

OXIDATION OF SUBSTITUTED CARBODIIMIDES AND UREAS¹

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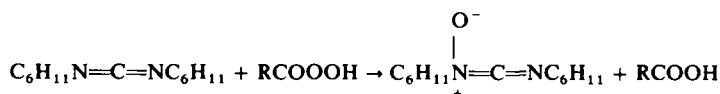
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Abstract—Pertrifluoroacetic acid oxidation of N,N'-dicyclohexylcarbodiimide and N,N'-diphenylsulfurdiimide yielded N-trifluoroacetyl-N,N'-dicyclohexyl urea and 2,2,2-trifluoroacetanilide as the major products. Sodium hypochlorite oxidation of N-hydroxy-N,N'-diphenyl thiourea and N-hydroxy-N,N'-diphenyl urea afforded 1,3,4,6-tetraphenyl-2,5-dithio-biurea and 1,2,4-triphenylsemicarbazide, respectively. The dimeric nature of these latter compounds implies the involvement of radical oxidation schemes.

INTRODUCTION

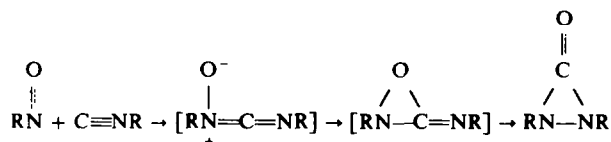
$$\begin{array}{c} \text{O}^- \\ | \\ \text{RN}=\text{C}=\text{NR} \\ + \end{array}$$

THE carbodiimide N-oxide system, $\text{RN}=\text{C}=\text{NR}$, represents a potential and interesting 1,3-dipolar intermediate, but no definite examples are known at present. One possible route to such a compound involves the oxidation of N,N'-dicyclohexylcarbodiimide (DCCI) with a peracid:



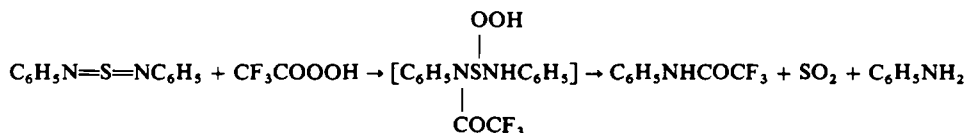
A literature search disclosed some earlier work on the reaction between DCCI and benzoyl peroxide.² N-Cyclohexyl isocyanate and N-cyclohexylbenzamide were formed with chloroform as the solvent, while in isopropanol the products were acetone, benzene, and N-benzoyl-N,N'-dicyclohexyl urea. If DCCI, an acid, and hydrogen peroxide or a peracid were used, then there was obtained either a symmetrical or unsymmetrical peroxide.³ A considerable amount of uncharacterized residue was reported here, too.

Later, the addition of 2-methyl-2-nitrosopropane to t-butyl isocyanide was postulated to form a carbodiimide N-oxide, followed by a valence isomerization to the oxaziridinimine, which in turn, finally produced the diaziridinone ring system:⁴

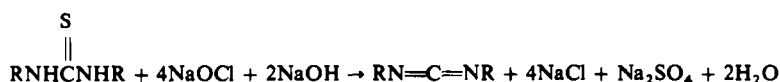


More recently, the oxidation of di-t-butylcarbodiimide with *m*-chloroperbenzoic acid was found to yield the corresponding di-t-butyl diaziridinone in low yield.⁵

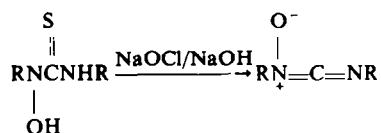
across the nitrogen-sulfur double bonds:



An alternative route was suggested by the reported reaction between a N,N'-disubstituted thiourea and basic sodium hypochlorite solution to form a N,N'-disubstituted carbodiimide:¹⁰



