methyl esters. The esters were saponified and aliquots of the mixture were diluted with the highly crystalline dipeptide acids which were recovered and recrystallized to constant activity.

We feel that the constancy of the $^{3}H/^{14}C$ ratios (Table I) of the products provides compelling evidence

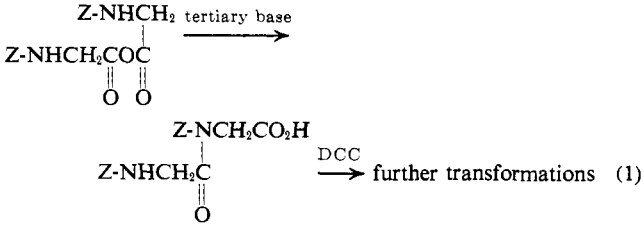
Table I

Peptide	$^{3}H/^{14}C$	Product distributions[a] DCC	Anhydride
Z-Gly-Gly-OH	3.71	1.01	1.04
Z-Gly-DL-Phe-OH	3.78	1.26	1.28
Z-Gly-L-Leu-OH	3.84	1.00	1.00
	Overall yields[b]	90%	95%

[a] Normalized to Z-Gly-L-Leu. [b] For coupling, transesterification, and saponification (based on acylating agent).

for a common product-determining step, *i.e.*, that the same acylating agents are involved in both reactions. The product distributions of the three polymer bound amines probably reflect resin loadings as well as their intrinsic nucleophilic properties and deserve little comment; however, the competition between the amine (on the solid phase) and the carboxylic acid (in solution) for the *O*-acylisourea (in solution) has a different outcome from that in solution. The *O*-acylisourea can be intercepted by amines and some phenols[7] in solution but not by polymer-bound amines during solid-phase peptide synthesis.

During solid-phase synthesis a 1:1 acid–DCC ratio is normally used, and, since these reagents are in excess with respect to the polymer-bound amine, the symmetrical anhydride must build up at the end of the reaction. Our result indicates that the anhydride is the acylating agent during the initial third of the reaction as well. Further, the relative insolubility of Z-Gly-OH makes the present experimental conditions unfavorable to anhydride formation; the common use of *t*-BOC amino acids as much more concentrated solutions during solid-phase synthesis should favor the anhydride mechanism, although steric factors may, in some cases, suppress anhydride formation. If the anhydride mechanism obtains in general, it would appear that the common use of excess DCC is superfluous or even deleterious during solid-phase synthesis. De Tar's demonstration of the lability of these anhydrides to tertiary bases, including DCC[8] (eq 1), is relevant here,



(1)

in that new acids are generated which would lead to side products of the sort that linear synthesis cannot tolerate. The report of loss of acylating power of DCC–acid–tertiary amine mixtures with time should be mentioned in this connection.[9]

We suggest that a 2:1 acid–DCC stoichiometry, or the preformed purified anhydride, be used in solid-phase peptide synthesis. We note that improved results have been reported recently with anhydrides.[10]

Acknowledgment. Financial support of this work by the Eli Lilly Co. and the Research Corporation is gratefully acknowledged.

anol and treated with roughly an equivalent of ethereal diazomethane solution and stored overnight in the refrigerator. Under these conditions polymer-bound Z-Gly-L-Leu was converted to the corresponding methyl ester with a reaction half-life of 1–2 hr.

(7) J. Kovacs, L. Kisfaludy, M. Ceprini, and R. Johnson, *Tetrahedron*, **25**, 2555 (1969).

(8) D. F. De Tar, R. Silverstein, and F. Rogers, Jr., *J. Amer. Chem. Soc.*, **88**, 1024 (1966).

(9) A. Tometsko, *Biochem. Biophys. Res. Commun.*, **50**, 886 (1973).

(10) T. Wieland, C. Birr, and F. Flor, *Angew. Chem., Int. Ed. Engl.*, **10**, 336 (1971). See also H. Hagenmaier and H. Frank, *Z. Physiol. Chem.*, **353**, 1973 (1972).

