DIRECT CARBONYLATION OF THE BENZOPHENONE SEMICARBAZONES AND BENZOPHENONE AZINE USING DICOBALT OCTACARBONYL¹

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ABSTRACT

Benzophenone semicarbazone (I) reacted with carbon monoxide at about 4000 p.s.i. and at 235-245° in the presence of preformed dicobalt octacarbonyl as catalyst to yield 3-phenyl-phthalimidine (II), 3-phenyl-2-(N-benzhydrylcarboxamido)phthalimidine (V), N,N'-dibenzhydrylurea (VII), and N-benzhydrylurea (VII). At 200-220° substance I gave compound VII, benzophenone azine (VIII), and benzophenone 4-benzhydrylsemicarbazone (IX). When the carbonylation product obtained in the second experiment but only the degradation and reduction products VIII, and IX, respectively. Carbonylation of benzophenone azine at 235-245° produced 3-phenylphthalimidine, whereas that of benzophenone 4-benzhydrylsemicarbazone at the same temperature yielded 3-phenylphthalimidine and 3-phenyl-2-(N-benzhydrylcarboxamido)phthalimidine.

Independent syntheses of the last compound and of benzophenone 4-benzhydrylsemicarbazone are described.

We have previously reported the synthesis of phthalimidines and N-carboxyanilide derivatives of phthalimidines by the direct incorporation of one and two carbon monoxide units into aromatic ketoximes and phenylhydrazones, respectively (1, 2). Because the kind of products obtained was dependent on temperature, we hoped to obtain information on the mechanism of the cyclization reaction by a further study of the direct carbonylation of other substrates containing the imino group (but containing different substituents on the nitrogen).

In this paper we report the results of a study of the carbonylation of aromatic imino compounds containing the ureido ($-NHCONH_2$), ureylene (-NHCONH-), and imino groups attached to the nitrogen of the C=N group. In particular, benzophenone semicarbazone, benzophenone 4-benzhydrylsemicarbazone, and benzophenone azine were carbonylated under a variety of reaction conditions. The last substance was included in this study since it is known that benzophenone semicarbazone decomposes above its melting point to yield benzophenone azine (3).

Benzophenone semicarbazone reacted with carbon monoxide at about 4000 p.s.i. and at 235–245° in the presence of preformed dicobalt octacarbonyl to give a mixture of reduction and carbonylation products (the latter are shown in Chart I) which were separated by chromatography on alumina. Most of the product directly crystallized out of the reaction mixture as a blue crystalline material (designated as A in experimental). This material was extracted with ethanol and then chromatographed to yield N,N'dibenzhydrylurea (VI) and 3-phenylphthalimidine (II). The structures of both of these substances were established by direct comparison with authentic samples of N,N'-dibenzhydrylurea (4) and 3-phenylphthalimidine (5).

The filtrate remaining after the removal of the blue material A was evaporated to dryness and the residue (B) then fractionated by alumina chromatography. Diphenylmethane (7% yield) and 1,1,2,2-tetraphenylethane (2%) were isolated from the residue

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ROSENTHAL AND MILLWARD: CARBONYLATION



Carbonylation of benzophenone semicarbazones and benzophenone azine

B and characterized by direct comparison (m.p. and infrared) with authentic samples of these substances. The fact that these compounds were present indicated that the high-purity carbon monoxide (containing about 0.01% hydrogen) acted as a reducing agent.

Compound V was unequivocally assigned the structure of 3-phenyl-2-(N-benzhydrylcarboxamido)phthalimidine on the following bases: (a) infrared analyses showed the presence of two carbonyls at 1684 and 1700 cm⁻¹, in excellent agreement with the spectrum of the previously reported N-carboxyanilide of 3-phenylphthalimidine (2); (b) refluxing compound V in 99% deuterium oxide gave a substance the infrared spectrum of which indicated the presence of an N—D grouping (see Experimental); (c) proton magnetic resonance analyses of the compound suggested a structure similar to that of 3phenylphthalimidine-N-carboxyanilide (absorption at δ equal to 6.09 and 6.20 indicated the presence of the two benzylic hydrogens; comparison of the n.m.r. of compound V with that of 3-phenylphthalimidine-N-carboxyanilide established that the peak at 6.20

was due to the CH of the HC Ph group). The structure of V was then confirmed by

direct comparison with an authentic sample of 3-phenyl-2-(N-benzhydrylcarboxamido)phthalimidine, prepared by the condensation of 3-phenylphthalimidine with benzhydrylisocyanate according to established procedures previously described (2, 6, 7).

