mesh were used for all kinetic work. Anal. Calcd for 20% ring substitution: Cl, 1.57 mmol/g. Found: Cl, 1.33 mmol/g.

B. Microporous Copolymers. Procedures used for the preparation of all microporous copolymers were similar to that described for the macroporous analogues, except that 4-methyl-2-pentanol was omitted.

Chloromethylation of XAD-2 and XAD-4 Resins. Procedures used for chloromethylating Rohm and Haas macroreticular resins were similar to those described for microporous polymers.[15] Prior to chloromethylation, these macroporous resins were extensively washed by using procedures described in the literature.[16]

Quaternization of Chloromethylated Copolymers with Tri-*n*-butylphosphine. Procedures similar to that used for the quaternization of macroporous chloromethylated polystyrene (10% divinylbenzene, 20% ring substitution) were followed for all macroporous copolymers. A 50-mL culture tube (Corning no. 9826, 25 × 150 mm) equipped with a Teflon-lined screw cap was charged with 1.0 g of macroporous copolymer (1.33 mmol of CH_2Cl) plus 10 mL of toluene. After the contents of the tube was purged with nitrogen for 5 min, tri-*n*-butylphosphine (2.69 g, 13.0 mmol) was added, and the tube was sealed, placed in an oil bath (90 °C) for 24 h, and then cooled to room temperature. The resin was filtered, extracted (Soxhlet) with toluene for 6 h, and dried under reduced pressure [6 h, 100 °C (0.05 mm)], yielding a polymer having a chloride ion content of 1.1 mmol/g (95% quaternization). Quaternization of the microporous polymers was carried out at 110 °C for 72 h (1 and 2% divinylbenzene), 120 h (5% divinylbenzene), or 168 h (10 and 20% divinylbenzene). Except for the 20% cross-linked microporous resins, where only 35–50% of the chloromethylene groups underwent displacement, the degree of quaternization was generally high (>80%). Chloromethylated XAD-2 and XAD-4 polymers required reaction times of 120 h at 90 °C to obtain fully quaternized resins.

Kinetic Methods. All kinetic experiments were performed at 90 °C using 50-mL culture tubes as reaction vessels and procedures identical with those previously described.[3] Stirring speeds of 1500 rpm were used in all cases.

Acknowledgment. We are grateful to Professor Keith Hall (University of Wisconsin, Milwaukee) for providing us with the use of his BET surface area apparatus and to the National Science Foundation for the purchase of a JEOL JSM-35 scanning electron microscope. We are also grateful to Mr. K. Ramasami and Mr. L. Wang for providing valuable technical assistance.

Registry No. Ethenylbenzene 1-(chloromethyl)-3-ethenylbenzene, 1-(chloromethyl)-4-ethenylbenzene 1,4-bisethenylbenzene copolymer tributylphosphine salt, 77080-45-6.

(15) Feinberg, R. S.; Merrifield, R. B. *Tetrahedron* **1974**, 3209.
(16) Farrall, M. J.; Frichet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877.

Phosphite-Mediated in Situ Carboxyvinylation: A New General Acrylic Acid Synthesis†

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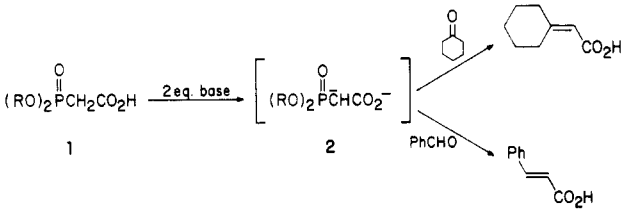
Received February 26, 1981

Sequential treatment of a 2-halo carboxylic acid with a dialkyl phosphite and an aldehyde or ketone in the presence of 3 equiv of sodium hydride in glyme constitutes a new general acrylic acid synthesis superior to conventional methods. An alkoxide-in-alcohol variant may be used with bromo- or chloroacetic acid and aryl aldehydes to produce cinnamic acids conveniently. The scope and other features of the synthesis are discussed.

The α,β-unsaturated carboxylic acid[1] moiety is a widely occuring structural subunit of many natural products and a versatile synthetic intermediate. In addition, many acrylic acids are of interest in their own right. Classical acrylic acid syntheses possess various shortcomings: the Perkin reaction succeeds only with aromatic aldehydes,[2] and the (Doebner) Knoevenagel reaction[3] suffers from unavailability of the requisite malonic acids, severe reaction conditions, long reaction times, and rapidly decreasing yields as the alkyl group of alkylmalonic acids becomes larger.[4]

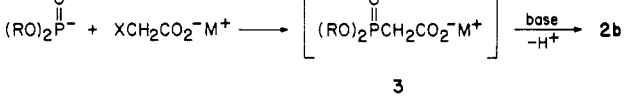
There are numerous acrylic ester syntheses, but these require an extra hydrolysis step to obtain the acrylic acid, and hydrolysis of α,β-unsaturated carboxylic esters can result in low yields.[5] Use of the Horner–Wadsworth–Emmons phosphonoacetate reagent, the most convenient route to acrylic esters,[6] is little used for the synthesis of α-substituted acrylates;[7] it necessitates preparation of the individual α-substituted phosphonoacetate reagents, and the product esters can isomerize to β,γ-unsaturated esters under the reaction conditions.[8]

Scheme I[a]



[a] a, R = $PhCH_2$;[9] b, R = C_2H_5.[10,11]

Scheme II



Along with Koppel and Kinnick[9] and Coutrot et al.,[10] we have carried out Horner–Wadsworth–Emmons-type

† Contribution No. 2871 from the Central Research and Development Department, E. I. du Pont de Nemours and Co.

