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PREPARATION OF CARBODIIMIDES BY THE REACTION OF THIOUREAS WITH DIETHYL AZODICARBOXYLATE*

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Abstract—A new synthesis of disubstituted carbodiimides from N,N'-disubstituted thioureas, diethyl azodicarboxylate and triphenyl phosphine has been achieved. The intermediates of the reaction have been isolated and found to be 1:1 adducts of the thioureas and diethyl azodicarboxylate, N^1,N^2-disubstituted—S—(N^3,N^4-biscarboethoxy)hydrazinoisothioureas which, on treatment with triphenyl phosphine at room temperature, afford the corresponding carbodiimides. Alternatively, the intermediates on heating under reflux in benzene or toluene, decompose to the carbodiimides, diethyl hydrazodicarboxylate and sulphur.

INTRODUCTION

CARBODIIMIDES are important in nucleotide and peptide fields,[2-3] and usually have been prepared by dehydrosulphurization or dehydration of thioureas or ureas. Recently, N,N'-disubstituted thioureas have been oxidized to the corresponding carbodiimides by variety of reagents.[3-5,†]

The synthesis of N,N'-diphenylcarbodiimide from N,N'-diphenylthiourea, diethyl azodicarboxylate and triphenyl phosphine, as reported,[1] is a convenient method for the preparation of carbodiimides and the reaction has now been investigated in detail.

RESULTS AND DISCUSSION

Diethyl azodicarboxylate (**1**) and N,N'-diphenylthiourea (**2a**) in THF react to yield one major product, which, without isolation, on adding of an equimolar amount of triphenyl phosphine (**4**) gives a 79% yield of diphenylcarbodiimide (**5a**).

In this manner, various carbodiimides were prepared in excellent yields as summarized in Table 1.

N,N'-di-p-chlorophenylthiourea (**2d**) afforded only a 40% yield of di-p-chlorophenylcarbodiimide (**5d**) and a considerable amount of a white solid was produced as a by product. The IR spectrum of this solid indicated a strong absorption at 1650 cm^{-1} attributed to a C=N bond. As diphenylcarbodiimide polymerizes on heating in the presence of tri-n-butyl phosphine,[7] and since TLC of the reaction mixture showed only three spots, **5d**, **6** and **7**, the polymerization of **5d** may take place during distillation. This reaction was not investigated further.

As shown in the Table 1, N-cyclohexyl-N'-phenylthiourea (**2f**) afforded a 79% yield of the unsymmetrical carbodiimide (**5f**), which on treatment with hydrochloric acid was converted to N-cyclohexyl-N'-phenylurea. Since no N,N'-dicylohexylurea

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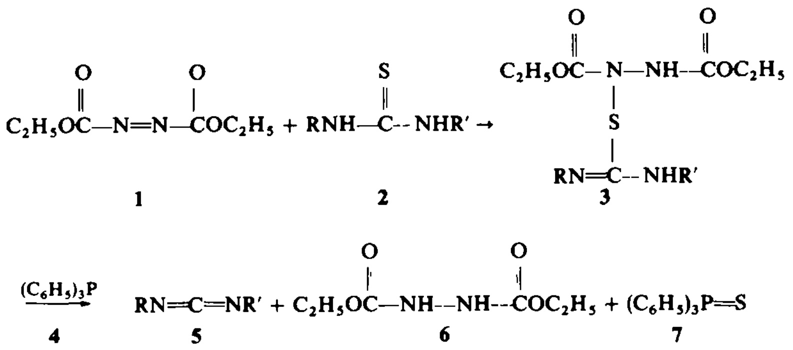
[*] A part of this work has appeared in a preliminary communication,[1] and was presented at the 21st Japan Chemical Society Meeting, Osaka, April 1968.

