Formation of Ketenimines by the Reaction of Thioamides with Diethyl Azodicarboxylate and Triphenylphosphine

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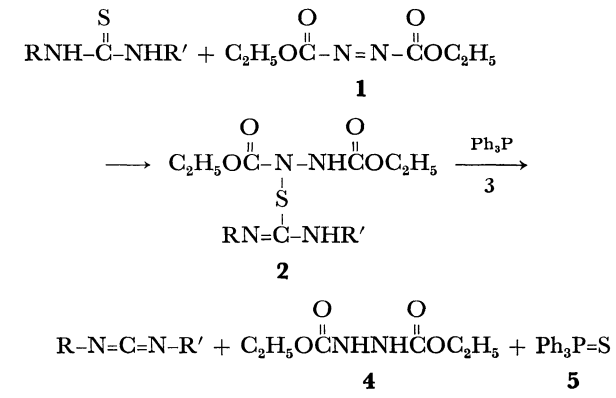
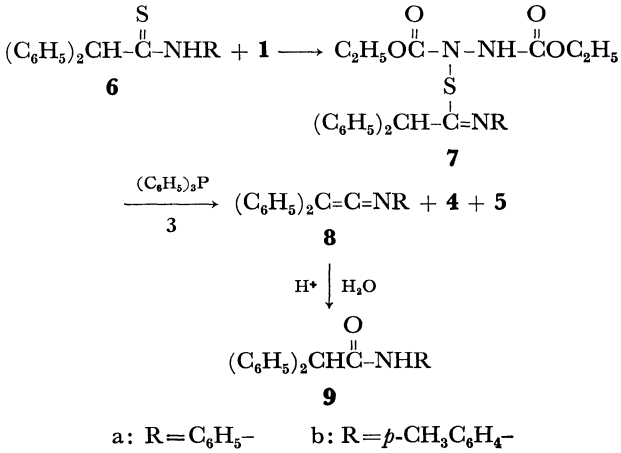
The reaction of diphenylacetothioanilide with diethyl azodicarboxylate and triphenylphosphine gave rise to the formation of diphenylketene(*N*-phenyl)imine. Similarly, the reaction of *N*-(*p*-tolyl)diphenylacetothioamide gave diphenylketene(*N*-*p*-tolyl)imine. On treatment with diethyl azodicarboxylate in the presence of sodium ethoxide, diphenylacetothioanilide afforded bis(*N*-phenylbenzalimidoyl) disulfide in a good yield. The intermediate of the formation of the ketenimines is also discussed.

Ketenimines have attracted considerable attention because of their importance as versatile reagent. Their use as condensing agents in the preparation of peptides[1] and nucleotides[2] has been examined. The preparation of ketenimines has been accomplished in various ways, 1) the interaction of phosphinimine and ketene,[3] 2) the reaction of diazomethane with nitriles,[4] 3) dehydrochlorination or dechlorination of imino chlorides,[5] 4) dehydration of amides,[6] 5) the Beckmann rearrangement,[7] 6) the reaction of α-haloxime with triphenylphosphine,[8] 7) photolysis of diphenyldiazomethane in the presence of isonitrile,[9] and 8) ring opening of isoxazolium salts.[10]

A new approach to the synthesis of disubstituted carbodiimides from *N*,*N*′-disubstituted thioureas using diethyl azodicarboxylate (**1**) and triphenylphosphine (**3**) was described in the preceding paper.[11] The reaction proceeds through the initial formation of an 1:1 adduct (**2**) of the thiourea and **1**. Formation of the carbodiimide couples to a redox system.

Since thioamides (**6**) are similar in structure to thioureas, **6** would be expected to react with **1** giving an 1:1 adduct (**7**). In view of the reactivity of **2**, we might expect that the **7** is desulfurized by **3** to give the corresponding ketenimine (**8**), diethyl hydrazodicarboxylate (**4**) and triphenylphosphine sulfide (**5**).





a: R=C_6H_5– b: R=*p*-$CH_3C_6H_4$–

Equimolar amounts of **1** and diphenylacetothioanilide (**6a**) in tetrahydrofuran (THF) were allowed to react for 4 hr, and then an equimolar amount of **3** was added. After the solution was kept standing for 7 days, the solvent was removed to give a yellow syrup. The infrared spectrum of the syrup shows a strong absorption at 2000 cm^{-1} which is attributed to N=C=C of the ketenimine. From the syrup, however, diphenylketen(*N*-phenyl)imine (**8a**) could not be isolated in pure state. In a repetition of the above experiment, the resulting yellow syrup was therefore treated with 2N hydrochloric acid to convert the **8a** into diphenylacetanilide (**9a**). The mixture was separated by column chromatography on silica gel to give **9a**, **4**, **5**, and triphenylphosphine oxide (**12**) in 35.5%, 98.0%, 36.1%, and 60.0% yields, respectively, and 63.0%

1) a) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961). b) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **34**, 2742 (1969). c) D. S. Kemp and S. W. Chien, *J. Amer. Chem. Soc.*, **89**, 2743 (1967).