(1) For convenience, α,β-unsaturated carboxylic acids will hereafter be referred to generically as acrylic acids in this paper.
(2) Johnson, J. R. *Org. React.* **1942**, *1*, 210.
(3) Jones, G. *Org. React.* **1967**, *15*, 203.

0022-3263/81/1946-2514$01.25/0

carboxyvinylation using a dialkyl (carboxymethyl)-phosphonate (1, Scheme I.)[11]

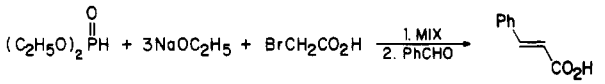
For our purposes 1 was conveniently prepared by an Arbuzov–Michaelis reaction between triethyl phosphite and benzyl chloroacetate followed by catalytic hydrogenolysis of the benzyl ester.[12] In our hands, **1b** furnished excellent yields of α,β-unsaturated carboxylic acids upon treatment with sodium hydride in glyme and an aldehyde or ketone. But, its use still requires a two-step synthesis of the preformed reagent **1**,[9,10,12] and this chemistry appeared to lack ready extension to α-substituted derivatives. Seeking an improved and more general route to acrylic acids, we reasoned that, in principle, Michaelis–Becker[13] alkylation of a dialkyl phosphite conjugate base with an alkali metal salt of a haloacetic acid, in the presence of 1 equiv of a base to deprotonate the initially formed alkylation product **3**, should yield the phosphoryl-stabilized anion **2** directly (Scheme II).

Herein we describe an operationally simple one-vessel synthesis of acrylic acids, which uses readily available starting materials and is applicable to the synthesis of a variety of α-substituted acrylic acids derived from both aliphatic and aromatic carbonyl substrates, on the basis of this simple concept.

Results and Discussion

Our initial investigations were conducted in alcoholic solution with an alkoxide base. As tacitly indicated above, simple stoichiometry considerations for this reaction demand the presence of 3 equiv of base/equiv of haloacetic acid and phosphite: 1 equiv to neutralize the carboxyl group, one to form the phosphite conjugate base, and one to deprotonate the intermediate phosphonate **3** to produce anion **2b**. Clearly, all 3 equiv must be present during the alkylation step, or the intermediate phosphonate **3** would quench the less acidic phosphite anion as alkylation proceeds, limiting the maximum theoretical yield to 50%.

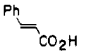
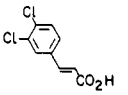
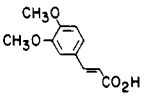
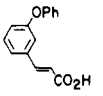
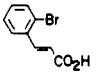
Thus reaction of 3 equiv of sodium ethoxide in ethanol containing diethyl phosphite (**4**) with bromoacetic acid and then with benzaldehyde afforded (*E*)-cinnamic acid (**5**) in 67% yield.



4 5

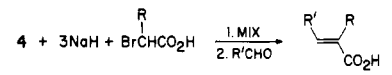
We have studied this reaction in some detail and have found that use of a 25% sodium methoxide in methanol solution,[14] dimethyl phosphite, and chloroacetic acid as reagents is most convenient. Using this optimized procedure, we have obtained yields of (*E*)-cinnamic acids in the range of 70–90%. Examples of cinnamic acids prepared by using this synthesis are presented in Table I.

Table I. Carboxyvinylation of Aryl Aldehydes with Chloroacetic Acid, Dimethyl Phosphite, and Sodium Methoxide in Methanol

benzaldehyde	product	yield, %
PARENT		89[a]
3,4-DICHLORO-		88[a]
3,4-DIMETHOXY-		74[b]
3-PHENOXY-		65–70[b,c]
2-BROMO-		54[a]

[a] Total crude crystalline yield. [b] Yield of purified product. [c] Results of three runs.

Scheme III

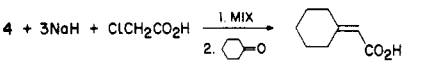


7–14

This simple procedure constitutes a very convenient, low-cost, and efficient synthesis of cinnamic acids. The facility of this reaction surpasses that of the classical Perkin[2] and Knoevenagel (Doebner)[3] reactions, in which high reaction temperatures and long reaction times or large excesses of the relatively expensive malonic acid are necessary to achieve comparable yields.

This procedure could not be extended to aliphatic carbonyl substrates. Clearly the problem lay with the alcoholic solvent since in previous work[9-11] cyclohexanone reacted with anion **2** generated directly from **1** in nonhydroxylic solvents to afford excellent yields of the olefinic acid.

To overcome these limitations, we used sodium hydride in 1,2-dimethoxyethane (glyme) as the base/solvent system. Addition of diethyl phosphite to a suspension of 3 equiv of 50% sodium hydride in mineral oil in glyme followed by addition of a solution of chloroacetic acid and then cyclohexanone led to a 54% yield of Δ^1,α-cyclohexeneacetic acid (**6**). After some adjustment of experimental conditions, this system afforded excellent yields of **6** (80%).

