Synthesis of Symmetrically N,N'-di-substituted Aliphatic Ureas by Reaction of *bis*(*o*-nitrophenyl) Carbonate with Primary Amines

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Symmetrical N,N'-dialkyl ureas were obtained from primary amines in very good yields using bis(o-nitrophenyl) carbonate. The reactions were carried out in dichloromethane at room temperature or in toluene under reflux conditions, the products either being precipitated directly from reaction mixture or isolated by removal of the byproduct, o-nitrophenol from reaction mixture by steam distillation.

Keywords: bis(o-nitrophenyl) carbonate, aliphatic amines, symmetrical N,N'- dialkyl ureas, steam distillation

In previously published studies [1,2] we have shown that *bis*(*o*-nitrophenyl) carbonate, reacts rapidly, under mild conditions with aliphatic amines to form *o*-nitrophenyl carbamates, new compounds of high reactivity.

The reactions of *bis*(*o*-nitrophenyl) carbonate with aromatic amines take place through the decomposition of the *o*-nitrophenyl carbamate intermediate into an aryl isocyanate which reacts more rapidly than the original carbonate, and before it is exhausted, with the amine in the reaction medium forming a symmetrical urea. It has not therefore been possible to isolate *N*-aryl-*o*-nitrophenyl carbamates, but a new method has been developed for the successful synthesis of symmetrical *N,N'*-disubstituted aromatic ureas[3].

Following up on the success obtained with aromatic ureas we have extended our studies to the reactions of *bis*(*o*-nitrophenyl) carbonate with aliphatic amines with the aim of obtaining the corresponding ureas. This paper presents the method of synthesis of symmetrical *N,N'*-disubstituted aliphatic ureas through reaction of *bis*(*o*-nitrophenyl) carbonate with excess of primary aliphatic amines.

Experimental part

Melting points were determined on Boetius apparatus (Carl Zeiss Jena). The IR spectra were recorded in KBr pellet for the solid compounds with a Jasco FT/IR-430 instrument. TLC analyses were carried out on pre-coated plates of silica gel 60 F_{254} (Merck). To visualize spots the plates were exposed under a UV 254 lamp. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DPX 200 MHz NMR spectrometer (200 and 50 MHz, respectively). Mass spectra were recorded on a MS Varian MAT 212 (MI). Elemental analysis was carried out on a Vario El instrument.

Preparation of symmetrical N,N'- dialkyl ureas 1-12

General Procedure

To a solution of *bis*(*o*-nitrophenyl) carbonate (0.2 g ,0.658 mmol) in toluene or dichloromethane (10 mL) was added the amine (2.3 equiv.). The reaction mixture was stirred at room temperature for several hours or refluxed for one hour (TLC control). The obtained urea was isolated through one of the following methods:

- by filtering off and washing with cold solvent;
- by separation using silica gel column chromatography, eluting with dichloromethane until the *o*-nitrophenol byproduct had been removed, and then with methanol;
- by removal of the byproduct, *o*-nitrophenol, from reaction mixture using steam distillation. The urea was then isolated from the resulting aqueous solution by water distillation, the residue being recrystallized from chloroforme-heptane

N,N'-Di-iso-propyl urea (1) Obtained in best yield (92%) by method **a)** as a white solid with mp 192-193°C.(Lit. 192-193°C [4];192°C[5]); $\nu_{C=O}$(cm^{-1})= 1617 (Lit. 1620 [4]) δ_H(200 MHz; $CDCl_3$) 1(d, 12H), 3.4(m, 2H), 5.5(s, 2NH); δ_C(50 MHz; $CDCl_3$) 23(4CH_3), 42(2CH), 157(C=O). m/z = 144