Compound VII was directly compared with an authentic sample of N-benzhydrylurea (8), prepared by the condensation of benzhydrylisocyanate with ammonia, and shown to be the same.

When the reaction temperature was reduced to 175–180°, benzophenone semicarbazone did not cyclize with carbon monoxide but pyrolyzed and was reduced to yield two major products, one of which was readily characterized as benzophenone azine (VIII). This assignment of structure is in accord with that of Borsche and Merkivitz (3), who first reported that the thermal decomposition of benzophenone semicarbazone yielded benzophenone azine. On the bases of elemental, infrared, and proton magnetic resonance

CANADIAN JOURNAL OF CHEMISTRY. VOL. 41, 1963

studies it appeared that the second product (compound IX in Experimental) was benzophenone 4-benzhydrylsemicarbazone. Confirmation of this assignment of structure was obtained by condensing benzhydrylamine with benzophenone semicarbazone to yield ammonia and benzophenone 4-benzhydrylsemicarbazone (identical in m.p. and infrared with compound IX).

At an intermediate temperature of $200-220^{\circ}$, benzophenone semicarbazone afforded the same reduction products as obtained at $175-185^{\circ}$, and in addition N-benzhydrylurea. It is noteworthy that these reactions therefore indicate that carbonylation of the semicarbazone to yield a urea takes place between $180-220^{\circ}$.

Although the mechanism of formation of benzophenone 4-benzhydrylsemicarbazone from benzophenone semicarbazone is obscure, it is probable that a portion of the latter substance was reduced by the carbon monoxide via some type of hydrogen-transfer process, as envisaged by Natta, Pino, and Ercoli (9), to yield benzhydrylamine which then condensed with the remaining portion of benzophenone semicarbazone to yield compound IX.

The fact that benzophenone azine and benzophenone 4-benzhydrylsemicarbazone were present in the product of the 200-220° experiment but were not in that of the higher temperature one suggested that one or both of these substances might be the reactive intermediates in the direct ring closure reactions to yield the phthalimidines. In order to test this hypothesis, both of these substances were carbonylated at 235–245°. Benzophenone azine yielded only 3-phenylphthalimidine, whereas benzophenone 4-benzhydrylsemicarbazone afforded both 3-phenylphthalimidine and 3-phenyl-2-(N-benzhydrylcarboxamido)phthalimidine. Since some unreacted benzophenone azine remained after it had been treated with carbon monoxide at 235–245° but none was present when benzophenone semicarbazone or benzophenone 4-benzhydrylsemicarbazone was carbonylated at the same temperature for the same time one might assume that stronger complexing had occurred between the semicarbazones and the catalyst than between benzophenone azine and the catalyst which facilitated the cyclization reaction to yield the phthalimidines.

The fact that diphenylmethane and 1,1,2,2-tetraphenylethane were present in the reaction product suggests strongly that benzhydryl free radicals were produced by thermal decomposition of the azo tautomer of the semicarbazone. Evidence for a similar tautomerization of arylhydrazones has been recently noted by Connor (10). The homolytic cleavage of the azo tautomer of the semicarbazone might be expected to yield nitrogen and benzhydryl free radicals. Abstraction of hydrogen from the substrate might then be expected to yield diphenylmethane. On the other hand one might envisage that benzophenone semicarbazone might be reduced by the small quantity of hydrogen present in the gas to benzhydrylamine and the latter might then undergo hydrogenolysis to yield diphenylmethane.

EXPERIMENTAL

General Considerations

(a) The high-pressure equipment has been described previously (1).

(b) In every carbonylation experiment preformed dicobalt octacarbonyl (11) was used, and high-purity carbon monoxide supplied by the Matheson Co., East Rutherford, N.J., was added to an initial pressure of about 2100 p.s.i. at room temperature.

(c) The aluminum oxide (calcined) "Analar" was procured from the British Drug Houses (Canada) Ltd., Toronto 14.

