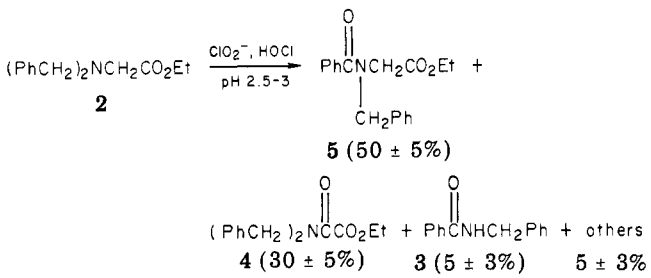
Table I. Products (mol %) of the Reaction of Acyclic Amines with Excess ClO_2 at pH 6.8

	PhCHO[a]	$PhCH_2NH_2$[a]	1	PhCH=NCH$_2$Ph[a]	$(HO)_2CHCO_2Et$[a]	3[a]	4	5	others
1[b]	trace	4	38[c]	27		16			15
1[d]	9	12	16[c]	25		24			14
2[b]	trace	0	23	12	27	5	21	4	8

[a] Identified on the basis of its mass spectrum. [b] One hour. [c] Starting material. [d] Two hours.

Scheme I



reactions of preformed ClO_2, loss of the more acidic proton from the initial aminium cation radical[10] appears to be the preferred process, whereas in the in situ case at low pH, direct abstraction of the α-hydrogen to give the more stable radical (benzyl vs. glycine α-carbon) may be favored. Thus the possibility of a difference in mechanism with the two reagents, preformed and in situ generated, suggested earlier by the observation of different ratios of cleavage products from benzyldimethylamines in the two cases,[2] remains to be investigated.

Experimental Section

A Hewlett-Packard Model 5985B gas chromatograph/mass spectrometer/data system (GC/MS/DS) equipped with a 180 × 0.2 cm glass column packed with 3% OV-1 on Gas Chrom Q was used for product analyses. High-resolution mass spectra were determined by the Middle Atlantic Mass Spectrometry Laboratory, The Johns Hopkins University School of Medicine. TLC separations were performed on Merck silica gel F-254 plates (0.25-mm thickness) with 1:1 hexane–ether as the eluant. The melting point (uncorrected) was determined on a Thomas-Hoover capillary apparatus. The ClO_2 solution (0.017 M) was prepared from reagent grade potassium persulfate and sodium chlorite.[11]

General Procedure for Chlorine Dioxide Oxidations. Solutions of the amine (1×10^{-2} mmol for 1, 5×10^{-3} mmol for 2) in acetonitrile (2.5 mL) and ClO_2 (2 mL of the 0.017 M solution in 0.5 mL of 0.1 M phosphate buffer, pH 6.8) were mixed and allowed to stand 1–2 h. For experiments at lower pH, dilute $HClO_4$ was added dropwise to the buffered ClO_2 solution before mixing. After the reaction, the mixtures were saturated with NaCl and, if necessary, adjusted to neutrality before extraction with CH_2Cl_2. The dried CH_2Cl_2 extracts were evaporated to dryness without heating, and the residues were dissolved in acetone for analysis by GC/MS.

Ethyl *N*,*N*-Dibenzyloxamate (4) and Ethyl *N*-Benzoyl-*N*-benzylglycinate (5) Formed with in Situ Generated ClO_2. A mixture of 2 (38 mg, 0.132 mmol), 0.16 M $NaClO_2$ (50 mL), 0.08 M NaOCl (50 mL), and 1 M $HClO_4$ (4.7 mL) had pH 2.6. It was stirred 1.5 h, adjusted to pH 6 with dilute KOH, and saturated with NaCl before extraction with two portions of CH_2Cl_2. The organic products (37 mg) were analyzed by GC/MS before separation and isolation of the two major amides by TLC: high-resolution mass spectrum, calcd for $C_{18}H_{19}NO_3$ m/e 297.1360, found for 4 m/e 297.1369, found for 5 m/e 297.1363. Characteristics of 4: mp 81–82 °C; IR (KBr) 1730, 1630 cm^{-1}; mass spectrum, m/e (relative intensity) 297 (1.5), 206 (97), 132 (21), 91 (100). Characteristics of 5: colorless syrup; IR (CCl_4) 1740, 1640 cm^{-1}; mass spectrum, m/e (relative intensity) 297 (1.2), 192 (90), 105 (100), 91 (23).

Registry No. 1, 103-49-1; 2, 77385-90-1; 3, 1485-70-7; 4, 80326-96-1; 5, 80326-97-2; PhCHO, 100-52-7; $PhCH_2NH_2$, 100-46-9; PhCH = NCH_2Ph, 780-25-6; $(HO)_2CHCO_2Et$, 64805-08-9; ClO_2, 10049-04-4.