N,N-Dicyclohexyl urea (2) Obtained in best yield (95%) as a white solid mp 227-229°C.(Lit. 228°C [4];229-230°C[6]); $\nu_{C=O}$(cm^{-1})= 1624 (Lit. 1635 [4]); δ_H(200 MHz; DMSO-d_6) 1.3(m, 12H), 1.8(m, 8H), 3.6(m, 2H), 6(s, 2NH); δ_C(50 MHz; DMSO-d_6) 24.3(4CH_2), 25.2(2CH_2), 33.3(4CH_2), 47.4(2CH), 156.5(C=O). m/z = 224

N,N'-Dibenzyl urea (3) Obtained in best yield (95%) as a white solid with mp 166-167°C; $\nu_{C=O}$(cm^{-1})= 1626; δ_H(200 MHz; $CDCl_3$) 4.22(d, 4H), 6.5(t, 2NH), 7.3 (m; 10H); δ_C(50 MHz; $CDCl_3$) 43(2CH_2), 126.7(CH), 127.1(4CH), 128.4(4CH), 141(2C), 158.3(C=O). m/z = 240

N,N'-Di-n-propyl urea (4) Obtained in 92% yield as a white solid with mp103-104°C (Lit. 102-103°C[7]); $\nu_{C=O}$(cm^{-1})= 1626; δ_H(200 MHz; $CDCl_3$) 0.90 (t, 6H), 1,47 (m, 4H), 3.12 (q, 4H), 5.25 (NH); δ_C(50 MHz; $CDCl_3$) 11.39 (2CH_3), 23.56 (2CH_2); 45.11 (2CH_2); 159.14 (C=O); Anal. calcd. for $C_7H_{16}N_2O$: C: 58.30; H: 11,18; N: 19.42; Found: C: 57.88; H: 10.67; N: 18.98.

N,N'-Di-n-butyl urea (5) Obtained in 99% yield as a white solid with mp70-72°C (Lit. 73°C[8]); $\nu_{C=O}$(cm^{-1})= 1618; δ_H(200 MHz; $CDCl_3$) 0.94 (t, 6H), 1,31 (m, 8H), 3.15 (C, 4H,), 5.56 (NH); δ_C(50 MHz; $CDCl_3$) 13.85 (2CH_3), 20.13 (2CH_2), 32.56 (2CH_2), 40.02 (2CH_2), 159.42 (C=O); Anal. calcd. for $C_9H_{20}N_2O$: C: 62.75; H: 11.70; N: 16.26; Found: C: 63.28; H: 12.15; N: 15.76.

N,N'-Di-iso-butyl urea (6) Obtained in 95% yield as a white solid with mp1 34-135°C (Lit. 135°C[8]); $\nu_{C=O}$(cm^{-1})= 1631; δ_H(200 MHz; $CDCl_3$) 0.90 (d, 12H), 1.71 (m, 2H), 2.96 (t, 4H), 5.50 (NH); δ_C(50 MHz; $CDCl_3$) 20.17 (4CH_3), 29.13 (2CH), 47.85 (2CH_2), 159.40 (C=O); Anal. calcd. for

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$C_9H_{20}N_2O$: C: 62.75; H: 11.70; N: 16.26; Found: C: 62.52; H: 11.41; N: 15.93.

N,N'-Di-sec-butyl urea (7) Obtained in 94% yield as a white solid with mp135-137°C (Lit. 136-137°C[8]); $\nu_{C=O}$(cm^{-1})= 1628; δ_H(200 MHz; $CDCl_3$) 0.90 (t, 6H), 1.08 (d, 6H), 1.40 (m, 4H), 3.66 (m, 2H), 4.68 (NH); δ_C(50 MHz; $CDCl_3$) 10.43 ($2CH_3$), 21.13 ($2CH_3$), 30.35 ($2CH_2$), 47.23 (2CH), 157.89 (C=O); Anal. calcd. for $C_9H_{20}N_2O$: C: 62.75; H: 11.70; N: 16.26; Found: C: 62.73; H: 11.53; N: 15.98.

