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A SPECIFIC INSERTION OF CARBENES INTO CARBON-CARBON BONDS

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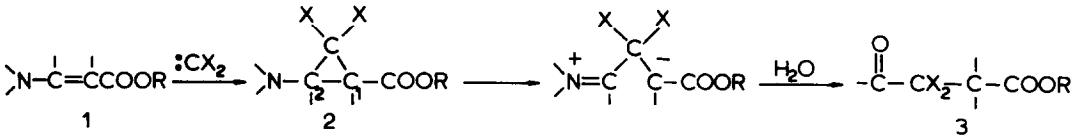
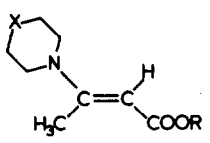
A 2-aminocyclopropane ester (2) may be expected, under hydrolytic conditions, to undergo ring-opening at the C_1-C_2 bond to yield a γ-keto ester 3[2a,b] (Scheme I).

Scheme I



Since such cyclopropane esters are accessible by addition of carbenes to enamine esters (1) - themselves readily available from the corresponding β-keto esters - the overall sequence would represent an operation whereby a β-keto ester is converted into a γ-keto ester in which the β-carbon is derived from the carbene employed. This communication presents results which demonstrate that the aforementioned reaction scheme constitutes a principally versatile procedure for the specific insertion of carbenes into C-C bonds.

The enamine esters 4a-d, 5a,b and 6a,b were prepared by the reaction of the corresponding β-keto esters with the appropriate secondary amines. Methylene ($:CH_2$) was generated according to the procedure of Sawada and Inouje[3] and dichlorocarbene was prepared by thermal decomposition of sodium trichloroacetate in DME. In a typical experiment involving $:CH_2$, the solution (ether/THF) of the carbene precursor was added dropwise to the enamine ester dissolved in ether. The mixture was refluxed for 2h and the reaction product(s) subjected to hydrolysis by addition of NH_4Cl solution (sat.) and refluxing for a further period of 3h. The γ-keto ester was isolated by either fractional distillation or column chromatography. Reactions



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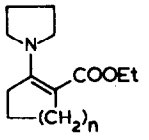
a. X = — , R = Me
b. X = CH_2, R = Me
c. X = O , R = Me
d. X = O , R = Et



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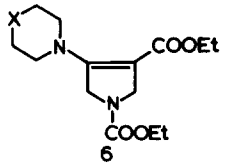
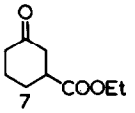
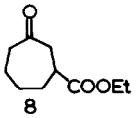
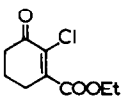
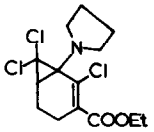
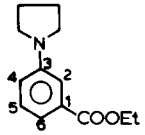
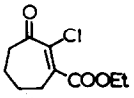
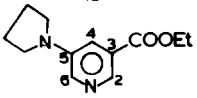
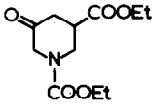
a. n = 1
b. n = 2



6

a. X = —
b. X = O

Table I

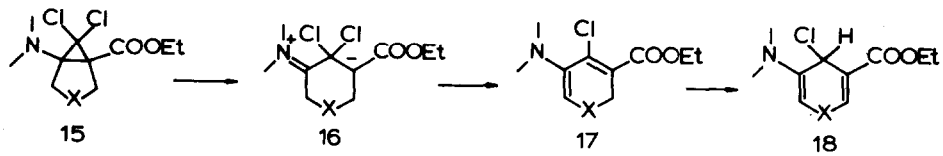
Enamine Ester	Carbene	Product(s)	Yield %
4a.	:CH_2	$CH_3COCH_2CH_2COOCH_3$	20
4b.	:CH_2	$CH_3COCH_2CH_2COOCH_3$	37
4c.	:CH_2	$CH_3COCH_2CH_2COOCH_3$	35
5a.	:CH_2	 7	10
5b.	:CH_2	 8	17
4d.	:CCl_2	$CH_3CO-C(Cl)=C(H)COOEt$ 9 (Cl),(H) cis : trans = 3 : 1	19
5a.	:CCl_2	 10(8%)  11(8%)  12 (32%)	
5b	:CCl_2	 13	11
6a	:CCl_2	 14	21
6b.	:CH_2	 15	10

