Effects of Substituents on the Nucleophilic Ring Opening of Activated Cyclopropanes

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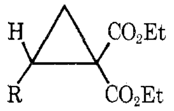
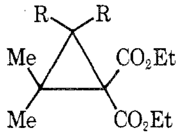
The propensity of suitably activated cyclopropanes to suffer ring opening upon reaction with nucleophiles has been recognized since the studies of Bone and Perkin.[1a-d] *Ordinarily, this type of reaction requires two geminal activating groups.*[2-4]

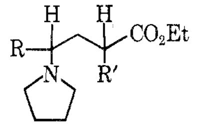
To our knowledge, there has been no systematic study of the effect of alkyl substitution on the direction or rate of opening of activated cyclopropanes. Such information could be of importance in extending this reaction to more complex synthetic objectives. Accordingly, we have prepared compounds **1**, **2**, and **3** and investigated their reactions with pyrrolidine.



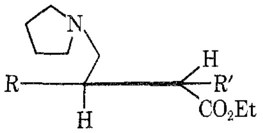
1, R = Et
4, R = $CH_2 = CH$



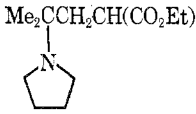
2, R = H
3, R = Me



6, R = Et; R′ = H
8, R = Et; R′ = CO_2Et
9, R = $CH_2 = CH$; R′ = CO_2Et



5, R = Et; R′ = H
7, R = Et; R′ = CO_2Et
10, R = $CH_2 = CH$; R′ = CO_2Et



$Me_2CCH_2CH(CO_2Et)_2$

11

Compound **1** was prepared by catalytic reduction (H_2, Pd/C) of diethyl 2-vinylcyclopropane-1,1-dicarboxylate (**4**).[5] Competing hydrogenolysis was not a problem with ethyl acetate as the solvent.[5,6] Compounds **2** and **3** were prepared by photochemically induced reactions of diethyl diazomalonate with isobutylene and tetramethylethylene, respectively, according to the procedure of Jones.[7]

Reaction of **1** with pyrrolidine at 110° for 50 hr gave a 40% yield of a mixture of four basic products. Starting **1** was recovered to the extent of 46%. The acid-soluble products, obtained in a ratio of 1:1.5:10:14.7 (analytical glc), were identified as **5**, **6**, **7**, and **8**, respectively. It seems reasonable that the decarbethoxylation reaction leading to **5** and **6** occurs after ring opening.[2]

Authentic **8** was prepared by catalytic hydrogenation of the known **9**,[8,9] obtained from the reaction of pyrrolidine with **4**. Hydrolysis, decarboxylation and reesterification converted **8** into authentic **6**. Compound **7** was obtained in pure form by regeneration from its picrate derivative, mp 113–113.5°, which was prepared by fractional crystallization from the mixture of amine picrates.

Since the mixture of **5**, **6**, **7**, and **8** was not amenable to preparative separation, the total basic fraction was subjected to hydrolysis–decarboxylation–reesterification. The resulting two-component mixture of **5** and **6** was separable by column chromatography on Florisil. Final purification of **5** was effected by preparative glc.

For the case of pyrrolidine as the nucleophile, there is a striking difference in the responses of the two cyclopropanes **1** and **4**. Thus, the vinyl compound, **4**, reacts with pyrrolidine to give exclusive substitution at the secondary carbon. No products corresponding to **10** were observed by two groups of workers.[8,9] Compound **1**, under the same circumstances, gives a 3:2 ratio of secondary (**6** + **8**); primary (**5** + **7**) modes of attack. These results can be construed as reflecting substantial dipolar character[10] in the ring opening of such activated cyclopropanes. Vinyl substitution would be expected to exert a considerably stronger directing influence due to allylic delocalization of the incipient positive charge. The finding that the rate of ring opening with pyrrolidine is very much faster[11] for **4** than for **1** is in accord with such a formulation.