(10) Y. L. Chow, W. C. Danen, S. F. Nelsen, and D. H. Rosenblatt, *Chem. Rev.*, **78**, 243 (1978).

(11) M. L. Granstrom and G. F. Lee, *J.—Am. Water Works Assoc.*, **50**, 1453 (1958).

Some Reactions of Lithium α-Lithiocyclopropanecarboxylate[1]

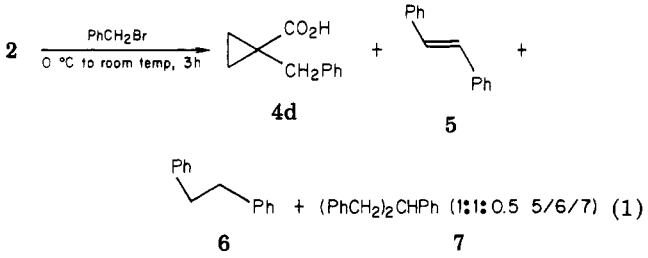
Philip M. Warner*[2] and Diem Le

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received August 10, 1981

The authors[3] of a recent paper on the chemistry of ethyl cyclopropanecarboxylate report that the dianion (2) of cyclopropanecarboxylic acid (1) failed to react with acetic acid-*d*, D_2O, benzyl bromide, or methyl iodide. By implication, this calls into question the reported[4] trapping of 2 with Me_3SiCl at 0 °C. Our interest in 2 stemmed from the notion that decarboxylation might be possible, whereby the theoretically significant[5] 1,1-dilithiocyclopropane (3) would arise. While we cannot report having achieved decarboxylation, we do document the successful alkylation of 2 (Scheme I).

Table I summarizes the results of treating 2 with various electrophiles at room temperature.[6] It should be noted that 2 was completely soluble at temperatures above 0 °C; below that, however, precipitation of the dianion occurred. The main conclusion is that alkylation of 2 does indeed occur, although the conversions tend to be low (not helped by adding HMPA[7]), and side reactions intercede. These latter include elimination (with *n*-BuI) and coupling reactions[8-10] (with benzyl bromide, eq 1). In an effort to



(1) This work was partially supported by a grant from the Iowa State University Research Foundation.

(2) Alfred P. Sloan Fellow, 1976–1980.

(3) Pinnick, H. W.; Chang, Y.-H.; Foster, S. C.; Govindan, M. *J. Org. Chem.* **1980**, *45*, 4505.

(4) Ainsworth, C.; Kuo, Y. N. *J. Organomet. Chem.* **1973**, *46*, 73.

(5) Collins, J. B.; Hill, J. D.; Jemmis, E. D.; Apeloig, Y.; Schleyer, P.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 5419.

(6) Perhaps the failure to observe alkylation reported in ref 3 was due to insufficient temperature or reaction times.

(7) The use of HMPA has been shown to decrease the yield of alkylation of α-branched acid enolates (Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1970**, *35*, 262. Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M., Jr. *Ibid.* **1972**, *37*, 451).

0022-3263/82/1947-0893$01.25/0

Scheme I

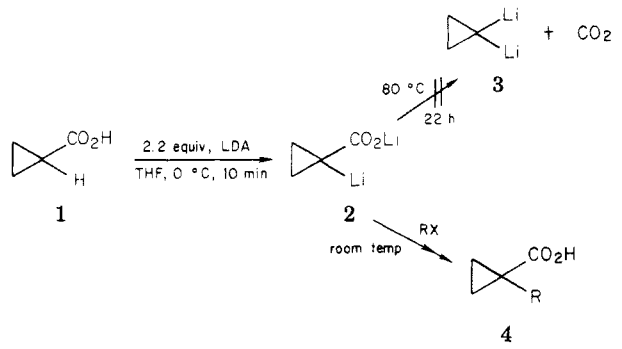


Table I. Yields of Alkylation Products from 2

RX	reaction time, h	% recovered 1	products	% yield
	3	70[a]	4a (R = allyl)	70[a,d]
MeI	1	47[a]	4b (R = Me)	89[a,d]
Me_3SiCl	3	0	4c (R = $SiMe_3$)	70[b,c]
$PhCH_2Br$	2	not determined	4d (R = CH_2Ph)	17[b]
n-BuI	3	100		