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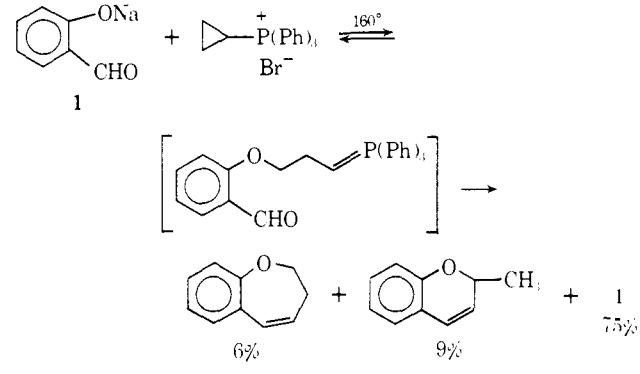
Carboethoxycylopropcyltriphenylphosphonium Fluoroborate. A Reagent for the Facile Cycloalkenylation of Carbonyl Groups

Sir:

Schweizer's exploratory studies on the reaction of cyclopropylphosphonium bromide with the sodium salt of salicylaldehyde have demonstrated that this reagent is of only limited utility as an annulation reagent.[1,2] This limitation is presumably a consequence of the difficulty of the ring opening step.[2]



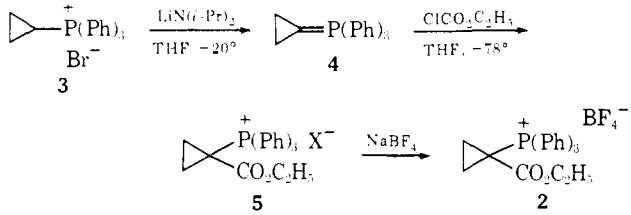
Since it is well documented that nucleophilic cleavage of cyclopropane rings is most facile when the cyclopropane ring bears two geminal electron-withdrawing groups,[3] it was therefore anticipated that cyclopropylphosphonium salt, **2**, which has a geminal carboethoxy group, should exhibit facile ring opening reactions.

(1) E. E. Schweizer, C. J. Berninger, and J. G. Thompson, *J. Org. Chem.*, **33**, 336 (1968).

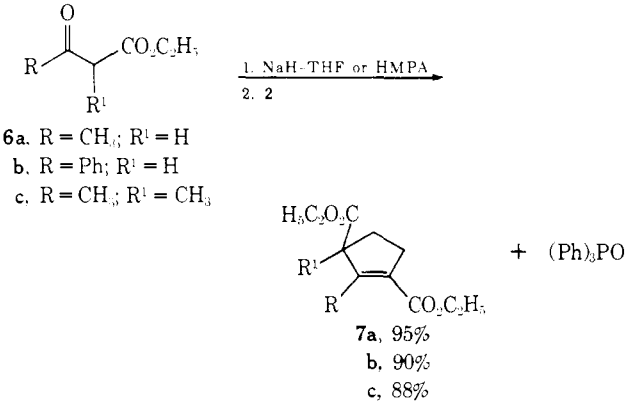
(2) E. E. Schweizer, T. Minami, and D. M. Crouse, *J. Org. Chem.*, **36**, 4028 (1971).

(3) (a) J. M. Stewart and H. H. Westberg, *J. Org. Chem.*, **30**, 1951 (1965); (b) J. E. Dolfini, K. Menich, P. Corliss, R. Cavanaugh, S. Danishefsky, and S. Chakrabartty, *Tetrahedron Lett.*, 4421 (1966); (c) S. Danishefsky, J. Dynak, and M. Yamoto, *J. Chem. Soc., Chem. Commun.*, 81 (1973); (d) E. J. Corey, P. L. Fuchs, *J. Amer. Chem. Soc.*, **94**, 4014 (1972); (e) G. Daviaud and Ph. Miginiac, *Tetrahedron Lett.*, 997 (1972); (f) D. J. Cram, *et al.*, *J. Amer. Chem. Soc.*, **95**, 4220, 4230, 4237 (1973).

