Preparation of Mono-, Di-, and Trisubstituted Ureas by Carbonylation of Aliphatic Amines with S,S-Dimethyl Dithiocarbonate

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Abstract: General procedures are reported to prepare N-alkylureas, N,N'-dialkylureas (both symmetrical and unsymmetrical), and N,N,N'-trialkylureas by carbonylation of aliphatic amines, employing S,S-dimethyl dithiocarbonate (DMDTC) as a phosgene substitute. All reactions were carried out in water. Symmetrical disubstituted ureas were prepared directly working at 60 °C with a molar ratio of DMDTC:amine = 1:2, preferably under nitrogen. Unsymmetrical ureas were prepared in two steps via S-methyl N-alkylthiocarbamate intermediates, which are formed selectively in the first step at room temperature. These intermediates react in the second step with ammonia or various aliphatic amines, both primary and secondary, at temperatures varying between 50 and 70 °C. All the target ureas were obtained in high yields (28 examples, average yield 94%) and with very high purity (generally >99.2%). Also to be noted is the recovery of a co-product of industrial interest, methanethiol, in an amount of two moles for each mole of DMDTC, with complete exploitation of the reagent.

Key words: ureas, carbonylation, amines, dithiocarbonates, thio-carbamates

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Substituted ureas have always attracted great attention by virtue of their numerous important applications.2–5 Indeed, they are widely used in the agricultural field as plant growth regulators and pesticides, particularly herbicides, in the medical field as tranquillizing, anticonvulsant, and antidiabetic agents as well as inhibitors of HIV-1 protease, etc., and in organic synthesis as starting materials (especially for the production of carbamates, isocyanates, polymers, and surfactants) and intermediates (especially for the production of pharmaceuticals, cosmetics, and agrochemicals). Moreover, ureas have found extensive applications in many other fields ranging from their use as dyes for cellulose fibers, antioxidants in gasoline, detergent additives, corrosion inhibitors, to polar solvents, etc. A great variety of procedures have been proposed for the preparation of substituted ureas.2,3,6 The procedures of widest use, which are also of practical interest for industrial productions, can be collected into three groups: (i) reaction of primary amines mainly with phosgene or its less toxic and less hazardous substitutes; (ii) reaction of primary and secondary amines with isocyanates, themselves prepared mainly from phosgene, in organic solvents; and (iii) reaction of primary and secondary amines with carbon dioxide, or carbon monoxide and oxygen, or carbon dioxide in addition to carbon monoxide and air, in the presence of various catalysts and under rather harsh conditions (at high pressure and high temperatures). Due to the growing importance of the variously substituted ureas, during the last years a great deal of research has been dedicated to the development of alternative, safer, and simpler procedures for their preparation.2–6

The present work is part of a wide ranging project that addresses the development of new, safe, and soft synthetic methodologies for the production of intermediates and products, particularly of industrial interest, based on the use of S,S-dimethyl dithiocarbonate (1, DMDTC). DMDTC is a reagent that can be easily prepared and in high yield on both the laboratory2 and industrial8 scale by rearrangement of the corresponding inexpensive O,S-dimethyl dithiocarbonate. DMDTC has already been used as a methanethiol precursor for the synthesis of organic sulfides,9 including triazine derivatives,10 as well as mesyl chloride and its derivatives.11 In more recent applications, DMDTC has been used as a phosgene substitute in the carbonylation of amines for the synthesis of N,N'-dialkylureas,12 N,N-dimethyl-N'-arylureas,13 and S-methyl N-alkylthiocarbamates.14 In this last role, unlike phosgene which is a highly toxic gaseous reagent, hazardous to handle and store, and difficult to measure,15 DMDTC is a liquid nontoxic reagent that can be measured, handled, and stored in complete safety. The present research reports the preparation of monosubstituted9, disubstituted symmetrical3 and unsymmetrical10, as well as trisubstituted ureas11 by reaction of DMDTC (1) with aliphatic amines (Schemes 1 and 2).

Scheme 1

As stated above, DMDTC was recently employed as a carbonylating reagent for primary aliphatic amines to give symmetrical and unsymmetrical N,N'-dialkylureas. With regard to the former, the reactions, carried out in methanol at 60 °C for 24 hours, supplied the products in 72% average yield (9 examples). With regard to the unsymmetrical ureas, the authors assert that the reaction between DMDTC and amines cannot be stopped at the first step,
because the substitution of the second methylthio group proceeds more rapidly. Thus, the reaction always leads to symmetrical ureas even when working with a notable reagent excess. To block the reaction at the first step and to avoid the successive formation of symmetrical ureas, the reactions between DMDTC and amines in an equimolar ratio were carried out in anhydrous THF under basic conditions (LDA) and nitrogen atmosphere, initially at –78 °C and then at room temperature (20 h). Under these conditions, the resulting S-methyl N-alkylthiocarbamates were deprotonated immediately after being formed, giving the corresponding lithium salts that, being relatively stable towards nucleophilic substitution, do not react further to give symmetrical ureas. Later treatment of the N-anions with an acid gave the thiocarbamates. Only two compounds were synthesized by this procedure, namely S-methyl N-benzylthiocarbamate (62% yield) and N,N'-p-(xylene)bis(thiocarbamate) (unreported yield). The reactions of these two thiocarbamates with various aliphatic amines were then carried out in methanol at 60 °C for 24 hours, resulting in the corresponding unsymmetrical N,N'-dialkylureas in modest yields. The average yield of the four examples reported was 47%.

