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INTERMOLECULAR DEHYDRATION BETWEEN ALCOHOLS AND ACTIVE HYDROGEN COMPOUNDS BY MEANS OF DIETHYL AZODICARBOXYLATE AND TRIPHENYLPHOSPHINE

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Preceding paper describes that the reaction of alcohols with phthalimide (pKa 8.3), diethyl azodicarboxylate (1) and triphenylphosphine (2) resulted in the formation of corresponding N-alkylphthalimides in good yields.[1] This reaction proceeds stereospecifically with complete inversion of the configuration at C-1 in the alcohol.

In this paper, we wish to report the intermolecular dehydration between alcohols and various active hydrogen compounds by means of 1 and 2.

When ethyl cyanoacetate (pKa$>$9) and n-propanol were allowed to react with equimolar amounts of 1 and 2 in tetrahydrofurane (THF) at room temperature, ethyl 2-cyanopentanoate was obtained in a 52% yield by preparative thin layer chromatography. Similarly, the reaction of malononitrile (pKa 11.2) and n-propanol with 1 and 2 led to the formation of n-propylmalononitrile in a 51% yield. Both C-alkylation and O-alkylation took place, ethyl acetoacetate (pKa 10.7) being used as an active methylene compound in the above reaction. On the other hand, ethyl malonate (pKa 13.3) could not undergo this type of reaction, presumably due to low acidity. These results are summarized in Table 1.

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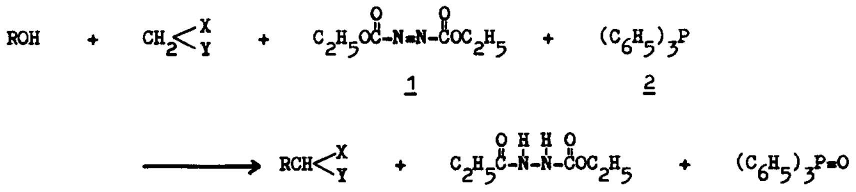
When ethyl cyanoacetate and (R)-(-)-2-octanol[2] ($[\alpha]_D$ -14.4°) were treated with 1 and 2, there was obtained ethyl 2-cyano-3-methylnonanoate (28%) which showed $[\alpha]_D$ +1.18±0.09 (14.68mg/1ml, benzene). Although the absolute configuration of the product has not yet been established, it may have S-configuration on the basis of recent experiments.[1, 3]

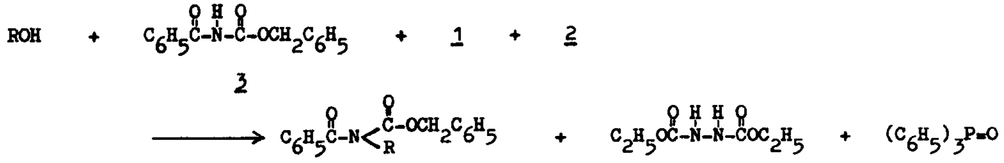


$$ROH + CH_2{<}^{X}_{Y} + \underset{1}{C_2H_5O\overset{O}{\overset{\|}{C}}-N{=}N-\overset{O}{\overset{\|}{C}}OC_2H_5} + \underset{2}{(C_6H_5)_3P}$$

$$\longrightarrow RCH{<}^{X}_{Y} + C_2H_5\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}OC_2H_5 + (C_6H_5)_3P{=}O$$

$X = Y = CN$
$X = CN,\ Y = CO_2C_2H_5$
$X = CH_3CO,\ Y = CO_2C_2H_5$

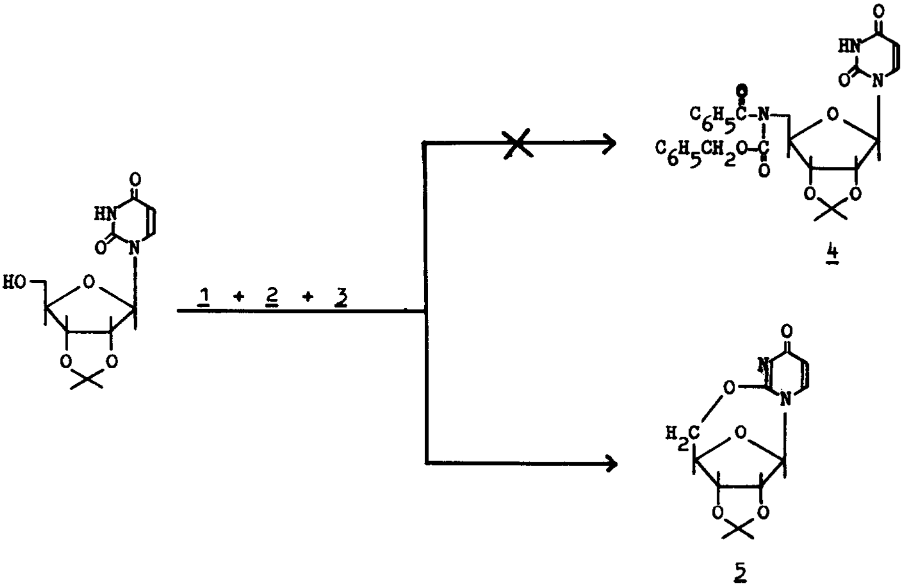
The reaction described above was further extended to the alkylation of amides. When benzamide (pKa 13-14) and p-nitrobenzamide were allowed to react with n-propanol, 1 and 2 in THF at room temperature, no N-n-propylbenzamide and N-n-propyl-p-nitrobenzamide were obtained. That no alkylation took place may be attributed to low acidity of the amides. Therefore, N-carbobenzoxybenzamide (3) was prepared from benzoyl isocyanate and benzyl alcohol. As expected, the reaction of 3 and alcohols with 1 and 2 resulted in the formation of N-carbobenzoxy-N-alkylbenzamides in about 70% yields. The results are summarized in Table 1.



