Addition of Alcohols to Mesityl Oxide Using an Acid Ion Exchange Resin Catalyst

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The preparation of diacetone alcohol ethers from mesityl oxide and alcohols with basic and acidic catalysts has been reported.[1-6] Hoffman[1] prepared these ethers with a sulfuric acid catalyst and a reaction time of 12 days while the same reaction described by Halbig and Treibs[4] required only 12 hr. Acid ion exchange resins have been used by a number of investigators for catalyzing various reactions,[7,8] but the utilization of an acid resin for preparing ethers of diacetone alcohol is a new observation. Dowex 50, a sulfonic acid ion exchange resin, effectively catalyzed the formation of ethers of diacetone alcohol from mesityl oxide and alcohols. The advantages of this catalyst were the reaction time was greatly reduced, the yields were excellent, and the catalyst was easily separated from the reaction solution.

EXPERIMENTAL

The Dowex 50 was converted to the acid form with 3*N* hydrochloric acid, washed with water, and then methanol. Sufficient resin was put in a vertical Pyrex tube 90 cm. long, 19 mm. ID, so that there was a catalyst bed 71 cm. deep. The catalyst bed occupied a total volume of 200 ml. of which 155 ml. was resin beads and 45 ml. was void volume.

The temperature used for all experiments was 25°.

Preparation of 4-methoxy-4-methyl-2-pentanone. A stock solution of equal volumes of methanol and mesityl oxide (2.86 moles of methanol per mole of mesityl oxide) was used. In run 2 of Table 1, 1800 ml. (7.88 moles of mesityl oxide and 21.9 moles of methanol) of the stock solution was passed over the ion exchange resin at an average rate of 0.616 ml. per min. The effluent was first distilled using an efficient glass column at 200 mm. until all of the methanol (b.p. 35°) was removed. The pressure was then reduced to 40 mm. for the removal of the unreacted mesityl oxide (b.p. 42°) followed by 4-methoxy-4-methyl-2-pentanone, confirmed by infrared, b.p. 74°/40 mm., n_D^{25} 1.4159, d_{25} 0.900, (Lit.[1] d_{25} 0.901).

In Table I the results of four runs made at varying feed rates are given.

Preparation of 4-ethoxy-4-methyl-2-pentanone. The same resin that was used above was used for this experiment after it was washed with ethanol. A solution composed of 24.9 moles of anhydrous ethanol and 9.7 moles of mesityl oxide was passed over the resin at a rate of 0.552 ml. per min. The reaction solution was then distilled at 170 mm. until all of the ethanol (b.p. 45°) was removed and then at 40 mm. for the mesityl oxide removal followed by 20 mm. for the 4-ethoxy-4-methyl-2-pentanone, b.p. 67°/20 mm., n_D^{25} 1.4152, d_{25} 0.884 (lit.[1] d_{25} 0.886). A 37 g. high boiling residue remained. A recovery of 7.04 moles of mesityl oxide and 2.19 moles of ether represented a conversion of 27% and a yield of 82% based on unrecovered mesityl oxide.

TABLE I

Run No.	Feed Rate, Ml./Min.	Volume of Stock Soln., Ml.	High Boiling Residue, G.	Mesityl Oxide	
				% Conv.	% Yield[a]
1	0.377	1585	35	57.0	88.2
2	0.616	1800	28	56.6	93.7
3	1.29	1800	27	46.5	94.0
4	2.41	1800	28	40.9	94.0

[a] Based on unrecovered mesityl oxide.

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(1) A. Hoffman, *J. Am. Chem. Soc.*, **49**, 530 (1927).
(2) A. Hoffman, U. S. Patent **1,729,255**.
(3) C. W. Simms, U. S. Patent **1,823,704**.
(4) P. Halbig and A. Treibs, U. S. Patent **2,217,167**.
(5) B. P. Geyer and S. A. Ballard, U. S. Patent **2,413,822**.
(6) J. B. Tindall, U. S. Patent **2,430,436**.
(7) F. Helfferich, *Angew. Chem.*, **66**, 241 (1954).
(8) F. C. Nachod and J. Schubert, editors, *Ion Exchange Technology*, Academic Press, Inc., New York, 1956, pp. 279–284.

Reaction of Alkyl and Aryl Silicon Isocyanates with Amines

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Silicon tetraisocyanate and alkyl and arylsilicon isocyanates have been extensively studied by Forbes and Anderson,[2,3] and by Eaborn.[4] Although it is known that silicon tetraisocyanate reacts with water to form silica no study has been made of the reaction of silicon isocyanates with primary and secondary aliphatic and aromatic amines.[5]

(1) For reprints: 3267 57th Avenue S.W., Seattle 16, Wash.
(2) G. S. Forbes and H. H. Anderson, *J. Am. Chem. Soc.*, **62**, 761 (1940); *J. Am. Chem. Soc.*, **66**, 1703 (1944); *J. Am. Chem. Soc.*, **67**, 1911 (1945); *J. Am. Chem. Soc.*, **69**, 1241 (1947); *J. Am. Chem. Soc.*, **70**, 1043, 1222 (1948).
(3) H. H. Anderson, *J. Am. Chem. Soc.*, **66**, 934 (1944); *J. Am., Chem. Soc.*, **72**, 193, 196, 2761(1950); *J. Am. Chem. Soc.*, **75**, 1576 (1953).
(4) C. Eaborn, *Nature*, **165**, 685 (1950).
(5) Incidentally to another study, Anderson reacted aniline with silicon tetraisocyanate, *n*-butylsilicon triisocyanate, diphenylsilicon diisocyanate, *n*-propylsilicon triisothiocyanate, diethylsilicon diisothiocyanate, and triethylsilicon isothiocyanate, but did not characterize the products, where formed. See H. H. Anderson, *J. Am. Chem. Soc.*, **73**, 2351 (1951).