2) a) F. R. Atherton, A. L. Morrison, R. J. Cremlyn, G. W. Kenner, A. R. Todd, and R. F. Webb, *Chem. Ind.* London, **1955**, 1183. b) R. J. Cremlyn, G. W. Kenner, and A. R. Todd, *J. Chem. Soc.*, **1960**, 4511. c) T. M. Jacob and H. G. Khorana, *J. Amer. Chem. Soc.*, **86**, 1630 (1964).

3) H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 887 (1921).

4) R. Dijkstra and H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **73**, 575, 695 (1954).

5) a) C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **75**, 657 (1953). b) C. L. Stevens and J. C. French, *ibid.*, **76**, 4398 (1954).

6) C. L. Stevens and G. H. Singhal, *J. Org. Chem.*, **29**, 34 (1964). b) H. J. Bestmann, J. Lienert, and L. Mott, *Ann. Chem.*, **718**, 24 (1968).

7) S. Hüng and W. Rehder, *Angew. Chem.*, **80**, 314 (1968).

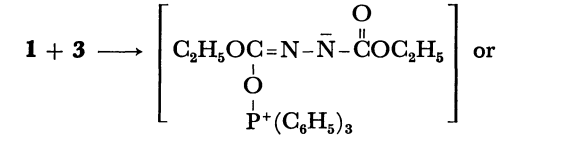
8) M. Masaki, K. Fukui, and M. Ohta, *J. Org. Chem.*, **32**, 3564 (1967).

9) J. A. Green and L. A. Singer, *Tetrahedron Lett.*, **1969**, 5093.

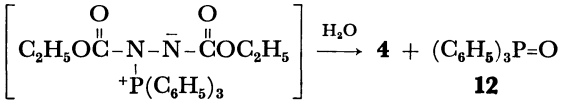
10) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **88**, 3169 (1966).

11) O. Mitsunobu, K. Kato, and F. Kakese, *Tetrahedron Lett.*, **1969**, 2473.

of **6a** was recovered. This indicates that up to 35.5% of **8a** was formed by the present procedure. Similarly, diphenylketene(*N*-*p*-tolyl)imine was formed in a 42.5% yield. The formation of **12** can be explained as follows. The addition reaction of **6a** to **1** is a time consuming step and on treatment the reaction mixture with **3**, unreacted **1** forms a quaternary phosphonium salt (**11**)[12] which is hydrolyzed to **4** and **12**. In fact, thin layer chromatography (tlc) of the solution resulting from the reaction of **1** and **6a** showed that the starting materials survived even after 7 days.



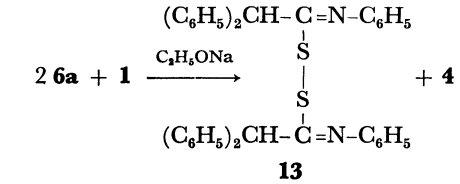
11a



11b

It was therefore considered desirable to accelerate the reaction of **1** with **6** for preparation of **8**. Thus, ethanol was used as solvent in place of THF. As expected, the reaction of **1** with **6a** in ethanol was shown to proceed more faster than in THF, namely, **1** and **6a** were consumed within 1 day as indicated by tlc. After treatment with **3**, followed by treatment with 2N hydrochloric acid, the products were separated by column chromatography. The yield of **8a** increased to a 61.2% and **5** was isolated in a 91.2% yield, although a small amount of **12** was still isolated.

Other attempts to promote the reaction met with no success. For example, when *p*-toluensulfonic acid or benzoyl peroxide was used as a catalyst, the starting materials remained in considerable extent after one day as indicated by tlc. On the other hand, when sodium ethoxide was used as a catalyst, the reaction proceeded in an unexpected direction. When one half of **1** was added to **6a** in THF in the presence of sodium ethoxide, the color of the solution immediately faded. However, when the remaining half was added, disappearance of the orange red of **1** was no longer observed. Thus, **1** was allowed to react with 2 mol of **6a** at room temperature and bis(*N*-phenylbenzalimidoyl) disulfide (**13**) was obtained in a 97% yield. The structure of **13** was confirmed by elementary analysis and infrared spectrum.



