

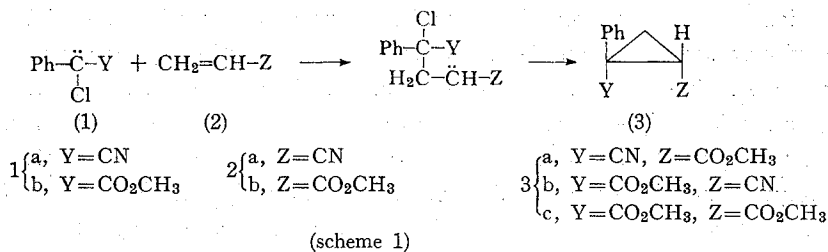
Cyclopropanation via the Michael Addition

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It was proved by means of product analysis and deuterium-labelling that the base-catalyzed reaction of phosphoenolpyruvate with active methylene compounds proceeded via nucleophilic addition, 1,3-proton shift and intramolecular displacement in the intermediate Michael adduct carbanion, ultimately to give cyclopropane derivatives.

A number of methods have been developed for preparing cyclopropanes, and advantage has been claimed for respective scheme of synthesis. Of these, two schemes via the Michael addition are of particular interest from the view-point of asymmetric synthesis and also of solvent polarity-dependence of stereochemistry. Both processes are initiated by the nucleophilic addition of carbanions to acrylates, followed by the 1,3-eliminative cyclization. One is the base-catalyzed condensation of α -haloester with α,β -unsaturated ester, the mechanism of which has been elaborated by McCoy.¹⁾ The striking solvent polarity-dependence of steric course in asymmetric synthesis of this type has been worked out by Inouye and his collaborators.²⁾

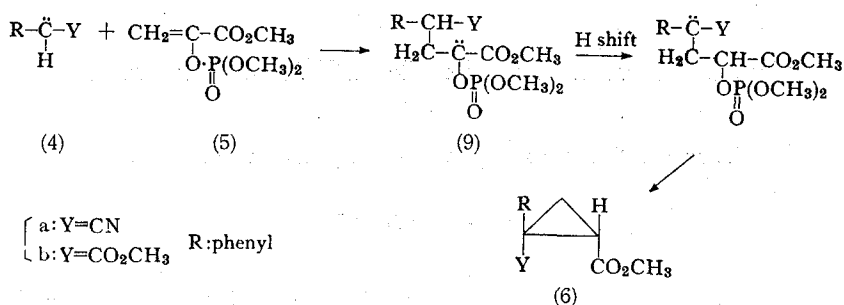


Another cyclopropanation has been achieved by Schmidt^{3a, b)} in the consecutive Michael addition of active methylene compounds to acrylates carrying an electronegative leaving group in α -position, and cyclization by 1,3-elimination. For this type of reaction, Schmidt^{3b)} suggested a mechanism involving the initial nucleophilic attack of carbanion to the polarized double bond of the Michael acceptor, followed by the probable 1,3-shift of proton in the intermediate adduct carbanion and then by the intramolecular nucleophilic displacement to form cyclopropane products.

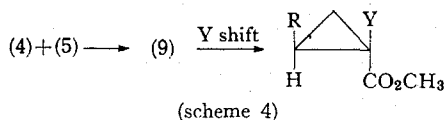
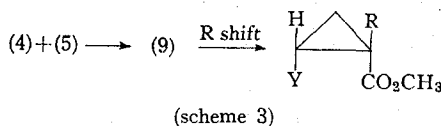
To date, however, no rigorous experimental evidence has been presented for this speculation. Alternative pathways could equally account for the cyclopropane formation in this system; say, cyclopropanation might possibly be attained also by 1,3-migration of either R or Y group, instead of proton, at the intermediary carbanion stage.

We wish, at this time, to describe the establishment of mechanism of this reaction

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(scheme 2)



(scheme 2) by means of product distribution analysis and deuterium labelling.

The NaH-catalyzed reaction of phenylacetonitrile (4a) with methyl dimethylphosphoenolpyruvate^{3b,4} (5) in DMF yielded a reaction mixture, which indicated 2 peaks on vpc of cyclopropane derivatives in addition to those attributable to unreacted starting materials. Preparative vpc of the reaction mixture gave methyl *cis*-, (6a) and *trans*-2-phenyl-2-cyanocyclopropane-1-carboxylates (6a). The structure and geometry of these isomers were fully substantiated by comparison of IR- and PMR-spectra with those of the authentic samples obtained by the reaction of phenylchloroacetonitrile (1a) with methyl acrylate (2b). The structure and geometry were further confirmed by acid hydrolysis into the corresponding cyclopropane-dicarboxylic acids (3c) of the well-defined structure and geometry. It was proved that during the hydrolysis, no isomerization took place at all under the conditions employed here.