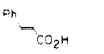
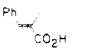
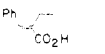
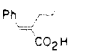
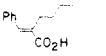
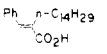
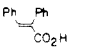
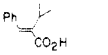
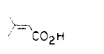
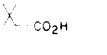
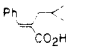
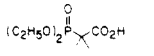
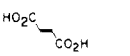
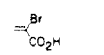


6

Not only does use of the sodium hydride/glyme system circumvent the ketone reactivity problem, but it also overcomes the other limitations of the alkoxide/alcohol system mentioned above. Most importantly, homologous 2-bromoalkanoic acids lead smoothly to 2-substituted alkenoic acids (Scheme III). There are no good general alternative synthetic routes to such acids. This is particularly significant because attempts to alkylate **2b** have been synthetically unpromising. Treatment of **2b** with iodomethane followed by another equivalent of sodium hydride and then benzaldehyde led to a 60–65% yield of

(4) Gensler, W. J.; Berman, E. *J. Am. Chem. Soc.* **1958**, *80*, 4949.
(5) Butler, C. G.; Callow, R. K.; Johnston, R. C. *Proc. R. Soc. London, Ser. B* **1961**, *155*, 417.
(6) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.
(7) Gallagher, G., Jr.; Webb, R. L. *Synthesis* **1974**, 122 and references therein.
(8) Wadsworth, W. S., Jr.; Emmons, W. D. *Org. Synth.* **1965**, *45*, 44.
(9) Koppel, G. A.; Kinnick, M. D. *Tetrahedron Lett.* **1974**, 711.
(10) Coutrot, P.; Snoussi, M.; Savignac, P. *Synthesis* **1978**, 133.
(11) Brittelli, D. R., unpublished results, **1974**.
(12) Martin, D. J.; Griffin, C. E. *J. Org. Chem.* **1965**, *30*, 4034. The authors of ref 9 and 10 seem to be unaware of this excellent synthetic route to **1b**.
(13) Worms, K. H.; Schmidt-Dunker, M. In "Organic Phosphorus Compounds"; Kosolapoff, G. M., Maier, L., Eds.; Wiley: New York, 1976, Vol. 7, p 27.
(14) Available from the Aldrich Chemical Co.

Table II. Carboxyvinylation of Benzaldehyde with 2-Bromoalkanoic Acids, Diethyl Phosphite, and Sodium Hydride in Glyme

halo acid	product		yield, %
BROMOACETIC (7)		(5)	85[a]
2-BROMOPROPIONIC (8)		(20)	100[a], 82[b]
2-BROMOBUTYRIC (9)		(21)	97[a]
2-BROMOPENTANOIC (10)		(22)	69[b]
2-BROMOHEXANOIC (11)		(23)	100[a]
2-BROMOHEXADECANOIC (12)		(24)	85[a]
2-BROMOPHENYLACETIC (13)		(25)	100[a]
2-BROMO-3-METHYLBUTYRIC (14)		(26)	~3[c]
		(27)	97[a]
2-BROMO-3,3-DIMETHYLBUTYRIC (15)		(28)	40
2-BROMO-4-METHYLPENTANOIC (16)		(29)	97[a]
2-BROMO-2-METHYLPROPIONIC (17)		(30)	66[b]
2-BROMOSUCCINIC (18)		(31)	56
2,3-DIBROMOPROPIONIC (19)		(32)	--[c]

[a] Total crude crystalline yield. [b] Yield of purified product. [c] By NMR.

an approximately 1:1 mixture of cinnamic and 2-methylcinnamic acids.

A summary of the scope of the synthesis with various 2-bromoalkanoic acids is given in Table II.

Especially noteworthy are the results with acids **9**–**12** in which increasing chain length does not affect the yields. By comparison, with the substituted malonic acid (Doebner) synthesis of **21**–**24**, declining yields begin with the two-carbon side-chain product **21** (40–60%) and drop to 20–40% with the four-carbon substituent of **23** and to 20% for a ten-carbon side chain.[4]

This chemistry is also applicable to the preparation of 2-phenylacrylic acids as illustrated by the conversion of **13** to **25**, but some limitations of the synthesis appear with acids **14** and **15**. Only a trace of 2-isopropylcinnamic acid (**26**) is seen (NMR) in the reaction employing **14**; substantially complete elimination to yield **27** occurs instead. With the *tert*-butyl-substituted acid **15**, no reaction occurs under the normal reaction conditions described above; under more forcing conditions (longer time and elevated temperature), the reduced acid **28** is produced. This can be regarded as the result of displacement on bromine rather than on carbon.

Branching farther out on the aliphatic side chain is not deleterious; **16** produced 2-isobutylcinnamic acid in excellent yield.

The reactivity pattern displayed by acids **7**–**16** is clearly noteworthy for its implications on the mechanism. These results parallel in a qualitative way the classical reactivity pattern for the effect of α-, β-, and γ-alkyl and α-phenyl substituents on rates of S_N2 alkylation[15] if the carboxylate is disregarded. That is, introduction of one or two substituents α (cf. conversion of **17** to **30**) or one substituent β to the center undergoing substitution does not produce a large effect on rate. Multiple β substitution greatly retards the reaction (acids **14** and **15**). The expected steric effect on a phenyl substituent is offset by its electronic effect. γ branching as in the isobutyl-substituted acid has no significant effect.

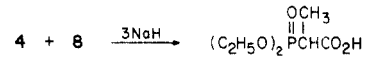
Although no kinetic measurements have been performed, a competition experiment between bromoacetic and 2-bromopropionic acids (molar ratio of phosphite/**7**/**8** of 1/2/2) has been examined; only cinnamic acid was produced (NMR).

The circumstantial evidence outlined above is consistent with an S_N2 process for the first step in the reaction. Specific experiments on optically active halo acid substrates, which could rule out the alternative mechanistic pathway proceeding through the intermediacy of an α-lactone, were rejected since the initially formed phosphonates would racemize via their achiral enolate anions.

Other limitations on the structure of the halo acid component are apparent in examples **18** and **19**. Acids bearing a good leaving group or an acidic hydrogen β to the carboxyl undergo facile elimination in preference to substitution.