Recently,14 we revisited the reaction of S,S-dimethyl dithiocarbonate (1) with benzylamine according to the literature protocol,13 with a 1:2 molar ratio in methanol at 60 °C for 24 hours. The literature13 reports the exclusive formation of N,N'-dibenzylurea in 85% yield. However our many tests14 showed the complete consumption of DMDTC, but the resulting N,N'-dibenzylurea (3j) was obtained only in 72% yield, together with two by-products, the intermediate S-methyl N-benzylthiocarbamate (5f; 7% yield), and methyl N-benzylcarbamate (5% yield), the last being formed by the reaction of 5f with the solvent methanol. These results demonstrate that the ureas obtained through reactions carried out in methanol at 60 °C for 24 hours are always impure, and therefore need further purification by means of crystallization or chromatography. In this research the same reaction, carried out at 60 °C for 24 hours in water instead of methanol, supplied N,N'-dibenzylurea (3j) in 95% yield and 99.2% purity, determined by GC analysis (Table 1, entry 12). The reaction was repeated, bubbling nitrogen into the mixture to drive out the methanethiol (4) as soon as it was formed (entry 13). Under such conditions the reaction time can be shortened to 5 hours and yield and purity of the urea 3j are still high (93% yield; 100% GC purity). On the basis of these results, DMDTC was reacted with various primary aliphatic amines in water at 60 °C, under vigorous stirring and preferably bubbling nitrogen into the reaction mixture (Scheme 1). The standard DMDTC-to-amine molar ratio was 1:2. Only in the case of amines with a boiling point less than 65 °C it was necessary to work with an excess of amine (entries 1–5, 11).

The best conditions were as follows: amine 2 in an aqueous solution (concentrations varying between 40% and 70% in weight; entries 1–5, 7, 8, 11–13), or neat when the amine was not water-soluble (entries 6, 10, 14–16), was slowly added to a suspension of DMDTC in water, maintained under vigorous stirring. The mixture was then heated to 60 °C with an oil bath, and heating and stirring were maintained until completion of the reaction, i.e., until the disappearance of DMDTC and the S-methyl N-alkylthiocarbamate 5 intermediate. When the amine had a high boiling point (above 100 °C) or when it was a solid substance, the reactions were preferably carried out under a nitrogen stream (entries 6, 8, 10, 13–16); under these conditions the reaction times were considerably shortened (compare entries 8 and 13 with, respectively, entries 7 and 12). The course of all the reactions was monitored by GC and GC-MS (entries 1–13) or TLC (entries 14–17) analysis. These analyses highlighted, right from the start and for most of the reaction time, the presence of the S-methyl N-alkylthiocarbamate intermediates 5 and the target products N,N'-dialkylureas 3, alongside the starting compounds, i.e., amines 2 and DMDTC (1). This last reagent is the first to disappear. Under the best conditions the reactions reached completion in times between 2 and 12 hours. As the ureas 3 are formed, they separated out from the reaction mixtures as colorless solid substances. At the end of the reactions the ureas were collected by different work-ups: (i) separation by decantation or by filtration under suction with subsequent drying of the products by treatment with anhydrous toluene or chloroform, and then, distillation of the toluene/water or chloroform/water azeotropes under reduced pressure; and (ii) extraction with an organic solvent that was then dried with sodium sulfate and evaporated under reduced pressure. All symmetrical N,N'-dialkylureas 3 were obtained in high yields, between 84 and 98% (the average yield of 13 examples was 93%) and in very high purity, greater than 99.2% (determined by GC and 1H NMR analyses). Table 1 shows
the reaction times, yields, purity, and melting points of the symmetrical N,N’-dialkylureas 3a–m, both crude and crystallized. A further merit of these reactions is that, alongside the urea formation, there is also a development of methanethiol (4) (two moles for each mole of DMDTC, Scheme 1). This last can be collected in an aqueous sodium hydroxide solution and recovered as sodium methanethiolate in yields higher than 95%.16

With regard to the unsymmetrical ureas, the N-alkyl (9), N,N'-dialkyl (10), and N,N,N'-trialkyl (11) ureas were prepared in two steps via the S-methyl N-alkylthiocarbamate intermediates 5 (Scheme 2). Recently,14 we demonstrated that, contrary to previous literature reports,12 the reactions between S,S-dimethyl dithiocarbonate (1) and primary aliphatic amines, even in strong excess, can be stopped at the first step with selective formation of S-methyl N-alkylthiocarbamates 5.

