[CONTRIBUTION FROM THE MORLEY CHEMISTRY LABORATORY, WESTERN RESERVE UNIVERSITY]

Use of Sodium Hydride in Alkylation of Urethans

RALPH L. DANNLEY AND MARVIN LUKIN[1]

Received August 2, 1956

By the use of sodium hydride, representative urethans have been alkylated with benzyl and primary alkyl halides in yields of 68–96%. The best results were obtained using excess alkyl halide or dimethylformamide as solvents. Secondary alkyl groups could not be introduced by the procedure. Although the alkylation of an *N*-perfluoroalkyl urethan (ethyl *N*-perfluoropropylcarbamate) was unsuccessful, an unusual hydrolysis product (ethyl *N*-perfluoropropionylcarbamate) was isolated.

The alkylation of urethans has received little attention since a compound which might be synthesized by this method can generally be prepared more readily from the appropriate secondary amine and a chloroformate. Such alkylations might be of use in the synthesis of novel urethans, however, for it is possible to obtain carbamates (*e.g.*, the N-perfluoroalkyl type) corresponding to primary amines which have never been isolated.

It was therefore decided to develop a general procedure for the alkylation of urethans. Kraft[2] had reported that treatment of ethyl carbamate with metallic sodium produced a salt which reacted with methyl iodide to give ethyl N-methylcarbamate. In developing a general procedure, however, sodium hydride appeared to be a more promising reagent than sodium for the step of salt formation. Sodium hydride has been used very successfully in the alkylation of simple amides[3] and has the advantage that it does not react with alkyl halides.[4]

The present work was undertaken with several objectives: first, to find whether sodium hydride could be used successfully in the alkylation of urethans; second, to select the solvents most desirable for use as diluents for the reaction mixtures; third, to determine yields from the reactions of typical alkylating reagents with representative urethans; and fourth, to attempt the alkyation of an N-perfluoroalkylurethan.

EXPERIMENTAL

Reagents. Sodium hydride (Metal Hydrides) and Eastman Kodak White-Label grades of ethyl N-methylcarbamate, *n*-butyl bromide, methyl iodide and benzyl chloride were used without purification. Allyl chloride was redistilled before use. Toluene and xylene were dried over sodium wire and dimethylformamide (Rohm & Haas) was dried with Drierite. The N-phenylurethan and N-benzylurethan were prepared from the respective amines and ethyl chlorocarbonate as described in a previous paper.[5]

Butylation of ethyl N-methylcarbamate. To a mixture of 72.1 g. (0.7 mole) of ethyl N-methylcarbamate and 191.8 g. (1.4 moles) of *n*-butyl bromide was added 19.2 g. (0.8 mole) of sodium hydride. The exothermic reaction caused the temperature to rise and the mixture refluxed spontaneously for about 0.5 hr. After stirring and refluxing for an additional 10 hr., the sodium bromide was removed by filtration. The salt cake was washed with two 100-ml. portions of ether and the ether washings were added to the filtrate. After removal of the ether and excess butyl bromide from the filtrate at atmospheric pressure, the residue was distilled *in vacuo* through a Todd column to give 91 g. (82% yield) of N-methyl-N-*n*-butylurethan (b.p. 91° at 20 mm.; n_D^{20} 1.4255; d_{25}^{25} 0.9159).

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.33; H, 10.78. Found: C, 60.77; H, 11.00.

Additional alkylations of N-methylurethan with butyl bromide were performed in various solvents as shown in Table I. In each instance the procedure was essentially identical with the experiment already described.

Benzylation of ethyl N-methylcarbamate. When a mixture of 72.1 g. (0.7 mole) of ethyl N-methylcarbamate, 177.1 g. (1.4 moles) of benzyl chloride and 19.2 g. (0.8 mole) of sodium hydride was stirred at room temperature, a very slow evolution of hydrogen occurred. Upon heating, the reaction became exothermic and benzyl chloride refluxed. The mixture was allowed to cool to 120° and maintained at this temperature for 18 hr. After addition of 10 ml. of ethanol to decompose the excess sodium hydride, 200 ml. of water were added and the aqueous layer separated and washed with three 75-ml. portions of ether. The combined organic layer and ether washings were dried over Drierite and distilled through a glass helices-packed column to yield 83.0 g. (61%) of ethyl N-methyl-N-benzylcarbamate, b.p. 100–101° (2.5 mm.), n_D^{20} 1.5052, d_{25}^{25} 1.049.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.84. Found: C, 68.14; H, 7.64.

