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Reaction of 4-Acetylsydnones

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Due to their unique mesoionic character, sydnones have been the subject of continued study since their discovery in 1935.[1] Although sydnones have been extensively investigated, little is known concerning the synthesis and reaction of 4-substituted sydnones. We reported the synthesis of 4-acetylsydnones by the reaction of sydnones with acid anhydrides in the presence of perchloric acid.[2] In this paper, we describe the reaction of 4-acetylsydnones whose structures are analogous to that of acetophenone.

Reaction of 4-acetyl-3-phenylsydnone (I) with benzaldehyde in the presence of alkali afforded 4-cinnamoyl-3-phenylsydnone (III), and 4-acetyl-3-benzylsydnone (II) reacted with benzaldehyde to give α-(4-cinnamoylsydnon-3-yl)stilbene (IV). 4-(Bromoacetyl)-3-phenylsydnone (V) and 3-benzyl-4-(bromoacetyl)sydnone (VI) were obtained by the reaction of I and II with bromine, respectively, in chloroform under irradiation of visible light. Corresponding dibromoacetyl derivatives, VII and VIII, were obtained when the above reaction was carried out in the presence of two equivalents mole of bromine. However, tribromoacetyl derivatives were not obtained even in the presence of three equivalents

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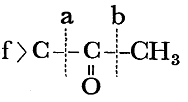
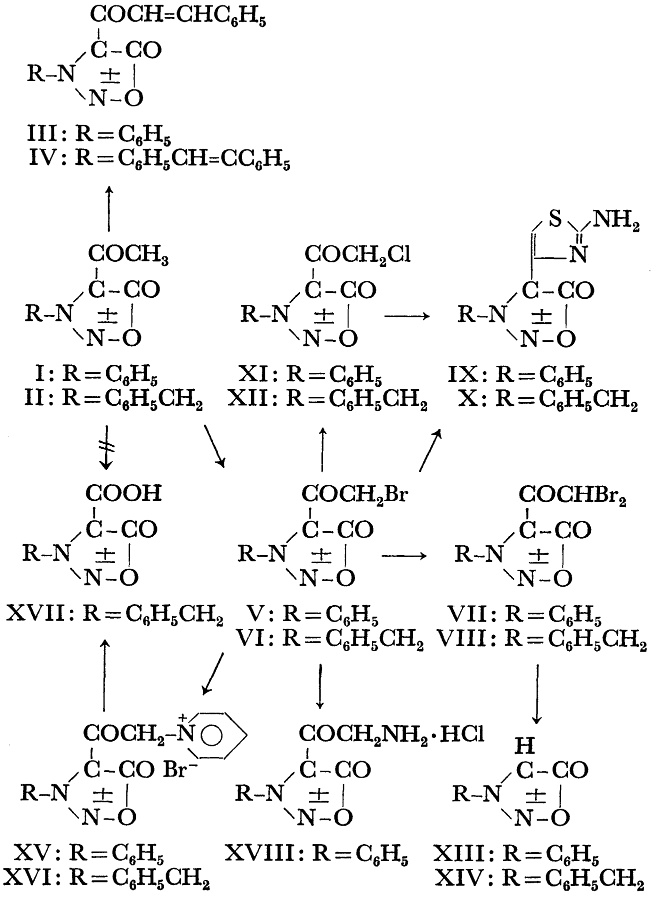
[1] J. C. Earl and A. W. Mckney, *J. Chem. Soc.*, **1935**, 899.