Table 1 Synthesis and Properties of Symmetrical N,N'-Dialkylureas 3a–m

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>Ratio 1/2</th>
<th>Procedure*</th>
<th>N₂</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)b</th>
<th>GC purity (%)</th>
<th>Mp (°C)</th>
<th>Recrystallized</th>
<th>Lit.</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>1:3</td>
<td>A –</td>
<td>2</td>
<td>3a</td>
<td>97</td>
<td>100</td>
<td>107.4–108.0</td>
<td>107.8–108.3 (toluene)</td>
<td>106¹²</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>1:4</td>
<td>A –</td>
<td>5</td>
<td>3b</td>
<td>96</td>
<td>100</td>
<td>110.0–111.2</td>
<td>111–112 (toluene)</td>
<td>111¹⁷</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Bu</td>
<td>1:2.1</td>
<td>B –</td>
<td>8</td>
<td>3c</td>
<td>95</td>
<td>99.8</td>
<td>73.6–74.1</td>
<td>74.1–75.0 (pentane)</td>
<td>71¹⁷</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>i-Bu</td>
<td>1:2.1</td>
<td>B –</td>
<td>10</td>
<td>3d</td>
<td>95</td>
<td>99.8</td>
<td>132.8–133.4</td>
<td>133.9–134.8 (Et₂O)</td>
<td>134¹⁷</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>s-Bu</td>
<td>1:3</td>
<td>B –</td>
<td>12</td>
<td>3e</td>
<td>86</td>
<td>100</td>
<td>136.7–137.6</td>
<td>137.1–137.5 (Et₂O)</td>
<td>134.8¹⁶b</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>n-C₅H₁₁</td>
<td>1:2</td>
<td>C +</td>
<td>6</td>
<td>3f</td>
<td>96</td>
<td>99.7</td>
<td>76.4–76.9</td>
<td>77.5–78.6 (MeOH)</td>
<td>76.¹⁶b</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>c-C₅H₁₁</td>
<td>1:2</td>
<td>B –</td>
<td>16</td>
<td>3g</td>
<td>85</td>
<td>95.5</td>
<td>232.1–232.9</td>
<td>232.6–233.2 (CHCl₃)</td>
<td>232–233¹⁷</td>
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<tr>
<td>8</td>
<td>C</td>
<td>+</td>
<td>5</td>
<td>3g</td>
<td>84</td>
<td>99.8</td>
<td>232.5–232.9</td>
<td>232.2–232.9</td>
<td>(CHCl₃)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>E¹</td>
<td>+</td>
<td>5</td>
<td>3g</td>
<td>84</td>
<td>99.2</td>
<td>232.4–232.9</td>
<td>(CHCl₃)</td>
<td></td>
<td></td>
<td></td>
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<td>10</td>
<td>n-C₁₀H₂₁</td>
<td>1:2</td>
<td>C +</td>
<td>4</td>
<td>3h</td>
<td>98</td>
<td></td>
<td>99.9–101.4</td>
<td>99.9–101.4 (CHCl₃)</td>
<td>101.¹⁶b</td>
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<tr>
<td>11</td>
<td>CH₂=CHCH₂</td>
<td>1:4</td>
<td>B –</td>
<td>6</td>
<td>3i</td>
<td>97</td>
<td>100</td>
<td>96.5–97.4</td>
<td>96.8–97.5 (toluene–pentane)</td>
<td>92–94¹²</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Bn</td>
<td>1:2</td>
<td>B –</td>
<td>24</td>
<td>3j</td>
<td>95</td>
<td>99.6</td>
<td>169.7–170.3</td>
<td>171.7–172.8 (EtOH)</td>
<td>172–173¹⁷</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>C</td>
<td>+</td>
<td>5</td>
<td>3j</td>
<td>93</td>
<td>100</td>
<td>170.9–171.5</td>
<td>(EtOH)</td>
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<td></td>
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<tr>
<td>14</td>
<td>4-MeC₈H₇CH₃</td>
<td>1:2</td>
<td>D +</td>
<td>7</td>
<td>3k</td>
<td>91</td>
<td></td>
<td>224.4–224.9</td>
<td>225.3–225.6 (MeOH)</td>
<td>215–216¹⁸b</td>
<td></td>
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<tr>
<td>15</td>
<td>4-ClC₈H₇CH₃</td>
<td>1:2</td>
<td>D +</td>
<td>8</td>
<td>3l</td>
<td>88</td>
<td></td>
<td>245.5–246.5</td>
<td>246.4–247.3 (MeOH)</td>
<td>242–243¹⁹</td>
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<tr>
<td>16</td>
<td>4-H₂NC₆H₄CH₂</td>
<td>1:2</td>
<td>D +</td>
<td>6</td>
<td>3m</td>
<td>80</td>
<td></td>
<td>203.5–204.3</td>
<td>203.5–204.3 (MeOH)</td>
<td>200–202¹²</td>
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</tr>
<tr>
<td>17</td>
<td>E¹</td>
<td>+</td>
<td>6</td>
<td>3m</td>
<td>90</td>
<td></td>
<td></td>
<td>203.5–204.3</td>
<td>(MeOH)</td>
<td></td>
<td></td>
</tr>
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</table>

*a All reactions were carried out in H₂O at 60 °C, under vigorous stirring.
*b Based on the starting DMDTC (1).
*The first step was carried out at r.t. and the second step at 60 °C.
*GC and ¹H NMR analyses of compound 10h are less significant because of its poor solubility in organic solvents; however, comparison of the mp of the crude product with that of the recrystallized one confirmed its purity.
*Purity was confirmed by TLC analysis (SiO₂; CHCl₃).
*Purity was confirmed by TLC analysis (SiO₂; CHCl₃–MeOH, 1:1).
working at ambient (20–25 °C) or lower temperatures. In accordance with the reported protocol,14 the reactions between DMDTC (1) and several primary aliphatic amines 2 (R1 = Me, Et, n-Bu, n-C6H13, c-C6H11, Bn), in a 1:2 molar ratio, were carried out in water at room temperature (Scheme 2, first step). The aim of the excess amine is two-fold: to shorten the reaction time and to obtain purer products in higher yields. After the disappearance of DMDTC, the reaction mixtures consisting of the formed thiocarbamates 5 and the unreacted amines were extracted with dichloromethane. The organic solutions were then washed with aqueous 5% hydrochloric acid to separate out the excess amine, which was later recovered almost quantitatively. Evaporation of the solvent left the crude S-methyl N-alkylthiocarbamates 5a–f in 95–100% yield and greater than 99% purity (determined by GC and 1H NMR analyses). The crude products obtained in this first step were then reacted directly in the second step with ammonia or different amines, in water and at temperatures varying between 50 °C and 70 °C.

The best conditions for the synthesis of N-alkylureas 9 were as follows: a 30% aqueous solution of ammonia (6: R2 = R3 = H) was added to the crude S-methyl N-alkylthiocarbamates obtained in the first step, either as such (5a–e) or to their solutions in 1,4-dioxane (5d–f). The molar ratio ammonia: 5 varied from 9:1 to 12:1. These mixtures were heated to 60–70 °C in an oil bath. GC and GC-MS analyses of the obtained solutions showed the progressive decrease of the starting thiocarbamates 5 and the progressive increase in the formed N-alkylureas 9. The reaction times varied from 3 to 6 hours. At the end of the reactions, the solvents were removed under reduced pressure, and the residues were dried by treatment with anhydrous toluene or chloroform and then, by under reduced pressure distillation of the toluene/water or chloroform/water azeotropes. Subsequent washings with small amounts of cold ethyl acetate (for 9b–e) or 1,4-dioxane (for 9a) or toluene (for 9f) afforded the pure (GC, GC-MS, 1H NMR) ureas 9a–f in overall yields, based on the starting DMDTC, varying from 92% to 96% (Table 2; 6 examples, average overall yield 94%).