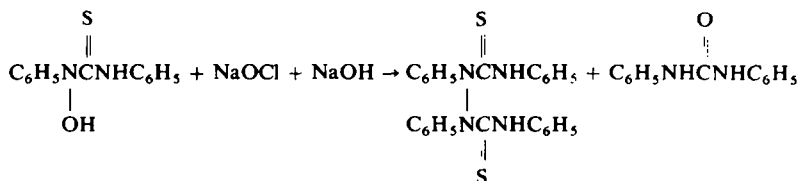
Therefore, one might be able to obtain the desired N-oxide from a N-hydroxy-N,N'-disubstituted thiourea under these same conditions. The proposed transformation is the following:



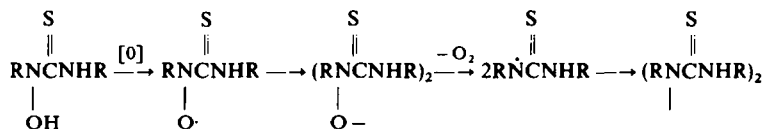
It was decided to investigate the same sequence with N-hydroxy-N,N'-diphenyl urea, as this intermediate was available, too.

Treatment of N-hydroxy-N,N'-diphenyl thiourea¹¹ with sodium hypochlorite and sodium hydroxide in dichloromethane afforded a dark-green oil, 1,3-diphenyl urea, and, as the chief product, an unknown, white solid. The elemental analysis revealed the absence of oxygen, while the mass spectrum suggested a possible dimeric formulation (*m/e* 455, C₂₆H₂₂N₄S₂⁺). The most logical structure was 1,3,4,6-tetraphenyl-2,5-dithio-biurea, which had been previously prepared from hydrazobenzene and mustard gas.¹² An alternative synthesis, involving the refluxing together of hydrazobenzene and phenyl isothiocyanate, gave the desired material. The two compounds had superimposable infrared spectra and undepressed m.ps.

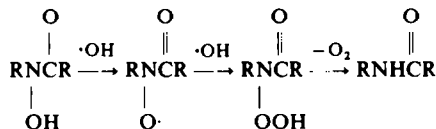
The main sequence observed is hence:



A tentative mechanism for the formation of the biurea is:



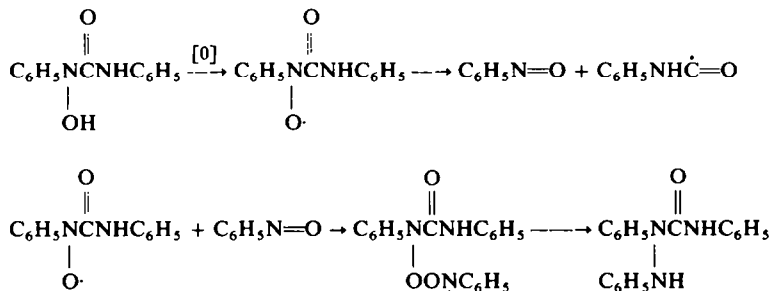
To justify the intramolecular loss of oxygen, a similar oxidation sequence for hydroxamic acids has been proposed:^{13, 14}



However, an ionic pathway,¹⁵ as well as a combination of these mechanisms,¹⁶ have been invoked to explain the last results.

Parallel products were seen when N-hydroxy-N,N'-diphenyl urea was treated with sodium hypochlorite and sodium hydroxide. A green oil, 1,3-diphenyl urea, and another white solid were separated from the reaction mixture. The unknown was identified as 1.2.4-triphenylsemicarbazide by the synthesis of an authentic sample, which was obtained by the addition of hydrazobenzene to phenyl isocyanate.

In this case the mechanism may proceed by a one electron abstracting oxidant. Thus:



In summary, the peracid oxidation of carbodiimides or sulfurdiimides and the hypochlorite oxidation of N-hydroxy thioureas or N-hydroxy ureas does not yield the carbodiimide N-oxide system. Other routes to this type of intermediate are under investigation.