Benzylation of ethyl N-phenylcarbamate. From a mixture of 33 g. of ethyl carbanilate, 5.28 g. of sodium hydride and 31.6 g. of benzyl chloride in 200 ml. of xylene kept at reflux for 24 hr. was obtained 51.0 g. (75% yield) of ethyl N-benzylcarbanilate, b.p. 135–136° (2.5 mm.), n_D^{20} 1.5677, d_{25}^{25} 1.099 (lit.[6] d_4^{25} 1.076). The procedure for isolation of the product was identical with that used in the preparation of ethyl N-methyl-N-benzylcarbamate.

Allylation of ethyl N-phenylcarbamate. The reaction of 82.5 g. of N-phenylurethan, 76.5 g. of allyl chloride, and 12.65 g. of sodium hydride in 150 ml. of dimethylformamide was quite vigorous. After the initial reaction subsided, the mixture was heated at gentle reflux for 6 hr. After decomposing the excess sodium hydride with 10 ml. of ethanol, 180 ml. of chloroform was added and the mixture was poured into 700 ml. of water. The aqueous layer was separated and extracted with additional chloroform. The combined chloroform solutions were dried over Drierite and distilled *in vacuo* to yield a fraction boiling from 98–102°

---

(1) From the thesis submitted by Marvin Lukin to the Graduate School of Western Reserve University in partial fulfillment of the requirements for the doctor's degree.

(2) F. Kraft, *Ber.*, **23**, 2785 (1890).

(3) W. Fones, *J. Org. Chem.*, **14**, 1099 (1949).

(4) S. Cristol, J. Ragsdale, and J. Meek, *J. Am. Chem. Soc.*, **71**, 1863 (1949).

(5) R. L. Dannley, M. Lukin, and J. Shapiro, *J. Org. Chem.*, **20**, 92 (1955).

(6) McBain, Harvey, and Smith, *J. Phys. Chem.*, **30**, 314 (1926).

TABLE I

REAGENTS AND PRODUCTS OF ALKYLATIONS PER MOLE OF STARTING ETHYL CARBAMATE

Starting Urethan	Alkylating Halide	Halide, Moles	NaH, Moles	Solvent	Solvent, Moles	Product Urethan, Moles
N-methyl	n-C_4H_9Br	2.00	1.14	None	—	0.82
N-methyl	n-C_4H_9Br[a]	1.50	1.00	Xylene	1.17	.43
N-methyl	n-C_4H_9Br[b]	1.50	1.07	Dimethylformamide	2.78	.60
N-methyl	n-C_4H_9Br[c]	0.97	0.97	$CHCl_3$	1.84	.10
N-methyl	$C_6H_5CH_2Cl$	2.00	1.14	None	—	.61
N-methyl	$C_6H_5CH_2Cl$[d]	1.55	1.17	Toluene	5.82	.54
N-methyl	$C_6H_5CH_2Cl$[e]	1.50	1.17	Dimethylformamide	1.82	.68
N-phenyl	$C_6H_5CH_2Cl$	1.25	1.10	Xylene	8.20	.75
N-phenyl	$C_6H_5CH_2Cl$[f]	1.25	1.10	Dimethylformamide	1.37	.66
N-phenyl	$CH_2{=}\overset{H}{C}{-}CH_2Cl$	2.00	1.10	Dimethylformamide	3.89	.93
N-benzyl	CH_3I[g]	2.00	1.10	Dimethylformamide	1.56	.79

[a] Refluxed 15 hr. [b] Temperature maintained at 60° for 12 hr. [c] Much sodium hydride left unreacted even though the mixture was refluxed for 18 hr. [d] Benzyl chloride added to a stirred mixture of sodium hydride and the urethan in toluene. The mixture was then refluxed for 30 hr. [e] Temperature maintained at 100° for 18 hr. [f] Temperature of 85° maintained for 18 hr. and chloroform used to extract the product. [g] Refluxed for 5 hr.

at 1.5 mm. To insure the absence of unalkylated urethan in the product, a benzene solution of the fraction was refluxed with 5 g. of sodium hydride for 3 hr. and then filtered. Distillation of the filtrate through a helices-packed column gave 95 g. (93% yield) of ethyl N-allyl-N-phenylcarbamate, b.p. 115–116° (4.5 mm.), n_D^{20} 1.5159; d_{25}^{25} 1.046.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.38. Found: C, 70.23; H, 7.28.