To prepare unsymmetrical N,N’-dialkylureas 10 and N,N,N’-trialkylureas 11 the crude S-methyl N-alkylthiocarbamates 5 obtained in the first step were directly reacted in the second step with amines, both primary (7: R2 = H; R3 = alkyl) and secondary (8: R2, R3 = alkyl), in water and at temperatures varying between 50 and 60 °C. The reactions were monitored by GC and GC-MS analyses, and all went to completion in 1 to 16 hours. The slowest reactions were also carried out under nitrogen, and this shortened the reaction times to 2–4 hours (compare entries 8 and 12 with, respectively, entries 7 and 11). Work-up as described above for symmetrical N,N'-dialkylureas 3, led also to the ureas 10 and 11, practically pure (GC purity 99.2–100%) and in overall yields of 93% to 100%, based on the starting DMDTC. The average yield of the nine examples considered was 96%. Table 2 shows the reaction conditions, overall yields of the two steps, purity, and the melting points of the unsymmetrical ureas 10a–f and 11a–c, both crude and crystallized. These reactions allowed also the recovery of the formed methanethiol (4) (2 moles for each mole of starting DMDTC).

### Table 2 Synthesis and Properties of N-Alkylureas 9a–f, Unsymmetrical N,N’-Dialkylureas 10a–e, and N,N,N’-Trialkylureas 11a–c

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Ratio 5/6–8</th>
<th>N2 Temp °C</th>
<th>Time (h)</th>
<th>Product Yield (%)a</th>
<th>GC purity (%)</th>
<th>Crude Mp (°C)</th>
<th>Recrystallized</th>
<th>Lit.</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1:12</td>
<td>65</td>
<td>3</td>
<td>9a 96c 100</td>
<td>101–102</td>
<td>101.9–102.1 (EtOH)</td>
<td>10217</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>1:12</td>
<td>70</td>
<td>6</td>
<td>9b 90d 100</td>
<td>93.2–93.3</td>
<td>93.3 (EtOH)</td>
<td>9217</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Bu</td>
<td>H</td>
<td>H</td>
<td>1:12</td>
<td>70</td>
<td>4</td>
<td>9c 95d 100</td>
<td>96.6–96.8</td>
<td>96.8 (EtOH)</td>
<td>9617</td>
<td></td>
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<tr>
<td>4</td>
<td>n-C6H13</td>
<td>H</td>
<td>H</td>
<td>1:12</td>
<td>70</td>
<td>6</td>
<td>9d 95d 99.5</td>
<td>110.3–111.2</td>
<td>110.8–111.2 (H2O)</td>
<td>107–10920</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>c-C6H11</td>
<td>H</td>
<td>H</td>
<td>1:9</td>
<td>70</td>
<td>6</td>
<td>9e 92d 100</td>
<td>193.6–194.5</td>
<td>193.8–194.5 (EtOH)</td>
<td>192–19317</td>
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<tr>
<td>6</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>1:9</td>
<td>60</td>
<td>6</td>
<td>9f 93 100</td>
<td>149.1–149.7</td>
<td>150.4–150.8 (EtOH)</td>
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<td>7</td>
<td>Me</td>
<td>c-C6H11</td>
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<td>1:1.2</td>
<td>60</td>
<td>16</td>
<td>10a 94 99.7</td>
<td>157.7–158.1</td>
<td>158.1–159.0 (MeOH)</td>
<td>157–15921</td>
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<td>1:1.05</td>
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<td>10a 94 99.4</td>
<td>157.0–157.6</td>
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<td>9</td>
<td>Me</td>
<td>H</td>
<td>Bn</td>
<td>1:1.2</td>
<td>60</td>
<td>4</td>
<td>10b 95 100</td>
<td>97.4–99.3</td>
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<td>97–9822</td>
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Table 2  Synthesis and Properties of N-Alkylureas 9a–f, Unsymmetrical N,N’-Dialkylureas 10a–e, and N,N,N’-Trialkylureas 11a–c (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Ratio</th>
<th>N₂</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product Yield (%)</th>
<th>GC purity (%)</th>
<th>Mp (°C)</th>
<th>Recrystallized</th>
<th>Lit.</th>
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<td>10</td>
<td>Et</td>
<td>H</td>
<td>Me</td>
<td>1:10 –</td>
<td>50</td>
<td>1</td>
<td>10c</td>
<td>97</td>
<td>100</td>
<td>54.0–54.5</td>
<td>54.3–54.7</td>
<td>52–53</td>
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<td>H</td>
<td>Bn</td>
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<td>60</td>
<td>3</td>
<td>10d</td>
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<td>101–102</td>
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<td>Bn</td>
<td>1:1 +</td>
<td>60</td>
<td>2</td>
<td>10e</td>
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<td>99.5</td>
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<tr>
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<td>H</td>
<td>Bn</td>
<td>1:3 +</td>
<td>60</td>
<td>7</td>
<td>10d</td>
<td>95</td>
<td>99.6</td>
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<tr>
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<td>Me</td>
<td>Et</td>
<td>Et</td>
<td>1:1.2 +</td>
<td>60</td>
<td>7</td>
<td>11a</td>
<td>94</td>
<td>100</td>
<td>–f</td>
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<tr>
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<td>Me</td>
<td>Bu</td>
<td>Bu</td>
<td>1:1.1 +</td>
<td>60</td>
<td>2</td>
<td>11b</td>
<td>95</td>
<td>99.2</td>
<td>44.2–44.9</td>
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<td>Pr</td>
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<td>60</td>
<td>5</td>
<td>11c</td>
<td>93</td>
<td>99.9</td>
<td>62.7–63.6</td>
<td>63.4–64.1</td>
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</tr>
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</table>

a The temperatures reported refer to the second reaction step; whereas the first step was carried out at r.t. (20–25 °C).

b Overall yield of the two steps, based on the starting DMDTC (1).
c Crude product, washed with 1,4-dioxane.
d Crude product, washed with EtOAc.
e Crude product, washed with EtOH.
f Oily colorless crystals, as reported.

