A GENERAL PROCEDURE FOR THE SYNTHESIS OF EPOXY-ALKYLATED AND ACYLATED HETEROCYCLES

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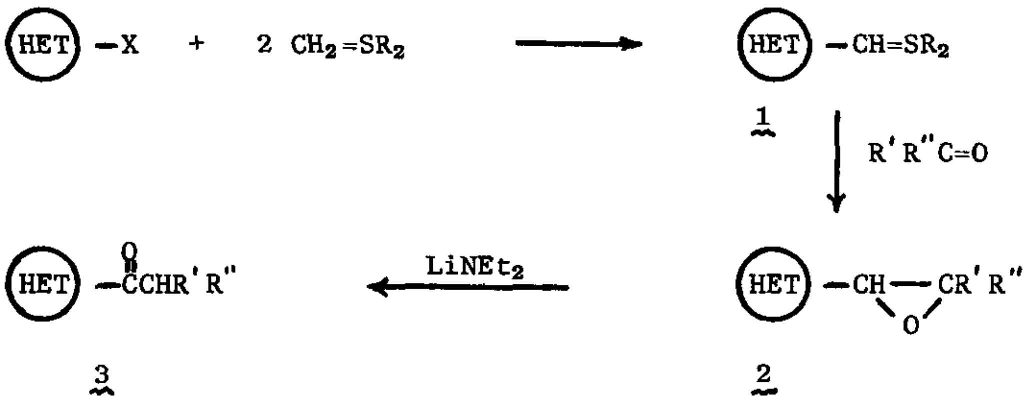
We have recently reported[1] a new procedure for the direct introduction of alkyl and alkenyl substituents into heterocyclic nuclei *via* nucleophilic displacement of suitable leaving groups by Wittig reagents. The new heterocyclic ylides thus formed were then subjected (*in situ*) to the normal reactions of Wittig reagents (hydrolysis to alkyl-substituted heterocycles, reaction with carbonyl compounds to give alkenyl-substituted heterocycles, etc.). Further, we have utilized[2] this procedure for a facile synthesis of quinine and related Cinchona alkaloids. We now report an extension of this method which employs sulfur ylides for the direct introduction of epoxy and acyl substituents into heterocyclic nuclei.

Although some methods are available for the introduction of oxygenated-alkyl substituents into heterocyclic nuclei [for example, reactions of heterocyclic N-oxides with alkyllithium compounds followed by addition of esters,[3] the Emmert reaction,[4] homolytic acylation of heterocycles by acyl radicals,[5] base-catalyzed reaction of ketones with N-alkoxy heterocycles,[6] direct acylation of heterocycles containing a replaceable hydrogen with an ester and aluminum amalgam,[7] reaction of 2-lithio-1,3-dithianes with α-haloheterocycles,[8] and treatment of trimethylsilylated heterocycles with aldehydes, acid chlorides and acid anhydrides[9]], they all possess limitations which severely limit their scope. In addition, it should be noted that epoxy substituents are not generally obtainable by peracid oxidation of olefins if a ring nitrogen atom is present.[10] Alternate routes to epoxy-substituted heterocycles involve multi-step, complicated procedures.[11]

The use of sulfonium ylides for the preparation of heterocycles with oxygenated alkyl substituents is depicted in general terms below:



Treatment of a heterocycle possessing an appropriate leaving group with two equivalents of a sulfonium ylide generates a new ylide (1) which, when treated *in situ* with a carbonyl compound, yields an epoxide (2).[12] Moreover, the epoxide may, without isolation, be rearranged with lithium diethylamide[13] to give an acyl derivative (3). Typical conversions are summarized in Tables I and II.

The general experimental procedure is illustrated as follows. To a suspension of diphenylmethylsulfonium tetrafluoroborate or perchlorate (2.5 equiv) in anhydrous 1,2-dimethoxyethane (DME) under dry nitrogen at -70° was added 2.5 equiv of lithium diisopropylamide, the reaction mixture stirred for 1 hr, and the appropriate heterocycle added (1 equiv). The reaction mixture was allowed to warm to -35° where it was maintained until formation of the new heterocyclic ylide (1) was complete (usually requiring 2-4 hrs, the reaction course being monitored by TLC).