[†] The reaction of *p*-quinones with thiourea have been resulted in the formation of 5-hydroxy-1,3-benzoxathiol-2-ones. S-(2,5-Dihydroxyaryl)thiouronium salts have been isolated as the intermediates.[6]



$$\underset{\mathbf{1}}{C_2H_5O\overset{O}{\overset{\|}{C}}-N=N-\overset{O}{\overset{|}{C}}OC_2H_5} + \underset{\mathbf{2}}{RNH-\overset{S}{\overset{\|}{C}}-NHR'} \rightarrow \underset{\mathbf{3}}{C_2H_5O\overset{O}{\overset{\|}{C}}-\underset{\underset{\underset{RN=C-NHR'}{|}}{\underset{S}{|}}}{N}-NH-\overset{O}{\overset{\|}{C}}OC_2H_5}$$

$$\xrightarrow[\mathbf{4}]{(C_6H_5)_3P} \underset{\mathbf{5}}{RN=C=NR'} + \underset{\mathbf{6}}{C_2H_5O\overset{O}{\overset{|}{C}}-NH-NH-\overset{O}{\overset{|}{C}}OC_2H_5} + \underset{\mathbf{7}}{(C_6H_5)_3P=S}$$

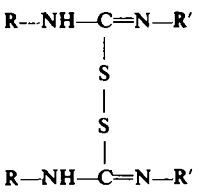
a: $R=R'=C_6H_5$-
b: $R=R'=$p-$CH_3C_6H_4$-
c: $R=R'=$p-$CH_3OC_6H_4$-
d: $R=R'=$p-ClC_6H_4-
e: $R=R'=$cyclo C_6H_{11}-
f: $R=C_6H_5$-, $R'=$cyclo C_6H_{11}-

and N,N'-diphenylurea could be detected by TLC, the disproportionation[3] of the unsymmetrical carbodiimide does not occur during the reaction.

Isolation of the reaction intermediate. The IR spectrum of the solution resulting from the reaction of **1** and **2a** shows that the C=O absorption of **1** (1785 cm^{-1}) has shifted to 1729 cm^{-1} and 1709 cm^{-1} and a new absorption due to C=N has appeared at 1630 cm^{-1}, and no C=O absorption attributed to **6** is present. TLC of the solution reveals a new spot as the reaction between **1** and **2a** proceeds and as further treatment with **4**, yields **5a**, a 1 : 1 adduct of **1** and **2a** is probably an intermediate in the reaction.

Equimolar amounts of **1** and **2a** react in THF to produce N^1,N^2-diphenyl-S-(N^3,N^4-biscarboethoxy)hydrazinoisothiourea (**3a**) as a white crystalline compound, which reacts with **4** to give a 66% yield of **5a**. Various 1 : 1 adducts (**3**) of **1** and **2** were successfully obtained and are summarized in Table 2.

Yoneda, *et al.*[8] demonstrated that mercaptans are oxidized to the corresponding disulphides by means of **1**. As this reaction is promoted by **4**,[9] an alternative pathway may involve the initial formation of bis(carbamidino)disulphides (**8**) as shown by the reaction of **1** and **2** in the presence of **4**.[1] In the oxidation of thioureas by bromine or thionyl chloride, bis(carbamidino)disulphides were isolated as hydrobromide salts.[10–18]



$$\begin{array}{c} R-NH-C=N-R' \\ | \\ S \\ | \\ S \\ | \\ R-NH-C=N-R' \end{array}$$

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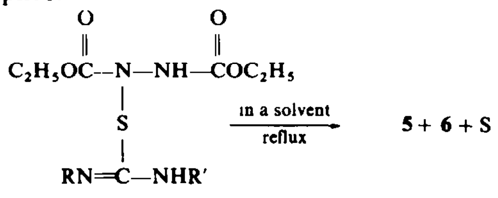
The disulphides on treatment with absolute ethanol lose an atom of sulphur to afford bis(carbamino)sulphides.[15,16] No carbodiimides have been reported to be formed. Thus it is not likely that bis(carbamidino)disulphide (**8**) is formed as an intermediate which in turn is desulphurized by **4** to give the **5**, **7** and **2**.

Thermal decomposition of the S-hydrazinoisothiourea. N^1,N^2-dicyclohexyl-S-(N^3,N^4-biscarboethoxy)hydrazinoisothiourea was not isolated in the reaction of **1** with **2e**, while **5e**, sulphur and **6** were formed as indicated by TLC. This suggests that **3** is unstable and decomposed to the corresponding **5**, sulphur and **6**.

