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Acylation of 3-Phenylsydnone with Carboxylic Acids and Phosphorus Pentoxide

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The successful mercuration (2) of 3-phenylsydnone (I) suggested to Tien and Hunsberger (3) that sydnones undergo electrophilic substitution as readily as thiophene. In support of this analogy they studied the mercuration of *N*-(3-pyridyl)sydnone (3) and the direct formylation of sydnones (4) by the Vilsmeier procedure (5). In addition, one can cite the remarkable similarity in reactivity of sydnones and thiophene towards bromination (6) and sulfonation with sulfur trioxide complexes (7).

Kato and Ohta (8) first synthesized methyl-4-(3-phenylsydnonyl) ketone (IIa) in 24% yield by reaction of the Grignard reagent, obtained from 3-phenyl-4-bromosydnone, with acetic anhydride at room temperature in absolute ether. Russian investigators (9) found boron trifluoride etherate to be an efficient catalyst for the acetylation of I and ethylsydnone with acetic anhydride. While the yields of ketones were not reported, these workers mentioned unsuccessful attempts to acylate I with acetic anhydride or benzoyl chloride in the presence of a variety of catalysts, *i.e.* aluminum chloride, stannic chloride and phosphoric acid, at a variety of temperatures.

The acylation of thiophene and furan in high yield with equimolar quantities of either an aliphatic or aromatic carboxylic acid and phosphorus pentoxide in refluxing benzene was achieved by Hartough and Kosak (10). Other investigators (11) reported earlier that catalytic amounts of phosphorus pentoxide effectively caused acylation of thiophene in yields of the order of 50% using acid anhydrides and acyl halides.

The application of the phosphorus pentoxide procedure (10) to 3-phenylsydnone (I) revealed the yield of ketone (II) to be dependent on the quantity of phosphorus pentoxide, duration of reaction and volume of benzene. Optimum yields of the alkyl-4-(3-phenylsydnonyl) ketones (IIa-IId) were obtained by refluxing three molar equivalents of phosphorus pentoxide with one each of the carboxylic acid and sydnone in 125 ml. of benzene for five hours. However, the scope of this preparative method appears to be limited. With pivalic and decanoic acids the sydnone I was recovered in near quantitative yield. Neither benzoic acid nor any of the *ortho*- and *para*-substituted benzoic acids employed to secure aryl-4-(3-phenylsydnonyl) ketones were effective. In comparison to thiophene (10) which readily benzoylates under similar reaction conditions, 3-phenylsydnone appears to be less nucleophilic or possesses a steric factor prohibitive to the attack on a bulky acylating complex.

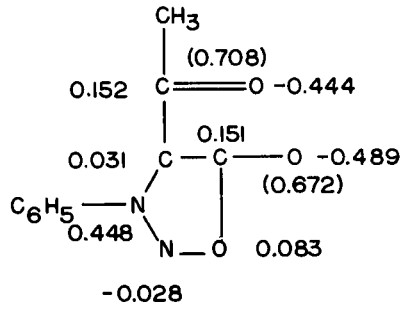


Figure 1. Molecular orbital calculations of charge densities and bond orders (in parentheses) for methyl-4-(3-phenylsydnonyl) ketone.

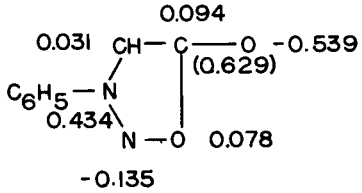
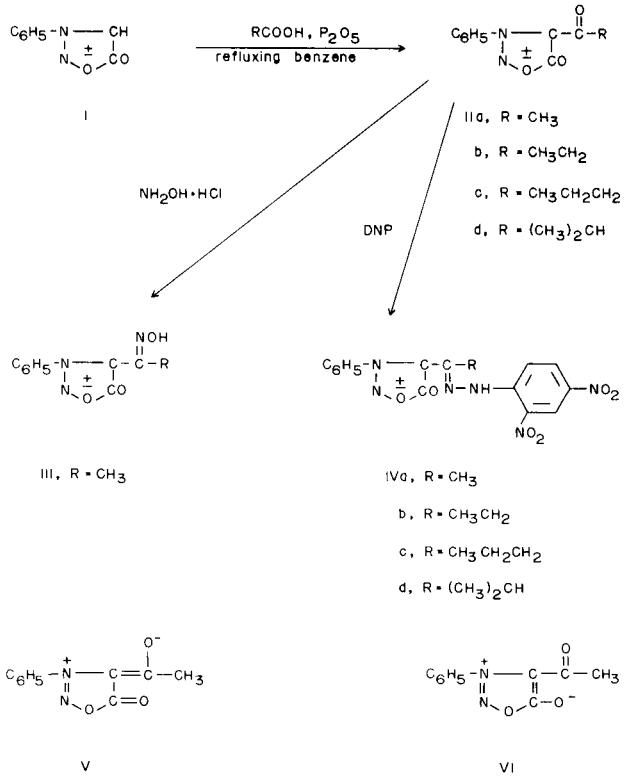


Figure 2. Molecular orbital calculations of charge densities and bond orders (in parentheses) for 3-phenylsydnone (18).