The alkylation step of this reaction sequence obviously constitutes a synthesis of 2-phosphonoalkanoic acids. But many of these phosphonates are water soluble and hydrolytically sensitive and are thus hard to isolate quantitatively. They are also difficult to purify. Vacuum distillation of **1b** leads to transesterification to an equilibrium mixture of *P,P*-diester and mixed phosphorus–carboxyl diester.[16]

Isolation of **30** and **33** confirms that such phosphonates are present in the reaction mixture. However, **33** was



33

isolated in only 30% yield. This clearly points out the difficulty in recovering **33** from the reaction mixture since **33** was isolated in greatly reduced yield compared to the quantity demonstrably present in solution by trapping with benzaldehyde (82–100%). Since the main utility of these phosphonates from the organic synthesis standpoint is for Horner–Wadsworth–Emmons-type olefination, we prefer not to isolate the phosphonates but to use their derived anions generated in situ. Indeed, one of the major advantages of the overall procedure is that it avoids the need to synthesize precursor reagents.

Some idea of the scope of carbonyl components which can be used may be gleaned from the entries in Table III. No attempts were made to optimize these particular reactions. Undoubtedly improvements could be made in individual cases. The limitations on the scope of this carboxyvinylation procedure are expected to be determined by both the well-known steric effects on S_N2 alkylations[15] and the carbonyl reactivity in phosphonate olefination.[6]

Not surprisingly, in light of experience with the Horner–Wadsworth–Emmons reagent, the stereochemical preference for this carboxyvinylation is for the production of (*E*)-acrylic acids. But the propensity for the carboxyanion to produce *E* olefins is even stronger than that of the ester. Kinstle and Mandanas showed that with in-

(15) Streitwieser, A., Jr. *Chem. Rev.* **1956**, *56*, 571.
(16) Magerlein, B.; Kagan, F. *J. Am. Chem. Soc.* **1960**, *82*, 593.

Table III. Carboxyvinylation of Representative Carbonyl Compounds with 2-Bromoalkanoic Acids, Diethyl Phosphite, and Sodium Hydride in Glyme

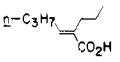
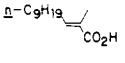
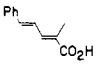
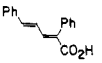
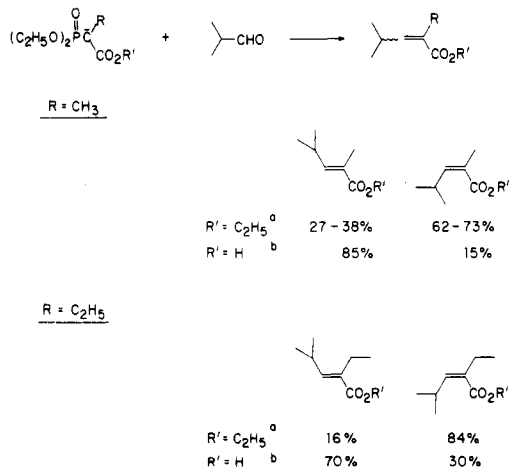
carbonyl substrate	halo acid	product	yield, %
CH_2O	9		53
n-C_3H_7CHO	10		55
n-$C_9H_{19}CHO$	8		64
	8		88
	13		91
	8		76
Ph_2CO	7		30

Table IV. Effect of Substitution on the Stereochemical Outcome of Carbethoxylation and Carboxyvinylation



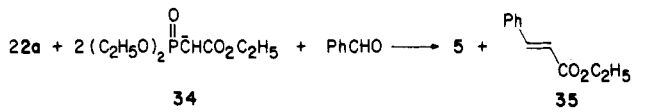
[a] Reference 17. [b] This work.

creasing steric bulk in both the phosphonate and carbonyl moieties, the *Z* olefinic ester may become the major product.[17] Their results are compared with the respective carboxy anion systems in Table IV. Even in the case of the 2-ethyl anion, which in the ester series gave predominantly the *Z* isomer, our carboxy anion still produced the *E* olefin by a greater than 2:1 margin. We interpret this to mean that the carboxylate, with its gegenion and associated solvent shell, behaves as though it were larger than the carboethoxy group.

The implication for synthesis is clear. In such substituted systems, olefins with complementary geometry may be obtained by proper choice of carboxyl functionality, and the carboxylate-bearing anion can be depended upon to furnish a higher proportion of *E*-olefin product.

Surprisingly, there is no significant reactivity difference between carboxylate- and carbethoxy-bearing anions. In a competition experiment, equimolar quantities of **2a** and **34** were allowed to compete for 25 mol % of benzaldehyde. A 50% yield of cinnamic acid and a 48% yield of ethyl cinnamate were produced. One potential advantage in the

(17) Kinstle, T. H.; Mandanas, B. Y. *J. Chem. Soc., Chem. Commun.* **1968**, 1699.



34 **35**

production of α,β-unsaturated carboxylic acid salts compared to the corresponding esters is that the salts are not subject to facile isomerization to β,γ-unsaturated isomers, which can be a problem with the esters produced from **34**.[8]

This sequential in situ carboxyvinylation promises to be a powerful synthetic method for α-substituted, α,β-unsaturated carboxylic acids. We have therefore examined experimental variables in some detail. The narrower scoped sodium methoxide-in-methanol modification has already been discussed, so we will deal here only with the sodium hydride/nonhydroxylic solvent system.

We have routinely used 1,2-dimethoxyethane (glyme) as the solvent for these reactions. We find that about 500 mL of glyme/0.1 mol of halo acid must generally be used or the mixture sets up to a thick gelatinous mass which hinders good mixing. The synthesis is also operable in toluene, heptane, ether, pyridine, *N,N*-dimethylformamide, and tetrahydrofuran, but we see no particular advantages with these solvents.