In preliminary small scale reactions to test the stability of **3**, a solution of **3a** or **3c** in benzene or toluene was heated under reflux for 8 hr. TLC of the solution showed the formation of the corresponding carbodiimide, sulphur and **6** only. If on the other hand, the reaction was carried out in boiling THF or dioxan, many side products were formed in addition to **5** and **6**. Therefore, the thermal decomposition of **3** depends on the solvent used rather than the reaction temperature. As expected, the thermal decomposition of **3b** in boiling benzene afforded a 93% yield of **5b** together with a small amount of sulphur.



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solvents: THF, benzene, dioxan or toluene

In the formation of carbodiimides by the present process, **1** is reduced to **6** and **4** is oxidized to **7**. In the thermal decomposition of **3**, the hydrogens and the sulphur of the thioureas are accepted in **1** and oxidized to sulphur respectively.*

This method for the preparation of carbodiimides is convenient and cheap as the diethyl hydrazodicarboxylate formed is readily oxidized to diethyl azodicarboxylate[21] which may be used again.

TABLE 1. THE REACTION OF N,N'-DISUBSTITUTED THIOUREAS (2) WITH DIETHYL AZODICARBOXYLATE (1) AND TRIPHENYL PHOSPHINE (4)

$RNH-C(=S)-NHR'$		Products			
		$RN{=}C{=}NR'$		$C_2H_5OC(=O)NH-NHC(=O)OC_2H_5$	$(C_6H_5)_3P{=}S$
R	R'	Yield %	b.p.°/mm	Yield %	Yield %
(a) C_6H_5-[a]	C_6H_5-	79	135–138/2	84	98
(b) p-$CH_3C_6H_4$-[b]	p-$CH_3C_6H_4$-	78		94	90
(c) p-$CH_3OC_6H_4$-[c]	p-$CH_3OC_6H_4$	81	162–163/0·08	78	84
(d) p-ClC_6H_4[c]	p-ClC_6H_4-	40	130/0·018	89	98
(e) cycloC_6H_{11}[c]	cycloC_6H_{11}-	79	105–107/1	87	83
(f) C_6H_5-[d]	cycloC_6H_{11}-	79	104–108·5/1	89	93

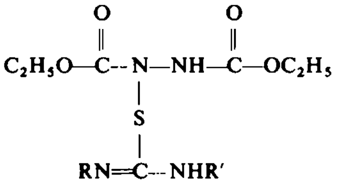
[a] The soln of 1 and 2 was allowed to stand for 3 hr and then 4 was added.

[b] The soln of 1 and 2 was allowed to stand overnight and then 4 was added.

[c] It takes about 3 days until the colour of the solution of 1 and 2e no longer changed.

* Strong heating of S-alkyl isothioureas have been known to eliminate mercaptans giving carbodiimides. The elimination has been effected by treating the isothiourea with silver nitrate or mercuric chloride in the presence of an acid acceptor.[3, 19, 20]

TABLE 2. PREPARATION OF N^1,N^2-DISUBSTITUTED—S—(N^3,N^4-BISCARBOETHOXY)HYDRAZINOISOTHIOUREAS



R	R'	m.p.°	Yield %		Analysis % C	H	N	IR cm^{-1} C=O	C=N
C_6H_5-	C_6H_5-	124–125·5	82	Calcd.	56·70	5·51		1730	1639
				Found	56·92	5·46		1709	
p-$CH_3OC_6H_4$-	p-$CH_3OC_6H_4$	107–110	76	Calcd.	54·30	6·08	12·06	1731	1634
				Found	54·65	5·56	12·27	1713	
p-ClC_6H_4-	p-ClC_6H_4-	89–91 (dec.)	83	Calcd.	48·44	4·28	13·58	1715	1633
				Found	49·74	4·30	11·52		
p-$CH_3C_6H_4$-	p-$CH_3C_6H_4$-	104·5 (dec.)	72					1753	1636
								1718	

EXPERIMENTAL

IR spectra were recorded on Nippon Bunko IR-G spectrometer and measured as KBr disks. IR spectra of the reaction solns were measured in a 0·05 cm matched cell (NaCl). TLC were carried on silica gel (Wako Gel B-O) plates with benzene as the solvent and spots were developed with iodine vapour. Compounds **2a**, **2b**, **2c**, **2d** and **2e** were prepared from the corresponding amines and CS_2; **2f** was prepared from phenyl isothiocyanate and cyclohexylamine. Diethyl azodicarboxylate was prepared by a known procedure.[21] Triphenyl phosphine is a commercial product and was purified by recrystallization from EtOH. The solvents were purified and dried by ordinary procedures.