N,N'-Di-tert-butyl urea (8) Obtained in 85% yield as a white solid with mp184-186°C; $\nu_{C=O}$(cm^{-1})= 1637; δ_H(200 MHz; DMSO-d_6) 1.19 (s, 18H); 5.44 (NH); δ_C(50 MHz; DMSO-d_6) 26.29 ($6CH_3$); 48.73 (2C); 157.04 (C=O); Anal. calcd. for $C_9H_{20}N_2O$: C: 62.75; H: 11.70; N: 16.26; Found: C: 62.29; H: 11.59; N: 16.01.

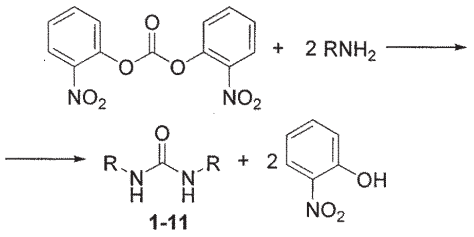
N,N'-Di-iso-pentyl urea (9) Obtained in 85% yield as a white solid with mp 45-47°C; $\nu_{C=O}$(cm^{-1})= 1624; δ_H(200 MHz; $CDCl_3$) 0.91 (d,12H), 1.41 (c, 4H), 1.55 (m, 2H), 3.17 (c, 4H), 5.37 (NH); δ_C(50 MHz; $CDCl_3$) 22.56 ($4CH_3$), 25.83 (2CH), 38.59 ($2CH_2$), 39.32 ($2CH_2$), 159.29 (C=O); Anal. calcd. for $C_{11}H_{24}N_2O$: C: 65.95; H: 12.08; N: 13.98; Found: C: 65.67; H: 11.93; N: 13.69.

N,N'-Di-allyl urea (10) Obtained in 95% yield as a white solid with mp 93-95°C (Lit. 91-93°C [9], 92°C[8]); $\nu_{C=O}$(cm^{-1})= 1626; δ_H(200 MHz; $CDCl_3$) 3.72 (t, 4H), 5.08 (m, 2H), 5.17(d, 2H); 5.83(m, 2H); 5.86 (NH); δ_C(50 MHz; $CDCl_3$) 42.63 ($2CH_2$), 115.11 ($2CH_2$), 135.65 (2CH), 159.07 (C=O); Anal. calcd. for $C_7H_{12}N_2O$: C: 59.98; H: 8.63; N: 19.98; Found: C: 59.71; H: 8.17; N: 19.61.

N,N'-Di-2-phenyl-ethyl urea (11) Obtained in 90% yield as a white solid with mp 139-141°C (Lit. 139.5-141°C [10]); $\nu_{C=O}$(cm^{-1})= 1615; δ_H(200 MHz; DMSO-d_6) 2.68 (t, 4H), 3.27 (c, 4H), 5.86 (NH), 7.27 (m, 10H); δ_C(50 MHz; DMSO-d_6) 39.43 ($2CH_2$), 40.02 ($2CH_2$), 125.81 (2CH), 128.15 (4CH), 128.6 (4CH), 139 (2C), 157.9 (C=O); Anal. calcd. for $C_{17}H_{20}N_2O$: C: 76.09; H: 7.51; N: 10.44; Found: C: 76.34; H: 7.57; N: 10.23.

Results and discussions

Given that *o*-nitrophenyl carbamates can be obtained by reaction between *bis*(*o*-nitrophenyl) carbonate with primary aliphatic amines in dichloromethane at room temperature within less than 10 min [2], we made use of the same conditions to obtain symmetrical aliphatic ureas (scheme 1), working with a carbonate : urea molar ratio of 1 : 3. The reactions carried out under these conditions involved *iso*-propyl amine, cyclohexyl amine and benzyl amine and required 4-5 h for completion (table 1), with the products being separated from the reaction mixture by column chromatography. Only *N,N'*-dicyclohexyl urea was precipitated from the reaction mixture.