In conclusion, this research has confirmed the validity of S,S-dimethyl dithiocarbonate (1) as an efficient phosgene substitute in the carbonylation of aliphatic amines to produce mono-, di-, and trisubstituted ureas.9–11 Indeed, the advantages of the set-up procedures, with respect to traditional ones using phosgene and isocyanates (prepared mostly from phosgene), can be summarized as follows: (i) use of an easily available reagent, low-cost, nontoxic and hazard-free, and therefore easy and safe to handle; (ii) use of a liquid reagent with the consequent simplification of its measurement and the equipment needed; (iii) exclusive use of a liquid reagent with the consequent simplification of its measurement and the equipment needed; (iv) easy isolation of the ureas that, being mostly not soluble in the water in which they are formed, they are easily collected by simple decantation or by suction filtration; and (v) formation of a co-product of industrial interest, methanethiol (4), in an amount of two moles for each mole of DMDTC. Methanethiol spontaneously goes out from the reaction mixtures and, when working on a large scale,16 it can be recovered almost quantitatively as sodium methanethiolate. Consequently, the new procedures exploit all of the DMDTC, with evident economic and ecological advantages. Furthermore, differently from methodologies using carbon dioxide or carbon monoxide/oxygen that usually require rather harsh conditions and sometimes the presence of catalysts, the new methodologies based on the use of DMDTC are very simple and call for neither solvents nor catalysts. Thus, given their simplicity and economic and ecological advantages, these new set-up procedures adapt well for use on both laboratory and industrial scales.

1H NMR and 13C NMR spectra were recorded on a Bruker Avance 200 spectrometer at 200 MHz and 50 MHz, respectively, in CDCl₃ or DMSO-d₆, unless otherwise noted. Mass spectra were recorded on an AT 5973N mass selective detector connected to an AT 6890N GC, cross-linked methyl silicone capillary column. Details for the reactions and yields for the pure (GC, GC-MS, TLC, 1H NMR) products are listed in Tables 1 and 2. The molecular structures of all products were confirmed by comparison of their physical (mp or bp) and spectral data (MS, 1H NMR) with those reported in the literature, or with those of authentic samples of analytical purity. All the amines were purchased from Aldrich and used without further purification. S,S-Dimethyl dithiocarbonate (1, DMDTC) was obtained from Oxon Italia S.p.A. (Italy) or prepared as described in the literature.²

N,N’-Dialkylureas 3a–m; Typical Procedures

N,N’-Dimethylurea (3a)

**Procedure A**  *Table 1, Entry 1:* An aq 40% soln of MeNH₂ (2, R¹ = Me; 2.33 g, 30 mmol; Aldrich) was added dropwise over a period of 5 min to DMDTC (1; 1.22 g, 10 mmol), previously heated in an oil bath at 60 °C, and maintained under stirring. The reaction was exothermic, the temperature raised at once to 67–68 °C and a colorless solution was obtained. Heating at about 60 °C was maintained until completion of the reaction that was monitored by GC and GC-MS analyses. After 1 h, the products were S-methyl N-alkylthiocarbamate (5a) and the title compound 3a, in a GC ratio of 1:3. After 2 h, the intermediate 5a disappeared and 3a was the only product. The solvent was removed under reduced pressure and the colorless solid residue was dried by addition of anhydrous toluene (4–5 mL) and subsequent distillation under reduced pressure of the toluene/H₂O.
azeotrope; yield: 0.85 g (97%); 100% purity (GC analysis); mp 107.6–107.9 °C; mp 107.8–108.3 °C (recrystallized from toluene) (Lit.17 mp 106 °C).

When the reaction was carried out in the presence of a great excess of MeNH2 (molar ratio of Lamine = 1:10), the reaction was complete after 10–15 min. Yield and GC purity of 3a were as above. N,N’-Dithiouretha (3b; entry 2) was also prepared according to Procedure A, using an aq 70% soln of EtNH2 (2, R2 = Et; Aldrich); the molar ratio of EtNH2 was 1:4.

**N,N’-Dithiouretha (3j)**

Procedure B; Table 1, Entry 12: The reaction was carried out according to Procedure A, starting from DMDTC (1: 1.22 g, 10 mmol) and an aq 40% soln of benzylamine (2, R1 = Bn; 2.14 g, 20 mmol) in H2O (5.35 mL). The mixture was maintained at 60 °C under vigorous stirring. After 2 h, GC and GC-MS analyses showed the disappearance of DMDTC. Beside the starting benzylamine, two products were present, the intermediate S-methyl N-benzylthio-carbamate (5j) and N,N’-dibenzyluretha (3j), in a ratio of about 1:1. During the reaction the target product 3j separated out from the mixture as a colorless solid; subsequent addition of H2O (ca. 3 x 3 mL) made the stirring easier. The reaction was complete after 24 h, when compound 5j disappeared, and 3j was the only product. The solid substance was separated by decantation and first treated with a 5% aq soln of HCl (20 mL) and then with H2O (20 mL). After filtration under reduced pressure, the solid was dried by subsequent additions of anhyd toluene or CHCl3 (3 × 20 mL). The mixture at 60 °C. After 6 h, the intermediate thiocarbamate disappeared and urea 3m was the only product (TLC analysis: CHCl3–MeOH, 1:1). After a work-up similar to that reported in Procedure D, the pure title compound 3m was obtained; yield: 2.43 g (90%); mp 203.6–204.4 °C; mp 203.6–204.4 °C (recrystallized from MeOH) (Lit.15 mp 200–202 °C).

Alternatively, the solid substance was collected by filtration under reduced pressure and then dissolved in CH3Cl–EtOH (8:1; 160 mL). The organic solution was washed successively with an aq 5% soln of HCl (20 mL) and H2O (50 mL), dried (Na2SO4) and then evaporated under reduced pressure. The crude residue was the title compound 3j; yield and purity were as above.