Reaction of **2** with pyrrolidine occurred quite slowly. After 40 hr at 120°, a 13% yield of adduct **11** was obtained. Starting **3** was recovered to the extent of 60%. The preferential attack at the tertiary center is again consistent with carbonium ion character[10] in the transition state for ring opening. However, the overall reaction at both the primary and tertiary centers is substantially retarded relative to **1**, presumably for reasons involving steric hindrance to attack. *Another factory could be the general stabilization of* ring structures with increasing substitution (Thorpe–Ingold effect).[12]

Either or both of these factors may be involved in the nonreaction of **3** with *pyrrolidine. After the two components were heated at* 120° for 42 hr, the recovery of **3** was 76%. No basic products were detected.

Further studies into nucleophilic opening of activated cyclopropanes are in progress.

Experimental Section[13]

Diethyl 2-Ethylcyclopropane-1,1-dicarboxylate (1). This compound was prepared in quantitative yield by catalytic (10% Pd/C) hydrogenation of **4**[8,9] in ethyl acetate. Compound **1** was obtained as a free-flowing oil: bp 58–60° (0.025 mm); λ (CCl_4) 5.79, 8.30, 8.85, 9.62, 9.82 μ; τ (CCl_4) 5.86 (2 H, q, $J = 7$ Hz), 5.88 (2 H, q, $J = 7$ Hz), 7.8–9.3 (14 H, m, containing t at 8.75, $J = 7$ Hz); *m/e* 214 (parent), 122 (base peak).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.40. Found: C, 61.94; H, 8.60.

Reaction of 1 with Pyrrolidine. Formation of 5, 6, 7, and 8. A solution of compound **1** (2.0 g, 9.33 mmol) and pyrrolidine (1.34 g, 18.9 mmol) was heated in a Fisher borosilicate pressure bottle at 110° for 50 hr. The product was diluted with ether and extracted with 5% aqueous HCl. Evaporation of the organic fraction gave 0.92 g of essentially pure **1**.

The acidic aqueous fraction was neutralized (cautious addition of solid sodium carbonate) and extracted with ether. Evaporation gave a residue of 0.92 g of basic material. Analytical glc (5 ft, 3% SE-30 column at 160°) indicated the presence of **5**, **6**, **7**, and **8** in a ratio of 1:1.5:10:14.7 using authentic samples as described below.

The total amine mixture was dissolved in 95% ethanol and treated with a saturated solution of picric acid. After heating and slow cooling, platelets were collected which were purified by recrystallization from absolute ethanol. Regeneration of amine **7** from this picrate (see below) indicated the crystals to be the ammonium picrate corresponding to **7**.

Anal. (for picrate) Calcd for $C_{21}H_{30}N_4O_{11}$: C, 49.02; H, 5.88; N, 10.89. Found: C, 48.76; 5.81; N, 10.80.

A suspension of this picrate in ether was shaken with dilute aqueous sodium acetate. The ether solution was dried and concentrated *in vacuo* to afford a residue of pure **7**: λ (CCl_4) 3.56, 5.71 (sh), 5.77 μ; τ (CCl_4) 5.87 (2 H, q, $J = 7$ Hz), 5.89 (2 H, q, $J = 7$ Hz), 6.58 (1 H, d, $J = 7$ Hz), 7.2–9.2 (14 H, m, containing t at 8.75, $J = 7$ Hz); *m/e* 285 (parent), 112 (base peak).

Purification 5 and 6. To 5 ml of 10% aqueous HCl was added 1.55 g of the crude amine mixture described above. The solution was heated under reflux for 3 hr and maintained at room temperature overnight. The solution was neutralized with aqueous KOH and the water removed *in vacuo*. The residue was thoroughly triturated with methylene chloride. Evaporation of the methylene chloride left a residue of 1.34 g. This was heated at 170° until cessation of gas evolution (~30 min). The crude mixture of amino monoacids (1.0 g) was dissolved in 10 ml of absolute ethanol, saturated with HCl, and heated under reflux overnight. Neutralization with aqueous KOH followed by extraction with ether gave 0.70 g (62%) of amino ester mixture **5** and **6**.

Chromatography of 250 mg of this mixture on 10 g of Florisil gave 27 mg of essentially pure **5** (eluted with 1:1 ether–hexane): λ (CCl_4) 3.58, 5.78, 8.50, 9.66 μ; τ (CCl_4) 5.97 (2 H, q, J = 7 Hz), 7.3–9.4 (21 H, m, containing t at 8.77, J = 7 Hz); *m/e* 213 (parent), 84 (base peak).

