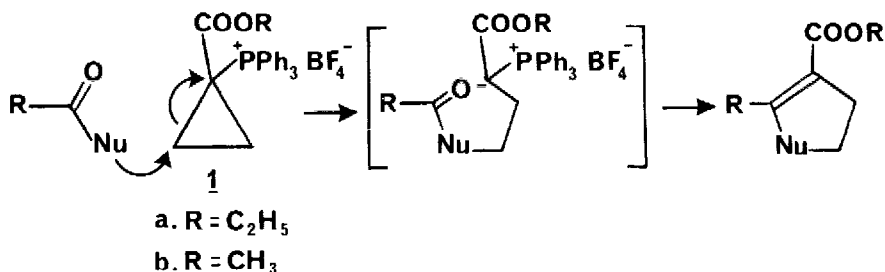


THE REACTION OF CARBOALKOXYCYCLOPROPYLTRIPHENYLPHOSPHONIUM
SALTS WITH IMIDE ANIONS: A THREE-STEP SYNTHESIS
OF + ISORETRONECANOL¹

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Summary Reaction between carboalkoxycyclopropyltriphenylphosphonium tetrafluoroborate (1a) and sodium succinimide affords the adduct (2a) which was converted in two additional steps into + isoretronecanol; some other condensations between (1a) and imide salts are described.

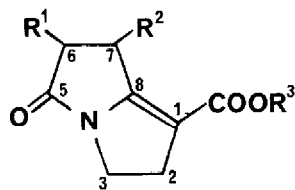
Carboalkoxycyclopropyltriphenylphosphonium tetrafluoroborate² (1a) has been shown to react with carbonyl-containing nucleophiles (for example, β -diketone anions², carboxylate anions³) as shown in Scheme 1. Nucleophilic opening of the activated cyclopropane ring is followed by intramolecular Wittig reaction to yield, for example, dihydrofurans³ (Nu = O).



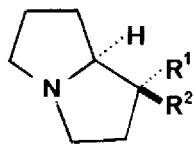
Scheme I

When the nucleophile and the carbonyl group are separated by one or two carbon atoms (e.g., 2-formylpyrrole, salicylaldehyde), the reaction proceeds analogously to afford products containing a six- or seven-membered ring.²

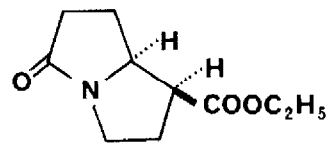
We have extended this reaction to include the use of imide anions as nucleophiles. Under the conditions previously reported for reaction of (1a) (hexamethylphosphoric triamide as solvent^{2,3}) no reaction occurred with sodium succinimide⁴ at temperatures up to 140°. However, if equimolar mixtures of the two reactants were heated to 140° for 4 hours without solvent⁵, a 50% yield of the expected product (2a)^{6,7} was obtained.



- a. $R^1 = R^2 = H, R^3 = C_2H_5$
 b. $R^1 = CH_3, R^2 = H, R^3 = C_2H_5$
 c. $R^1 = H, R^2 = CH_3, R^3 = C_2H_5$
 d. $R^1 = R^2 = H, R^3 = CH_3$

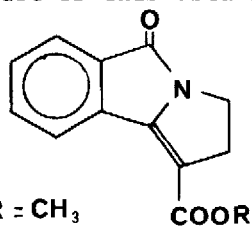


- a. $R^1 = H, R^2 = CH_2OH$
 b. $R^1 = CH_2OH, R^2 = H$



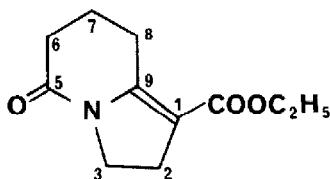
The use of sodium 2-methylsuccinimide afforded a 10:1 mixture⁸ of the products (2b)⁹ and (2c) in 60% yield. The major product results from intramolecular Wittig reaction of the intermediate (Scheme I) at the less hindered carbonyl group.