The reaction mixture was then treated with an excess (4-5 equiv) of the appropriate aldehyde or ketone in anhydrous DME, allowed to come to room temperature, and stirred for 18 hr. Excess solvent was removed under reduced pressure and the residue treated by either of the following procedures. (a) To obtain epoxy-substituted heterocycles, the residue was suspended in water and extracted with ether, the combined dried extracts concentrated under reduced pressure, and the residual material added to an excess of mercuric chloride in 25% aqueous ethanol. The precipitated solid was collected by filtration and washed, and the heterocycle was freed by treatment of the salt with an excess of diisopropylethylamine in ethanol-hexane solution, filtration, and concentration of the filtrate under reduced pressure. The product was purified by distillation or recrystallization. (b) To obtain acylated heterocycles, the residue was taken up in anhydrous ether and added to a solution of lithium diethylamide in anhydrous ether under dry nitrogen at -20°. The mixture was allowed to warm to room temperature, refluxed for 1 hr, and then hydrolyzed by pouring into water. The organic layer was separated and the aqueous layer extracted with ether. The combined ether extracts were either treated with mercuric chloride as above or extracted with dilute aqueous acid, the aqueous layer made alkaline and the resulting solution extracted with ether. The combined ether extracts were dried, evaporated under reduced pressure, and the product purified by distillation or recrystallization.

Thus, by a proper choice of the starting ylide, heterocycle,

TABLE I. Synthesis of Epoxy-Alkyl Substituted Heterocycles

Starting Material	Carbonyl Compound	Product	Yield %
2-Methylsulfonyl-quinoline	Propionaldehyde	1-Ethyl-2-(2-quinolyl)-oxirane	37
"	Benzaldehyde	1-Phenyl-2-(2-quinolyl)-oxirane	47
"	Acetone	1,1-Dimethyl-2-(2-quinolyl)-oxirane	17
4-Methylsulfonyl-quinoline	Propionaldehyde	1-Ethyl-2-(4-quinolyl)-oxirane	62
"	Benzaldehyde	1-Phenyl-2-(4-quinolyl)-oxirane	58
1-Methylsulfonyliso-quinoline	Propionaldehyde	1-Ethyl-2-(1-isoquinolyl)-oxirane	42
"	Benzaldehyde	1-Phenyl-2-(1-isoquinolyl)-oxirane	65
4-Chloroquinazoline	Propionaldehyde	1-Ethyl-2-(4-quinazolinyl)-oxirane	50
"	Benzaldehyde	1-Phenyl-2-(4-quinazolinyl)-oxirane	48
2-Chloroquinoxaline	Propionaldehyde	1-Ethyl-2-(2-quinoxalinyl)-oxirane	65
2-Chlorobenzoxazole	Propionaldehyde	1-Ethyl-2-(2-benzoxazoyl)-oxirane	62
"	Benzaldehyde	1-Phenyl-2-(2-benzoxazoyl)-oxirane	70
1,3-Dimethyl-6-chloro-uracil	Benzaldehyde	1-Phenyl-2-(6-(1,3-dimethyl)-2,4-dioxopyrimidinyl))oxirane	52

TABLE II. Synthesis of Acylated Heterocycles.

Starting Material	Carbonyl Compound	Product	Yield %
2-Methylsulfonyl-quinoline	Propionaldehyde	Propyl 2-quinolyl ketone	45
"	Acetaldehyde	Ethyl 2-quinolyl ketone	57
"	Acetone	Isopropyl 2-quinolyl ketone	51
"	Cyclohexanone	Cyclohexyl 2-quinolyl ketone	52
"	Benzaldehyde	Benzyl 2-quinolyl ketone	65
4-Chloroquinazoline	Acetaldehyde	Ethyl 4-quinazolinyl ketone	36
"	Propionaldehyde	Propyl 4-quinazolinyl ketone	37
2-Methylsulfonyl-quinoxaline	Benzaldehyde	Benzyl 2-quinoxalinyl ketone	19
"	Propionaldehyde	Propyl 2-quinoxalinyl ketone	39
2-Methylsulfonylpyrazine	Acetaldehyde	Ethyl 2-pyrazinyl ketone	33
1-Methylsulfonyliso-quinoline	Cyclohexanone	Cyclohexyl 1-isoquinolyl ketone	60
"	Propionaldehyde	Propyl 1-isoquinolyl ketone	56
2-Chlorobenzoxazole	Propionaldehyde	Propyl 2-benzoxazoyl ketone	57

and carbonyl compound, a wide variety of oxygenated-alkyl substituted heterocycles may be prepared. The synthetic potential of this direct and unequivocal method for heterocycle functionalization was recently illustrated by " one-pot" syntheses of racemic erythro-rubanol, cinchonidine, and cinchonine.[2]

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