The reaction of N,N'*-diphenylthiourea* (**2a**) *with diethyl azodicarboxylate* (**1**) *and triphenyl phosphine* (**4**)

(a) Triphenyl phosphine (2·62 g, 0·01 mole) in 10 ml THF was added dropwise to **2a** (2·28 g, 0·01 mole) and **1** (1·74 g, 0·01 mole) in 20 ml THF at room temp. After standing overnight, the solvent was removed under reduced pressure and the residue was extracted with light petroleum (b.p. 30–60°) to separate soluble material from the remainder. The light petroleum extract was concentrated and distilled to give diphenylcarbodiimide, b.p. 85–90°/0·2 mm, 1·27 g, 65%.

The light petroleum-insoluble material was applied to a column (2·5 × 40 cm) of alumina in benzene. The column was eluted first with benzene (1·5 l) and then with ethanol (1·5 l). Triphenyl phosphine sulphide (2·38 g, 81%) was obtained from the benzene fraction and purified by recrystallization from EtOH, m.p. 163·5–164·5°. Diethyl hydrazodicarboxylate (1·28 g, 72%) was obtained from the EtOH fraction and recrystallized from benzene, m.p. 134°. In this manner, **5b** was obtained in a 42% yield, b.p. 131–133°/0·2 mm; m.p. 51–53°.

(b) A soln of **1** (1·74 g, 0·01 mole) in THF was added dropwise to **2a** (2·28 g, 0·01 mole) in 20 ml THF at room temp. The orange-red of the soln was gradually faded during about 3 hr. The IR spectrum of the soln shows that C=O absorption of **1** has shifted to 1729 cm^{-1} and 1709 cm^{-1} and C=N absorption appeared at 1630 cm^{-1}. The TLC of the soln revealed a new spot as the starting materials disappeared. Then **4** (2·62 g, 0·01 mole) in 20 ml THF was added at room temp and the soln was kept one day. The solvent was removed under reduced pressure and the residue was worked up as described to give N,N'-diphenylcarbodiimide (1·63 g, 79%, b.p. 135–138°/2 mm), triphenyl phosphine sulphide (2·88 g, 98%, m.p. 159–161°) and diethyl hydrazodicarboxylate (1·48 g, 84%).

Similarly, **5b**–**5f** were obtained* and the results are summarized in Table 1.

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* If the light petroleum extract contained **6**, after removal of the light petroleum, the residue was taken up in benzene, filtered over Al_2O_3 and then distilled to give pure carbodiimides.

Synthesis of N^1,N^2*-disubstituted-S-*(N^3,N^4*-biscarboethoxy)hydrazinoisothioureas* (**3**)

General procedure. Diethyl azodicarboxylate (1·74 g, 0·01 mole) in THF (20 ml) was added dropwise to an ice-cooled soln of N,N'-disubstituted thiourea (0·01 mole) in 20 ml THF. The soln was allowed to stand overnight at room temp and then the solvent was removed under reduced pressure leaving a white crystalline mass which was dissolved in 150 ml ether and precipitated with light petroleum (ice cooling). The product was collected by filtration. The yields and the m.ps are summarized in Table 2.

The reaction of N^1,N^2*-diphenyl—S—*(N^3,N^4*-biscarboethoxy)hydrazinoisothiourea* (**3a**) *with triphenyl phosphine*

Triphenyl phosphine (1·31 g, 0·005 mole) in 5 ml THF was added dropwise to **3a** (2·01 g, 0·005 mole) in 20 ml THF at room temp. After standing overnight, the solvent was removed under reduced pressure and the residue was extracted with light petroleum (6 ml × 5) to separate soluble material from the remainder. Diphenylcarbodiimide was obtained from the extract by distillation, 0·64 g, 66%, b.p. 100–104°/0·07 mm. The light petroleum-insoluble material was applied to a column of alumina. Elution with benzene followed by EtOH gave **7** (74%) and **6** (91%) respectively.

