magnitude) is predicted for E between the two cases.[13] In particular, E is predicted to increase as the proportion of the diallyl radical structure increases.

The zero-field splitting parameters listed in Table I allow the esters to be divided into two categories. The mono and para substituted derivatives have smaller E values than do the ortho and meta derivatives. This is consistent with the triplet of the mono and para derivatives having a larger contribution of the *p*-quinoidal structure while the triplet of the ortho and meta derivatives assumes more of the diallyl radical structure. The variation of E for the mono and para substituted derivatives attests to the sensitivity of this parameter to asymmetry since the values decrease in the order $\mathbf{1} > \mathbf{4} > \mathbf{7}$. Calculations which include the effect of the substituent and nonplanar structures are in progress.[14]

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(14) N. C. Baird, unpublished results.
(15) On leave from the University of Aarhus, Aarhus, Denmark.

D. R. Arnold,* J. R. Bolton, J. A. Pedersen[15]
Photochemistry Unit, Department of Chemistry
University of Western Ontario, London 72, Canada
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A Facile Method for Alkylation and Alkenylation of Heterocycles

Sir:

Despite the plethora of synthetic methods available for the introduction and manipulation of functional groups in heterocyclic systems,[1] there exists no general method for alkylation or alkenylation on carbon. We describe in this communication a facile procedure for the introduction of alkyl and alkenyl groups at positions activated toward nucleophilic substitution reactions, utilizing as starting materials halo-substituted heterocycles, which number among the most readily accessible derivatives of heterocyclic systems.

Existing methods for the direct introduction of alkyl substituents into heterocyclic nuclei appear to be severely limited in scope; these include reactions of parent heterocycles or their *N*-oxides with Grignard or organolithium reagents,[2-5] electrophilic alkylation of *in situ* produced dihydro derivatives,[6] the reaction of chloro derivatives with salts of active methylene compounds,[7-9] the reaction of certain parent heterocycles with methylsulfinyl carbanion to give methylated derivatives,[10] the reaction of pyrazines with aldehydes and ketones in the presence of a solution of an alkali or alkaline earth metal in liquid ammonia,[11] the reaction of protonated heteroaromatic bases with alkyl radicals,[12,13] and the Reissert reaction[14,15] and certain specialized variations thereof,[16,17] which seem to be largely restricted to quinolines, isoquinolines, and phenanthridines.

Our new procedure involves treatment of a chloroheterocycle with 2 equiv of an appropriate Wittig reagent. The new ylide which is formed *in situ* is either hydrolyzed to give an alkyl-substituted heterocycle, or subjected to the normal reaction of Wittig reagents with carbonyl compounds to elaborate an olefinic side chain.[18] Typical conversions are summarized in Tables I and II.

The general experimental procedure is as follows. To a suspension of the appropriate phosphonium salt (2.2 equiv) in anhydrous 1,2-dimethoxyethane (DME) under dry nitrogen at -30 to $-35°$ was added 2.2 equiv of *n*-butyllithium in hexane, the reaction mixture was stirred for 1 hr, and the appropriate chloro-substituted heterocycle (1 equiv) was added. The reaction mixture was allowed to warm to room temperature and was then either stirred under reflux (for unreactive chloro derivatives) or at room temperature (for reactive chloro derivatives).

For hydrolysis to alkyl-substituted heterocycles, sodium carbonate (1 equiv) in water was added, and the mixture was refluxed for 3 hr, evaporated under reduced pressure, and then worked up by either of the two following procedures. (a) The mixture was suspended in chloroform or ether and extracted with dilute aqueous acid, the combined aqueous layers were made alkaline with sodium hydroxide, and the resulting mixture was then extracted with ether. The combined ether extracts were dried and evaporated and the product was purified by distillation or recrystallization. (b) The mixture was extracted with hot ether, the combined ether extracts were concentrated under reduced pressure, and the residual material was treated with an excess of mercuric chloride in 25% aqueous ethanol. The precipitated salt was then collected by filtration and washed, and the heterocycle was freed by treatment of the mercuric chloride salt with hydrogen sulfide followed by aqueous base.