Ureas 3c-e-g.i were also prepared (entries 3–5,7,11) according to Procedure B. It should be noted that under the adopted conditions (H2O, 60 °C with stirring) ureas 3c-e-i emulsified as soon as they were formed. Instead, when the reaction mixtures were allowed to cool to r.t., the ureas separated out as colorless solids.

**Procedure C; Table 1, Entry 13:** A stream of N2 was bubbled through the mixture, prepared as described in Procedure B (entry 12) and maintained at 60 °C under stirring, to remove the methanethiol (4) as it was formed. This can be collected in an aq 50% soln of NaOH and recovered as sodium methanethiolate. The progress of the reaction was monitored by GC analysis: DMDTC (1) disappeared after 1 h and the intermediate 3j after 5 h. When the reaction was complete, the mixture was worked up as described for Procedure B. The crude title compound 3j was obtained in 93% yield (2.23 g); 99.6% purity (GC analysis); mp 170.9–171.5 °C.

According to Procedure C, ureas 3f-h were also prepared (entries 6,8,10). When the amines were not water-soluble (2, R1 = n-C6H13, n-C4H9), they were added neat (respectively 2.02 g and 3.14 g, 20 mmol) to a suspension of DMDTC (1: 1.22 g, 10 mmol) in H2O (5–10 mL), under vigorous stirring (entries 6,10).

**N,N’-Bis(4-methylthiouretha (3k)**

Procedure D; Table 1, Entry 14: 4-Methylbenzylamine (2.42 g, 20 mmol) was added in one portion to a suspension of DMDTC (1: 1.22 g, 10 mmol) in H2O (15 mL) maintained at 60 °C under vigorous stirring. Then Na2CO3 was bubbled through the mixture. After 15–20 min, a colorless solid began to separate out. The amount of precipitate increased during the reaction; to make the stirring of the mixture easier, successive portions of H2O (2 × 5 mL) were added after 2 and 4 h. The progress of the reaction was monitored by TLC (SiO2; CHCl3). After 1 h, DMDTC disappeared and two products were present, the intermediate S-methyl N-(4-methylthiobenzyl)thiocarbamate and the urea 3k, the first as the major product. After 7 h, the intermediate disappeared and 3k was the only product. The solid substance was separated by decantation and first treated, under stirring, with a 5% aq soln of HCl (20 mL) and then with H2O (20 mL). After filtration under reduced pressure, the solid substance was dried by subsequent additions of anhyd toluene or CHCl3 (3 × 20 mL) and distillation under reduced pressure of the toluene/H2O or chloroform/H2O azeotropes. The residue was the pure title compound 3k; yield: 2.44 g (91%); mp 224.4–224.9 °C; mp 225.4–225.6 °C (recrystallized from MeOH) (Lit.18mp 204–205 °C; Lit.19 mp 215–216 °C).

**N,N’-Bis(4-chlorobenzyl)uretha (3l) and N,N’-bis(4-aminobenzyl)uretha (3m)** were also prepared according to Procedure D (entries 15 and 16).

**N,N’-Bis(4-aminobenzyl)uretha (3m)**

Procedure E; Table 1, Entry 17: The reaction was carried out in two steps. According to the procedure previously reported,17 in the first step 3-methyl N-(4-aminobenzyl)thiocarbamate was prepared starting from DMDTC (1: 1.22 g, 10 mmol) and 4-aminobenzylamine (2.44 g, 20 mmol) in H2O (15–20 mL) at 20–25 °C for 16 h, under stirring. After this time, the starting DMDTC disappeared and S-methyl N-(4-aminobenzyl)thiocarbamate [MS: m/z = 196 (M+)*] was the only product formed. Then Na2CO3 was bubbled through the mixture at 60 °C. After 6 h, the intermediate thiocarbamate disappeared and urea 3m was the only product (TLC analysis: CHCl3–MeOH, 1:1). After a work-up similar to that reported in Procedure D, the pure title compound 3m was obtained; yield: 2.43 g (90%); mp 203.6–204.4 °C; mp 203.6–204.4 °C (recrystallized from MeOH) (Lit.15 mp 200–202 °C).

**N,N’-Dicyclohexyluretha (3g)** was also prepared (entry 9) according to Procedure E.

Details for the reactions of entries 1–17 are reported in Table 1; spectral data are given below.

**N,N’-Dimethyluretha (3a)**

1H NMR (CDCl3): δ = 2.73 (d, J = 4.6 Hz, 6 H, 2 × CH3), 5.41 (m, 2 H, 2 × NH); identical to that reported.26

MS (EL 70 eV): m/z (%) = 88 (100, [M+]*), 58 (68, [CH3NHCO]), 44 (7), 31 (19), 30 (54), 28 (17); identical to that reported.26

**N,N’-Diethy luretha (3b)**

1H NMR (400 MHz, CDCl3): δ = 1.05 (t, J = 7.0 Hz, 6 H, 2 × CH3), 3.09 (dq, J = 7.0 Hz, 4 H, 2 × CH2), 5.40 (m, 2 H, 2 × NH); identical to that reported.26

MS (EL 70 eV): m/z (%) = 116 (100, [M+]*), 101 (12, [M+ – CH3]), 72 (11), 44 (75), 30 (66), 29 (15); identical to that reported.26

**N,N’-Dibutyl uretha (3c)**

1H NMR (CDCl3): δ = 0.91 (t, J = 7.2 Hz, 6 H, 2 × CH3), 1.25–1.54 [m, 8 H, 2 × CH2(CH3)2], 3.15 (t, J = 6.6 Hz, 4 H, 2 × CH2NH), 4.60 (m, 2 H, 2 × NH); identical to that reported.26

MS (EL 70 eV): m/z (%) = 172 (42, [M+]*), 130 (16), 129 (14), 101 (17), 100 (13), 87 (11), 72 (11), 57 (19), 44 (41), 41 (22), 30 (100); identical to that reported.26