EXPERIMENTAL

M.p.s were determined with a Reichert "Thermopan" apparatus and are uncorrected. IR spectra, from KBr pellets, were recorded on a Perkin-Elmer 257 spectrometer. NMR spectra were obtained on a Varian Associates' A-60 spectrometer using TMS as an internal standard. Mass spectra were measured on an A.E.I. MS-9 spectrometer at 70 electron-volts. TLC employed iodine or sodium dichromate-sulfuric acid as the detecting agents. Evaporations were performed under reduced pressure (water pump) in a rotary evaporator at minimum temp. Microanalyses were provided by Galbraith Laboratories, Inc., Knoxville, Tennessee. All solvents were reagent grade and the light petroleum had boiling range 30-60°. MgSO₄ was used for drying purposes.

Oxidation of N,N'-dicyclohexylcarbodiimide. Pertrifluoroacetic acid, freshly prepared from H₂O₂ (1.87 g of a 90% soln, 0.05 mole) and trifluoroacetic anhydride (11.55 g, 0.055 mole), was added dropwise over a 3 hr period to a stirred soln of N,N'-dicyclohexylcarbodiimide (10.3 g, 0.05 mole) in dry dichloromethane (50 ml) held at 0°. The milky mixture was neutralized with NaHCO₃ aq and filtered to afford N,N'-dicyclohexyl urea (0.6 g), identical in all aspects with an authentic sample. The organic phase was washed with water, dried, and evaporated to leave a solid. Crystallization from light petroleum and then from cyclohexane gave fine white crystals of N-trifluoroacetyl-N,N'-dicyclohexyl urea (7.8 g) m.p. 138° (lit.⁷ 139°); ν_{max} 3460 (NH), 3340 (NH), 2940, 2870, 1710 (C=O), 1680 (CONH amide I), 1530 (CONH amide II), 1270-1190 (CF₃).

1150. and 730 cm^{-1} ; m/e 320 ($\text{C}_{15}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_2^+$), parent, very small, 195 ($\text{C}_8\text{H}_{12}\text{F}_3\text{NO}^+$) 1%, 152 ($\text{C}_3\text{F}_3\text{N}_2\text{O}_2^+$) 37%, 98 ($\text{C}_6\text{H}_{12}\text{N}^+$) 32%, 82 ($\text{C}_6\text{H}_{10}^+$) 100%, and 67 (CF_2OH^+) 91%; 435 (singlet, NH) and 130–60 (multiple cyclohexyl) Hz (CDCl_3). (Found: C, 56.39; H, 7.30; N, 8.63; F, 17.71. Calc. for $\text{C}_{15}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_2$ (320.35): C, 56.24; H, 7.24; N, 8.74; F, 17.79).

Under these same conditions, *N,N'*-dicyclohexyl urea was recovered unchanged.

A basic reaction using a mixture of H_2O_2 (1.12 g of a 90% soln, 0.03 mole) in water (5 ml), NaOH (0.5 g, 0.0125 mole) in EtOH (10 ml) and *N,N'*-dicyclohexylcarbodiimide (4.12 g, 0.02 mole) in dichloromethane (50 ml) at 0° afforded *N,N'*-dicyclohexyl urea.

A neutral reaction was attempted with pertrifluoroacetic acid, freshly prepared from trifluoroacetic anhydride (13.9 g, 0.066 mole) and H_2O_2 (2.0 g of a 90% soln, 0.055 mole), that was added dropwise over a 15 min period to a stirred mixture of finely ground disodium hydrogen phosphate (20 g) and *N,N'*-dicyclohexylcarbodiimide (10.3 g, 0.05 mole) in dichloromethane (30 ml). The products were *N,N'*-dicyclohexyl urea and *N*-trifluoroacetyl-*N,N'*-dicyclohexyl urea, as well as a yellow oil. This last material was apparently a peroxide, as it gave a positive Ferrox test,⁸ and possessed infrared absorptions bands attributed to such a function.

