One-Pot Synthesis of \(N,N,N',N'-\)Tetrasubstituted Ureas and Oxomalonamides by Oxidative Carbonylation of Lithium Amides at Atmospheric Pressure

Norma S. Nudelman,* Elizabeth S. Lewkowicz, Daniel G. Pérez
Departamento de Química Orgánica, Facultad de Ciencias Exactas, Universidad de Buenos Aires, Pab. II, P. 3, Ciudad Universitaria, 1428 Buenos Aires, Argentina

\(N,N,N',N'\)-tetrasubstituted ureas have been obtained in good yields by reaction of lithium aliphatic amides in tetrahydrofuran solution with carbon monoxide under mild conditions (0°C, 1013 mbar) followed by treatment with oxygen prior to work up. \(N,N,N',N'\)-tetrosubstituted oxomalonamides (oxopropanediamides) can be obtained under similar reaction conditions by carrying out the reaction in the presence of known amounts of the pure amine. Besides being an useful synthetic method, the present studies afford new evidence of the mechanism of the reaction.

In addition to the rapid development of synthesis gas chemistry for the industrial generation of bulk materials\(^1\)–\(^4\) there is a recent interest in the use of carbon monoxide as a building block in the synthesis of higher value fine chemicals in smaller volume.\(^3\)–\(^6\) There are numerous examples for its use in the synthesis of \(N\)-substituted formamides, especially using transition-metal catalysts.\(^7\)–\(^11\)

\(N,N\)-disubstituted ureas are usually prepared by reaction of isocyanates or phosgene with amines or by direct carbonylation of amines or nitro compounds in the presence of a transition-metal complex.\(^11\),\(^12\) Ureas have also been obtained by oxidative carbonylation of amines by various oxidizing agents.\(^13\) The oxidative carbonylation of amines by carbon monoxide and oxygen in the presence of a catalyst system containing a palladium-group metal and either an alkali metal halide or an onium halide\(^14\)–\(^17\) has been reported.

Surprisingly, no methods based on carbonylation of amines have been described for the preparation of oxomalonamides. Recently, we have reported the synthesis of \(N,N\)-disubstituted formamides and glyoxal-amides by the carbonylation of lithium amides.\(^18\) Here we describe the preparation of \(N,N,N',N'\)-tetrasubstituted ureas and oxomalonamides in good yield from lithium amides and carbon monoxide at atmospheric pressure under mild conditions, followed by \textit{in situ} oxidation.

\begin{center}
\begin{tabular}{ccc}
\hline
\textbf{I–4} & \textbf{R}^1 & \textbf{R}^2 \\
\hline
\textbf{a} & Bu & Bu \\
\textbf{b} & \(c\text{-C}_6\text{H}_{11}\) & \(c\text{-C}_6\text{H}_{11}\) \\
\textbf{c} & \(\epsilon\text{-Pr}\) & \(c\text{-C}_6\text{H}_{11}\) \\
\hline
\end{tabular}
\end{center}

Scheme A
Table 1. Reaction of Lithium Dialkylamides with Carbon Monoxide

<table>
<thead>
<tr>
<th>Amide</th>
<th>Solvent</th>
<th>( R_2NH/ ) ( R_2NLi )</th>
<th>Yield (%) of Products:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1a</td>
<td>THF*</td>
<td>(4 : 5)</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>(1 : 5)</td>
<td>–</td>
</tr>
<tr>
<td>1b</td>
<td>THF/BrLi</td>
<td>(4 : 5)</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>(1 : 5)</td>
<td>–</td>
</tr>
<tr>
<td>1c</td>
<td>THF/hexane (5 : 1)</td>
<td>(4 : 5)</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>hexane</td>
<td>(1 : 5)</td>
<td>12</td>
</tr>
</tbody>
</table>

* Reaction at \(-78^\circ C\). For all the other cases \(0^\circ C\).

Carbonylation of lithium dicyclohexylamide\(^{19}\) \((1b)^{20}\) produces three main products: dicyclohexylformamide \((2b)\), dicyclohexylglyoxylamide \((3b)\), and tetracyclohexyltartronamide \((4b)\); \(N,N,N',N'-\)tetracyclohexylhydroxypropanediamide \((\text{Scheme A})\).

A careful evaluation of the different factors influencing the carbonylation reactions of several lithium amides, resulted in development of conditions for the synthesis of compounds having structure 3 in 85–100% yields.\(^{18}\)

Factors such as the amine/lithium amide ratio, solvents and cosolvents, addition of "inert" salts, among others, were now examined and adjusted to lead the reaction toward production of one of the other two products: compounds 2 or 4. Table 1 shows the optimum conditions for conversion of lithium amides 1a–c to either substituted formamides 2 in variable yields or to tartronamides 4 in high yield.