Scheme 1

Table 1
SYNTHESIS OF N,N'-DIALKYL UREAS IN DICHLOROMETHANE AT ROOM TEMPERATURE

R	Time in CH_2Cl_2 at r.t.	Urea	η[%]
iso-propyl	4h	**1**	87
cyclohexyl	4h	**2**	78
benzyl	5h	**3**	70

The syntheses were repeated in toluene under reflux using 2.3 equivalents of amine. Each of the three ureas previously obtained in yields of below 90% over an extended timescale was synthesised under these new conditions in only 1h and was also isolated from the reaction mixture by precipitation in very high yield.

The investigation was extended to other primary aliphatic amines; these reactions also went to completion within an hour. However of the whole range of ureas presented in table 2 only *N,N'*-di-*tert*-butyl urea and *N,N'*-di-2-phenyl-ethyl urea could be isolated directly by precipitation. In the other situations the byproduct, o-nitrophenol was removed by steam distillation. In most cases simple cooling of the resulting nitrophenol-free aqueous solution resulted in precipitation of the urea. If the urea did not precipitate, the solution was evaporated to dryness, with the residue being purified by recrystallization from chloroform-heptane. The desired final products were obtained with very good yield the method being also applicable for the syntheses involving other non-hydrolizable compounds.

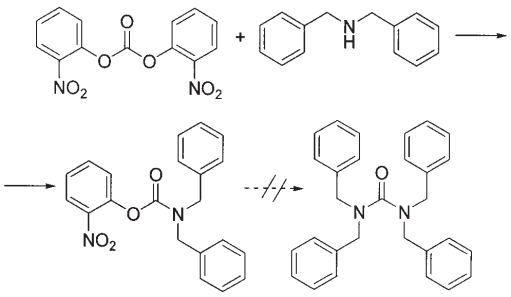
The results of studies on the behaviour of some amine isomers in comparison with *bis*(*o*-nitrophenyl) carbonate have been published previously [1,2]. The work reported here is concerned with demonstrating the usefulness of this carbonate for the synthesis of symmetrically disubstituted aliphatic ureas.

Table 2
SYNTHESIS OF N,N'-DIALKYL UREAS IN TOLUEN UNDER REFLUX

R	Urea	η (%)	$\nu_{C=O}$ [cm^{-1}]
iso-Propyl	**1**	92[a)]	1617
Cyclohexyl	**2**	95[a)]	1624
Benzyl	**3**	95[a)]	1626
n-Propyl	**4**	99[b)]	1626
n-Butyl	**5**	92[b)]	1620
iso-Butyl	**6**	95[b)]	1631
sec-Butyl	**7**	94[b)]	1629
tert-Butyl	**8**	85[a)]	1637
iso-Pentyl	**9**	85[b)]	1629
Allyl	**10**	95[b)]	1629
β-Phenyl-ethyl	**11**	90[a)]	1617

a) Precipitation in reaction medium
b) By steam distillation

An attempt was made to obtain tetra-substituted ureas but, probably due to steric hindrance effects, the reactions did not proceed beyond the *N,N'*-dialchyl-*o*-nitrophenyl carbamate step, despite treatment under reflux conditions both with a non-polar solvent (toluene) and a polar one (acetonitrile). The reaction of dibenzyl amine was followed in this way until a 1 : 6 molar ratio of carbonate : amine was reached after 40 h of reflux treatment, but only traces of desired ureas were obtained, the major product being *N,N'*-dibenzyl-*o*-nitrophenyl carbamate (scheme 2).



Scheme 2

Conclusions

In summary, we have developed an efficient methodology for symmetrical *N,N'*-dialkyl ureas synthesis using *bis*(*o*-nitrophenyl)carbonate as substitute of phosgene or isocyanates. The desired products are isolated in high yields. The method has two advantages: 1) *bis*(*o*-nitrophenyl)carbonate is more reactive and more soluble in a wide range of solvents than many other carbonates; 2) when the desired products (in this case aliphatic ureas) cannot be isolated from the reaction mixture by precipitation the byproduct, *o*-nitrophenol, can be removed by steam distillation.

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