(d) All melting points were obtained on a Leitz heating stage and are uncorrected. The infrared analyses were done on a Perkin-Elmer spectrophotometer, Model 21, using a sodium chloride crystal. Microanalyses

ROSENTHAL AND MILLWARD: CARBONYLATION

were done by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, im Max-Planck Institut fur Kohlenforschung, Mulheim (Ruhr), Germany, and by Mrs. Aldridge of this department. The n.m.r. spectra were obtained on a Varian A-60 instrument using tetramethylsilane as the internal standard (set at $\delta = 0$).

Carbonylation of Benzophenone Semicarbazone at 235-245°

To a mixture of 10.0 g of benzophenone semicarbazone (0.04 mole) in 45 ml of dry purified benzene were added 3.0 g of preformed dicobalt octacarbonyl and 2100 p.s.i. of carbon monoxide. The mixture was heated to 235–245° (at about 4000 p.s.i.) for 150 minutes. The bomb was then cooled overnight (the pressure drop at room temperature was 40 p.s.i., equal to 0.019 mole of carbon monoxide) and vented. The vented gas contained no basic material. The reaction product consisted of 7.4 g of a blue solid (A) and a brown liquid (essentially free of catalyst) which on evaporation yielded 4.6 g of a brown solid (B).

3-Phenylphthalimidine (from Blue Solid A)

The blue solid (A) was extracted with ethanol for 24 hours in a Soxhlet apparatus, yielding 4.3 g of crystalline material. Chromatography of 0.105 g of this substance on alumina using benzene-chloroform (5:1) as developer yielded 0.019 g (10%) of N,N'-dibenzhydrylurea. Further elution of the column with chloroform afforded 0.054 g (25%) of solid which on recrystallization from ethanol had a melting point of 222-224°. The mixed melting point of the latter substance (II) and an authentic sample of 3-phenylphthalimidine (5) was 222-224°. The infrared spectra of the two compounds were identical.

Separation of Substances in Solid B

Solid B was separated into five components by thin-layer chromatography (12) on silica gel using chloroform as a developer and concentrated nitric acid – sulphuric acid as a detector.

A 2.17-g portion of material B dissolved in a minimum of benzene was chromatographed on an alumina column $(133 \times 54 \text{ mm diameter})$. The following developers were then added consecutively with elutions as indicated: (1) 600 ml of benzene – petroleum ether $(30-60^{\circ})$ (1:1) eluted 0.283 g (8%) of liquid III; (2) 300 ml of benzene eluted 0.050 g (2%) of solid IV; (3) 400 ml of benzene yielded no material; (4) 600 ml of benzene eluted a trace; (5) 800 ml of benzene gave 0.328 g (8%) of solid V; (6) 1200 ml of benzene-ethanol (99:1) eluted nothing; (7) 500 ml of benzene-ethanol (98:2) yielded 0.595 g (15%) solid VI; (8) 300 ml of benzene-ethanol (98:2) gave no material; (9) 400 ml of benzene-ethanol (5:1) gave 0.312 g (7%) sirup VII.

Characterization of Fractions

Diphenylmethane (III)

Fraction III was purified by vapor phase chromatography using a silicone column at 270° C. Scratching of the liquid induced crystallization, m.p. 25°; mixed melting point with an authentic sample of diphenylmethane was 24–25°. The infrared spectrum of compound III was identical with that of an authentic sample of diphenylmethane.

1,1,2,2-Tetraphenylethane (IV)

Compound IV was recrystallized from ligroin, m.p. $215-217^{\circ}$. Anal. Found: C, 93.69; H, 6.40. Calc. for $C_{28}H_{22}$: C, 93.40; H, 6.64. The infrared spectrum of compound IV was identical with that of an authentic sample of 1,1,2,2-tetraphenylethane (13), prepared by the reduction of tetraphenylethylene.

3-Phenyl-2-(N-benzhydrylcarboxamido)phthalimidine (V)

Compound V was recrystallized twice from benzene – petroleum ether (b.p. 30–60°); m.p. 200–201°; mixed m.p. of compound V with an authentic sample of 3-phenyl-2-(N-benzhydrylcarboxamido)phthalimidine, 199–200°.