Oxidation of N,N'-diphenylsulfurdiimide. Petrifluoroacetic acid, prepared from trifluoroacetic anhydride (1.16 g, 0.0055 mole) and H_2O_2 (0.19 g of a 90% soln, 0.0055 mole) in dichloromethane (15 ml) was added dropwise to a chilled, stirred soln of *N,N'*-diphenylsulfurdiimide (1.07 g, 0.005 mole) in dichloromethane (30 ml). The black soln was taken to dryness and the residue was chromatographed in benzene over silica gel. The first fraction gave a semi-solid, which on crystallization from ligroin yielded pale beige needles of 2,2,2-trifluoroacetanilide (0.25 g), m.p. 86° (lit.⁹ 88°); ν_{max} 3450 (NH), 3330 (NH), 1700 (sec amide), 1600, 1545 (sec amide), 1500 (aromatic), 1450 (aromatic), 1350, 1285, 1240, 1190–1150 (CF_3), 920, 895, 755 (aromatic), 730, and 690 (aromatic) cm^{-1} , identical in all aspects with an authentic sample.

The second fraction on evaporation yielded a dark red oil that was shown to be a mixture on the basis of TLC on silica gel. No further work was attempted on this material.

N-Hydroxy-N,N'-diphenyl-thiourea. Phenylhydroxylamine (40.0 g, 0.37 mole) was added to phenyl isothiocyanate (56.0 g, 0.35 mole) in ether (350 ml) at 0°. After standing at room temp for 3 hr, the solvent was evaporated and the residue was crystallized from EtOAc–light petroleum to afford a sticky, yellow solid (61.0 g). A portion of this material was dissolved in 1N NaOH filtered, and then acidified with 1N HCl. The ppt was collected, dried, and crystallized in the form of shiny white plates, m.p. 110° (lit.¹¹ 111°); ν_{max} 3460 (NH), 3350 (NH), 3020 (CH, aromatic), 2770, 1600 (aromatic), 1530, 1490 (aromatic), 1350 (sulfonamide), 1240 (thioketone), 1000, 950, 765, and 700 cm^{-1} ; 472–411 (complex, aromatic) and 32 (singlet, ROH) Hz (CDCl_3).

Oxidation of N-hydroxy-N,N'-diphenyl-thiourea. Freshly prepared NaOCl soln¹⁷ (8.0 ml of a 16.4% soln, 0.177 mole) was added dropwise to a stirred mixture of *N*-hydroxy-*N,N'*-diphenyl-thiourea (10.74 g, 0.044 mole) in water (44 ml) and dichloromethane (26 ml) while the temp was maintained at 8°. After standing in the refrigerator overnight, the reaction was filtered to remove unreacted starting material (2.2 g). The organic layer was separated, washed, dried, and evaporated to leave a dark yellow solid. Chromatography over silica gel and elution with chloroform gave three major fractions. The first produced a solid that was crystallized first from chloroform–ligroin and then from dichloromethane to afford shiny, pale yellow crystals of 1,3,4,6-tetraphenyl-2,5-dithio-biurea (1.6 g), m.p. 162°; ν_{max} 3445, 3340, 3130 (NH), 2950 (aromatic), 1590 (aromatic), 1530 amide NH), 1490 (aromatic), 1445 (thioketone), 1360, 1265, 1200, 765, 725, 695 (phenyl), and 635 cm^{-1} ; m/e (30 electron volts) 455 ($\text{C}_{26}\text{H}_{22}\text{N}_4\text{S}_2^+$) parent, less than 1%, 286 ($\text{C}_{19}\text{H}_{16}\text{N}_3^+$) 2%, 228 ($\text{C}_{13}\text{H}_{11}\text{N}_2\text{S}^+$) 83%, 194 ($\text{C}_{13}\text{H}_{10}\text{N}_2^+$) 63%, 135 ($\text{C}_7\text{H}_5\text{NS}^+$) 100%, 118 94%, and 109 88%; 620–600 (broad, singlet), 523 (singlet, NH), 471–453 (complex, aromatic), 449–417 (complex, aromatic), and 297–287 (broad, singlet) Hz (deuteriopyridine). (Found: C, 68.56; H, 5.16; N, 12.29; S, 14.25. Calcd. for $\text{C}_{26}\text{H}_{22}\text{N}_4\text{S}_2$ (454.59): C, 68.69; H, 4.88; N, 12.34; S, 14.10).