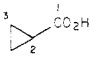
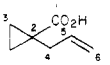
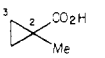
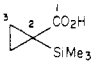
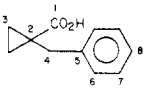
[a] Yield determined by ^1H NMR (internal standard). [b] Isolated yield. [c] Ainsworth and Kuo[4] reported obtaining a 90% yield (at −78 °C) of trimethylsilyl α-(trimethylsilyl)cyclopropanecarboxylate, which quantitatively hydrolyzed to 4c in H_2O. Although our workup conditions were hydrolytic, we also observed the silylated ester upon examination of the crude material prior to the workup. [d] Yield based on unrecovered starting 1.

avoid elimination, we added CuI[12] prior to attempted *n*-BuI trapping; no improvement was observed. Similarly, inverse addition of **2** to benzyl bromide did not increase the yield of **4d**.

Perhaps surprisingly, **2** did not apparently react with either CO_2 or CH_2O over a 6-h period at room temperature. After 6 days at room temperature, a mixture containing **2** and benzaldehyde led only to recovered **1** and the Cannizzaro products from PhCHO. This failure[13] to yield aldol-type products may be contrasted with the rapid self-condensation reported[3] for α-lithioethyl cyclopropanecarboxylate. An explanation may lie in the stability of **2** (indeed, **2** remained unchanged after 22 h at 80 °C). Thus aldol formation, which is reversible, may be thermodynamically unfavorable in this instance.[15]

In summary, while **2** is rather unreactive, it is definitely alkylated with MeI, allyl bromide, benzyl bromide, and Me_3SiCl.

Table II. ^{13}C NMR Data[a] for Various Cyclopropane Carboxylic Acids

compd	chemical shifts[b] (relative intensities) C_1	C_2	C_3	others
 1	181.5 (87.8)	12.55 (289)	8.78 (611)	
 4a	182.2 (105)	22.62 (165)	15.74 (765)	C_4, 36.70 (434); C_5, 175.24 (269); C_6, 116.44 (364)
 4b	183.1 (107)	18.27 (204)	17.36 (1020)	Me, 18.73 (581)
 4c	183.5 (157)	10.67 (148)	13.27 (1090)	Me, −2.60 (1030)
 4d	182.1 (123)	23.61 (117)	16.00 (982)	C_4, 37.78 (524); C_5, 139.16 (154); C_6, C_7, 129.28 (743); 128.17 (843); C_8, 126.29 (498)

[a] All spectra were obtained in $CDCl_3$. [b] Chemical shifts are reported in parts per million downfield from Me_4Si.

Experimental Section

General Methods. All reactions were carried out under N_2 in vessels which had been flame dried and cooled under N_2. Cyclopropane carboxylic acid (**1**) was dried overnight over molecular sieves and distilled prior to use. All other organic reagents were stored and distilled from CaH_2. THF was distilled from $LiAlH_4$. *n*-BuLi was standardized via titration with diphenylacetic acid. ^1H NMR spectra were obtained by utilizing Perkin-Elmer R20B and Varian A60 spectrometers. ^{13}C NMR spectra were measured on a JEOL FX90Q spectrometer. IR spectra were measured on a Beckman IR4250 instrument, while high-resolution mass spectra were obtained with a Varian MS902 spectrometer. All melting points are uncorrected.

Preparation of Lithium α-Lithiocyclopropanecarboxylate (2). A 100-mL round-bottomed flask was charged with 3.1 mL (22 mmol) of diisopropylamine and 10 mL of THF. To the magnetically stirred solution was added dropwise, at 0 °C, 1 equiv (9.2 mL of a 2.4 M solution in hexane) of *n*-BuLi, and the resulting LDA solution then stirred for 10 min more. Cyclopropanecarboxylic acid (**1**, 10 mmol) dissolved in 10 mL of THF was then added dropwise over a 10-min period at 0 °C. After the addition was complete, the dianion solution was stirred for another 10 min before the electrophiles were added.

1-Allylcyclopropanecarboxylic Acid (4a). To a solution of 10 mmol of **2** was added dropwise, at 0 °C, 20 mmol of allyl bromide dissolved in 5 mL of THF (the addition of HMPA effected no change). When the initially exothermic reaction had subsided, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature, whereupon it was stirred for 3 h more.

Quenching of the reaction mixture with 10 mL of H_2O was followed by a standard workup procedure. This consisted of extracting the organic layer once with 20 mL of a 1 M NaOH solution and then combining the basic aqueous layers. These were then cooled in an ice bath and acidified with concentrated HCl. The resulting mixture was washed three times with Et_2O. The combined ether extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and freed from solvent on a rotary evaporator.