**N,N’-Dioctyl uretha (3d)**

1H NMR (CDCl3): δ = 0.89 (d, J = 6.7 Hz, 12 H, 4 × CH3), 1.62–1.82 (m, 2 H, 2 × CH2), 2.97 (d, J = 6.8 Hz, 4 H, 2 × CH2), 5.18 (m, 2 H, 2 × NH); identical to that reported.12
Preparation of Mono-, Di-, and Trisubstituted Ureas

N,N'-Di(1-butylurea) (3c)
1H NMR (CDCl3): δ = 0.91 (t, J = 7.4 Hz, 6 H, 2 × CH3(CH2)2); 1.12 (app t, J = 6.5 Hz, 6 H, 2 × CH2CH3), 1.38–1.52 (m, 4 H, 2 × CH2), 3.59–3.72 (m, 2 H, 2 × CH), 4.09 (m, 2 H, 2 × NH); identical to that reported.6b

MS (EI, 70 eV): m/z (%) = 172 (6, [M+]), 143 (32), 79 (25), 44 (100); identical to that reported.6b

N,N'-Dihexylurea (3f)
1H NMR (CDCl3): δ = 0.88 (d, J = 5.6 Hz, 6 H, 2 × CH2), 1.30 [m, 12 H, 2 × CH2(CH2)3CH3], 1.46–1.52 (m, 4 H, 2 × CH2CH3), 3.15 (app t, J = 6.5 Hz, 4 H, 2 × CH2NH), 4.42 (m, 2 H, 2 × NH); identical to that reported.6b

MS (EI, 70 eV): m/z (%) = 224 (53, [M+]), 143 (44), 100 (11), 59 (44), 99 (29), 70 (19), 61 (28), 56 (100), 43 (33), 41 (33), 21 (100), 29 (11); identical to that reported.6b

N,N'-Dicyclohexylurea (3g)
1H NMR (CDCl3): δ = 0.99–1.27, 1.57–1.84 (2 m, 10.5:9.5, 20 H, 10 × CH2), 3.34–3.49 (m, 2 H, 2 × CH); identical to that reported.6b

MS (EI, 70 eV): m/z (%) = 244 (53, [M+]), 143 (44), 100 (11), 59 (44), 99 (29), 70 (19), 61 (28), 56 (100), 43 (13), 41 (14); identical to that reported.6b

N,N'-Dicyclohexylurea (3h)
1H NMR (CDCl3): δ = 0.88 (t, J = 6.7 Hz, 6 H, 2 × CH2); 1.26–1.72 (m, 32 H, 2 × CH2CH(CH3)2), 3.12–3.14 (m, 4 H, 2 × CH2NH), 4.37 (m, 2 H, 2 × NH); NMR data are not reported, as measurement of NMR spectra was difficult because of the very low solubility of 3h in organic solvents.6b

MS (EI, 70 eV): m/z (%) = 340 (23, [M+]), 255 (26), 241 (27), 158 (19), 112 (21), 99 (42), 57 (20), 56 (21), 55 (33), 44 (30), 43 (40), 41 (34), 30 (100); identical to that reported.6b

N,N'-Diallylurea (3i)
1H NMR (CD2OD): δ = 3.76 (app d, J = 5.1 Hz, 4 H, 2 × CH2NH), 5.07 (dd, J = 10.3, 1.3 Hz, 2 H, 2 × CH), 5.17 (dd, J = 17.2, 1.3 Hz, 2 H, 2 × CH); 5.77–5.96 (m, 2 H, 2 × CH); identical to that reported.6b

MS (EI, 70 eV): m/z (%) = 140 (4, [M+]), 99 (8), 98 (13), 85 (14), 75 (80), 56 (100), 54 (8), 41 (43), 39 (20), 30 (20), 28 (17).

N,N'-Dibenzylurea (3j)
1H NMR (CDCl3): δ = 4.22 (d, J = 5.9 Hz, 4 H, 2 × CH2NH), 4.34 (t, J = 5.9 Hz, 2 H, 2 × NH), 7.17–7.35 (m, 10 H, 2 × C6H5); similar to that reported.6b

MS (EI, 70 eV): m/z (%) = 240 (50, [M+]), 149 (21), 107 (11), 106 (100), 91 (51), 79 (18), 77 (12), 65 (12); identical to that reported.6b

N,N'-Bis(4-methylbenzylurea) (3k)
1H NMR (CDCl3): δ = 2.26 (s, 6 H, 2 × CH3), 4.16 (d, J = 6.0 Hz, 4 H, 2 × CH2), 6.33 (t, J = 6.0 Hz, 2 H, 2 × NH), 7.09 (d, J = 8.6 Hz, 4 H, 2 × ArH), 7.13 (d, J = 8.6 Hz, 4 H, 2 × ArH). The title compound is known,13b but the spectral data are not reported.

13C NMR (CDCl3): δ = 22.55 (2 × CH3), 44.58 (2 × CH2), 128.87, 130.63 (4 × CH, ArH), 137.42, 139.70 (4 × C, ArH), 159.92 (C=O).

N,N'-Dibis(chlorobenzyl)urea (3l)
1H NMR (DMSO-d6): δ = 4.20 (d, J = 6.1 Hz, 4 H, 2 × CH2), 6.53 (t, J = 6.1 Hz, 2 H, 2 × NH), 7.25 (d, J = 8.4 Hz, 4 H, 2 × ArH), 7.37 (d, J = 8.4 Hz, 4 H, 2 × ArH); similar to that reported.13b

MS (EI, 70 eV): m/z (%) = 308 (19, [M+]), 183 (19), 167 (29), 142 (32), 140 (100), 138 (24), 132 (92), 127 (23), 125 (75), 106 (46), 89 (25), 77 (38), 75 (23), 32 (22).