For the synthesis of \(N,N,N',N'-\)tetrasubstituted ureas, 5, the carbonylation is carried out under the conditions that favor the formation of compounds 2. For the preparation of \(N,N,N',N'-\)tetrasubstituted oxomalanamides, 6, the reaction conditions are those that lead to the production of compounds 4. In both cases, the carbonylation reaction mixture is treated with dry oxygen before workup (Scheme B).

The results are shown in Table 2. It can be observed that substituted ureas are produced in variable yields while the procedure is excellent for the synthesis of substituted oxomalanamides.

By comparison with the results in Table 1 it is surprisingly observed that the yield of compounds 6 is always higher than that of compounds 4, while that is not the case when comparing the yields of compounds 5 and 2, suggesting that the mechanisms are not straightforward.

Formation of ureas from the oxidative carbonylation of 1 indicates that the precursor to 2 is not the carboxamoyl, 7, as reported previously,\(^{26}\) but another intermediate, 8, produced by the addition of a second molecule of 1 to 7 (Scheme C).

Scheme C

Ureas are proved to be formed by the oxidation of intermediate 8. In fact, 8a was prepared from the reaction of 1a with 2a and by further treatment with oxygen, 5a was obtained in good yield.

Oxomalanamides are produced by the oxidation of dilithium tartronamides, intermediate 10. Compound 10a was independently prepared by the reaction of 4a with 1a; its further treatment with oxygen renders 6a as the main product, and tetrabutylxolalamide, 11a (less than 10%)(Scheme D).

The physical and spectral characteristics of compounds 5 and 6 are gathered in Tables 3 and 4. By comparing the reaction conditions and the yields obtained by conventional procedures (see experimental section) with those of Table 2, it can be observed that the present reaction

Table 2. Oxidative Carbonylation of Lithium Dialkylamides

<table>
<thead>
<tr>
<th>Amide</th>
<th>Solvent</th>
<th>Method</th>
<th>( R_2NH/ ) ( R_2NLi )</th>
<th>Yield (%) of Products:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>1a</td>
<td>THF*</td>
<td>A</td>
<td>(4 : 5)</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>B</td>
<td>(1 : 5)</td>
<td>7</td>
</tr>
<tr>
<td>1b</td>
<td>THF/BrLi</td>
<td>A</td>
<td>(4 : 5)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>B</td>
<td>(1 : 5)</td>
<td>4</td>
</tr>
<tr>
<td>1c</td>
<td>THF/hexane (5 : 1)</td>
<td>A</td>
<td>(4 : 5)</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>hexane</td>
<td>B</td>
<td>(1 : 5)</td>
<td>6</td>
</tr>
</tbody>
</table>

* Reaction at \(-78^\circ C\). For all the other cases \(0^\circ C\).
Bu₂NLi + Bu₂N\(\overset{O}{\underset{\text{Bu₂NLi}}{\to}}\) OH

\[\text{Bu₂N} = \text{Bu₂N} + \text{Bu₂NLi}\]

\[\text{Bu₂NLi} + \text{Bu₂N} = \text{Bu₂N} + \text{Bu₂NLi}\]

\[\text{Bu₂NLi} + \text{Bu₂N} = \text{Bu₂N} + \text{Bu₂NLi}\]

\[\text{Bu₂NLi} + \text{Bu₂N} = \text{Bu₂N} + \text{Bu₂NLi}\]

Scheme D

has the following advantages over the classical methods: a) is one-step; 2) the reaction time is very short; 3) amine is the starting material; 4) the yields are higher. Although full results are presented only for three different amines, the reaction was also tested with other amines such as: diethylamine, dipropylamine, dipentylamine, piperidine and morpholine.

The only observed limitation is the pKₐ-value of the amine; good yields of compounds 5 and 6 are obtained for amine whose pKₐ in tetrahydrofuran is lower than 35. Morpholine, for instance, failed to yield 5 or 6, producing only 1-formylmorpholine.

IR spectra were recorded on a Perkin-Elmer 121 spectrophotometer using KBr pellets for solid and KBr plates for liquid materials. ¹H- and ¹³C-NMR spectra were measured on a Varian 100 MHz spectrometer. Mass spectra were obtained on a Varian Mat spectrometer. Solvents and amines were dried in the usual manner,¹a distilled and stored under a nitrogen atmosphere. Solvents were distilled from lithium benzenophene ketyl immediately prior to use.

**Lithium Dialkylamides 1; General Procedure:**

The corresponding R¹R²NH (7.4 mmol) is added dropwise by cannula to a stirred solution of BuLi in hexane (7 mL, 0.7 N) cooled in an ice bath. The precipitated lithium amide is centrifugated, the solution is removed, and the white crystals are washed with hexane (3 × 5 mL) followed by centrifugation each time. The resulting solid is dried under vacuum at r.t. Atmospheric pressure is restored by flushing with dry, O₂-free N₂.

For the case of lithium isopropylecyclohexylamine (1c), which is soluble in hexane, the preparation is similar but, since no solid is formed, the solvent is distilled at reduced pressure through a cannula until the total volume left is nearly 1.5–2 times the volume of the added amine. The resulting syrup is dissolved in the desired solvent and used immediately.

**N,N,N',N'-Tetrasubstituted Ureas 5 and N,N,N',N'-Tetrasubstituted Oxomalonamides 6; General Procedure:**

A round-bottomed flask containing a Teflon-coated stirring bar is heated in a vacuum oven at 130–150 °C for at least 30 min and then cooled in a dried N₂ atmosphere. Ligron (3–4 mL) is added and heated to boiling until almost complete evaporation. With the remaining ligron still boiling, the flask is capped with a no-air stopper, it is left to cool at r.t. and then put into an ice bath with vigorous magnetic stirring. A solution of R¹R²NLi (0.5 M) in THF (7–8 mL) containing free amine in a ratio R¹R²NH/R¹R²NLi (4:5, Method A) to yield product 5 and (1:5, Method B) to yield product 6 is added by cannula. When necessary the cosolvent or the lithium salt is then added. The stirred solution is exposed to CO at ca. 1013 mbar. The bulk of the CO is absorbed within the first 3–4 min, and the gas absorption is complete in 10–15 min after this, dry O₂ is flushed into the flask and distilled H₂O (1–2 mL) is added. The remaining CO is evacuated, THF (10 mL) and then

---

**Table 3. N,N,N',N'-Tetrasubstituted Ureas 5 Prepared**

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Molecular Formula</th>
<th>IR (cm⁻¹)</th>
<th>¹H-NMR (CDCl₃/TMS) δ, J (Hz)</th>
<th>¹³C-NMR (CDCl₃/TMS), δ</th>
<th>MS (70 eV) m/z (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>38</td>
<td>C₁₄H₁₄N₂O₂ (284.5)</td>
<td>2900, 1635, 1460, 1305</td>
<td>0.85 (t, 2H, J = 6), 1.0–1.6 (m, 16H), 3.1 (t, 8H, J = 6)</td>
<td>14.1, 20.6, 31.3, 48.3</td>
<td>284 (M⁺, 1), 241 (2), 156 (44), 57 (100)</td>
</tr>
<tr>
<td>5b</td>
<td>62</td>
<td>C₁₅H₁₆N₂O₂ (388.6)</td>
<td>2970, 1680, 1430</td>
<td>1–2 (m, 40H), 4.3 (m, 4H)</td>
<td>25.4, 26.3, 31.2, 54.9</td>
<td>388 (M⁺, 0.4), 305 (2), 208 (53), 43 (100)</td>
</tr>
<tr>
<td>5c</td>
<td>54</td>
<td>C₁₅H₁₆N₂O₂ (308.5)</td>
<td>2950, 1670, 1420, 1360</td>
<td>1.5–2.4 (m, 32H), 3.7 (m, 4H)</td>
<td>20.8, 25.4, 26.1, 31, 45.7, 54.6</td>
<td>308 (M⁺, 0.2), 265 (2), 168 (54), 86 (100)</td>
</tr>
</tbody>
</table>

* a) Satisfactory microanalyses obtained: C ± 0.18, H ± 0.09, N ± 0.15.

b) IR- and ¹H-NMR spectra are consistent with literature data (ref. 29).

**Table 4. N,N,N',N'-Tetrasubstituted Oxomalonamides 6 Prepared**

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Molecular Formula</th>
<th>IR (KBr) (cm⁻¹)</th>
<th>¹H-NMR (CDCl₃/TMS) δ, J (Hz)</th>
<th>¹³C-NMR (CDCl₃/TMS), δ</th>
<th>MS (70 eV) m/z (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>77</td>
<td>oil</td>
<td>C₁₈H₂₄N₂O₃ (340.5)</td>
<td>2850, 1650, 1460, 1380</td>
<td>0.8 (m, 12H), 1–1.6 (m, 16H), 3.4 (m, 8H)</td>
<td>14.1, 20.6, 31.3, 48.3, 164.8</td>
<td>340 (M⁺, 93), 325 (24), 312 (47), 297 (45), 100 (100)</td>
</tr>
<tr>
<td>6b</td>
<td>78</td>
<td>200–201 (hexane)</td>
<td>C₂₀H₂₆N₂O₃ (444.6)</td>
<td>2870, 1650, 1300</td>
<td>1–1.8 (m, 32H), 2.7 (m, 8H), 3.05 (m, 2H), 4 (m, 2H)</td>
<td>25.7, 25.9, 26.1, 26.6, 31.2, 31.5, 56.6, 56.7, 167.9, 168.2</td>
<td>444 (M⁺, 0.4), 333 (3), 208 (83), 83 (100)</td>
</tr>
<tr>
<td>6c</td>
<td>71</td>
<td>133–134 (H₂O)</td>
<td>C₁₈H₂₆N₂O₃ (364.5)</td>
<td>2800, 1630, 1440, 1360</td>
<td>0.9 (d, 6H, J = 7), 1.45 (d, 3H, J = 6.5), 1.5 (d, 12H, J = 7), 1–1.8 (m, 12H), 2.7 (m, 4H), 3.1 (m, 4H), 4 (m, 2H), 4.3 (m, 2H)</td>
<td>20.6, 25.9, 26.9, 31.4, 47.2, 57.6, 165.7, 165.8</td>
<td>364 (M⁺, 0.7), 293 (2), 168 (99), 83 (100)</td>
</tr>
</tbody>
</table>

* a) Satisfactory microanalyses obtained: C ± 0.10, H ± 0.08, N ± 0.12.
NaHCO₃ (500 mg, 6 mmol) is added; after careful mixing the organic phase is quantitatively analyzed by GC. For preparative purposes, after quenching the reaction the organic layer is diluted with five volumes of Et₂O. The Et₂O extract is washed with 10% HCl (2 x 5 mL), sat. aq NaHCO₃ (5 mL) and H₂O (2 x 5 mL). The organic phase is dried; distillation of the solvent at reduced pressure afforded a yellow oil. The reaction mixture is chromatographed in a silica gel column using the eluents CH₂Cl₂ and EtOAc (Table 3, 4).

**Independent Synthesis of Oxidation Products 5 and 6; General Procedures:**

Most of the substituted ureas and oxomalonamides isolated from oxidative carbonylation of lithium amides in this paper have not been previously described. They are characterized by means of elemental analysis, IR, ¹H and ¹³C-NMR spectroscopy and mass spectrometry. The data (Tables 3 and 4) are identical to those of authentic samples prepared by independent methods.

N,N,N',N'-Tetraalkyl Substituted Ureas 5: Ethyl chloroformate (80 mg, 0.74 mmol) is added to a stirred solution of R¹R²RNLi (3.5 mmol) in THF (5 mL) and stirring is continued at rt. for 1 d. The reaction is quenched with H₂O (10 mL) and Et₂O (10 mL) and then added. The organic layer is washed with 10% HCl (2 x 10 mL) and H₂O (2 x 5 mL), dried (MgSO₄) and concentrated at reduced pressure. GLC shows that the resulting oil is pure. The obtained yields (calculated with respect to amine) vary in the range 20–30% depending on the amine used.

N,N,N',N'-Tetraalkyl Substituted Oxomalonamides 6: MnO₂ is used as oxidizing reagent.⁵³ MnO₂ (100 mg, 1.1 mmol) is suspended in a solution of N,N,N',N'-tetraalkylhydroxylammonaldehyde (50 mg, 0.11 mmol), prepared as previously described,¹⁸ in CH₂Cl₂ (8 mL) and the stirred mixture is refluxed for 5 h. The mixture is filtered, the precipitate washed with Et₂O and the whole filtrate is vacuum distilled. The residue is purified by preparative TLC (silica gel, EtOAc as eluent). The yields vary in the range 50–60% depending on the amine. For the reaction of (t-Pr)₂C₆H₁₃N[Li-SeO₂]₂₈ instead of MnO₂ is used, and the mixture refluxed for 6 h.

This research has been supported by the National Research Council from Argentina (CONICET). E.L. is a grateful recipient of a CONICET fellowship.

Received: 4 January 1990; revised: 17 April 1990


20. Although lithium dialkylamides are usually written as monomers (and so will be used hitherto) it is known¹² that they exist as dimers,²³ trimeres,²³ and tetramers.²⁴ It is highly probable that they also form complexes with the carbon monoxide¹⁵ before reaction.