For comparison, isomeric methyl 1-phenyl-2-cyanocyclopropane-1-carboxylates (7a), which might be expected from 1,3-migration of phenyl group in the intermediate (9a), were prepared by an analogous reaction (scheme 1) of methyl phenylchloroacetate (1b) with acrylonitrile (2a). Spectral comparison as well as their physical properties unequivocally revealed that the isomers obtained from scheme 2 were quite different in both structure and geometry from those in scheme 1, although acid hydrolysis of cyano-compounds ultimately led to the same dicarboxylic acids respectively. The operation of phenyl 1,3-migration at the intermediary stage can, therefore, be safely excluded. The fact that any peaks of cyclopropane products other than *cis*-6a and *trans*-6a were not detected at all in vpc of the reaction product from scheme 2, and exclusion of phenyl migration as well, discouraged us to test any further the possibility of 1,3-migration of cyano-group. In all probabilities, it seems very unlikely that the 1,3-cyano group migration is operative in the present system.

By exclusion, the probability of 1,3-proton shift was greatly enhanced and additional

convincing evidence was provided by deuterium labelling experiment. Although Schmidt^{3b)} simply postulated an intramolecular 1,3-proton shift, an intermolecular process which involves a protonation in α -position of the intermediate carbanion, proton being supplied by active methylene compounds or solvent medium, and subsequent removal of γ -proton, could successfully account for the cyclopropane formation as well. Actually this might be feasible under the reaction conditions employed by Schmidt (NaH, DMSO, 45°C).

In order to avoid the intervention of intermolecular protonation process at all, the reaction must be conducted in aprotic solvent under conditions as mild as possible. The NaH-catalyzed reaction of deuterated active methylene compounds, methyl phenylacetate- α - d_2 ⁵⁾ (95% deuteration)* and phenylacetonitrile- α - d_2 (95% deuteration), with equimolar phosphoenolpyruvate (5) was conducted at 40°C in DMF which is believed to be aprotic under the conditions. Addition of equimolar NaH was made all at once so as to ensure an irreversible conversion of active methylene compounds into the corresponding carbanions. After 2.5 hr's stirring, the reaction was quenched with water and neutralized with hydrochloric acid. Under these circumstances, the concentration of active methylene compounds as such is kept low enough from the initial stage, so that an intermolecular protonation process in which active methylene compounds as well as solvent medium may participate can be safely circumvented.

In Table I are summarized the results of deuterated cyclopropane formation according to this scheme. The ring proton signals of both *trans*-1-phenylcyclopropane-1,2-dicarboxylate¹⁾ (3c) and *trans*-2-phenyl-2-cyanocyclopropane-1-carboxylate¹⁾ (3a) showed an ABX-type splitting of the same pattern over nearly the same range of magnetic field (Fig. 1). Since Schmidt^{3b)} has found that the methine signal appears in the lowest field with diethyl *trans*-1-phenyl-cyclopropane-1,2-dicarboxylate, the quartet at δ 2.63

Table I. Deuteration in Cyclopropane-Products

Substrate	% deuteration of substrate	% reaction yield	% deuteration in products	
			methine	other positions
PhCD ₂ COOCH ₃	95	30	<i>cis</i> 85	0
			<i>trans</i> 90	
PhCD ₂ CN	95	30	<i>cis</i> 90	0
			<i>trans</i> 75	

* Methyl phenylacetate- α - d_2 was prepared by refluxing phenylacetic acid in DCl-D₂O solution, followed by addition of methanol and then diazomethane. Phenylacetonitrile- α - d_2 was obtained by stirring phenylacetonitrile in deuterium oxide in the presence of potassium *t*-butoxide at ambient temperature. The position and extent of deuteration in these compounds were determined by PMR-means. As these molecules contain no proton to be referred to as criterion, it is impossible by themselves to determine whether or not any deuteration takes place on benzene nuclei. The conditions of preparation for phenylacetonitrile- α - d_2 reasonably rules out the possibility of deuteration on benzene nucleus, but methyl phenylacetate- α - d_2 falls under this suspicion. PMR-analysis of the latter acid, which resulted from proton-exchange of carboxylic deuterium of the deuteration product, in comparison with methyl ester thereof, revealed that no deuterium is present in both carboxylic acid and ester-methyl groups, and integration showed the complete agreement with the expected values for 5 phenyl protons as referred to 1 carboxylic proton or 3 ester-methyl protons. In this way, it was concluded that deuteration of active methylene compounds (4a and 4b) used here was located solely in α -position and the extent was 95% respectively as determined by integration.