V VI

Acidic hydrolysis of the acylsydnones II should yield 2-ketocarboxylic acids which would react with the phenylhydrazine released from the acid decomposition of the sydnone ring to yield a phenylhydrazone of the ketoacid. However, all the acylsydnones prepared showed an unusual resistance to acidic hydrolysis. After heating each sydnone in 9*N* hydrochloric acid for 2.5 hours on a steam bath the cooled reaction solution deposited unchanged sydnone (II).

As a result of their stability in acidic media and the unexplainable difficulty in securing oximes other than III, the four ketones were successfully converted to 2,4-dinitrophenylhydrazones IV.

The ultraviolet spectra of the four acylated sydnones (IIa-d) showed identical absorption maxima at 238 and 324 mμ. 3,4-Diphenylsydnone showed maxima at 245 and 340 mμ (12) while the parent sydnone (I) absorbed at 235 and 310 mμ (13). Thus it appears the substitution of I with an acyl function extends the conjugation but not as extensively as with diarylsydnones. The absorptions at 238 and 324 mμ are tentatively assigned to $\pi \rightarrow \pi^*$ transitions since heteroaromatic ketones do not normally show the low intensity $n \rightarrow \pi^*$ transitions (14).

The infrared carbonyl absorption of sydnones occurs between 5.66-5.82 μ (1767-1718 cm^{-1}) region (3,15). The four acylsydnones prepared in this study showed two very strong absorptions at 5.59 μ (1789 cm^{-1}) and 6.00 μ (1667 cm^{-1}). The latter absorption is attributed to the acyl function which is below the frequency ranges for aryl ketones (1700-1680 cm^{-1}) but within the range for α,β-unsaturated ketones (1685-1665 cm^{-1}) (16). It is quite evident that the acyl function is conjugated with the electron donating ring system. Kishimota and Ohta (17) have suggested that there is a significant contribution from resonance form V to the total structure of methyl-4-(3-phenylsydnonyl) Ketone (IIa). A molecular orbital calculation, using the ω-Huckel technique previously employed by Kier and Roche (18) for sydnones, reveals that the aceto group carbonyl is polarized though less so than the sydnone exocyclic oxygen (compare Figures 1 and 2). Furthermore, the bond order of the aceto group carbonyl shows somewhat more double bond character than the sydnone exocyclic oxygen. These calculations imply some contribution from the contributing resonance structure V, in a valence bond representation of the compound, but a relatively greater contribution from structure VI. These calculations correlate quite well with the spectroscopic findings on the structure of the acylsydnones.

Previous studies on the sydnones (19,20) and on the isoconjugate mesoionic pseudooxatriazoles (21) have revealed a very modest hypotensive activity in the former and a significant hypotensive activity in the latter series. Accordingly, the sydnones described here were tested for hypotensive action in dogs. The four compounds (IIa-d) were found to be moderately hypotensive when administered i.v., in doses of 10 mg/Kg. The blood pressure drop in each case was about 10% and of short duration. The LD_{50} for acute toxicity in mice was about 700 mg/Kg for the four compounds. The hypotensive activity was found to be intermediate between sydnones (20) and the mesoionic pseudooxatriazoles (21).

EXPERIMENTAL

All melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. All combustion analyses were performed by Weiler and Strauss, Microanalytical Laboratories, Oxford, England. Infrared spectra were measured on a Perkin-Elmer Infracord Model 137 using the potassium bromide pellet technique. Ultraviolet spectra were obtained with a Bausch and Lomb 505 Spectrophotometer, all samples being dissolved in alcohol. *N*-Phenylglycine was purchased from Eastman Distilleries, Inc., N. Y. and used without further purification in the preparation of 3-phenylsydnone according to the procedure of Earl and Mackney (22).

Methyl-4-(3-phenylsydnonyl) Ketone (IIa).

To a suspension of 21.3 g. (0.15 mole) of phosphorus pentoxide in 125 ml. of sodium dried, thiophene free, benzene (Eastman) in a three-necked 250 ml. round bottom flask fitted with a reflux condenser equipped with a calcium chloride drying tube was added 8.1 g. (0.05 mole) of 3-phenylsydnone. The magnetically stirred mixture was heated to reflux and 2.86 ml. (0.05 mole) of glacial acetic acid added dropwise, through a dropping funnel, over a 10 minute period. The stirred reaction mixture was refluxed for 5 hours during which the resultant clear solution turned brown-black. After cooling to room temperature, the benzene was decanted and the remaining black residue

washed twice with 20 ml. of benzene. The combined washings and decantate were evaporated to dryness to yield a yellow solid. Two recrystallizations from ethanol gave 6.1 g. (59.7%) of a pale yellow crystalline powder, m.p. 141.5-142.5°. Ultraviolet spectrum showed λ max, 238 (ε, 7,960); 324 mμ (ε, 6,340). The product gave a superimposable infrared spectrum and no depression in melting point on admixture with the products from the Japanese (8) and Russian (9) methods.