Reaction of cyclopropyltriphenylphosphonium bromide[4] **3** with lithium diisopropylamide in tetrahydrofuran (−20°) smoothly produced a solution of ylide **4**. Subsequent treatment of **4** with ethyl chloroformate (−78°, 1.1 equiv) produced the known carboethoxycyclopropyltriphenylphosphonium salt **5**.[5] Exchange of the counterion with $NaBF_4$[6] and crystallization ($CHCl_3$–ether) provided nonhygroscopic phosphonium salt **2**[7] (80% overall from **3**).



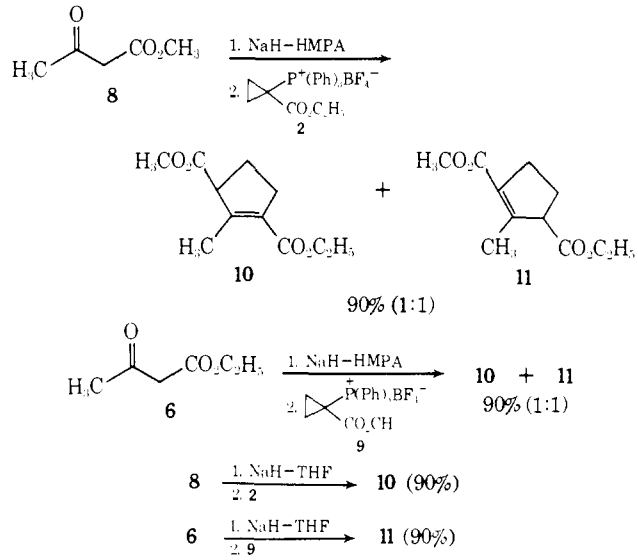
It was gratifying to find, in accord with expectations, that **2** proved to be an excellent reagent for the cycloalkenylation of carbonyl compounds. For example, reaction of β-keto esters (**6a–c**) (as their sodium enolates) with **2**, either as a suspension in tetrahydrofuran at reflux or in hexamethylphosphoric triamide (HMPA) solution at room temperature, smoothly produced cyclopentene diesters (**7a–c**) in excellent yield.[8,9]



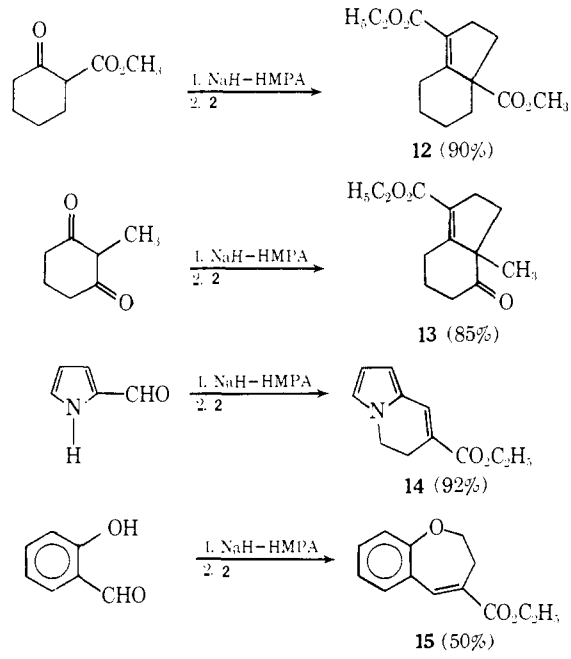
6a, R = CH_3; R^1 = H
b, R = Ph; R^1 = H
c, R = CH_3; R^1 = CH_3