The reaction mixture does not need to be heated; indeed, heating may prove deleterious to yields. The reaction has proceeded well at autogenous temperature and the effect of external heating has not been systematically examined.

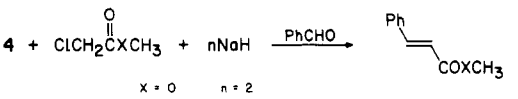
Better yields seem to be obtained if the reaction mixture is stirred vigorously during addition of the halo acid. Presumably this is effective since it prevents local aggregates of unreactive crystalline carboxylate salt from building up.

In some cases, particularly in reactions involving 2-bromophenylacetic acid (**13**), the initially formed phosphonate does not undergo complete deprotonation under the reaction conditions, presumably because of a steric or other kinetically inhibiting effect on proton transfer. In such cases, adding a small amount of an alcohol as a messenger base is helpful to complete anion formation after initial hydrogen evolution ceases.

Bromo- or chloro-substituted acids seem to function equally in the only cases (acetic and propionic acid series) where comparisons have been made. The bromo derivatives of higher acids were generally used simply because of their commercial availability.

Diethyl phosphite is the phosphite of choice. Use of dimethyl phosphite leads to agglomeration and formation of an insoluble phase, longer chain phosphites afford more viscous reaction mixtures, and the alkylation step proceeds much more slowly. Diethyl thiophosphite ($(C_2H_5O)_2P(S)H$) is also effective, although it offers no advantages over diethyl phosphite.

The in situ procedure can be extended to preparation of α,β-unsaturated esters and amides. Reaction of diethyl phosphite, sodium hydride, and either methyl chloroacetate or *N*-methyl chloroacetamide followed by treatment with benzaldehyde afforded the corresponding cinnamic acid derivatives in 100% and 54% yields, respectively.



Conclusions

This in situ acrylic acid synthesis possesses several significant advantages over conventional acrylic acid and ester syntheses.

Starting materials are much more readily available and inexpensive. A wide variety of 2-halo carboxylic acids are commercially available or are easily prepared. The 50% sodium hydride in mineral oil dispersion is an inexpensive, safe, and easy-to-handle base. Operationally, the reaction is very convenient and simple to carry out. Product isolation is facilitated by simplified extractive removal of byproducts, and purification is often more convenient because of the crystalline nature of a majority of acrylic acids. Indeed, in many cases the products as isolated are sufficiently pure for further synthetic transformations (for example, esterification or reduction to saturated alcohols).

Experimental Section

General Methods. All reactions were run under a positive pressure of dry nitrogen. Infrared spectra were determined on a Perkin-Elmer 137 spectrophotometer and are reported in reciprocal centimeters. ^{1}H NMR spectra were determined in the indicated solvent on a Varian A-60 spectrometer and are reported in δ units (parts per million) downfield from tetramethylsilane as the internal reference. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet; br, broad. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Benzaldehyde was purified just prior to use by washing with aqueous $NaHCO_3$ solution, drying ($MgSO_4$), and distillation. All other chemicals were reagent grade and were used as received. Sodium hydride was employed as a 50% dispersion in mineral oil, and the weights reported are for the dispersion.

Preparation of Diethyl (Carboxymethyl)phosphonate (1b). The phosphonate was prepared by Martin and Griffin's method[12] with one modification. We find, in confirmation of Magerlein's report,[16] that distillation of **1b** results in transesterification to give as a product **1b** containing ~12% of $(C_2H_5O)P(O)(OH)CH_2C-O_2C_2H_5$. We found it best to purify the benzyl ester carefully and after the subsequent catalytic hydrogenolysis, the product **1b** was obtained simply by filtration of catalyst and removal of solvent in vacuo. Product thus obtained is clean (NMR), free of the isomeric diester, and sufficiently pure for further use.

Preparation of (*E*)-Cinnamic Acid (5). To 4.0 mL (31 mmol) of diethyl phosphite and 6.5 g (93 mmol) of 97% sodium ethoxide[14] in 100 mL of absolute ethanol was added dropwise a solution of 4.32 g (31 mmol) of bromoacetic acid in 25 mL of absolute ethanol. The mixture was stirred for 15 min and then heated to 50 °C for 20 min, at which time the mixture became homogeneous. Benzaldehyde (3.15 mL, 31 mmol) was added, and the mixture was stirred for 1.5 h. The solution was then poured into water and washed with ether, which was discarded. The aqueous layer was acidified to pH 4 with concentrated HCl and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and evaporated in vacuo to afford 3.0 g (67%) of (*E*)-cinnamic acid: mp 132–135 °C (lit.[2] mp 131.5–132.5 °C); IR ($CHCl_3$) 3600–2400, 1700, 1620, 1600 cm^{-1}; NMR ($CDCl_3$) δ 6.43 (1, d, J = 16 Hz, $=CHCO_2H$), 7.2–7.6 (5, m, C_6H_5), 7.80 (1, d, J = 16 Hz, PhCH=), 11.90 (1, s, CO_2H).

Preparation of Cinnamic Acids Using Sodium Methoxide in Methanol. General Procedure. To 20 mL of 25% sodium methoxide in methanol[14] (93 mmol) in 50 mL of methanol was added 31 mmol of dimethyl or diethyl phosphite and then 31 mmol of bromo- or chloroacetic acid. The mixture was heated under reflux for 2 h, and then 31 mmol of the aromatic aldehyde was added. The resulting mixture was stirred for 45 min, and then the solution was poured into water and washed once with ether. The aqueous layer was acidified to pH 4 with concentrated HCl and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated in vacuo to yield the crystalline acid.