The thermal decomposition of N^1,N^2*-dipehnyl—S—*(N^3,N^4*-biscarboethoxy)hydrazinoisothiourea* (**3a**)

Small-scale experiment. A soln of **3a** in a solvent (THF, benzene, dioxan or toluene) was heated under reflux. The reaction was monited by TLC. When benzene or toluene was used as the solvent, almost all the **3a** was consumed during about 1 hr and **5a**, **6** and S were indicated by TLC. On the other hand, when the reaction was carried out in THF or dioxan, many other spots were observed in addition to those of expected products. The formation of **5a** was further ascertained as follows. The soln was refluxed for several hr, kept standing overnight and the solvent was removed under reduced pressure. The residue was extracted with light petroleum, evaporated under reduced pressure, to give an oily substance which was identified to be **5a** by comparison of its IR spectrum with that of an authentic sample.

The thermal decomposition of **3c** showed the same solvent dependency as N,N'-diphenyl derivatives.

Preparative-scale experiment. A soln of **3b** (2·28 g, 1/150 mole) in 150 ml of benzene was heated under reflux for 11 hr. The soln was concentrated and the residue was extracted with light petroleum leaving **6**, 1·02 g, 87%, m.p. 133–134°. The light petroleum extract was distilled to give **5b** (1·83 g, 93%, b.p. 114°/0·02 mm) which was contaminated with a small amount of sulphur.

REFERENCES

[1] O. Mitsunobu, K. Kato and F. Kakese, *Tetrahedron Letters* 2473 (1969)

[2] H. G. Khorana, *Chem. Revs.* **53** 145 (1953)

[3] F. Kurzer and K. Douraghi-Zadeh, *Ibid.* **67**, 107 (1967)

[4] S. Furumoto and Hirao, *Abstract of the 22nd Japan Chemical Society Meeting* III-1608, Tokyo, April (1970)

[5] S. Furumoto, *Nippon Kagaku Zasshi* **91**, 359 (1970)

[6] P. T. S. Lau and M. Kestner, *J. Org. Chem.* **33**, 4426 (1968)

[7] R. Richter, *Chem. Ber.* **101**, 174 (1968)

[8] F. Yoneda, K. Suzuki and Y. Nitta, *J. Am. Chem. Soc.* **88**, 2328 (1966)
F. Yoneda, K. Suzuki and Y. Nitta, *J. Org. Chem.* **32**, 727 (1967)

[9] K. Kato and O. Mitsunobu, *Ibid.* **35**, November issue (1970)

[10] P. K. Srivastava and Y. R. Rao, *J. Indian Chem. Soc.* **40**, 803 (1963); *Chem. Abstr.* **60**, 1734 (1964)

[11] P. K. Srivastava, *Indian J. Chem.* **1**, 432 (1963); *Chem. Abstr.* **60**, 2921 (1964)

[12] P. K. Srivastava, *Ibid.* **2**, 154 (1964); *Chem. Abstr.* **61**, 2968 (1964)

[13] P. Klatsmanyi-Gabor, T. Meisel and L. Erdey, *Acta Chim. Acad. Sci. Hung.* **40**, 99 (1964); *Chem. Abstr.* **61**, 9419 (1964)

[14] F. Kurzer and Ph. M. Sanderson, *J. Chem. Soc.* 4461 (1957); *Ibid.* 1058 (1959); *Ibid.* 3336 (1963)

[15] G. Barnikow and J. Bödeker, *Chem. Ber.* **100**, 1394 (1967)

[16] P. K. Srivastava and M. Saleem, *Tetrahedron Letters* 2725 (1968)

[17] B. V. Kopylova, M. N. Khasanova and R. Kh. Freidlina, *Clzb. Khim. Zh.* **12**, 29 (1968); *Chem. Abstr.* **70**, 68240 (1969)

[18] T. Kodama, K. Uehara, K. Hisada and Y. Kodama, *Yuki Gosei Kagaku Kyokai Shi* (*Journal of Synthetic Organic Chemistry, Japan*) **26**, 674 (1968)

[19] P. Schlack and G. Keil, G. P. 173460; *Chem. Abstr.* **62**, 1605 (1965)

[20] A. F. Ferris and B. A. Schutz, *J. Org. Chem.* **28**, 71 (1963)

[21] N. Rabjohn, *Org. Syn.* Coll. Vol. 3, 375 (1955)