with $:CCl_2$ were carried out by slowly adding the enamine esters (in DME) to a solution of $Cl_3CCOONa$ in DME at 50°, followed by refluxing the mixture. The precipated NaCl was filtered off and the reaction product(s), after hydrolysis, separated by chromatography. The isomeric mixture obtained by the reaction of $:CCl_2$ with 4d was separated by GLC. The results are presented in Table I. Structures of the products followed from their spectroanalytical data.

The formation of methyl levulinate, from 4a-c, as well as that of the cyclic γ-keto esters 7, 8 and 15 is consistent with Scheme I and requires no comment. It is also obvious that reaction of dichlorocarbene with 4d, 5a and 5b would lead to primary carbene insertion products (Scheme I) which, in each case, lose a chloride ion to yield the unsaturated esters 9, 10 and 13.

The formation of compounds 11, 12 and 14 falls outside the scope of Scheme I and consequently deserves an explanation. Evidence for the structure of 11 was derived from its IR($CHCl_3$): 1718 cm^{-1} (unsaturated ester); NMR($CDCl_3$): δ 1.28 t (3H, OCH_2 CH_3) 1.50-3.50 m (13H, ring and pyrrolidine protons), 4.22 q (2H, OCH_2CH_3); and MS($C_{14}H_{18}Cl_3NO_2$) spectra. An important process in the mass spectrometer comprised the loss of a $CHCl_2$ fragment from the molecular ion (m/e 254=100%). Product 12 was identified from the following spectral data. IR($CHCl_3$): 1712, 1612 cm^{-1}; NMR($CDCl_3$): δ 1.32 t (3H, OCH_2CH_3), 1.80-2.10 m (4H, $-CH_2-N-CH_2$), 4.31 q (2H, $-OCH_2CH_3$), 6.40-6.85 m (1H, H_2), 7.05-7.45 m (3H, $H_4+H_5+H_6$). Especially revealing for the structure of 14 (m.p. 38-42°) were the singlets in its NMR spectrum for the C_2-, C_6- and C_4-protons at δ 8.50, 8.08 and 7.35, respectively. Scheme II describes the sequence of intermediates via which products 11, 12 and 14 may be formed. Addition of $:CCl_2$ to enamine esters 5a and 6a would result in adducts 15a and 15b, respectively. Ring-opening in the expected fashion (16a,b), followed by elimination of the elements of HCl, will lead to cyclic dienes 17a,b. The 1,2-dihydrobenzene and 1,2-dihydropyridine (17ab) derivatives would be expected to possess a distinct tendency towards isomerization to the corresponding 1,4-dihydro derivatives (18a,b) by virtue of relief of the steric strain due to the presence of three bulky substituents on adjacent

Scheme II



15 16 17 18

a. X = CH_2 ; b. X = NCOOEt

carbon atoms, in the former systems. Addition of an equivalent of $:CCl_2$ to the enamine bond of 17a gives rise to the cyclic ester 11. Formation of 12 may be accounted for by the loss of HCl, under the reaction conditions, from intermediate 18a. Analogously, loss of a chloride ion from 18b would yield an acyl pyridinium salt which should readily hydrolyse to 14 during work up of the reaction mixture.

While the reported yields of the insertion products may be qualified as from low to modest, it should be noted that thus far no attempts have been made to optimalize the reaction conditions.

*Correct spectroanalytical data have been obtained for all compounds described in this communication.

1. To whom all inquiries should be addressed.

2. (a) S.A.G. de Graaf and U.K. Pandit, Tetrahedron, 29, 2141 (1973);

   (b) E. Wenkert, C.A. McPherson, El. Sanchez and R.L. Webb, Synth.Comm.,3(4), 255 (1973).

3. S. Sawada and Y. Inouje, Bull.Chem.Soc. Japan, 42, 2669 (1969). The reaction with 6b was carried out according to the procedure described by E. Wenkert et. al, J. Amer.Chem.Soc., 92, 7428 (1970).