(*E*)-Cinnamic Acid (5). The above procedure was used to afford 4.1 g (89%) of **5** (mp 131–132 °C) identical with the above sample.

3′,4′-Dichloro-(*E*)-cinnamic Acid. Use of the general procedure gave the product: 5.92 g (88%); mp 214–216 °C (from methanol); IR (Nujol mull) 3300–2500, 1700, 1660, 1620 cm^{-1}; NMR (Me_2SO-d_6) δ 6.65 (1, d, J = 16 Hz, $CHCO_2H$), 5.97 (1, d, J = 16 Hz, $CH=CHCO_2H$), 7.68 (2, s, aromatic 5, 6-H), 8.00, (1, s, aromatic 2-H), 11.0–11.5 (1, br, CO_2H). Anal. Calcd for $C_9H_6Cl_2O_2$: C, 49.80; H, 2.79. Found: C, 49.53; H, 2.95.

3′,4′-Dimethoxy-(*E*)-cinnamic Acid. The general procedure provided the product: 4.77 g (74%); mp 181–183 °C (from methanol); IR ($CHCl_3$) 3600–2500, 1690, 1630, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 3.82 (3, s, OCH_3), 3.83 (3, s, OCH_3), 6.47 (1, d, J = 14 Hz, $=CHCO_2H$), 6.9–7.4 (1, d, J = 14 Hz, $CH=CHCO_2H$). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.21; H, 5.63.

3′-Phenoxy-(*E*)-cinnamic Acid. This substance was prepared by the general procedure (5 times the above scale): 24.32 g (65%); mp 113–115 °C (from CH_3OH); IR (Nujol mull) 3300–2200, 1700, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 6.60 and 7.65 (2, AB, J_{AB} = 16 Hz, CH=CH), 7.0–7.7 (9, m, aromatic), 11.33 (1, br, CO_2H). Anal. Calcd for $C_{15}H_{12}O_3$: C, 75.00; H, 5.03. Found: C, 75.17; H, 5.20.

2′-Bromo-(*E*)-cinnamic Acid. This substance was prepared by the general procedure: 3.80 g (54%); mp 217.5–218.5 °C (from methanol); IR (Nujol mull) 3600–2400, 1700, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 6.41 (1, d, J = 16 Hz, $=CHCO_2H$), 7.4 (4, br, aromatic), 7.76 (1, d, J = 16 Hz, PhCH=), 10.72 (1, s, CO_2H). Anal. Calcd for $C_9H_7BrO_2$: C, 47.61; H, 3.11. Found: C, 47.78; H, 3.16.

Preparation of Acrylic Acids Using Sodium Hydride in Glyme. General Procedure. A mixture of 4.0 mL (31 mmol) of diethyl phosphite and 4.46 g (93 mmol) of 50% sodium hydride in mineral oil in 100 mL of 1,2-dimethoxyethane under nitrogen was treated with a solution of 31 mmol of α-halo carboxylic acid in 30 mL of 1,2-dimethoxyethane, and the mixture was stirred until hydrogen gas evolution ceased. Then 31 mmol of aldehyde or ketone was added, and the mixture was stirred for 1 h. The mixture was then quenched by addition of 5 mL of ethanol and poured into 500 mL of water. The strongly basic solution was washed with ether to remove mineral oil (ether extract discarded), acidified to pH 4 with concentrated hydrochloric acid and extracted with ether. The latter ether solution was dried ($MgSO_4$) and evaporated in vacuo to afford the product.

(*E*)-Cinnamic Acid (5). Use of chloroacetic acid and benzaldehyde afforded 3.89 g (85%) of **5**, identical with material obtained above.

2-Cyclohexylideneacetic Acid (6). With chloroacetic acid and cyclohexanone, the above procedure afforded compound **6**: 3.45 g (80%); mp 90–91.5 °C (lit.[18] mp 90–92 °C); IR ($CHCl_3$) 3600–2400 (OH), 1700 (C=O), 1650 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60 (6, s, $CH_2CH_2CH_2CH_2CH_2C=$), 2.17 (2, s, $CH_2CH_2CH_2CH_2CH_2CH_2C=$), 2.77 (2, s, $CH_2CH_2CH_2CH_2CH_2C=$), 5.50 (1, s, $=CHCO_2H$), 11.40 (1, s, CO_2H). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.45; H, 8.61.

2-Methylcinnamic Acid (20). The general procedure when used with 2-bromopropionic acid and benzaldehyde yielded 5.06 g (100%) of **20**. Recrystallization from petroleum ether gave acid **20**: 4.15 g (82%); mp 77–79 °C (lit.[4] mp 79–81 °C); IR ($CHCl_3$) 3600–2400, 1700, 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.15 (3, d, J = 1.5 Hz), CH_3), 7.43 (5, s, aromatic), 7.84 (1, q, J = 1.5 Hz, HC=), 11.42 (1, s, CO_2H).

2-Ethylcinnamic Acid (21). Use of 2-bromobutyric acid and benzaldehyde gave **21**: 5.31 g (97%); mp 105–106.5 °C (*n*-butyl chloride) (lit.[4] mp 103–104°); IR ($CHCl_3$) 3600–2400, 1700, 1620, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 1.12 (3, t, J = 7 Hz, CH_2CH_3), 2.47 (2, q, J = 7 Hz, CH_2CH_3), 7.40 (5, s, aromatic), 7.58 (1, s, =CH), 11.2–12.2 (1, br, CO_2H). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.90; H, 6.79.