7a, 95%
b, 90%
c, 88%

In the case of unsubstituted β-keto esters the double bond in the resulting cyclopentene diester **7** was found to equilibrate when using HMPA as solvent but was regiostable when the reaction was conducted in THF. Although the isomerization reaction is not detectable in the reaction **6** → **7**, because of the symmetry of the product, it can be conveniently demonstrated by using different ester groups on the cyclopropylphosphonium salt and on the β-keto ester. Specificially, reaction of the sodium enolate of methyl acetoacetate (**8**) with reagent **2** in HMPA produces a 1:1 mixture of diesters **10** and **11**. The same 1:1 mixture is also produced in the reaction of the sodium enolate of ethyl acetoacetate (**6**) with carbomethoxycyclopropyltriphenylphosphonium fluoroborate (**9**).[7] Repetition of the same two reactions in THF, however, regiospecificially (>95%) produces the desired diesters **10** and **11**, respectively.[9]



The following four examples further demonstrate the utilty of phosphonium salt **2** as a cycloalkenylation reagent.[9]



The mechanism of the above reactions (illustrated for **8** → **10**) can be most simply viewed as a nucleophilic attack of the enolate on reagent **2** to produce a stabilized ylide **16**. Ylide **16** then rapidly cyclizes to the product in an intramolecular Wittig reaction.[10,11]

(4) Obtained from Willow Brook Laboratories, Waukesha, Wis.

(5) H. J. Bestman, Th. Denzel, R. Kunstmann, and J. Lengyel, *Tetrahedron Lett.*, 2895 (1968).

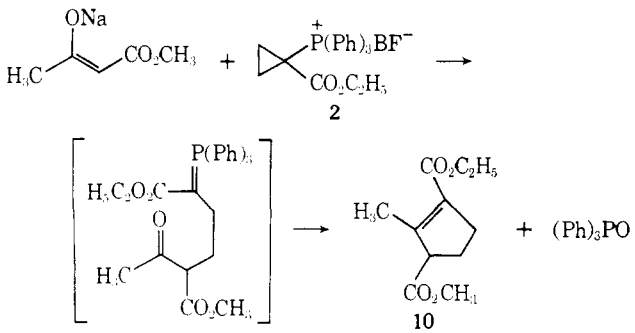
(6) E. Vedejs, J. P. Bershas, and P. L. Fuchs, *J. Org. Chem.* **38**, 3625 (1973).

(7) **2** (mp 179–181°): nmr ($CDCl_3$, δ) 7.5–7.9, 15 H, m; 4.01, 2 H, q (*J* = 7 Hz); 2.10–2.35, 2 H, m; 1.20–1.75, 2 H, m; 0.85, 3 H, t (*J* = 7 Hz). *Anal.* Calcd for $C_{24}H_{24}BF_4O_2P$: C, 62.36; H, 5.23; P, 6.70. Found: C, 62.14; H, 5.23; P, 6.95%. Similarly prepared was carbo*methoxy*cyclopropyltriphenylphosphonium fluoroborate (**9**) 60% yield (mp 157–159°).

(8) The substrate (1.0 mmol) is added at room temperature to NaH (1.2 mmol) in THF or HMPA (5.0 ml) to produce a homogeneous solution. Reagent **2** is added to the above solution (as the solid, 1.1–1.2 mmol) and the mixture is stirred until the consumption of starting material is complete (8–36 hr at 25° for HMPA, 12–72 hr at 65° for THF). These reactions may also be run in DMF or DMSO (16–72 hr, at 25°). The product is isolated by extraction of HMPA–H_2O with hexane or evaporation of THF and stirring the residual salts with hexane. Plug filtration of the crude product through SiO_2 (5–10 g) with ether elution to remove triphenylphosphine oxide produces pure cycloalkenylated products. All yields refer to isolated product.

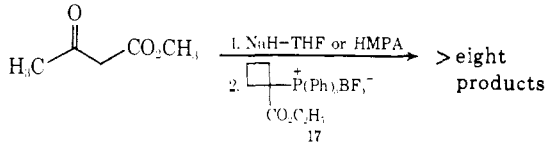
(9) Satisfactory ir, nmr, mass spectral, and exact mass data have been obtained for all new compounds.