The adduct (2a) possesses the carbon skeleton of the pyrrolizidine alkaloid bases isoretronecanol (3a) and trachelanthamide (3b). An efficient conversion of (2a) to (3a) could be effected by initial catalytic reduction (10% palladium on carbon, ethanol, 60 p.s.i.) to give a quantitative yield of the ester (4)¹⁰ which, upon reduction with lithium aluminium hydride in refluxing tetrahydrofuran¹¹, gave a 62% yield of \pm isoretronecanol (3a)¹² (picrate mp 188-189°; Lit. mp¹³ 189-190°, (3b) picrate¹⁴ mp 174-175°). The product is thus obtained in three steps in an overall yield of 31%.

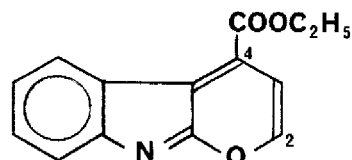


- a. $R = CH_3$
 b. $R = C_2H_5$

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6



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The potential scope of the reactions of the carboethoxy phosphonium salt (1a), and the carbomethoxy analogue (1b)¹⁵ (prepared in 69% yield from cyclopropyltriphenylphosphonium bromide, using the procedure of reference 2) was examined by condensation with other amide and imide substrates as shown in Table I.

In all cases equimolar amounts of (1a) or (1b) and the imide or amide salt were heated to 140° for 1-4 hours. No attempt was made to optimize yields, though it was noted that the yield of (2a) was relatively insensitive to variations in the molar ratio of the reactants, and the time and temperature of the reaction. The carbomethoxy phosphonium salt gave markedly inferior yields

TABLE I

<u>Phosphonium Salt</u>	<u>Substrate</u>	<u>Product</u>	<u>Yield, %</u>
(1b)	sodium succinimide	(2d) ¹⁶	8
(1a)	potassium phthalimide	(5a) ¹⁷	80
(1b)	potassium phthalimide	(5b) ¹⁸	3
(1a)	sodium glutarimide ¹⁹	(6) ²⁰	25
(1a)	sodium salt of isatin ²¹	(7) ²²	10

in the two reactions attempted. The pyrano [2,3-b] indole product (7) results from initial nucleophilic attack of the oxygen rather than the nitrogen of the amide anion, followed by intramolecular Wittig reaction to give the presumed initial product, 2,3-dihydro-(7) from which the isolated product (7) was formed by means of an oxidation reaction.²³ The product is unexpected in that alkylation of isatin salts usually occurs on the nitrogen atom.²⁴

Acknowledgement We thank Dr. M. Maddox for assistance with the ¹³C NMR data.

References and Notes

- Contribution No. 560 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, California.
- P.L. Fuchs, J. Am. Chem. Soc., **96**, 1607, 1974.
- W.G. Dauben and D.J. Hart, Tetrahedron Lett., 4353, 1975.
- Prepared by addition of succinimide to a methanolic solution of one equivalent of sodium methoxide, followed by addition of 5 volumes of ether to precipitate the product.
- These conditions are similar to those employed for the reactions between succinimide and other amides and various stabilized phosphonium ylids. W. Flitsch and B. Mütter, Chem. Ber., **104**, 2847, 1971, W. Flitsch and M. Peters, ibid, **103**, 805, 1970; Tetrahedron Lett., 1161, 1969.
- All new compounds gave C, H and N microanalyses within $\pm 0.4\%$ of theory. Melting points are uncorrected, ¹H and ¹³C NMR spectra were obtained in CDCl₃ solutions on Varian HA 100 and Bruker WH-90 spectrometers respectively. Shifts are reported in ppm downfield from tetramethylsilane. Infrared frequencies are reported to the nearest 5 cm.⁻¹. Ultraviolet spectra were taken in methanol solution.
- Isolated by chromatography on silica gel (5:2 toluene:acetone) mp 53-55^o (ether-hexane), UV 280 nm (ϵ 19600); IR (KBr) 1715, 1680, 1640 cm.⁻¹ ¹³C NMR 103.28 (C₁); 32.02 (C₂); 40.99 (C₃); 172.20 (C₅); 33.81 (C₆); 21.07 (C₇); 160.01 (C₈); 14.53 (CH₃); 59.82 (OCH₂); 165.54 (ester carbonyl). MS 195 (M⁺).