Attempted alkylation of urethans with secondary halides. In the two experiments tried (the *s*-butylation of ethyl N-methylcarbamate and the isopropylation of N-phenyl urethan) olefins were formed by dehydrohalogenation of the halides and the starting urethans were recovered unchanged.

Attempted alkylation of ethyl N-perfluoropropylcarbamate. Although the desired alkylation was not obtained, an unusual hydrolysis of the urethan was observed. Ten grams (0.039 mole) of N-perfluoropropylurethan[7] were added dropwise to a suspension of 0.98 g. (0.041 mole) of sodium hydride in 16.03 g. (0.117 mole) of butyl bromide. The reaction mixture was maintained at room temperature for 18 hr. and then refluxed for a day. The excess hydride was decomposed with wet ether and 10 ml. of water added. The organic layer was separated and the aqueous layer extracted with ether. The combined ethereal solutions were dried over Drierite and distilled to give 1.45 g. (16% yield) of ethyl N-perfluoropropionylcarbamate (m.p. 60–61°).

Anal. Calcd. for $C_6H_6F_5NO_3$: C, 30.65; H, 2.58; F, 40.40. Found: C, 30.66; H, 2.68; F, 39.5.

The identity of this product was proved through alcoholysis of an 0.5-gram sample in 4 ml. of refluxing anhydrous ethanol. Two ml. of this solution were distilled and the residue evaporated and distilled *in vacuo* to give 35 mg. (b.p. 73° at 12 mm.) of ethyl carbamate. After recrystallization from ligroin the urethan melted at 49–50° and addition of an authentic sample of ethyl carbamate did not depress the melting point.

The 2-ml. distillate was dissolved in anhydrous ether and the ether solution saturated with anhydrous ammonia. Evaporation of the solvent left 117 mg. of perfluoropropionamide, m.p. 95–96° (lit.[8] m.p. 95–95.5°).

The ethyl N-perfluoropropionylcarbamate undoubtedly was formed by hydrolysis of unchanged urethan while working up the reaction mixture.

Other methods of alkylation of this urethan were attempted without success. Use of dimethylformamide as a solvent, substitution of methyl iodide for the butyl bromide, and replacement of the sodium hydride with silver oxide all produced oils of high boiling point and low fluorine content.

DISCUSSION

The alkylation of urethans through the use of sodium hydride generally proceeded in good yield using an excess of the alkylating halide as a reaction medium. The use of excess halide, however, may sometimes be undesirable either due to the cost or unavailability of the reagent. Of several diluents tried, dimethylformamide generally gave rise to the best yields. The advantage in yield is not as remarkable as that observed by Sheehan and Bolhofer[9] in the use of dimethylformamide in the analogous Gabriel synthesis, but may again be related to its solvent properties for the salts formed as intermediates in the reaction.

The use of secondary halides led to olefin formation and recovery of the original urethan. Since alkyl halides do not react with sodium hydride, the dehydrohalogenation must result from reaction with the sodium derivative of the urethan. In contrast, Fones[3] did succeed in alkylating acetanilide in 53% yield with isopropyl bromide using sodium hydride as the condensing agent. The success of Fones may be due to the lower basicity of the salt of the simple anilide as compared to the salt of the urethan.

The alkylation of the N-perfluoroalkyl urethans was unsuccessful despite a variety of modifications of the general procedure. The inability to alkylate

---

(7) A. Albrecht, D. Husted, U. S. Patent **2,617,817**; *Chem. Abstr.*, **47**, 8774 (1953).

(8) R. Haszeldine and K. Leedham, *J. Chem. Soc.* 1548, (1953).

(9) J. Sheehan and W. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).

may be attributed to predominant competitive reactions of the fluorine atoms alpha to the nitrogen. The great reactivity of such fluorine atoms has been previously reported.[10]

Acknowledgment. We are indebted to the Research Corporation for financial aid in support of this work.

CLEVELAND, OHIO

---

[10] (*a*) D. Barr and R. Haszeldine, *J. Chem. Soc.*, 2532 (1955); (*b*) R. L. Dannley and M. Lukin, *J. Org. Chem.*, 21,1036 (1956); (*c*) R. L. Dannley, R. G. Taborsky, and M. Lukin, *J. Org. Chem.*, 21, 1318 (1956).