(10) An additional example of an intramolecular Wittig reaction of a stabilized ylide is the reaction of enollactones with methylenetriphenylphosphorane to yield α,β-unsaturated ketones: C. A. Henrick, E. Boehme, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, **90**, 5926 (1968).



16 10

Attempts to utilize homologous reagent **17** in these reactions have been unrewarding.[12]



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Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

(11) Thus far, efforts to detect a stabilized ylide intermediate have not been successful; this suggests that ring opening may be the rate limiting step in these reactions.

(12) Carboethoxycyclobutyltriphenylphosphonium fluoroborate (17) may be prepared from cyclobutyltriphenylphosphonium bromide[13] by a procedure analogous to the one used for the synthesis of **2** (**17**: 63% yield (mp 162–163°)).

(13) K. V. Scherer, Jr., and R. S. Lunt III, *J. Org. Chem.*, **30**, 3215 (1965).

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Azetidinone Sulfenic Acids. Isolation of Crystalline Sulfenic Acids from Penicillin Sulfoxides and a Study of Their Reactivities

Sir:

It has been 10 years since the sulfenic acid II was postulated as an intermediate in the important thermal rearrangement of penicillin sulfoxide (I) to desacetoxycephalosporin (IV).[1] While some derivatives or salts of sulfenic acids have been made,[2] compounds with this reactive function have defied isolation and in reality have only been known as a transient species. We wish to report the actual crystallization of this key intermediate sulfenic acid, IIa, and the isolation of other sulfenic acids in stable forms.

When the penicillin sulfoxide ester Ia was refluxed in ethyl acetate for 10 min and then evaporated to dryness, a mixture of the sulfoxide Ia and the sulfenic acid IIa was obtained in a 4:1 ratio. Recrystallization from ethyl acetate–ether gave sulfoxide Ia (60%). Evaporation of the filtrate and crystallization from methylene dichloride–cyclohexane yielded the pure sulfenic acid, IIa, mp 152–153° (10%).

The structure IIa was supported by nmr ($CDCl_3$–DMSO-d_6, 1:1) δ 2.0 (3 H, s, vinyl methyl), 5.6 and 5.9 (2 H, d, J = 4.5 Hz, *cis*-azetidinone protons), 5.01 and 5.19 (allylic and methylene protons), 7.25 (1 H, s, exchangeable with D_2O, –SOH);[3] infrared spectrum (KBr, cm^{-1}) showed four carbonyl absorptions, 1779 and 1720 (phthalimido), 1760 (azetidinone), and 1740 (ester), as well as a broad absorption at 3160 (OH) and intense bands at 1179, 1154, and 770 cm^{-1} which we assign to the S–O function; and high resolution mass spectrum, m/e 497 M^+. The crystalline α,β-unsaturated sulfenic acid isomer IIIb, mp 147–149°, was obtained in high yield by hydrolysis (methanol, 0°, 2 hr) of its trimethylsilyl sulfenic ester:[4] nmr ($CDCl_3$–DMSO-d_6) δ 2.22 and 2.33 (6 H, 2s), 5.67 and 5.83 (2 H, 2d, J = 5 Hz), 7.56 (1 H, s, exchangeable with D_2O, –SOH); infrared (5% $CHCl_3$) ν_{max} 3570 cm^{-1} (broad) sulfenic acid–OH.

Other sulfenic acids obtained by removal of the trimethylsilyl protecting function were IIb, amorphous, nmr ($CDCl_3$) δ 7.34 (1 H, s, exchangeable with D_2O, –SOH) and the above crystalline IIa.