In this case there resulted 0.782 g of product, determined (^1H NMR, internal standard) to contain 70% **I** and a 70% yield of **4a** based on depleted **1**. A pure sample of **4a** was obtained via distillation [bp 68 °C (0.2 torr)]: ^1H NMR (CCl_4) δ 11.2 (s, 1 H), 6.1–5.5 (m, 1 H), 5.2–4.8 (m, 2 H), 2.3 (d, 2 H), 1.3–0.7 (A_2B_2, 4

(8) For discussions of possible mechanisms leading to *trans*-stilbene and bibenzyl, see: (a) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: New York, 1974; pp 151–3. (b) Harris, T. D.; Roth, G. P. *J. Org. Chem.* **1979**, *44*, 2004.

(9) Although formation of *trans*-stilbene and bibenzyl from the reaction of benzyl halides with alkyllithiums is well documented,[8] that of 1,2,3-triphenylpropane is not.

(10) 1,2,3-Triphenylpropane has been obtained from the photolysis of benzylmercuric iodide[11a] and the Na/NH_3 reduction of benzyl chloride.[11b]

(11) (a) Hey, D. H.; Shingleton, D. A.; and Williams, G. H. *J. Chem. Soc.* **1963**, 1958. (b) Verkade, P. E.; deVries, K. S.; Wepster, B. M., *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 637.

(12) Kitatani, K.; Hiyama, T.; and Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3288.

(13) Additionally, treatment[14] of **1** with $MgBr_2$ or $ZnCl_2$ prior to carbonyl compound addition was of no avail.

(14) Mulzer, J.; Brüntrup, G.; Finke, J.; and Zippel, M. *J. Am. Chem. Soc.* **1979**, *101*, 7723.

(15) Such is also the case in some aldols leading to cyclization. For example, see: Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219.

H); ^{13}C NMR, see Table II; IR (CCl_4) 3400–2400 (br), 1690, 1635 cm^{-1}; mass spectrum, calcd for $C_7H_{10}O_2$ m/e 126.0681, found m/e 126.0684.

1-Methylcyclopropanecarboxylic Acid (4b). To a solution of 10 mmol of **2**, at 0 °C, was added dropwise 1.3 mL (20 mmol) MeI in 2 mL THF. After the addition was complete, the ice bath was removed and the solution stirred for 1 h. The standard workup afforded 0.874 g of a light yellow oily residue, which was identified (^1H NMR) as 47% 1 and an 89% yield of **4b** based on the 53% of 1 converted. The identity of **4b** was confirmed by comparison of the ^1H NMR spectrum and a GC trace (3% OV1) with those of an authentic commercial sample (Aldrich).

1-(Trimethylsilyl)cyclopropanecarboxylic Acid (4c). To a solution of 10 mmol of **2**, at 0 °C, was added dropwise 2.5 mL (20 mmol) of Me_3SiCl in 2.5 mL of THF. After the exothermic reaction had subsided, the ice bath was removed and the mixture stirred for 3 h. The standard workup afforded 1.165 g of crude product as white crystals. Recrystallization (pentane) gave a 70% yield of **4c**, mp 131–134 °C (lit.[4] mp 106 °C). Despite the large difference between the present and past-reported melting points, the ^1H NMR (CCl_4) [δ 11.3 (s, 1 H), 1.3–0.6 (A_2B_2, 4 H), 0.05 (s, 9 H)] followed closely that reported:[4] for the ^{13}C NMR, see Table II; mass spectrum, calcd for $C_7H_{14}O_2SiCH_3$ m/e 143.0528, found m/e 143.0536.

1-Benzylcyclopropanecarboxylic Acid (4d). To a solution of 10 mmol of **2**, at 0 °C, was added dropwise a solution of 1.5 mL (12 mmol) of benzyl bromide in 1.5 mL of THF. The mixture first turned brown but became light yellow toward the end of the addition. After removal of the ice bath and stirring for 2 more h, the standard workup gave a solid which was recrystallized (hexane) to yield **4d**: 303 mg (17%); mp 102–104 °C; ^1H NMR (CCl_4) δ 12.3 (s, 1 H), 7.2 (s, 5 H), 3.0 (s, 2 H), 1.4–0.8 (A_2B_2, 4 H); ^{13}C NMR, see Table II; IR (CCl_4) 3400–2400, 1700, 1610, 1500 cm^{-1}; mass spectrum, calcd for $C_{11}H_{12}O_2$ m/e 176.0837, found m/e 176.0836.

The intial organic layer, after base extraction, was washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated. Three products (*trans*-stilbene, bibenzyl, 1,2,3-triphenylpropane) were observed and isolated by GC (3% OV1 on Chromosorb W, 12 ft × 8 mm); they were identified by spectral comparison with authentic samples.