N,N'-Bis(4-amino benzyl)urea (3m)
1H NMR (DMSO-d6): δ = 4.01 (d, J = 5.5 Hz, 4 H, 2 × CH2), 4.91 (br s, 4 H, 2 × NH2), 6.02 (t, J = 5.5 Hz, 2 H, 2 × NH), 6.49 (d, J = 8.3 Hz, 4 H, 2 × ArH), 6.89 (d, J = 8.3 Hz, 4 H, 2 × ArH); identical to that reported.12a

MS (direct, 70 eV): m/z (%) = 270 (75, [M+]), 177 (79), 164 (100), 121 (94), 106 (92), 94 (83); identical to that reported.12a

S-Methyl N-Alkylthiocarbamates 5a–f; S-Methyl N-Hexylthiocarbamate (5d); Typical Procedure

According to the procedure previously reported,14 hexylamine (2.02 g, 20 mmol) was added dropwise over a period of 10 min to a suspension of S,S-dimethyl dithiocarbamate (1; 1.22 g, 10 mmol) in H2O (5 mL), under vigorous stirring. The reaction was mildly exothermic, and during the addition the temperature of the mixture was maintained at 20–25 °C with an ice-water bath. The progress of the reaction was monitored by GC and GC-MS analyses. During the reaction an emulsion was formed. Stirring at r.t. (20–25 °C) was maintained until disappearance of 1 (2 h). The mixture was then treated with cold CH2Cl2/1% HCl (2:1, 100 mL). The aqueous soln was separated and extracted with CH2Cl2 (30 mL). The combined organic extracts were washed with H2O (30 mL), dried (Na2SO4), and evaporated under reduced pressure to give crude 5d; yield: 1.75 g (ca. 100%); 99.9% purity (GC analysis); mp 56.5–57.5 °C (pentane). Studies regarding biological activities of compound 5d are reported in the literature,24 but its physical and spectral data are not reported.

The title compound DMDTC (5d) was obtained in 98.6% (the by-product present was N,N'-dihexylurea; MS: m/z = 228 (M+)). The crude product was washed with cold (0 °C) EtOAc (1–2 mL). The title compound 5d was obtained pure (GC analysis) (100%); mp 106.8–108.0 °C; GC purity 92.6% [the by-product present was N,N'-dihexylurea; MS: m/z = 228 (M+)]. The crude product was washed with cold (0 °C) EtOAc (1–2 mL). The title compound 5d was obtained pure (GC analysis) (100%); mp 106.8–108.0 °C; GC purity 92.6% [the by-product present was N,N'-dihexylurea; MS: m/z = 228 (M+)]. The crude product was washed with cold (0 °C) EtOAc (1–2 mL). The title compound 5d was obtained pure (GC analysis) (100%); mp 106.8–108.0 °C; GC purity 92.6% [the by-product present was N,N'-dihexylurea; MS: m/z = 228 (M+)]. The crude product was washed with cold (0 °C) EtOAc (1–2 mL). The title compound 5d was obtained pure (GC analysis) (100%); mp 106.8–108.0 °C; GC purity 92.6%.
(m, 5 H, C₆H₅); the title compound is known, but the spectral data are not reported.

1C NMR (CDCl₃): δ = 15.43 (CH₃), 23.99, 27.96, 31.58, 32.50, 42.02 (CH₂), 45.89 (CH₃C₆H₅), 128.65 (CH, ArH), 128.82, 130.01 (2 CH₂, ArH), 140.80 (C), 159.85 (C=O).

MS (El, 70 eV): m/z (%) = 234 (100, [M⁺]), 191 (13), 164 (10), 106 (70), 107 (18), 91 (72), 79 (11), 65 (10), 44 (12), 30 (23).

N,N-Diethyl-N'-methyleneurea (11a)

1H NMR (CDCl₃): δ = 1.09 (t, J = 7.1 Hz, 6 H, 2 CH₂CH₃), 2.77 (d, J = 4.0 Hz, 3 H, CH₃), 3.20–3.33 (m, 2 H, CH₂CH₃), 3.38 [app t, J = 7.1 Hz, 4 H, N(CH₂CH₂CH₂CH₂), 4.46 (m, 1 H, NH); identical to that reported.²⁵

MS (El, 70 eV): m/z (%) = 108 (47, [M⁺]), 115 (33), 72 (27), 58 (100), 44 (24).

N,N-Dibutyl-N'-methyleneurea (11b)

1H NMR (CDCl₃): δ = 0.93 (t, J = 7.4 Hz, 6 H, 2 CH₃CH₂), 1.21–1.40 and 1.40–1.59 (2 m, 1:1, 8 H, 2 CH₂CH₂CH₂), 2.80 (d, J = 4.5 Hz, 3 H, CH₃), 3.16 [app t, J = 7.5 Hz, 4 H, N(CH₂CH₂CH₂CH₂)], 4.24 (m, 1 H, NH); identical to that reported.²⁵

MS (El, 70 eV): m/z (%) = 186 (18, [M⁺]), 143 (32), 87 (10), 86 (100), 58 (13), 57 (10), 44 (31).

N,N-Dipropyl-N'-ethyleurea (11c)

1H NMR (CDCl₃): δ = 0.89 (t, J = 7.4 Hz, 6 H, 2 CH₃CH₂), 1.13 (t, J = 7.2 Hz, 3 H, CH₃), 1.55 (app q, J = 7.5 Hz, 4 H, 2 CH₂CH₂CH₂), 3.13 [app t, J = 7.5 Hz, 4 H, N(CH₂CH₂CH₂CH₂)], 3.20–3.33 (m, 2 H, CH₂NH), 4.24 (m, 1 H, NH).

1C NMR (CDCl₃): δ = 12.80 (2 CH₃CH₂), 17.14 (CH₃CH₂), 23.19 (2 CH₂CH₂CH₂), 37.01 (CH₂CH₂), 50.46 (2 CH₂CH₂CH₂), 159.14 (C=O).

MS (El, 70 eV): m/z (%) = 172 (19, [M⁺]), 143 (24), 72 (100), 43 (10).


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References

(1) Professor Emeritus, University of Turin, Italy.


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References

(1) Professor Emeritus, University of Turin, Italy.

For example, for toxicity of phosgene, see:


