Tetrahedron Letters No. 38, pp 3381 - 3384, 1976. Pergamon Press. Printed in Great Britain.

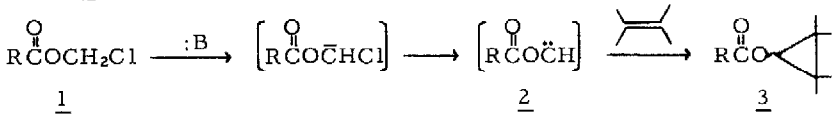
SYNTHESIS OF CYCLOPROPANOLS VIA ACYLOXYCARBENE INTERMEDIATES

R. A. Olofson,* Kenneth D. Lotts, and Gary N. Barber
Chemistry Department, The Pennsylvania State University
University Park, Pennsylvania 16802

(Received in USA 14 June 1976; received in UK for publication 9 August 1976)

Electrophilic, nucleophilic, and radical reagents cause cyclopropanols to undergo a wealth of highly selective, ring-opening rearrangements under mild conditions.[1] However, these processes have been exploited only rarely in complex syntheses because present routes to cyclopropanols lack either generality or practicality.[1] Though cyclopropyl esters are cleanly converted to cyclopropanols by treatment with $LiAlH_4$ or MeMgX,[1] these attractive precursors are themselves usually difficult to make.[2]

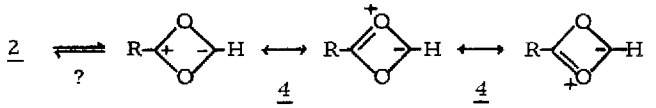
In theory, cyclopropyl esters (3) can be formed by the base-initiated α-elimination of HCl from chloromethyl esters (1) with concomitant trapping by alkenes of the intermediate acyloxycarbenoids[3] (2).

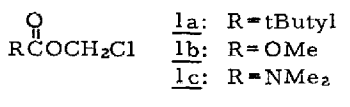


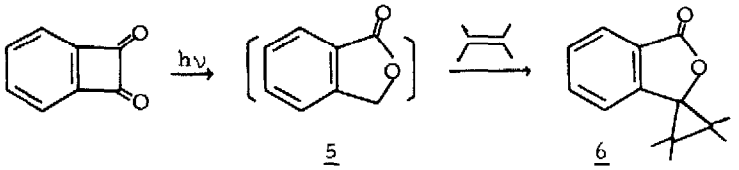
1 2 3

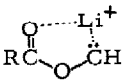
For such a route to work in practice, the base chosen must not only be strong enough to accomplish the desired proton abstraction but must also shun other reaction sites in 1 such as the highly electrophilic carbonyl or the activated chloromethyl group (to displace halide). Such side reactions might seem insurmountable. However, recent successes using the H^+arpoon base, lithium 2,2,6,6-tetramethylpiperidide (LiTMP), developed in this laboratory[4] in situations with similarly stringent selectivity requirements encouraged us to test the hypothesis, 1→[2]→3. Further motivation was provided by Beak and Farney's report that LiTMP deprotonates N,N-dimethylbenzamide to produce $PhCONMe\bar{C}H_2$.[5] Acyloxycarbenes (2) are also of interest because they might cyclize to the theoretically fascinating Hückel 6π-electron system (4), the formally neutral equivalent of a cyclobutadienyl dianion.[6] Moreover, only a

single acyloxycarbene has been reported previously -- the phenyl-stabilized cyclic species (5) formed by rearrangement on photolysis of benzocyclobutadienoquinone and trapped with alkenes as the spiro derivatives (6)[7] -- and 5 is geometrically prohibited from cyclizing to 4.







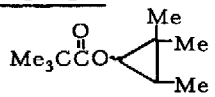
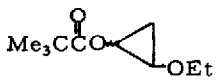
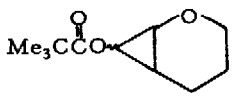
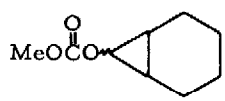
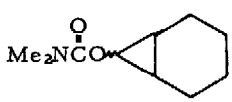
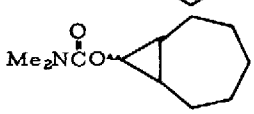
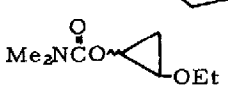
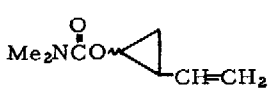


5 6 8

Three chloromethyl esters were tested in the scheme, 1→3, the commercially available pivalate[8] (1a) and the readily synthesized carbonate[9] (1b) and carbamate[10] (1c). Some representative reactions are summarized in Table I. Best yields were obtained when ca 1.1 equivalents of LiTMP[4] were added (ca 30 minutes) to a refluxing ethereal solution of the chloromethyl ester (one equiv.) containing a severalfold excess of the alkene. Work-up was accomplished by standard extraction-distillation methods after another 30 minutes; prolonged reaction times decreased yields. From the data in Table I, it is evident that the carbonate (1b) is substantially inferior to the other two reagents tested. In most experiments, leftover 1 could be recovered, an indication that alternate base-induced decompositions of starting materials and products are significant. To test the latter hypothesis, the 7-norcaryl pivalates and N,N-dimethylcarbamates were exposed to LiTMP at 25°. Product disappearance was observed with the syn isomers being destroyed several times more rapidly than the anti compounds. Thus, the syn:anti (cis:trans) ratios given in Table I probably do not accurately reflect the preferred geometry of the carbenoid addition.

No evidence was found for the presence of the 6π-electron cyclic species (4) in the reaction medium. To test for its intervention as an equilibrium component, carbonyl ^{18}O-enriched (8.6±0.8%) chloromethyl carbonate (1b) was made by hydrolysis of $(MeO)_4C$ in ^{18}O-enriched water buffered with sodium formate-formic acid[11] followed by photochemical chlorination of the initially formed dimethyl carbonate.[9] Mass spectral analysis of the 7-norcaryl methyl carbonates (7) isolated from reaction with LiTMP in ether-cyclohexene showed 6.2±0.8% carbonyl ^{18}O-enrichment with no excess label in the norcaryl oxygen (-0.7±2.2%). Analysis of the anti-7-norcaranol (0.6±0.4% excess ^{18}O) isolated after reduction of a small sample of 7 with $LiAlH_4$ confirmed the absence of scrambling. The noninvolvement of 4 in these reactions may be a consequence of the geometrical constraints imposed by special bonding interactions in the intermediate carbenoid such as those depicted in 8. To test this rationalization, the successful generation of a free acyclic acyloxycarbene would be most desirable.

Table I. Reaction of Chloromethyl Esters with LiTMP and Alkenes.

Alkene	Product	Yield[a]	Syn:anti (cis:trans)[b]	Bp (°C) at (torr)
Reaction with $Me_3CCO_2CH_2Cl$:				
2-Methyl-2-butene		35%	1.3:1	49-54° (3)
CH_2=CHOEt		30%	1:2.0	56-57.5° (1.5)
Dihydropyran		39%	1.0:1	87-89°(2)
Reaction with $MeOCO_2CH_2Cl$:				
Cyclohexene		10%	1:1.3	80-81° (2.5)
Reaction with $Me_2NCO_2CH_2Cl$:				
Cyclohexene		25% (30%)	1:1.2	92.5-93° (1.5)
Cycloheptene		20% (24%)	1.2:1	83-84° (0.3)
CH_2=CHOEt		30% (33%)	1:3.0	106-108°(20)
Butadiene		21%	3.2:1	83-84° (4)

[a] Yields given are for pure products after isolation by distillation. Values in parentheses are corrected for starting chloromethyl ester recovered during work-up. All compounds are new and were prepared as described in text. Satisfactory combustion analyses were obtained for all isomer pairs. High and low resolution mass spectra and IR and NMR data are also in accord with the assigned structures.

[b] Ratios were determined by gas chromatographic separation and independent NMR analysis. Syn and anti isomer assignments were based on the discovery by L. M. Jackman and S. Sternhell (Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd Edition, Pergamon Press, London, 1969) that the cis vicinal NMR coupling constants of the cyclopropyl protons in any isomer pair are always larger than the corresponding trans J values. Some structures were confirmed by cleavage to known cyclopropanols or by independent synthesis.

To confirm the known conversion of cyclopropyl esters to cyclopropanols[1,2] (vide supra), selected cyclopropyl pivalates and carbamates from Table I were cleaved in high yield to the corresponding cyclopropanols by treatment with $LiAlH_4$ or MeLi. Thus, the present scheme can be recommended as a rapid and convenient synthesis of small samples of many cyclopropanols. Attempts to make this route more attractive in larger scale preparations by increasing yields are underway.

Acknowledgements. We are grateful to the U. S. Public Health Service (GM 13980) and McNeil Laboratories, Inc. for grants in support of this research.

References

1) D. H. Gibson and C. H. DePuy, Chem. Revs., 74, 605 (1974); C. H. DePuy, Fortschr. Chem. Forsch., 40, 74 (1973). Similar cyclopropyl ester and ether ring cleavages are also known.

2) The best general synthesis of cyclopropyl esters consists of four steps beginning with the reaction of ethyl diazoacetate with an alkene: C. H. DePuy, Accts. Chem. Res., 1, 33 (1968) and ref. 1.

3) The terms "carbene" and "carbenoid" are used almost interchangeably here. Though no definitive experiments have been performed, the chemistry described best fits the intermediacy of a carbenoid species.

4) R. A. Olofson and C. M. Dougherty, J. Amer. Chem. Soc., 95, 581, 582 (1973).

5) P. Beak and R. Farney, J. Amer. Chem. Soc., 95, 4771 (1973). However, a different fate is reported for alkyl benzoates on treatment with LiTMP: C. J. Upton and P. Beak, J. Org. Chem., 40, 1094 (1975).

6) J. S. McKennis, L. Brener, J. R. Schweiger, and R. Pettit, Chem. Commun., 365 (1972); E. E. Nunn and R. N. Warrener, ibid., 818 (1972); W. Adam, Tetrahedron Lett., 1387 (1963); R. D. Rieke and P. M. Hudnall, J. Amer. Chem. Soc., 95, 2646 (1973).

7) H. A. Staab and J. Ipaktschi, Chem. Ber., 101, 1457 (1968).

8) Made by the $ZnCl_2$ catalyzed reaction of pivaloyl chloride with formaldehyde; used as an amine masking reagent: M. Rasmussen and N. J. Leonard, J. Amer. Chem. Soc., 89, 5439 (1967). These chloromethyl esters were chosen to avoid problems with competitive enolate formation.

9) Made by photochemical chlorination of dimethyl carbonate: V. Grignard, G. Rivat, and E. Urbain, C. R. Acad. Sci., Paris, 169, 1143 (1919).

10) New, bp 51-52° at 2 torr; satisfactory microanalysis and spectral data. Made by reaction of Me_2NH with the known chloromethyl chloroformate.

11) This labelling result is in accord with the known mechanism of ortho ester hydrolysis: A. M. Wenthe and E. H. Cordes, J. Amer. Chem. Soc., 87, 3173 (1965).