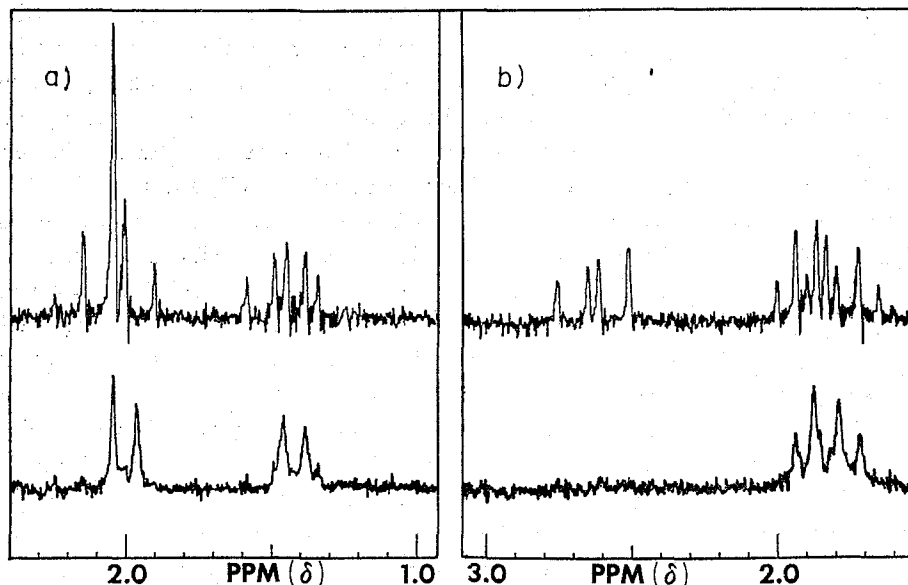


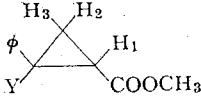
Fig. 1. The ring proton PMR spectrum (to TMS in CCl_4) of dimethyl 1-phenylcyclopropane-1,2-dicarboxylate (3c) and dimethyl 1-phenyl-2-deuteriocyclopropane-1,2-dicarboxylate (6b).
a) *cis*-form b) *trans*-form

(CCl_4) for 3c and the quartet at $\delta 2.69$ for 3a can be assigned to methine proton in both cyclopropanes. This methine signal at $\delta 2.6$ disappeared in PMR of both *trans*-deuteriocyclopropanes derived from deuterated active methylene compounds (4a, 4b) according to the present scheme, suggests that the deuterium atom in *trans*-cyclopropanes obtained by the present system holds the 1-methine position on the ring as was expected and that the methylene is not deuterated. In *cis*-series, the ring proton signals of the same pattern were observed in both compounds (Fig. 1), but the complicated multiplet near $\delta 2.2$, probably due to overlap of both methine and methylene protons, made impossible the clear-cut isolation of methine proton signal, contrary to the *trans*-counterparts. In the corresponding *cis*-deuteriocyanocyclopropanes derived from deuterated starting materials, however, the multiplet at $\delta 2.2$ disappeared, instead a doublet at $\delta 2.1$ was observed. The proton signals of *cis*-6a,b were completely identical with those of the authentic *cis*-1-deuteriocyclopropane (3c) which was obtained via the synthetic scheme of the well-established steric course^{1b,d)} from acrylate-*a-d*.* These

* Methyl acrylate-*a-d* was obtained by the reaction sequence starting from β -bromo-, or β -chloropropionic acid, involving deuteration in refluxing $\text{DCl-D}_2\text{O}$, esterification with diazomethane and dehydrohalogenation in hot quinoline. The deuterium substitution in *a*-position of the acrylate was rationalized by the synthetic scheme, since the complete deuteration in *a*-position of the parent β -halopropionic acids had been confirmed by PMR comparison with the corresponding protium compound. The acrylate-*a-d* was subjected to the NaH -catalyzed condensation^{1,2)} with methyl phenylchloroacetate in DMF at room temperature, which afforded isomeric cyclopropanes carrying a methine deuterium. This scheme of synthesis obviously provides convincing evidence for the methine deuterium in the cyclopropane products. Since the *trans*-isomer was proved to have no deuterium in the ring methylene position, it is deduced to be also the case with the *cis*-isomer from the same batch. Consequently, these isomeric cyclopropanes via scheme 1 can serve as reference for location and estimation of deuterium in the cyclopropanes from scheme 2.