A demonstration of the reactive nature of sulfenic acid IIa was obtained when a 50% conversion to penicillin sulfoxide (Ia) occurred (3 hr, 38°, $CHCl_3$ solution) as evidenced by nmr studies. Expected ring closure of the sulfenic acid IIa and IIb to the cephalosporin derivatives IVa and IVb occurred upon treatment with methane sulfonic acid in benzene–dimethylacetamide.[5]

Further evidence supporting the structural assignment of IIa derives from chemical reactions.[6] The oxidation of IIa with sulfuryl chloride (methylene chloride, room temperature) afforded the sulfinyl chloride Va[7] in almost quantitative yield and reaction with methane sulfonic acid (1 equiv, room temperature) gave VIa in a high yield.[8]

When the sulfenic acid IIb was treated with a trace of triethylamine in anhydrous benzene, there was obtained a crystalline isothiazolone derivative, VIIb,[9] in high

(1) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **85**, 1896 (1963); **91**, 1401 (1969); R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Accounts Chem. Res.*, **6**, 32 (1973).

(2) K. Fries, *Chem. Ber.*, **45**, 2965 (1912); T. C. Bruice and P. T. Markiw, *J. Amer. Chem. Soc.*, **79**, 3150 (1957); W. Jenny, *Helv. Chim. Acta*, **41**, 317, 326 (1958); J. R. Shelton and K. E. Davis, *J. Amer. Chem. Soc.*, **89**, 718 (1967); B. C. Pal, M. Uzil, D. G. Doherty, and W. E. Cohn, *ibid.*, **91**, 3634 (1969).

(3) The allylic proton is weakly coupled with the trans vinyl proton. Incidentally, the nmr spectrum of IIa is very similar and almost superimposable on the spectrum of the sulfinyl chloride Va reported previously (see ref 7).

(4) The trimethylsilyl ester was obtained by refluxing sulfoxide Ib with 100% excess silylating agents (2:1 molar ratio of trimethylsilyl chloride and hexamethyldisilazane) plus a trace of triethylamine. The trimethylsilyl esters of the β,γ-unsaturated sulfenic acids IIa and IIb were obtained from sulfoxide Ia and Ib, respectively, with the silylating agents only. See T. S. Chou, *Tetrahedron Lett.*, in press.

(5) Reference samples of compound IVa (mp 186–188°, $[\alpha]^{25}D$ –7.2° (*c* 1.0, $CHCl_3$)) and compound IVb (mp 176–177°, $[\alpha]^{25}D$ –4.7° (*c* 1.0, $CHCl_3$)) were prepared by procedures described in G. E. Gutowski, B. J. Foster, C. J. Daniels, L. D. Hatfield, and J. W. Fisher, *Tetrahedron Lett.*, 3433 (1971). Compound IVb had been previously prepared, S. Kukolja and S. R. Lammert, *J. Amer. Chem. Soc.*, **94**, 7169 (1972).

(6) Paper to be presented (S. Kukolja) at a Symposium on New Sulfur Chemistry sponsored by the Division of Petroleum Chemistry at the 167th Meeting of the American Chemical Society, Los Angeles, Calif., March 31–April 5, 1974.

(7) S. Kukolja and S. R. Lammert, *Angew. Chem.*, **85**, 40 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 67 (1973).

(8) The nmr ($CDCl_3$) spectrum of amorphous VIa: δ 1.83 (3 H, s), 3.61 and 3.50 (2 H, abq, J = 15 Hz), 3.56 (3 H, s), 5.38 (2 + 1 H, s), 5.46 (1 H, d, J = 4.5 Hz), 5.65 (1 H, d, J = 4.5 Hz), and 7.50–8.50 Hz (8 H, m, ar H).

(9) The isothiazolone VIIb has a melting point >230° dec, nmr ($CDCl_3$) δ 1.95 (3 H, s), 2.40 (3 H, s), 3.75 (3 H, s), 7.83 (4 H, m), and 8.40 (1 H, s); high resolution mass spectrum shows molecular ion at m/e 358 and a base peak at m/e 299 ($M - CO_2CH_3$). The intense peak at m/e 187 characteristic of a β-lactam compound with a phthalimido side chain is missing.