13

Concerning the intermediate of the present reaction, two possibilities could be considered, the initial formation of **7** and the formation of bis(*N*-arylbenzalimidoyl) disulfide (**13**).[13] In order to confirm the reaction path, the reaction of **1** with an equimolar amount of **6a** in THF was followed by infrared absorption spectrum. The spectrum indicated that the intensity of the C=O absorption of **1** gradually decreased and new absorptions appeared at 1740 cm^{-1} (C=O) and 1645 cm^{-1} (C=N) with the progress of reaction. The tlc of the solution revealed a new spot[15] which disappeared, on treatment of the solution with **3**, and the spot of the ketenimine was observed. That the disulfide is not an intermediate was further proved by a separate experiment in which **13** was treated with an equimolar amount of **3**. No **8a** was formed as indicated by tlc.

An attempt was made to isolate the proposed intermediate, **7**. However, from the reaction solution of **1** and **6a**, only a yellow oily substance was obtained which could not be purified.

The present procedure is unique since the reaction is coupled to a redox system, namely, triphenylphosphine is oxidized to triphenylphosphine sulfide and diethyl azodicarboxylate is reduced to diethyl hydrazodicarboxylate.

Experimental

Solvents were purified and dried in the usaual way. Tri phenylphosphine was of commercial grade and was used after recrystallization from ethanol. Diphenylacetic acid[16] and diethyl azodicarboxylate[17] were prepared according to published procedures. IR spectra were recorded on a Nippon Bunko IR-G spectrometer and measured as KBr disk. IR spectra of the reaction solution 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 vapor.

Diphenylacethyl Chloride. A modification of the procedure used for the preparation of glutarimide-*β*-acetyl chloride[18] was used. A mixture of diphenylacetic acid (30 g) and thionyl chloride (26 g) was heated at 100°C for 15 min. On being cooled to room temperature, 3 drops of dimethylformamide were added to the solution and refluxed for 15 min during which time vigorous evolution of HCl and SO_2 took place. Diphenylacethyl chloride was isolated by distillation; 26 g, 80%, bp 121—122°C/3mmHg.

Diphenylacetothioanilide and N-(p-*Tolyl)diphenylacetothioamide.* A modification of the procedure in literature[19] was used.

12) a) D. C. Morrison, *J. Org. Chem.*, **23**, 1072 (1958). b) V. A. Ginsburg, M. N. Vasiléva, S. S. Dubov, and A. Y. Yakubovich, *Zh. Obshch. Khim.*, **30**, 2854 (1960); *Chem. Abstr.*, **55**, 17477 (1961). c) E. Brunn and R. Huisgen, *Angew. Chem.*, (*Int. Ed. Engl.*), **8**, 513 (1969).

13) Oxidation of thioamides was investigated and, in certain cases, corresponding disulfides were obtained.[14]

14) a) F. Hodosan and N. Serban, *Bull. Soc. Chim. Fr.*, **1959**, 507. b) K. Heyns and W. V. Benbenburg, *Chem. Ber.*, **89**, 1303 (1956). c) H. Rivier and J. Zeltner, *Helv. Chim. Acta*, **20**, 691 (1937). d) J. R. Schaeffer, C. T. Goodhue, H. A. Risley, and R E. Stevens, *J. Org. Chem.*, **32**, 392 (1967).

15) A small amount of bis(*N*-arylbezalimidoyl) disulfide was formed at the same time.

16) C. S. Marvel, F. D. Hager, and E. C. Caudle, "Organic Syntheses," Coll. Vol. I, p. 224 (1956).

17) J. C. Kauer, "Organic Syntheses," Coll. Vol. IV, p. 411 (1962).

18) Y. Egawa, M. Suzuki, and T. Okuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 589 (1963).

19) a) W. Walter, J. Curts, and H. Pawelzik, *Ann.*, **643**, 29 (1961); *Chem. Abstr.*, **55**, 24652 (1961). b) L. F. Fieser and M. Fieser, "Reagents for Organic Syntheses," John Wiley & Sons, Inc., New York (1967), p. 333.

Twenty grams of diphenylacetanilide and 35 g of phosphorus pentasulfide were suspended in 150 m*l* of dioxane and stirred for 30 min at 80°C. The material was then extracted with dioxane and the combined extract was evaporated to dryness *in vacuo*. The residue was crystallized from xylene and diphenylacetothioanilide amounted to 17 g (78%), mp 187—188°C. In a similar way, *N*-(*p*-tolyl)diphenylacetothioamide was obtained in an 80% yield, mp 190—191°C.