(*E*)-2-*n*-Propylcinnamic Acid (22). 2-Bromopentanoic acid and benzaldehyde were used to yield **22**: 4.08 g (69%); mp 88–91 °C (petroleum ether) (lit.[19] mp 93 °C); IR (Nujol mull) 3300–2400, 1670, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (3, t, J = 7 Hz, CH_3), 1.63 (2, m, $CH_2CH_2CH_3$), 2.52 (2, m, $CH_2CH_2CH_3$), 7.42 (5, s, aromatic), 7.85 (1, s, CH=), 12.32 (1, s, CO_2H).

(*E*)-2-*n*-Butylcinnamic Acid (23). The procedure with 2-bromohexanoic acid and benzaldehyde afforded **23**: 6.35 g

(18) Beesley, R. M.; Thorpe, J. F.; Ingold, C. K. *J. Chem. Soc.*, **1915**, 1099

(19) Bogert, M. T.; Davidson, D. *J. Am. Chem. Soc.* **1932**, *54*, 334.

(100%); mp 82–84 °C (petroleum ether) (lit.[20] mp 83–84 °C); IR (Nujol mull) 3200–2400, 1650, 1600 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (3, t, J = 7 Hz, CH_3), 1.2–1.8 (4, m, $CH_2CH_2CH_3$), 2.57 (2, m, $=CHCH_2$), 7.37 (5, s, aromatic), 7.83 (1, s, CH=C), 12.65 (1, s, CO_2H).

(*E*)-2-*n*-Tetradecylcinnamic Acid (24). 2-Bromohexadecanoic acid and benzaldehyde were used to give **24**: 9.1 g (85%); mp 83–84 °C (ethanol); IR ($CHCl_3$) 3600–2400, 1690, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (27, s, n-$C_{13}H_{27}$), 2.58 (2, m, $=CCH_2C_{13}H_{27}$), 7.38 (5, s, aromatic), 7.80 (1, s, CH=), 10.83 (1, s, CO_2H). Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.89; H, 10.37.

(*E*)-2-Phenylcinnamic Acid (25). The procedure employing 2-bromophenylacetic acid and benzaldehyde afforded **25**: 6.96 g (100%); mp 170–172 °C (lit.[21] mp 172 °C); IR ($CHCl_3$) 3600–2400, 1680, 1610, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 5.6–6.9 (1, br, CO_2H), 6.9–7.5 (10, m, aromatic), 7.80 (1, s, =CH).

Attempted Preparation of 2-(1-Methylethyl)cinnamic Acid (26). Use of 2-bromo-3-methylbutyric acid and benzaldehyde afforded 3.47 g of a crystalline substance. NMR showed peaks at δ 1.93, 2.18, 5.72, and 11.1 which were from **27**. Integration of these signals established that 26 and 27 were present in the ratio 3:97.

Attempted Preparation of 2-(1,1-Methylethyl)cinnamic Acid. Use of **15** and benzaldehyde afforded 5.07 g of a liquid which NMR showed to be a 100% yield of a 40:60 mixture of **28** and **15**.

2-(2-Methylpropyl)cinnamic Acid (29). 2-Bromo-4-methylbutyric acid and benzaldehyde yielded **29**: 6.15 g (97%); mp 73.5–74.5 °C (petroleum ether); IR ($CHCl_3$) 3600–2400, 1680, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.11 (6, d, J = 6.5 Hz, $CH(CH_3)_2$), 1.97 (1, m, $CH(CH_3)_2$), 2.53 (2, d, J = 7 Hz, CH_2CH), 7.33 (5, s, aromatic), 7.82 (1, s, CH=), 11.87 (1, s, CO_2H). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.77; H, 7.84.

2-(Diethoxyphosphinyl)-2-methylpropionic Acid (30). To 2.97 g of 50% sodium hydride in mineral oil and 4.0 mL of diethyl phosphite in 100 mL of glyme was added 5.18 g of 2-bromo-2-methylpropionic acid in 40 mL of glyme. The mixture was stirred 96 h and then quenched by addition of a solution of 3.4 g of hydrogen chloride gas in 25 mL of glyme. The resulting mixture was filtered through diatomaceous earth and evaporated in vacuo to afford 6.05 g of a liquid. Vacuum distillation yielded 4.59 g (66%) of **30**: bp 120–135 °C (0.3 mm); IR (neat) 3600–2400, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (6, t, J = 7 Hz, CH_2CH_3), 1.47 (6, d, J_{P-H} = 16.5 Hz), $C(CH_3)_2$), 4.18 (4, dt, J = 7 Hz, J_{P-H} = 7 Hz, CH_2CH_3), 11.38 (1, s, CO_2H). Anal. Calcd for $C_8H_{17}PO_5$: C, 42.86; H, 7.64. Found: C, 42.57; H, 7.74.

2-Ethylacrylic Acid. From formaldehyde and 2-bromobutyric acid on 3 times the above scale was obtained 4.93 g (53%) of 2-ethylacrylic acid: bp 95–98 °C (25 mm); IR (neat) 3600–2400, 1690, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (3, t, J = 7 Hz, CH_2CH_3), 2.34 (2, q, J = 7 Hz, CH_2CH_3), 5.63 (1, s, =CH cis to CO_2H), 6.28 (1, s, =CH trans to CO_2H), 11.45 (1, s, CO_2H).