Infrared spectrum of compound V (KBr): 3260 (w), 3050 (w), 3020 (w), 2930 (w), 1700 (s), 1684 (s), 1607 (w), 1593 (w), 1582 (w), 1528 (s), 1493 (m), 1465 (w), 1453 (w), 1359 (m), 1340 (m), 1324 (m), 1295 (w), 1236 (m), 1201 (w), 1185 (m), 1158 (w), 1137 (m), 1090 (w), 1083 (m), 1024 (w), 894 (w), 849 (w), 770 (m), 762 (m), 750 (s), 738 (s), 727 (s), 697 (s). Nuclear magnetic resonance signals (given in δ units; spectra

obtained in deuterated chloroform): 6.09 (HC—Ph₂, area = 1 H), 6.20 (HC—Ph, area = 1 H), 7.20 (aromatic H, area = 15 H), 7.48 (phenylphthalimidine, aromatic H, area about 4 H), 9.45 (N—H, doublet, area 1 H). Anal. Found: C, 80.8; H, 5.29; N, 6.58. Calc. for $C_{28}H_{22}N_2O_2$: C, 80.35; H, 5.30; N, 6.70.

Exchange Reaction of 3-Phenyl-2-(N-benzhydrylcarboxamido)phthalimidine with D₂O

3-Phenyl-2-(N-benzhydrylcarboxamido)phthalimidine was refluxed for 17 hours in 10 ml of D₂O containing 0.05 g of K_2CO_3 . The product was obtained in the usual way. The infrared spectrum showed a strong N—D band at 2430 cm⁻¹ and a lowering of the carbonyl band to 1695 cm⁻¹.

Synthesis of Authentic 3-Phenyl-2-(N-benzhydrylcarboxamido)phthalimidine

Diphenylacetic acid was first converted into diphenylacetyl chloride according to the procedure of Stollé and Wolf (7). Diphenylacetyl chloride (5.0 g), dissolved in 35 ml of acetone, was added dropwise through a separatory funnel into a well-stirred solution of sodium azide (2.9 g) in 10 ml of water at such a rate that the temperature did not exceed 15°. Stirring was continued for a further 75 minutes; then 20 ml of cold aqueous

CANADIAN JOURNAL OF CHEMISTRY. VOL. 41, 1963

sodium bicarbonate (10%) was added. The reaction mixture was poured into 50 ml of ice-cold water and extracted with three 40-ml portions of cold ethyl ether. The combined extract was washed with cold aqueous sodium bicarbonate (10%) and then with cold water, dried over anhydrous magnesium sulphate, filtered into 100 ml of dry benzene, and warmed to 65° for 90 minutes. Removal of the benzene *in vacuo* yielded 3.32 g (73% of theoretical) of the crude isocyanate, which was subsequently distilled at 112° and 0.08 mm Hg, n_D^{26} 1.5765. The infrared spectrum showed the characteristic strong absorption at 2270 cm⁻¹ and a medium absorption at 2130 cm⁻¹. The benzhydrylisocyanate (0.48 g) was then condensed with 3-phenylphthalimidine (0.48 g) following the procedure previously described (2) to yield 0.89 g (93% of theoretical) of 3-phenyl-2-(N-benzhydrylcarboxamido)phthalimidine; m.p. 198–199°; Anal. Found: C, 80.37: H, 5.41. Calc. for $C_{28}H_{22}N_2O_2$: C, 80.35; H, 5.30.

N, N'-Dibenzhydrylurea (VI)

Compound VI was rechromatographed on alumina using benzene-chloroform (4:1). The first fraction from this column was decolorized with norite and recrystallized from ethyl acetate; m.p. 289-290°. Infrared spectrum of purified compound VI in KBr: 3290 (m), 3050 (w), 3020 (w), 2890 (w), 1623 (s), 1568 (s), 1490 (m), 1451 (m). As this spectrum suggested that compound VI was a urea, an authentic sample was prepared by allowing benzhydrylisocyanate to react with the moisture in the air. The product recrystallized from acetone had a melting point of 291-291.5°; mixed melting point of compound VI and authentic N,N'-dibenzhydrylurea, 290-291°. The literature melting point for this compound is 269-270° (4). Anal. Found: C, 82.81; H, 6.47; N, 6.95. Calc. for $C_{27}H_{24}N_2O$: C, 82.61; H, 6.16; N, 7.14.