*Preparation of Bis(*N*-phenylbenzalimidoyl) Disulfide (**13**).* To a solution of 0.303 g (0.001 mol) of diphenylacetothioanilide and a catalytic amount (one heaping of spatula) of sodium ethoxide in 14 m*l* of tetrahydrofuran (THF) was added dropwise to 0.087 g (0.0005 mol) of diethyl azodicarboxylate in 6 m*l* of THF. The color of the reaction mixture immediately faded. The solution was then evaporated under reduced pressure and the residue was chromatographed on silica gel (2.3 cm × 15 cm) to separate the products. Elution with benzene gave bis(*N*-phenylbenzalimidoyl) disulfide (0.29 g, 97%) which was dissolved in THF and precipitated with petroleum ether to give a pure sample, mp 169—170°C.

Found: N,4.39%. Calcd for $C_{40}H_{32}N_2S_2$:N,4.63%. IR(KBr) 1625 cm^{-1}(C=N) ; no N–H absorption.

Elution next with methanol gave diethyl hydrazodicarboxylate(0.087 g, 98%, mp 130—131°C).

Reaction of N-(p-*Tolyl)diphenylacetothioamide with Diethyl Azodicarboxylate and Triphenylphosphine.* To a stirred solution of 0.317 g (0.001 mol) of *N*-(*p*-tolyl)diphenylacetothioamide and 0.262 g (0.001 mol) of triphenylphosphine in 18 m*l* of THF was added 0.174 g (0.001 mol) of diethyl azodicarboxylate in an atmosphere of nitrogen at room temperature. After the solution was kept standing for 7 days at room temperature, it was evaporated *in vacuo*. The residue was dissolved in 10 m*l* of acetone and 4 m*l* of 2N hydrochloric acid and allowed to stand overnight to convert the diphenylketene-*N*-(*p*-tolyl)imine to *N*-(*p*-tolyl)diphenylacetamide. On being concentrated to dryness, the products were chromatographed on silica gel (2.3 cm × 50 cm). Elution with benzene gave two unknown substances (0.007 g and 0.002 g), recovered *N*-(*p*-tolyl)diphenylacetothioamide (0.148 g, 46.7%), triphenylphosphine sulfide (0.157 g, 53.4%), *N*-(*p*-tolyl)diphenylacetamide (0.128 g, 40.4%), diethyl hydrazodicarboxylate (quantitative) and triphenylphosphine oxide (0.135 g, 46.0%).

Reaction of Diphenylacetothioanilide with Diethyl Azodicarboxylate and Triphenylphosphine. a) THF as Solvent. To a solution of diphenylacetothioanilide (0.303 g, 0.001 mol) and triphenylphosphine (0.262 g, 0.001 mol) in THF (14 m*l*) was added dropwise diethyl azodicarboxylate (0.174 g, 0.001 mol) in THF (6 m*l*). After the solution had been kept standing for 7 days and subjected to the same work-up, diphenylacetanilide, diethyl hydrazodicarboxylate, triphenylphosphine sulfide, and triphenylphosphine oxide were obtained in 35.5%, 98.0%, 36.1%, and 60.0% yields, respectively, along with a small amount of an unknown product. Sixty three percent of diphenylacetothioanilide was recovered unchanged.

A change in the order of the addition does not affect the yield of the amide. The reaction also proceeds at 0°C. Triphenylphosphine in THF was added to diphenylacetothioanilide and diethyl azodicarboxylate in THF at 0°C. After the solution was allowed to stand in a refrigerator for 7 days and subjected to the same work-up, diphenylacetanilide was obtained in a 40.8% yield.

b) Ethanol as Solvent. To a stirred solution of 0.303 g (0.001 mol) of diphenylacetothioanilide in 5 m*l* of ethanol was added dropwise 0.174 g (0.001 mol) of diethyl azodicarboxylate in 6 m*l* of ethanol at 40°C. After 1 day at 40°C, diphenylacetothioanilide and diethyl azodicarboxylate were consumed as indicated by tlc and then the reaction mixture was evaporated *in vacuo* to give a yellow oily substance. Triphenylphosphine (0.262 g, 0.001 mol) was added and it was then dissolved in 6 m*l* of THF and kept standing for 7 days at room temperature. On being evaporated and treated with dilute hydrochloric acid in a similar manner as described above, the products were separated by columm chromatography (eluate: benzene) on silica gel to give an unknown compound (0.016 g), bis(*N*-phenylbenzalimidoyl) disulfide (0.011 g), triphenylphosphine sulfide (0.268 g, 91.2%), diphenylactanilide (0.176 g, 61.2%), diethyl hydrazodicarboxylate (0.166 g, 94.3%) and triphenylphosphine oxide (0.022 g, 8%).