For five preparations the yield of ketone ranged from 51-59% after two recrystallizations.

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.87; H, 3.80; N, 13.78.

Ethyl-4-(3-phenylsydnonyl) Ketone (IIb).

This compound was prepared by the same procedure described for IIa above, using identical molar equivalents of reactants. The propionic acid (3.7 ml., 0.05 mole) was added in three equal portions. A vigorous reaction took place after each addition of the acid. Refluxing five hours turns the solution dark yellow. The yellow solid obtained on evaporation of the benzene decantate and washings gave, after two recrystallizations from ethanol, 4.6 g. (42.2%) of a white crystalline powder, m.p. 92.5-94°. The ultraviolet spectrum showed λ max, 238 (ε, 12,820); 324 mμ (ε, 10,640).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.38; H, 4.38; N, 13.24.

n-Propyl-4-(3-phenylsydnonyl) Ketone (IIc).

This compound was prepared as described for IIb, using 0.05 mole of *n*-butyric acid. After two recrystallizations from ethanol, 5.1 g. (43.9%) of pale yellow needles were isolated, m.p. 72.5-74°. The ultraviolet spectrum showed λ max, 238 (ε, 10,910); 324 mμ (ε, 9,400).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.07. Found: C, 61.95; H, 5.52; N, 11.98.

Isopropyl-4-(3 phenylsydnonyl) Ketone (IId).

This compound was prepared in an identical manner to that described for IIb, using 0.05 mole of isobutynic acid. Two recrystallizations from ethanol gave 4.65 g. (40.1%) of a pale yellow product, m.p. 113.5-115°. The ultraviolet spectrum showed λ max, 238 (ε, 14,580); 324 mμ (ε, 12,500).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.07. Found: C, 62.26; H, 5.38; N, 12.30.

Methyl-4-(3-phenylsydnonyl) Ketoxime (III).

To methyl-4-(3-phenylsydnonyl) ketone (1.0 g., 0.005 mole) in 5 ml. of ethanol was added 1.0 g. (0.015 mole) of hydroxylamine hydrochloride and 5 ml. of pyridine. The solution was refluxed for 2 hours on a steam bath and cooled to room temperature. The amber liquid was decanted and evaporated to a white solid which was triturated with 5 ml. of water and filtered. The white crystalline residue was recrystallized twice from ethanol to give 0.45 g. (41.1%) of white crystals, m.p. 193.5-195°. In eight preparations the yields ranged from 36-44%.

Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.75; H, 4.32; N, 19.17.

Attempts to characterize the other three ketones IIb-d were either unsuccessful, starting ketone being recovered unchanged, or the oxime was unstable and failed to give accurate combustion analyses and reproducible melting points.

Preparation of 2,4-Dinitrophenylhydrazone Derivatives.

The following general procedure was employed to prepare derivatives IVa-d listed below.

The acylsydnone (0.5 g.) in 20 ml. of 95% ethanol was treated with freshly prepared 2,4-dinitrophenylhydrazine reagent and the solution left at room temperature for *ca.* 12 hours after which crystallization was complete. The crude hydrazone was filtered, added to 30 ml. of ethanol and heated on a steam bath. Ethyl acetate was added dropwise to the hot ethanol until the hydrazone completely dissolved. After remaining overnight at room temperature the solution deposited the hydrazone in analytically pure form.

Methyl-4-(3-phenylsydnonyl) Ketone 2,4-Dinitrophenylhydrazone (IVa).

Melting point 234-236°, yield 42.5%.

Anal. Calcd. for $C_{16}H_{12}N_6O_6$: C, 50.00; H, 3.15; N, 21.87. Found: C, 49.87; H, 3.20; N, 22.00.

Ethyl-4-(3-phenylsydnonyl) Ketone 2,4-Dinitrophenylhydrazone (IVb).

Melting point 242-243°, yield 48.1%.

Anal. Calcd. for $C_{17}H_{14}N_6O_6$: C, 51.26; H, 3.54; N, 21.10. Found: C, 51.35; H, 3.20; N, 20.99.

n-Propyl-4-(3-phenylsydnonyl) Ketone 2,4-Dinitrophenylhydrazone (IVc).

Melting point 239-240°, yield 47.4%.

Anal. Calcd. for $C_{18}H_{16}N_6O_6$: C, 52.43; H, 3.91; N, 20.38. Found: C, 52.27; H, 4.09; N, 20.00.

Isopropyl-4-(3-phenylsydnonyl) Ketone 2,4-Dinitrophenylhydrazone (IVd).

Melting point 178-179.5°, yield 23.7%.

Anal. Calcd. for $C_{18}H_{16}N_6O_6$: C, 52.43; H, 3.91; N, 20.38. Found: C, 52.44; H, 4.03; N, 20.27.

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(1a) To whom all inquiries should be addressed. (b) The molecular orbital and pharmacological studies were supported, in part, by a grant (GM-13100-01) from the National Institutes of Health. Present address L.B.K.: Battelle Memorial Institute, Columbus, Ohio.

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