8. GLC analysis, 5 ft. 3% SE-30; 170°.
9. Isolated by fractional crystallization of the mixture of (2a) and (2b) obtained by chromatography of the crude product (silica gel, 1:1 ethyl acetate:hexane) mp 57-61° (methylene chloride-hexane); UV 280 nm (ϵ 19600); ^{13}C NMR 103.15 (C_1); 31.73 (C_2); 41.09 (C_3); 175.26 (C_5); 40.51 (C_6); 29.65 (C_7); 158.55 (C_8); 17.30 (CH_3); 14.53 (CH_2CH_3); 59.82 (OCH_2); 165.57 (ester carbonyl)
10. Oil; IR (film) 1715, 1680 cm^{-1} ^{13}C NMR 45.61 (C_1); 30.00 (C_2); 41.25 (C_3); 172.72 or 175.75 (C_5); 30.33 (C_6); 22.27 (C_7); 63.30 (C_8) 14.27 (CH_3); 60.92 (OCH_2); 172.72 or 175.75 (ester carbonyl)
11. For the procedure used, see S. Danishefsky, R. McKee and R.K. Singh, J. Am. Chem. Soc., **99**, 4783, 1977.
12. Oil; MS 141 (M^+) 124, 110.
13. N.J. Leonard and T. Sato, J. Org. Chem., **34**, 1066, 1969.
14. N.J. Leonard and S.W. Blum, J. Am. Chem. Soc., **82**, 503, 1960.
15. mp 80-87° ($\text{CH}_2\text{Cl}_2\text{-Et}_2\text{O}$), 155-158° ($\text{CHCl}_3\text{-Et}_2\text{O}$); see also Ref. 2.
16. mp 82-84° (ether-hexane); UV 279 nm (ϵ 23100); IR (KBr) 1710, 1680, 1630 cm^{-1} MS 181 (M^+), 166, 150.
17. mp 172-174° (ethyl acetate-hexane); IR (nujol mull) 1695, 1645 cm^{-1} ^1H NMR 3.29 (t, J9Hz, 2H); 3.85 (s, 3H); 3.92 (t, J9Hz, 2H); ca. 7.6 (m, 2H); ca 7.8 (m, 1H); ca. 8.5 (m, 1H); MS 229 (M^+), 198, 170.
18. mp 111-114° (ethyl acetate-hexane); UV 214, 283, 345 nm (ϵ 27600, 7600, 7600); IR (nujol mull) 1680, 1640 cm^{-1} ; ^1H NMR 1.42 (t, J7Hz, 2H); 3.33 (t, J9Hz, 2H); 3.85 (t, J9Hz, 2H); 4.37 (q, J7H, 2H); ca. 7.7 (m, 3H); ca. 8.5 (m, 1H) MS 243 (M^+), 214, 198.
19. Prepared as described in reference 4.
20. mp 67.5-70° (ether-hexane); UV 283 nm (ϵ 23400); IR (KBr) 1680, 1660, 1615 cm^{-1} ^{13}C NMR 14.47 (CH_3); 19.34 (C_7); 23.47 (C_8); 26.56 (C_6); 32.28 (C_2); 44.28 (C_3); 59.88 (OCH_2); 108.71 (C_7); 152.08 (C_9); 166.03 (ester carbonyl); 168.79 (C_5).
21. Prepared by refluxing isatin and an equivalent of NaH in toluene.
22. mp 156-7° (methanol); IR (nujol) 1705 cm^{-1} ^1H NMR 1.39 (t, J7Hz, 3H); 4.35 (q, J7Hz, 2H); 6.74 (d, J3Hz, 1H); 7.04 (d, J3Hz, 1H); 7.0-7.6 (m, 4H). MS 241 (M^+), 196, 169. These data are in accord with (7) or the isomeric 2-ester. The latter compound is excluded on mechanistic grounds.
23. Since all reactions were run under nitrogen, the nature of the oxidation reaction is not obvious.
24. cf references cited by F.D. Popp in *Advances in Heterocyclic Chemistry*, A.R. Katritzky and A.J. Boulton, Editors, Academic Press, New York, 1975; Volume 18, pp. 1-58.

(Received in USA 14 August 1980)