Further elution with ether provided 63 mg of pure **6**, whose infrared, nmr, and mass spectra were identical with those of the same compound when obtained from pure 8 (see below).

Preparation of Pure Amino Diester 8 by Hydrogenation of 9. A solution of 1.003 g (3.53 mmol) of **9**[8,9] in ethanol was hydrogenated at atmospheric pressure with an uptake of 88 ml of gas (theoretical, 82 ml) in 1 hr. Filtration and removal of the solvent at reduced pressure gave 0.992 g of 8 distilling at 80° (0.005 mm): λ (CCl_4) 3.55, 5.71, 5.76 μ; τ (CCl_4) 5.87 (4 H, q, J = 7 Hz), 6.57 (1 H, t, J = 7 Hz), 7.2–9.3 (22 H, m, containing t at 8.77, J = 7 Hz); *m/e* 285 (parent), 112 (base peak).

Anal. (of picrate, mp 63–64°) Calcd for $C_{21}H_{30}N_4O_{11}$: C, 49.02; H, 5.88; N, 10.89. Found: C, 49.10; H, 6.03; N, 10.75.

Conversion of 8 to 6. A solution of 460 mg (1.62 mmol) of 8 in 2 ml of 20% aqueous HCl was heated under reflux for 20 hr. The residue remaining after removal of the water *in vacuo* was heated at 170° until cessation of gas evolution. This residue of crude amino monoacid was dissolved in absolute ethanol. The solution was saturated with anhydrous HCl and heated under reflux overnight. The ethanol solution was neutralized with 20% aqueous KOH. Extraction with methylene chloride followed by evaporation afforded a residue of 161 mg of crude amino ester. Distillation *in vacuo* at 100–110° (0.005 mm) gave 80 mg (24%) of **6:** λ (CCl_4) 3.59, 5.79, 8.51 μ; τ (CCl_4) 5.95 (2 H, q, J = 7 Hz), 7.3–9.3 (21 H, m, containing q at 8.84, J = 7 Hz); *m/e* 213 (parent), 112 (base peak).

Preparation of Diethyl 2,2-Dimethycyclopropane-1,1-dicarboxylate (2). To a 150-ml quartz immersion type photolysis cell, equipped with a Vycor filter and a Dry Ice condenser, was added 125 ml of isobutylene (bp −6°) and 3.6 g (0.0193 mmol) of diethyl diazomalonate. The system was purged with nitrogen and attached to a bubble counter. The solution was maintained at ±5° (circulating pump using ethanol coolant cooled by Dry Ice–acetone bath) and irradiated with a Hanovia 500-W high-pressure mercury immersion lamp until cessation of gas evolution (*ca.* 5 hr). The solution was concentrated by warming to room temperature and the residue was vacuum distilled to give 3.0 g (0.014 mol, 72%) of **2** collected at 46° (0.005 mm): λ (CCl_4) 5.79, 8.1, 9.1 μ; τ (CCl_4) 5.88 (4 H, J = 7 Hz), 8.71 (3 H, s), 8.79 (11 H, s and t, J = 7 Hz); *m/e* 214 (parent), 122 (base peak).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.74. Found: C, 61.84; H, 8.34.

Reaction of Compound 2 with Pyrrolidine. Formation of 11. To a 100-ml glass pressure flask was added 3.0 g (14.1 mmol) of **2** and 1.0 g (14.1 mmol) of pyrrolidine. The vessel was purged with nitrogen, sealed, and heated at 120° for 40 hr. The solution was diluted with ether and extracted with 5% aqueous HCl. The organic fraction was dried and concentrated *in vacuo* to give 1.82 g (60%) of recovered **2.** The aqueous fraction was carefully made basic with solid Na_2CO_3 and extracted with ether. The ether fraction was dried and concentrated *in vacuo.* The residue was distilled at 80–87° (0.005 mm) to give 0.47 g (1.65 mmol, 13%) of **11:** λ (CCl_4) 3.53, 5.72, 5.78 μ; τ (CCl_4) 5.95 (4 H, q, J = 7 Hz), 6.40 (1 H, t, J = 6 Hz), 7.3–7.8 (4 H, m), 8.0–8.9 (12 H, m, containing t, J = 7 Hz at 8.9), 9.04 (6 H, s); *m/e* 285 (parent), 112 (base peak).