[2] H. Tien and M. Ohta, This Bulletin, **45**, 2944 (1972).

mole of bromine. Compound V reacted with thioures to give sydnone-substituted thiazole derivative IX, and VI afforded X. Treatment of V and VI with calcium chloride in DMSO afforded chloroacetyl derivatives, XI and XII, which reacted with thiourea to give IX and X, respectively. Haloform reaction of neither I nor II proceeded, and resulted in a recovery of the starting material. Treatment of V with sodium hydroxide and bromine yielded 3-phenylsydnone (XIII). Brief heating of an aqueous sodium hydroxide solution of VII afforded XIII, and VIII yielded 3-benzylsydnone (XIV) by the same treatment. These results show that mono- and dibromoacetylsydnones are unstable to alkali. Pyridinium salts, XV and XVI, were obtained by treatment of V and VI with pyridine, respectively. Compound XVI afforded 3-benzylsydnone-4-carboxylic acid (XVII) by treatment with alkali, while XV did not afford corresponding carboxylic acid but 3-phenylsydnone was obtained. 4-(Aminoacetyl)-3-phenylsydnone hydrochloride (XVIII) was obtained by the reaction of V with hexamethylenetetramine followed by treatment with hydrochloric acid. 3-Benzyl-4-morpholinoacetylsydnone was obtained by treating VI with morpholine. The behavior of bromo derivatives and pyridinium salts toward alkali described above suggests that the substituents at position 3 and ω-position of side chain affect, to some extent, the mode of cleavage at bond a or b of  $\rangle C\overset{a}{\vdots}\underset{\overset{\|}{O}}{C}\overset{b}{\vdots}CH_3$ grouping.



Experimental

4-Cinnamoyl-3-phenylsydnone (III). Compound I (2.0 g) was suspended in an alkaline solution (sodium hydroxide 0.5 g, water 5 ml, ethanol 3 ml) and 1.0 g of benzaldehyde was added and the reaction mixture was stirred for 10 min at room temperature. The precipitates were collected and washed well with water and then with cold ethanol. Recrystallization from ethanol afforded yellow needles with a mp of 145—147 °C (yield 52%).

Found: C, 69.86; H, 4.11; N, 9.59%. Calcd for $C_{17}H_{12}O_3N_2$: C, 70.71; H, 4.20; N, 9.78%. IR: 1785, 1655, 1590, 1420, 1040 cm^{-1}.

α-(4-Cinnamoylsydnon-3-yl)stilbene (IV). Compound IV was prepared form II and benzaldehyde by the same method as mentioned above. Recrystallization from isopropyl alcohol afforded colorless prisms with a mp of 105—106 °C (yield 30%).

Found: C, 75.73; H, 5.14; N, 7.20%. Calcd for $C_{25}H_{18}O_3N_2$: C, 76.13; H, 4.60; N, 7.10%. IR: 1780, 1650, 1470, 1050, 1038 cm^{-1}.

4-Bromoacetylsydnones, V and VI. To a solution of I (2.0 g) in 30 ml of chloroform, 1.6 g of bromine was added under irradiation of visible light. After 15 min, the color of bromine bleached. The solvent was removed *in vacuo* and the residue was recrystallized from ethanol to give pale yellow crystals with a mp of 110—111 °C (yield 70%).

Found: C, 42.69; H, 2.76; N, 10.00%. Calcd for $C_{10}H_7O_3N_2Br$: C, 42.40; H, 2.47; N, 9.89%. IR: 3050, 2975, 2925, 1790, 1680, 1420, 1010, 770, 680 cm^{-1}.

By the same method, VI was obtained from 8.8 g of II and 6.4 g of bromine in 100 ml of chloroform. Recrystallization from ethanol gave colorless needles with a mp of 64.5—65.5 °C (yield 70%).

Found: C, 44.48; H, 3.06; N, 9.63%. Calcd for $C_{11}H_9O_3N_2Br$: C, 44.44; H, 3.06; N, 9.43%. IR: 3000, 1780, 1760, 1660, 1465, 1035, 735, 705 cm^{-1}.

