup>	1.73 (s, 2 pip-CH <sub>2</sub> ); 3.13 (s, NCH <sub>3</sub> )
<b>8</b>	100	151	1.35 (s, <i>p-t</i> -C <sub>4</sub> H <sub>9</sub> ); 1.40 (s, 2 <i>o-t</i> -C <sub>4</sub> H <sub>9</sub> ); 1.5-1.7 (br. signal, 6 pip-CH <sub>2</sub> ); 3.4-3.8 (2 br. signals, $\alpha$ -N-pip-CH <sub>2</sub> ); 7.39 (s, 2 arom. H)
<b>9</b>	90	79 ([11] 80°)	
<b>11</b>	71	159	2.93 (s, NCH <sub>3</sub> ); 4.18 (s, NCH <sub>2</sub> )
<b>12</b>	61	180/0.1 <sup>a</sup> )	2.88 (s, NCH <sub>3</sub> ); 3.28 and 3.74 (2 <i>pseudo-t</i> , NCH <sub>2</sub> ); 5.30 ( <i>pseudo-t</i> , OCH)
<b>13</b>	55 from <b>12</b> 68 from <b>7d</b>	75 ([12] 76)	
<b>14 · HCl</b>	57	180 ([13] 180)	

<sup>a</sup>) Air temperatures measured during bulb to bulb distillation with a Büchi GKR-50.

first with 2N HCl in THF/H<sub>2</sub>O and then with aqueous KOH in EtOH/H<sub>2</sub>O, gave the alkaloid **13** (68%) and the amine **14** (57%), respectively<sup>5</sup>).



All new compounds showed correct elemental analyses and were fully characterized by spectroscopic data, some of which are given in the accompanying *Table*. The substances described previously (**4a** [5], **9** [11], **13** [12] and **14** [13]) had physical properties identical with those given in the literature.

The results reported here extend the methodology of  $\alpha$ -N-CH-acidification [14] and increase the variety of conditions by which steric carbonyl protection can be achieved and subsequently removed.

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<sup>5</sup>) Yields are of non-optimized, preliminary experiments.