[CONTRIBUTION NO. 998 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Pyridylethylation of Active Hydrogen Compounds. VI. Reactions of Ketones, Alkylpyridines, and Alkylquinolines with 2- and 4-Vinylpyridine[1,2,3]

GEORGE MAGNUS AND ROBERT LEVINE

Received August 29, 1956

A study has been made of the conjugate addition reactions of a series of ketones with 4-vinylpyridine and of four alkylpyridines and two alkylquinolines with 2- and 4-vinylpyridine.

In 1947 Doering and Weil published a classical paper[4] in which they demonstrated elegantly that 2- and 4-vinylpyridine undergo conjugate addition reactions with a representative group of nucleophilic reagents. We have extended their observations and in previous papers from this laboratory the reactions of 2-vinylpyridine with ketones[5,6] and of both 2- and 4-vinylpyridine with ammonia,[2] amines,[2,7,8] amides,[2] and nitriles[2] were discussed.

The present paper is concerned with the reactions of 4-vinylpyridine with a series of ketones and of both 2- and 4-vinylpyridine with several alkylated tar bases. Apparently the only previously reported direct pyridylethylation of a ketone with 4-vinylpyridine appears in a paper by Levine and Wilt,[5] who obtained a 21.5% yield of phenyl γ-(4-pyridyl)-propyl ketone by the interaction of a 2:1:0.2 molar ratio of acetophenone, 4-vinylpyridine and sodium for a reaction time of 4 hr. This compound also has been prepared indirectly by the ketonic cleavage of ethyl α-[β-(4-pyridyl)ethyl]benzoylacetate,[9] which was obtained by the reaction of 4-vinylpyridine with ethyl benzoylacetate.

In the present study the reaction between acetophenone, 4-vinylpyridine and sodium has been reinvestigated. The interaction of a 2:1 molar ratio of ketone to 4-vinylpyridine for periods of 2, 4, and 6 hr. (Table I) gave mixtures of the monopyridylethylated product, phenyl γ-(4-pyridyl)-propyl ketone (16 to 18%) and the dipyridylethylated product, 3-benzoyl-1,5-di-(4-pyridyl)pentane, (65 to 73%). Even when a molar ratio of ketone to vinylpyridine of 4:1 was used in an attempt to greatly increase the amount of mono- and decrease the dipyridylethylated product, these derivatives were obtained in 21.6% and 36% yields, respectively. These results appear to indicate that 4-vinylpyridine reacts more readily with the initially formed monopyridylethylated compound to give the dipyridylethylated derivative than it does with acetophenone to give the monopyridylethylated compound.

The reaction of a 2:1 molar ratio of *p*-methylacetophenone to 4-vinylpyridine gave a low yield of the mono- (18.2%) and a higher yield of the dipyridylethylated (46.8%) product. Although under similar conditions the reaction of propiophenone with 4-vinylpyridine gave a high yield (88.5%) of the monopyridylethylated product, when this reaction was repeated using a 1:2 ratio of ketone to 4-vinylpyridine, essentially equal amounts of the mono- (43.4%) and the dipyridylethylated (41.0%) products were obtained.

Five symmetrical ketones have been condensed with 4-vinylpyridine (Table I). It may be seen that with the exception of acetone, each of these ketones was monopyridylethylated in fair to good yield. In the cyclohexanone reaction a mixture of a considerable amount of self-condensed ketone, 2-(1-cyclohexenyl)cyclohexanone, 40.8% of the mono-

---

[1] This paper is based on part of a thesis presented by George Magnus to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

[2] For the previous paper in this series, see G. Magnus and R. Levine, *J. Am. Chem. Soc.*, **78**, 4127 (1956).

[3] This work was performed under Contract No. AT(301)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

[4] W. von E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, 69, 2461 (1947).

[5] R. Levine and M. H. Wilt, *J. Am. Chem. Soc.*, **74**, 342 (1952).

[6] M. H. Wilt and R. Levine, *J. Am. Chem. Soc.*, **75**, 1368 (1953).

[7] H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, 77, 4913 (1955).

[8] H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, 77, 5434 (1955).

[9] V. Boekelheide and J. H. Mason, *J. Am. Chem. Soc.*, **73**, 2356 (1951).