N-Benzhydrylurea (VII)

Compound VII was recrystallized from benzene and then from hot water; m.p. 148–149°. The mixed melting point of an authentic sample of N-benzhydrylurea, prepared from benzhydrylisocyanate and ammonia, was 148–149° (literature m.p. is 143° (8)). Anal. (compound VII): Found: C, 73.89; H, 6.45; N, 12.33. Calc. for $C_{14}H_{14}N_2O$: C, 74.28; H, 6.23; N, 12.38.

Carbonylation of Benzophenone Semicarbazone at 200-220°

A 2.2-g aliquot of the product obtained from the carbonylation of benzophenone semicarbazone at 200–220° for 2.5 hours was chromatographed on alumina and yielded the following: 0.071 g of diphenylmethane (4%), 0.28 g (8%) of benzophenone azine (VIII), 0.85 g of benzophenone semicarbazone (35%), 0.45 g (11%) of a substance (IX) having a melting point of 179–181°, and 0.09 g of N-benzhydrylurea (4%).

Anal. (Compound IX): Found: C, 79.60; H, 5.67; N, 10.58; O, 4.11; mol. wt., 369 (Rast). Calc. for $C_{27}H_{23}N_3O$: C, 79.97; H, 5.72; N, 10.36; O, 3.95; mol. wt., 405. Nuclear magnetic resonance signals (deutereo-chloroform) of compound IX: 6.25 (HC—Ph₂, doublet, area 1 H), 6.95 (NH, area = 1 H), 7.32 (aromatic H, area = 20 H), 7.72 (NH, area = 1 H). Infrared spectrum (KBr): 3410 (m), 3150 (w), 3060 (w), 1668 (s), 1580 (m), 1495 (s), 1445 (m), 1365 (w), 1325 (w), 1230 (w), 1180 (m), 1105 (s), 1005 (m), 1025 (m), 945 (w), 910 (w), 862 (w), 835 (w), 782 (m), 753 (ls, 735 (m), 695 (s). The infrared spectrum of benzophenone semicarbasene showed peaks at 3460, 3190, and 1700 cm⁻¹.

Hydrolysis of compound IX with dilute sulphuric acid yielded benzophenone (isolated as benzophenone 2,4-dinitrophenylhydrazone).

Synthesis of Benzophenone 4-Benzhydrylsemicarbazone

A mixture of 0.38 g of benzophenone semicarbazone and 0.47 g of benzhydrylamine was heated at 120° for 4 hours. The reaction was accompanied by the evolution of ammonia. The residue was recrystalized from 25 ml of ethanol; yield, 0.47 g (74%), m.p. 179.5–180.5°; mixed melting point with compound IX was 179–180°. The infrared spectra of both compounds were the same.

Carbonylation of Benzophenone Semicarbazone at 175-180°

Similarly, 15.3 g of benzophenone semicarbazone was dissolved in chlorobenzene and treated with carbon monoxide at $175-180^{\circ}$ for 2.5 hours. Chromatography of 3.3 g of the product on alumina yielded 0.11 g of diphenylmethane, 0.05 g of 1,1,2,2-tetraphenylethane, 1.0 g of benzophenone azine (35%), 0.75 g of substance IX (24%), and 1.4 g of unreacted starting material.

Carbonylation of Benzophenone Azine

Benzophenone azine was carbonylated at $235-245^{\circ}$ for 2.5 hours under conditions similar to those used in the first experiment. Chromatography of the product yielded 63% of 3-phenylphthalimidine and unreacted starting material.

Carbonylation of Benzophenone 4-Benzhydrylsemicarbazone

The benzene solution obtained from the carbonylation of 0.47 g of benzophenone 4-benzhydrylsemicarbazone at 235–245° for 2.5 hours was boiled for 30 minutes to destroy the catalyst, filtered, and evaporated to dryness under vacuum. Chromatography of this residue on alumina as described previously yielded 0.044 g of diphenylmethane (11%), about 0.015 g of benzophenone (about 7%), 0.030 g of 3-phenyl-2-(N-benzhydrylcarboxamido)phthalimidine (6%), 0.04 g of N,N'-dibenzhydrylurea (9%), and 0.170 g of 3-phenylphthalimidine (70%). The yields are based on mole quantities possible from each moiety of the starting material.

2508

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2509