Anal. (of methiodide, mp 92–94°) Calcd for $C_{16}H_3NO_4I$: C, 44.97; H, 7.07. Found: C, 44.68; H, 7.31.

Formation of Diethyl Tetramethylcyclopropane-1,1-dicarboxylate (3). To a 150-ml quartz immersion type photolysis cell, equipped with a reflux condenser, was added 125 ml of tetramethylethylene and 2.0 g (10.7 mmol) of diethyl diazomalonate. The system was purged with nitrogen and attached to a bubble counter. The solution was maintained at 18° (tap water) and irradiated until cessation of gas evolution (6 hr) with a Hanovia 500-W high-pressure mercury immersion lamp. The solution was concentrated under reduced pressure and distilled to give 1.9 g (7.75 mmol, 73%) of **3:** bp 64° (0.02 mm); λ (CCl_4) 5.79, 8.15 μ; τ (CCl_4) 5.91 (4 H, q, J = 7 Hz), 8.78 (t, J = 7 Hz), and 8.79 (s) (total = 18 H; *m/e* 242 (parent), 227 (base peak).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.84; H, 9.26.

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Registry No. —**1,** 16783-06-5; **2,** 16783-05-4; **3,** 53166-31-7; **4,** 7686-78-4; **5,** 53166-32-8; **6,** 53166-33-9; **7,** 53166-34-0; **7** picrate, 53166-35-1; **8,** 53166-36-2; **8** picrate, 53166-37-3; **9,** 53166-38-4; **11,** 53166-39-5; **11** methiodide, 53166-40-8; pyrrolidine, 123-75-1; isobutylene, 115-11-7; diethyl diazomalonate, 5256-74-6; tetramethylethylene, 563-79-1.

References and Notes

(1) (a) W. A. Bone and W. H. Perkin, *J. Chem. Soc.,* **67,** 108 (1895); (b) R. H. Best and J. F. Thorpe, *ibid.,* 685 (1909); (c) J. M. Stuart and H. H. Westberg, *J. Org. Chem.,* **30,** 1951 (1965); (d) J. E. Dolfini, K. Menich, P. Corliss, R. Cavanaugh, S. Danishefsky, and S. Chalsrabartly, *Tetrahedron Lett.,* 4421 (1966).

(2) The only striking exceptions to this rule are found in an instance of mercaptide attack[3] and in situations where the cyclopropane is part of an even more strained system.[4a,b]

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(9) S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.,* 821 (1972).

(10) A. B. Chmurny and D. J. Cram, *J. Amer. Chem. Soc.,* **95,** 4237 (1973), and following papers.

(11) In the case of **1** 46% is recovered after 50 hr at 110°. In the case of **1** only 7% is recovered after 50 hr at 100°. However, a precise ratio for the relative rates of ring opening is complicated by the formation of decarbethoxylation products **5** and **6** from **1** and some deterioration of starting materials under these forcing conditions.

(12) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N.Y., 1962, pp 197–202, and references therein.

(13) Boiling points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137 infracord spectrophotometer. Nmr spectra were obtained from a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained from an LKB-9000 system *via* direct insertion. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Ring-Opening Reactions of 2-Benzoylcyclopropane Isocyanate

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In an extension of some previous work it was felt that the mixed carbonic anhydrates of *cis-* (**1**) and *trans-* 2-benzoylcyclopropanecarboxylic acid (**2**)[1] could be used to prepare the benzoylcyclopropane isocyanates, **5** and **6.** These latter materials were required as intermediates in the synthesis of the benzoylcyclopropylamines which were to serve as models for the preparation of a series of azabicyclic compounds.

The anhydrides, **1** and **2,** were smoothly converted to the isomeric carboxazides, **3** and **4,** respectively, by reaction with sodium azide. These carboxazides rearranged to give the isomeric isocyanates, **5** and **6,** on refluxing in toluene.