Cyclopropanation

Table II. PMR-Data of Cyclopropane Derivatives via Schemes 1 and 2

							
Y	H ₁		chemical shift (δ) ^{a)}				
			H ₁	H ₂₍₃₎	H ₃₍₂₎	COOCH ₃ ^{d)}	Y=COOCH ₃ ^{d)}
CN ^{c)}	D	<i>cis</i> ^{b)}	—	1.78	2.21	3.82	—
		<i>trans</i>	—	1.91	2.20	3.51	—
	H	<i>cis</i>	2.2	—	1.7	3.83	—
		<i>trans</i>	2.69	2.1	—	3.50	—
COOCH ₃	D	<i>cis</i>	—	1.42	2.01	3.68	3.58
		<i>trans</i>	—	1.75	1.92	3.37	3.58
	H	<i>cis</i>	2.1	—	1.4	3.68	3.59
		<i>trans</i>	2.63	1.8	—	3.36	3.57

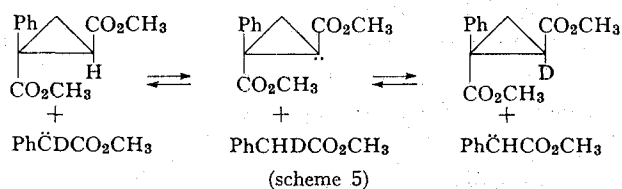
a) in ppm to TMS in CCl₄.b) *cis-trans* refers to the relationship between the groups Y and COOCH₃.c) Band 2240 cm⁻¹ (CN group) was observed for all cyclopropanes.

d) Assignment was made with reference to 1-phenyl-1-methoxycarbonyl-2-deuterio-2-methoxycarbonylcyclopropane obtained via scheme 1.

findings combined together cogently support the location of the deuterium atom at ring 1-position in the *cis*-isomers too. Not to mention, complete agreement in PMR was obtained also between the *trans*-isomers (6a,b) and the authentic specimens.^{1b,d)} Extent of deuteration in the ring methine position for isomeric forms was estimated by integration as shown in the Table I.

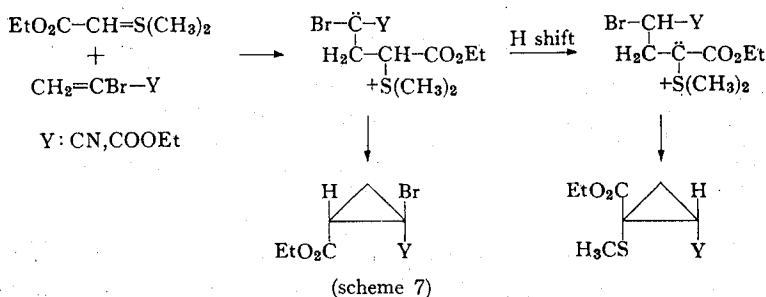
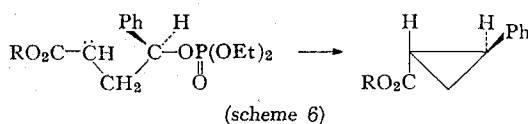
It, therefore, was evidenced that 1,3-deuteron shift did operate in the intermediate for the present cyclopropanation. Not to mention, the possibility of phenyl migration by which formation of the same product as that via 1,3-proton shift might be accounted for in case of 1-phenylcyclopropane-1,2-dicarboxylate (6a), can safely be rejected based on the evidence presented above (*vide supra*).

Should any other unknown mechanism have operated in the present process to yield non-deuterated cyclopropane products, the ultimate formation of deuterio-cyclopropanes might as well be explained by invoking a base-catalyzed exchange between acidic ring proton and acidic deuterium in the reagent as illustrated below (scheme 5). In view of the nearly complete retention of isotopic purity from reagents to cyclopropane products, however, it can hardly be expected that such a pathway plays a prime role in the present



process. A slight discrepancy found in % deuteration between the reagents and the resultant products may be ascribed to computational error inherent to PMR integration technique and/or to a partial deuterium-protium exchange during the workup in water.