4-(Dibromoacetyl)sydnones, VII and VIII. To a solution of I (5.0 g) in 100 ml of chloroform, a little portion of chloroform solution of bromine (9.0 g/60 ml) was added under irradiation of visible light. After the initiation of the reaction, residual bromine solution was added dropwise and the solution was refluxed by heating with the tungsten lamp for 1 hr. During the irradiation, evolved hydrogen bromide was repelled by the stream of N_2. The solvent was removed *in vacuo* to give oily residue, to which a small amount of petroleum ether was added to crystallize. Reprecipitation of VII from a benzene solution with *n*-hexane afforded pale yellow prisms with a mp of 86—87 °C (yield 67%).

Found: C, 33.47; H, 1.86; N, 7.52%. Calcd for $C_{10}H_6O_3N_2Br_2$: C, 33.17; H, 1.66; N, 7.74%. IR: 1785, 1690, 1420, 1005, 770 cm^{-1}.

By the same method, VIII was prepared from 2.2 g of II and 3.2 g of bromine. Reprecipitation from a benzene solution with *n*-hexane afforded colorless needles with a mp of 80.5—81.5 °C (yield 80%).

Found: C, 35.11; H, 2.13; N, 7.45%. Calcd for $C_{11}H_8O_3N_2Br_2$: C, 35.25; H, 2.19; N, 7.57%. IR: 3000, 1760, 1682, 1470, 1000, 705 cm^{-1}.

Reaction of V with Thiourea. A solution of 1.4 g of V and 0.4 g of thiourea in 20 ml of ethanol was refluxed for 10 min. The precipitates were collected by filtration and dissolved in dilute ethanol (1: 1) and the solution was neutralized with sodium hydrogen carbonate. The precipitates were recrystallized from ethanol to give IX as yellow needles with a mp of 181—182 °C (yield 70%).

Found: C, 50.68; H, 3.13; N, 21.79; S, 12.10%. Calcd for $C_{11}H_8O_2N_4S$: C, 50.77; H, 3.08; N, 21.54; S, 12.31%.

IR: 3425, 3280, 3150, 1750, 1630, 1215 cm^{-1}.

Reaction of VI with Thiourea. Compound VI was treated with thiourea as mentioned above to give X. Recrystallization from ethanol gave X as yellow needles with a mp of 125—127 °C (yield 66%).

Found: C, 52.39; H, 3.73; N, 20.42; S, 11.98%. Calcd for $C_{12}H_{10}O_2N_4S$: C, 52.55; H, 3.65; N, 20.44; S, 11.68%. IR: 3375, 3295, 3200, 3120, 1745, 1730, 1620, 1520, 1325, 1180 cm^{-1}.

4-(Chloroacetyl)sydnones, XI and XII. Compound V (2.8 g) was dissolved in 20 ml of DMSO which was saturated with calcium chloride, and the solution was allowed to stand at room temperature for 48 hr. The reaction mixture was poured into ice-water and the precipitates were collected. Recrystallization from ethanol afforded colorless plates with a mp of 127—129 °C.

Found: C, 50.18; H, 2.94; N, 11.76%. Calcd for $C_{10}H_7O_3N_2Cl$: C, 50.31; H, 2.94; N, 11.74%. IR: 3060, 2990, 2945, 1790, 1775, 1693, 1280 cm^{-1}. NMR τ ($CDCl_3$) 2.15—2.60 (m, 5H), 5.33 (s, 2H).

By the same method, XII was prepared from VI and calcium chloride. Recrystallization from ethanol afforded colorless needles with a mp of 67—70 °C (yield 24%).

Found: C, 52.21; H, 3.59; N, 11.18%. Calce for $C_{11}H_9O_3N_2Cl$: C, 52.27; H, 3.56; N, 11.09%. IR: 1798, 1765, 1690, 1680, 1448, 1385, 1268, 1010 cm^{-1}.

Pyridinium Salt of VI (XVI) and 3-Benzylsydnone-4-carboxylic Acid (XVII). Compound VI was dissolved in 17 ml of pyridine and precipitates separated in a few minutes. Ether (30 ml) was added to the reaction mixture and precipitates were collected and recrystallized from ethanol, mp above 300 °C (yield 27%).