We wish to report that reaction of amines with silicon isocyanates of the above type results in cleavage of the isocyanate group from the silicon atom with formation of theoretical yields of the corresponding monosubstituted urea.

Silicon tetraisocyanate and isocyanates of empirical formula $R_xSi(NCO)_y$, where R is methyl or phenyl and x and y are 1, 2, or 3, were prepared by reaction of R_xSiCl_y with silver (iso)cyanate in anhydrous benzene.[2,3] Treatment of these isocyanates either alone or in anhydrous benzene with allylamine, diallylamine, aniline, benzylamine, *o*- or *p*-toluidine, produced theoretical yields of the corresponding urea. In every case the NCO: NH_2 ratio was 1:1. No evidence was obtained for the formation of ureidosilanes, and the fate of the silicon-containing moiety was not determined.[6]

EXPERIMENTAL

Allylurea from phenylsilicon triisocyanate. In a typical reaction, phenylsilicon triisocyanate (2.31 g., 0.01 mole) was added, dropwise, to a well-stirred mixture of allylamine (1.71 g., 0.03 mole) in anhydrous benzene (10 ml.). After the initial strongly exothermic reaction had moderated the mixture was heated on the steam bath for 2 hr., then allowed to cool. The white solid was washed thoroughly with benzene, yield 3.94 g. (98%). Recrystallization from isopropyl alcohol gave a white crystalline product of m.p. 85.0°. The mixed melting point of this product with authentic allylurea was undepressed.

Anal. Calcd. for $C_4H_8N_2O$: N, 28.0. Found: N, 27.9.

Similarly, allylurea was produced by reaction of allylamine with silicon tetraisocyanate, methylsilicon triisocyanate, dimethylsilicon diisocyanate, trimethylsilicon isocyanate, and diphenylsilicon diisocyanate.

Products of reaction with other amines. Reaction of aniline, benzylamine, diallylamine, *o*-, and *p*-toluidines with the above silicon isocyanates produced 95–100% yields of, respectively, phenylurea, benzylurea, *N,N*-diallylurea, *o*-, and *p*-tolylurea, which gave undepressed mixed melting points with the authentic ureas and analyzed correctly for nitrogen.

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(6) Further work is in progress to determine the nature of the silicon-containing fragment.

Disulfides

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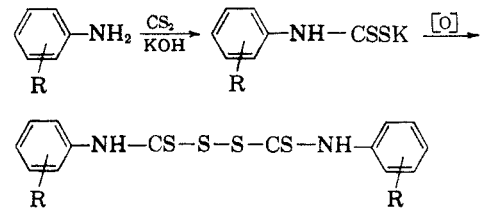
Chemotherapeutic activity can be conceived as due to the interference of the agent in the progression of the parasites metabolic reaction. This interference takes the form of inactivation or displacement of a metabolite essential to the parasite (*a*) by oxidizing a substance that requires to be reduced, (*b*) by molecular combination forming an inactive product, or (*c*) by competition with an enzyme associated with the essential metabolite.[1-3]

It was reported by Srinivasan[4] that paludrine can inhibit the oxygen uptake of the malarial parasite. He is of the opinion that the drug acts through inhibition of the activity of some —SH groups essential for the respiration of the parasite.

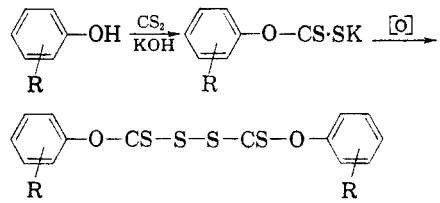
It was, therefore, decided to prepare some —S—S— compounds as potential antimalarials, since these compounds might be active by oxidizing some of the —SH groups essential to the parasite. The potency of thiuramdisulfides as bacterial poisons as well as the antimalarial activity exhibited by them in experimental malaria led us to prepare some analogous disulfides.

These compounds were made by first treating various amines with carbon disulfide in presence of aqueous potassium hydroxide and then oxidizing the thiocarbamido derivative with sodium nitrite, methyl alcohol, and hydrochloric acid.



o-, *m*-, *and p*-Aminobenzoic acids and the three aminobenzene sulfonic acids were thus treated to give the corresponding bisaryl thiuram disulfides.

The dixanthogens are a class of compounds closely related in structure and hence it was decided to prepare some derivatives of this type to study their effect in experimental malaria. The preparation of these compounds follows a similar route, different phenol carboxylic and phenol sulfonic acids being used instead.



These compounds were quite active in inhibiting the respiration of *Plasmodium gallinaceum in vitreo*, using the Warburg technique. However, only diphenylxanthogen-*p,p'*-disulfonic acid and *N,N'*-diphenylthiuram disulfide-*p,p'*-disulfonic acid were active *in vivo* against *P. gallinaceum* in chicks. Detailed pharmacological data will be published elsewhere.

(1) D. D. Woods, *Brit. J. Exp. Pathol.*, **21**, 274, (1940).
(2) P. Fildes, *Lancet*, **1**, 955, (1940).
(3) E. M. Lourie, *Ann. Rev. Microbiol.*, **1**, 237, (1947).
(4) V. R. Srinivasan, a thesis submitted for the Ph.D., Madras University.