Registry No. 1, 1759-53-1; 2, 80375-26-4; **4a**, 80360-57-2; **4b**, 6914-76-7; **4c**, 31469-29-1; **4d**, 27356-91-8; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; MeI, 74-88-4; Me_3SiCl, 75-77-4; *trans*-stilbene, 103-30-0; bibenzyl, 103-29-7; 1,2,3-triphenylpropane, 26898-17-9.

Diels–Alder Reaction of Heterocyclic Azadienes. 2. "Catalytic" Diels–Alder Reaction of in Situ Generated Enamines with 1,2,4-Triazines. General Pyridine Annulation

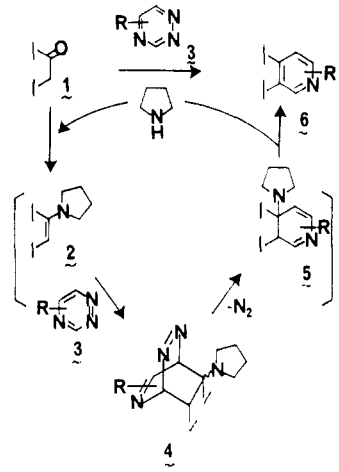
Dale L. Boger,*[1a] James S. Panek, and Michael M. Meier[1b]

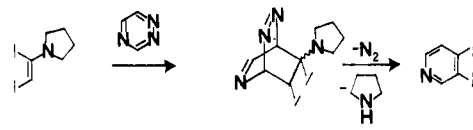
Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045

Received October 28, 1981

As part of an effort to develop short synthetic routes to naturally occurring alkaloids[2] we have had the occasion to investigate methods for the construction of substituted pyridines. These studies led to the development of a simple pyridine annulation based on the regiospecific inverse electron-demand Diels–Alder reaction of enamines with 1,2,4-triazine (eq 1).[3] Despite the convenience and

Scheme I





(1)

simplicity of this pyridine annulation, two immediate limitations surfaced which have proven to restrict the applicability of the reaction. First there is the requirement for a preformed pyrrolidine enamine, a venture approached with some concern when complex or valuable synthetic intermediates are involved. This problem is further compounded by the instability of some enamines, which often precludes their purification and occasionally isolation. A second and puzzling limitation discovered in our initial studies is the unique behavior of cyclohexanone pyrrolidine enamines. Although pyrrolidine enamines of aliphatic or five- and seven-membered cyclic ketones afforded the annulated pyridines in high yield (64–78%), a series of cyclohexanone pyrrolidine enamines uniformly yielded the pyridine products in modest yields (22–40%).[3] In this latter case, the problems reside in the final aromatization step (loss of pyrrolidine)[3] and persisted despite considerable effort to optimize the reaction conditions for elimination.

Herein, we disclose a convenient solution to the first of these limitations, which fortuitously serves to eliminate the unusual behavior of pyrrolidine enamines derived from six-membered cyclic ketones. The solution, which we refer to as a "catalytic" Diels–Alder reaction, constitutes a novel variant of the conventional Diels–Alder reaction. Experimentally we have demonstrated that the cycloaddition reaction of 1,2,4-triazine with pyrrolidine enamines proceeds under *exceptionally mild conditions*, often being exothermic, indicating that successful efforts to prepare the enamine in the presence of 1,2,4-triazine would result in the concomitant cycloaddition and subsequent pyridine formation. This further suggested that the process might well be capable of being conducted catalytically, under mild conditions. Thus, catalytic and/or in situ generation of a pyrrolidine enamine (1 → 2) in the presence of a 1,2,4-triazine (3) precedes the ensuing inverse electron-

(1) (a) Chicago Community Trust/Searle Scholar Recipient, 1981–1984. (b) National Science Foundation Undergraduate Research participant, 1980 (NSF-URP Grant No. SPI-8026418); Sterling-Winthrop Undergraduate Research Fellow, 1981.

(2) Typified by (+)-sesbanine, purported cytotoxic constituent of *Sesbania drummondii*. See: Powell, R. G.; Smith, C. R., Jr.; Weisleder, D.; Muthard, D. A.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 2784. Powell, R. G.; Smith, C. R., Jr. *J. Nat. Prod.* **1981**, *44*, 86. Also typified by streptonigrin, antitumor antibiotic isolated from cultures of *Streptomyces flocculus*. See: Gould, S. J.; Weinreb, S. M. *Prog. Chem. Org. Nat. Prod.*, in press.

(3) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179.

0022-3263/82/1947-0895$01.25/0