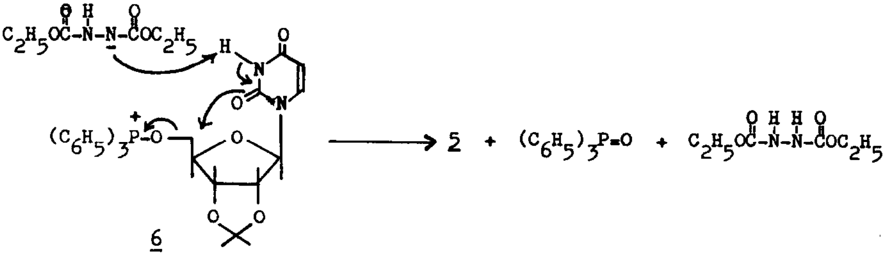
$$ROH + \underset{3}{C_6H_5\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-OCH_2C_6H_5} + 1 + 2$$

$$\longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}-N{<}^{\overset{O}{\overset{\|}{C}}-OCH_2C_6H_5}_{R} + C_2H_5O\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}OC_2H_5 + (C_6H_5)_3P{=}O$$

Next, an attempt was made to react 2', 3'-O-isopropylideneuridine with 1, 2 and 3 with a view to prepare 2', 3'-O-isopropylidene-5'-deoxy-5'-(N-benzoyl-N-carbobenzoxy)aminouridine (4). Contrary to our expectation, no 4 could be isolated but 2', 3'-O-isopropylidene-O^2: 5'-cyclouridine (5) was isolated in about 60% yield (mp 275°-277°C, λ_{max}^{EtOH} 238mμ, λ_{min}^{EtOH} 212mμ).



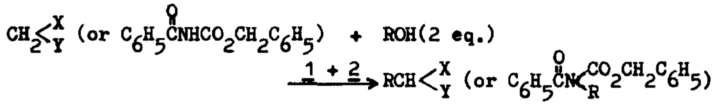
Similarly, when 2', 3'-O-isopropylideneuridine was treated with 1 and 2 in the presence or absence of phthalimide, 5 was obtained in 68% and 80% yields, respectively. These results can be explained by assuming the formation of a quaternary phosphonium salt (6). The hydrogen atom at N-3 in the uracil ring (pKa of uridine is 9.25) was abstracted by the anion of diethyl hydrazodicarboxylate, followed by intermolecular electron transfer giving 5 and triphenylphosphine oxide.



Similar mechanism for the formation of cyclonucleosides have been proposed by Verheyden and Moffatt.[4]

Condensation of alcohols with strong acids such as carboxylic or phosphoric acid can be achieved by the use of dehydrating reagents. There are no reports, however, of direct condensations of alcohols with weak acids under mild conditions. The work described in this paper indicates that intermolecular dehydration between alcohols and weak acids of pKa 11 can be effected by means of 1 and 2. Further applications of the reaction to the nucleosides and peptides are in progress.

Table 1. Alkylation of Active Hydrogen Compounds



$$CH_2{<}^{X}_{Y} \text{ (or } C_6H_5\overset{O}{\overset{\|}{C}}NHCO_2CH_2C_6H_5) + ROH(2\text{ eq.}) \xrightarrow{1\,+\,2} RCH{<}^{X}_{Y} \text{ (or } C_6H_5\overset{O}{\overset{\|}{C}}N{<}^{CO_2CH_2C_6H_5}_{R})$$

Yields of $RCH{<}^{X}_{Y}$ *				Yields of $C_6H_5\overset{O}{\overset{\|}{C}}N{<}^{CO_2CH_2C_6H_5}_{R}$ *	
R	X	Y	%	R	%
n-C_3H_7-	-CN	-$CO_2C_2H_5$	52	C_2H_5-	66
n-C_3H_7-	-CN	-CN	51	n-C_3H_7-	66
n-C_3H_7-	-$COCH_3$	-$CO_2C_2H_5$	10**	n-C_4H_9-	68

* Satisfactory IR and NMR data were obtained for these products.

** O-Alkylated product was obtained in a 28% yield. The ratio of C-alkylation to O-alkylation was determined by NMR spectrum.

REFERENCES

1. O. Mitsunobu, M. Wada and T. Sano, J. Am. Chem. Soc., February issue (1972).
2. A. W. Ingersoll, "Organic Reactions", Vol. 2, John Wiley and Sons, Inc., New York, 1960. Optical rotation was measured with JASCO ORD/UV-5.
3. (a) O. Mitsunobu and M. Eguchi, Bull. Chem. Soc. Japan, **44**, 3427 (1971). (b) W. Gerrard and W. J. Green, J. Chem. Soc., 2550 (1951). (c) R. G. Weiss and E. I. Snyder, J. Org. Chem., **35**, 1627 (1970) and references therein.
4. J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., **35**, 2319 (1970).