The second set of fractions left a solid that was crystallized from chloroform–ligroin and then from dichloromethane to give 1,3-diphenyl urea (0.5 g), m.p. 232°, identical in all aspects with an authentic sample.

The third set of fractions, after evaporation, consisted of a small quantity of dark green oil. TLC on aluminium oxide revealed four major spots. No further work was done on this material.

1,3,4,6-Tetraphenyl-2,5-dithio-biurea. Hydrazobenzene (2.0 g, 0.011 mole) and phenyl isothiocyanate (30 ml) were refluxed in an oil bath at 130° for 6 hr. Light petroleum was added to the cooled mixture and the resulting solid was collected and crystallized from benzene to yield 1,3,4,6-tetraphenyl-2,5-dithio-biurea (1.0 g), m.p. 164° (lit.¹² 168°). The IR spectrum was identical to the product isolated from the oxidation of *N*-hydroxy-*N,N'*-diphenyl-thiourea.

Oxidation of N-hydroxy-N,N'-diphenyl-urea. The oxidation of N-hydroxy-N,N'-diphenyl-urea (10.04 g, 0.044 mole) was done as described for the corresponding thiourea. After 1 hr the black soln was filtered to give a beige solid (1.2 g), m.p. 232°, identified as 1,3-diphenyl-urea by comparison with an authentic sample.

The filtrate was reduced in volume (ca 3 ml) and chromatographed over silica gel using chloroform for development. Two major fractions were obtained by this procedure. The first consisted of dark red oils (2.3 g), while the second was a red solid. After a wash with MeOH to remove most of the color, the remaining material was crystallized from chloroform–light petroleum to yield 1,2,4-triphenylsemicarbazide (2.4 g), m.p. 221°; ν_{\max} 3450 (NH), 3365 (NH), 3260 (NH), 1655 (sec amide), 1593 (amide), 1590, 1530, 1440, 1328, 1312, 1295, 1215, 758, 745, and 690 (phenyl) cm^{-1} ; 470–408 (multiple, aromatic) and 199 (singlet, NH) Hz (deuteriodimethylsulfoxide); m/e 303 ($\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}^+$) parent 92%, 185 ($\text{C}_{12}\text{H}_{12}\text{N}_2^+$) 11%, 173 ($\text{C}_{10}\text{H}_{10}\text{N}_3\text{O}^+$) 74%, 174 100%, 109 ($\text{C}_4\text{H}_3\text{N}_3\text{O}^+$) 41%, 83 and 82 ($\text{C}_2\text{HN}_3\text{O}^+$) 100%. (Found: C, 75.17; H, 5.48; N, 13.42. Calc. for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}$ (303.35); C, 75.22; H, 5.65; N, 13.85).

1,2,4-Triphenylsemicarbazide. Hydrazobenzene (5.0 g, 0.027 mole) and phenyl isocyanate (3.2 g, 0.027 mole) in benzene were stirred for 2 days at room temp. The solid product was collected and crystallized from chloroform–MeOH (9:1) to give white crystals of 1,2,4-triphenylsemicarbazide (4.1 g), m.p. 219°. The IR spectrum was identical to the product isolated from the oxidation of N-hydroxy-N,N'-diphenyl-urea.

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