For conversion to alkenyl-substituted heterocycles, the above reaction mixture was treated directly with an excess (about 4 equiv) of the appropriate aldehyde or ketone in anhydrous DME, and then stirred for 24 hr at room temperature. Excess solvent was removed by

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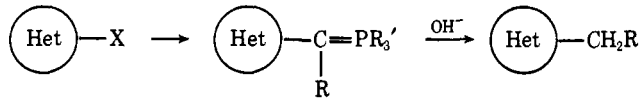
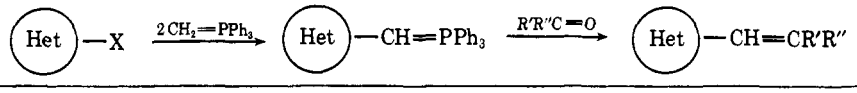
Table I. Synthesis of Alkyl-Substituted Heterocycles



Starting material	Reacting ylide	Product	Yield, %
2-Chloroquinoline	$CH_2{=}PPh_3$	Quinaldine	82[a]
	$CH_3CH{=}PPh_3$	2-Ethylquinoline	75[a]
	$n\text{-}C_3H_7CH{=}PPh_3$	2-*n*-Butylquinoline	58[a]
	$PhCH{=}P(n\text{-}Bu)_3$	2-Benzylquinoline	72[b]
2-Methyl-4-chloroquinoline	$CH_2{=}PPh_3$	2,4-Dimethylquinoline	79[a]
1-Chloroisoquinoline	$PhCH{=}P(n\text{-}Bu)_3$	1-Benzylisoquinoline	76[b]
6,7-Dimethoxy-1-chloroisoquinoline	$3,4\text{-}(CH_3O)_2C_6H_3\text{-}CH{=}P(n\text{-}Bu)_3$	Papaverine	74[a]
6-Chloropurine[c]	$CH_2{=}PPh_3$	6-Methylpurine	73

[a] Worked up by method a. [b] Worked up by method b. [c] *Via* the tetrahydropyranyl derivative (R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis, and A. Jackson, *J. Amer. Chem. Soc.*, **83**, 2574 (1961)).

Table II. Synthesis of Alkenyl-Substituted Heterocycles



Starting material	Carbonyl compd[d]	Product[a,b]	Yield, %
2-Bromopyridine[c]	Benzaldehyde	2-Styrylpyridine	32
2-Chloropyrazine	Propionaldehyde	2-(1-Butenyl)pyrazine	35
	Benzaldehyde	2-Styrylpyrazine	52
2-Chloroquinoline	Propionaldehyde	2-(1-Butenyl)quinoline	62
	Benzaldehyde	2-Styrylquinoline	65
	Thiophene-2-carboxaldehyde	1-(2-Thienyl)-2-(2-quinolyl)ethylene	52
	Acetone	2-(2-Methyl-1-propenyl)-quinoline	55
	Cyclohexanone	2-Quinolylidenecyclohexane	54
	Acetophenone	2-(α-Methylstyryl)-quinoline	46
	Benzophenone	1,1-Diphenyl-2-(2-quinolyl)ethylene	47
2-Methyl-4-chloroquinoline	Benzaldehyde	2-Methyl-4-styrylquinoline	69
1-Chloroisoquinoline	Benzaldehyde	1-Styrylisoquinoline	68
2-Chloroquinoxaline	Propionaldehyde	2-(1-Butenyl)quinoxaline	42
	Benzaldehyde	2-Styrylquinoxaline	53
2-Chlorobenzoxazole	Benzaldehyde	2-Styrylbenzoxazole	72

[a] Based on nmr coupling constants, only trans 1,2-disubstituted ethylenes were formed. [b] Satisfactory microanalytical data were obtained for all new compounds. [c] 2-Chloropyridine was virtually unreactive.

evaporation under reduced pressure and the residue worked up by method b above.

This new alkylation and alkenylation reaction is applicable to a broad range of heterocyclic systems, including pyridine itself. It should prove to be particularly useful in the synthesis of isoquinoline alkaloids, as indicated by the direct synthesis of papaverine in 74% yield directly from 1-chloro-6,7-dimethoxyisoquinoline and the Wittig reagent prepared from veratryl chloride and tri(*n*-butyl)phosphine; this result is to be contrasted with a reported optimum yield of papaverine of 17% by the Reissert procedure.[19] We have converted 6-chloropurine to 6-methylpurine in a single step in 73% yield; higher alkyl and alkenyl purine derivatives related to kinetin should be readily accessible by extensions of this route, and such investigations are in progress. Specific application of the alkenylation procedure to the total synthesis of quinine will be reported independently.

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(20) NIH Predoctoral Fellow, 1969–1972.

Edward C. Taylor,* Stephen F. Martin[20]
Department of Chemistry, Princeton University
Princeton, New Jersey 08540
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