Mention must be made here also to a conceivable mechanism involving the generation of carbene and insertion to C-D bond in adduct carbanion, which could equally lead to the cyclopropanes in question. In relevant 1,3-eliminative cyclopropanations, however, the intramolecular nucleophilic displacement was preferred by the authors^{6,7)} to carbene mechanism in spite of their far more favored molecular environments for carbene formation. *A priori* consideration of energetics also cogently supports the intramolecular displacement in accord with the principle of least motion,⁸⁾ than the carbene mechanism. It, then, follows that operation of carbene insertion is also unlikely.



In conclusion, it is deduced that the present cyclopropanation proceeds by 1,3-proton shift in the Michael adduct carbanion, followed by intramolecular nucleophilic displacement to give cyclopropanes.

EXPERIMENTAL

Melting and boiling points were uncorrected. PMR spectra were taken on a Varian Model A-60 spectrometer and IR on a Hitachi EPI spectrophotometer.

Phenylacetonitrile- α - d_2 (4a): Phenylacetonitrile (1 g) was stirred in deuterium oxide (10 ml) containing potassium *t*-butoxide (150 mg) at room temperature for 48 hr, and then extracted with ether. Phenylacetonitrile- α - d_2 boiling at 118°C/20 mmHg, n_D^{20} 1.5028; 800 mg, was recovered. The isotopic purity was 95% in α -position as determined by PMR: δ (CCl₄) 7.31 (5H, s; phenyl); IR, 2250 (CN).

Methyl phenylacetate- α - d_2 (4b): Phenylacetic acid (1 g) was dissolved in deuteriochloric acid (20 ml) and the solution was refluxed for 24 hr. After the period, the acid was taken up in ether and dried over anhydrous sodium sulfate. Ether was evaporated and the residue was dissolved in methanol and again the solvent was removed to give crystalline product. Phenylacetic- α - d_2 acid mp 94°C, yield 900 mg; isotopic purity 95%. The standard method with diazomethane gave methyl phenylacetate- α - d_2 , bp 105°C/20

mmHg, n_D^{20} 1.5045, yield 900 mg. PMR signals of both ester-methyl and methylene protons of this ester appeared in the same region δ 3.6–3.7 (CCl_4), which made it impossible to evaluate each separately. The integrated number of these protons was 3.1 relative to 5 phenyl protons. PMR: δ (CCl_4) 7.28 (5H, s; phenyl), 3.67 (3H, s; COOCH_3). Monodeuteriomethyl acrylate- α - d : β -Bromopropionic acid (3 g) was dissolved in deuteriochloric acid (20 ml) and refluxed for 48 hr. After the period, the acid was taken up in ether and was esterified with diazomethane to give a fraction boiling at 60–80°C/30 mmHg, 700 mg. This fraction consisted of methyl β -bromo-, and β -chloropropionates as analyzed by vpc. The mixed ester (700 mg) was dissolved in quinoline (700 mg) and the mixture was heated in nitrogen atmosphere. Repeated distillations of the reaction mixture gave methyl acrylate- α - d , bp 74–6°C, yield 200 mg (45%). The isotopic purity of the acrylate was unable to estimate by itself since this molecule had no proton to be referred. However, the parent β -halo-esters were deuterated in their α -position as high as 90% or so, as estimated with reference to β -bromo-, and β -chloropropionic acids, so that the isotopic purity of the same order may well be inferred to the acrylate derived therefrom. 30% Deuteration in ester-methyl group of the acrylate was deduced from PMR analysis of the ultimate cyclopropane products obtained via scheme 1.

Methyl dimethylphosphoenolpyruvate (5): The literature method³⁾ was followed for preparation. bp 110–113°C/0.7 mmHg, n_D^{26} 1.4315; yield 65% PMR; δ (CCl_4) 5.59 (1 H, t; vinyl) 5.88 (1 H, t; vinyl). IR 1640 cm^{-1} (terminal ethylene).

Cyclopropanation according to scheme 2 was carried out under the same conditions specified by Schmidt^{3b)} with a slight but important modification. The reactants in equimolar amount (0.5 mole) were allowed to react in DMF at 40°C for 2.5 hr, being catalyzed by NaH (0.5 mole) in a lot. Usual work-up gave the cyclopropane derivatives. (For PMR data, see Table II).

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