Found: C, 51.24; H, 3.87; N, 11.10%. Calcd for $C_{16}H_{14}O_3N_3Br$: C, 51.06; H, 3.72; N, 11.17%. IR 1780, 1675, 1635, 1480, 1005 cm^{-1}.

Pyridinium salt (0.75 g) thus obtained was added to a sodium hydroxide solution (sodium hydroxide 0.4 g, water 15 ml), and the solution was heated at 50 °C for 10 min. After filtering off the precipitates, filtrate was made acidic to Congo red with concentrated hydrochloric acid and kept to stand overnight at room temperature. Separated oily product was dissolved in methanol and treated with activated charcoal. Solvent was removed *in vacuo* to give XVII as colorless crystals. Recrystallization from hot water afforded colorless needles with a mp of 154—156 °C (yield 11%, calcd from pyridinium salt).

Found: C, 54.16; H, 3.81; N, 12.85%. Calcd for $C_{10}H_8O_4N_2$: C, 54.55; H, 3.64; N, 12.73%. IR: 3100—2500 (br), 1825 (sh), 1785, 1680, 1500, 1493, 1220, 1100 cm^{-1}.

Pyridinium Salt of V (XV) and its Treatment with Alkali. Compound XV was prepared from V and pyridine as mentioned above. Recrystallization from 90% ethanol afforded XV as pale yellow crystals with a mp of 226—228 °C (dec.).

Found: C, 49.49; H, 3.31; N, 11.45%. Calcd for $C_{15}H_{12}O_3N_3Br$: C, 49.72; H, 3.31; N, 11.60%. IR: 3025, 3010, 1780, 1685, 1640, 1492, 1470, 1435, 1015, 755, 685 cm^{-1}.

Pyridinium salt (1.8 g) thus obtained was heated at 50—60 °C in an alkaline solution (sodium hydroxide 1 g, water 30 ml) for 10 min. Precipitates were collected and washed with water. Recrystallization from ethanol gave 0.3 g of 3-phenylsydnone.

4-(Aminoacetyl)-3-phenylsydnone hydrochloride (XVIII). To a chloroform solution of V (5.6 g/30 ml), a chloroform solution of hexamethylenetetramine (2.8 g/30 ml) was added and the reaction mixture was stirred for 24 hr at room temperature. Precipitates were collected and washed with chloroform. The precipitates were added to ethanol–concentrated hydrochloric acid (20—8.5 ml) and the solution was stirred for 3 days at room temperature. In the course of stirring, precipitates were dissolved completely and then the reaction product separated out. Precipitates were collected and stirred for 10 min in 10 ml of water. Recrystallization from methanol gave XVIII, mp 180 °C (yield 78%).

Found: C, 46.68; H, 4.11; N, 16.11%. Calcd for $C_{10}H_{10}O_3N_3Cl$: C, 46.86; H, 3.91; N, 16.41%. IR: 3000—2850 (br), 1790, 1690 cm^{-1}.

3-Benzyl-4-morpholinoacetylsydnone. To a chloroform solution of VI (3.0 g/20 ml), a chloroform solution of morpholine (1.75 g/20 ml) was added under cooling with ice-water and the reaction mixture was kept at low temperature for 2 hr. Precipitates were filtered off and filtrate was concentrated *in vacuo*. Resulted oily product was dissolved in benzene and precipitates were filtered off. The benzene solution was concentrated and a small amount of petroleum ether was added to crystallize. Reprecipitation from acetone solution with ether afforded orange prisms with a mp of 121—123 °C (yield 97%).

Found: C, 59.62; H, 5.68; N, 13.71%. Calcd for $C_{15}H_{17}O_4N_3$: C, 59.39; H, 5.65; N, 13.86%. IR: 2955, 2875, 1840, 1770, 1755, 1673, 1432, 1110, 985, 710 cm^{-1}.