2-(Diethoxyphosphinyl)propionic Acid (33). With the same method that let to **30**, 2-bromopropionic acid yielded 2.06 g (31%) of **33**: bp 125 °C (0.2 mm); IR (neat) 3700–2400, 1700, 1260 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (6, t, J = 7 Hz, OCH_2CH_3), 1.48 (3, dd, J = 7 Hz, J_{P-H} = 15 Hz, $PCHCH_3$), 3.06 (1, dq, J = 7 Hz, J_{P-H} = 24 Hz, $PCHCH_3$), 4.19 (4, dt, J = 7 Hz, J_{P-H} = 7 Hz, OCH_2CH_3), 10.42 (1, s, CO_2H). Anal. Calcd for $C_7H_{15}PO_5$: C, 40.01; H, 7.19. Found: C, 3953; H, 7.34.

(*E*)-2-*n*-Propyl-2-hexenoic Acid. Use of the general procedure with 2-bromopentanoic acid and n-butyraldehyde yielded the product: 2.67 g (55%); bp 128–134 °C (12 mm); IR (neat) 3600–2500, 1700, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (6, m, CH_3), 1.2–1.8 (4, m, CH_2CH_3), 2.0–2.5 (4, m, $CH_2CH{=}CH_2$), 11.9 (1, s, CO_2H).

(*E*)-2-Methyl-2-dodecenoic Acid. From 2-bromopropionic acid and n-decanaldehyde was obtained 4.20 g (65%) of (*E*)-2-methyl-2-dodecenoic acid: mp 33–35 °C (lit.[22] mp 33 °C); IR (Nujol mull) 3400–2400, 1690, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.8 (17, m, C_8H_{17}), 1.83 (3, d, J = 1.5 Hz, $=CCH_3$), 2.20 (2, m, CH_2C=), 6.91 (1, td, J = 7.5 Hz, J' = 1.5 Hz), 10.53 (1, s, CO_2H).

(*E,E*)-2-Methyl-5-phenyl-2,4-pentadienoic Acid. This substance (10.3 g, 88%) was obtained by using the general procedure on twice the above scale with 2-bromopropionic acid and (*E*)-cinnamaldehyde: mp 159–161.5 °C (n-butyl chloride); IR (Nujol) 2600–2500, 1670, 1610, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 2.03 (3, s, CH_3), 7.05 (1, s, $=CHCH=$) 7.21 (1, s, $PhCH=$), 7.0–7.8 (5, m, aromatic), 7.56 (1, s, $=CHCH=$). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.71; H, 6.46.

(*E,E*)-2,5-Diphenyl-2,4-pentadienoic Acid. Use of (*E*)-cinnamaldehyde and 2-bromophenylacetic acid furnished 7.07 g (91%) of the title compound with NMR and IR spectra identical with those of authentic material.

2-Cyclohexylidenepropionic Acid. Cyclohexanone and 2-bromopropionic acid furnished the product: 3.40 g (76%); mp 65–67 °C (lit.[23] mp 68.5 °C); IR ($CHCl_3$) 3600–2500, 1675, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.1–1.8 (8, m, ring CH_2), 1.90 (3, s, CH_3), 2.2–2.8 (4, $(CH_2)_2C$=), 11.28 (1, s, CO_2H).

3,3-Diphenylacrylic Acid. Chloroacetic acid and benzophenone yielded 2.1 g (30%) of 2,2-diphenylacrylic acid: mp 158–160 °C (lit.[24] mp 160–162 °C); IR ($CHCl_3$) 3600–2500, 1680, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 6.34 (1, s, =CH) 7.32 (10, s, aromatic).

(*E*)- and (*Z*)-2,4-Dimethyl-2-pentenoic Acids. From 2-bromopropionic acid and 2-methylpropionaldehyde there was obtained 3.4 g (85%) of the mixture of isomers: bp 122–125 °C (15 mm); IR (neat) 3700–2400, 1690, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (6, d, J = 7 Hz, $(CH_3)_2CH$), 1.83 (3, d, J = 1.5 Hz, CH_3), 2.60 (1, m, $CH(CH_3)_2$), 5.80 (15% of 1, d, J = 10 Hz, CH=C, *Z* isomer), 6.70 (85% of 1, d, J = 10 Hz, CH=C, *E* isomer), 10.50 (1, s, CO_2H).

(*E*)- and (*Z*)-2-Ethyl-4-methyl-2-pentenoic Acids. From 2-bromobutyric acid and 2-methylpropionaldehyde was obtained 6.3 g (71%) of the mixture of isomers: bp 127–132 °C (15 mm); IR (neat) 3600–2400, 1690, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (6, d, J = 7 Hz, $CH(CH_3)_2$), 1.05 (3, t, J = 7 Hz, CH_2CH_3), 2.40, (1, m, $CH(CH_3)_2$), 5.78 (30% of 1, d, J = 10 Hz, (*Z*)-CH=C), 6.70 (70% of 1, d, J = 10 Hz, (*E*)-CH=C), 11.52 (1, s, CO_2H).

Competition Reaction between 2a and 34. To 3.30 g (81 mmol) of a 59.3% suspension of sodium hydride in mineral oil in 125 mL of glyme was added dropwise a solution of 5.36 mL (27 mmol) of ethyl (diethoxyphosphinyl)acetate and 5.30 g (27 mmol) of **1** in 50 mL of glyme. The mixture was stirred until hydrogen gas evolution ceased and then treated with 1.35 mL (13.5 mmol) of benzaldehyde. The mixture was stirred for 2.0 h, quenched by addition of ethanol, and poured into water. The mixture was extracted with ether, the ether layer was dried ($MgSO_4$) and evaporated in vacuo, and the residue was Kugelrohr distilled to yield 1.16 g (49%) of ethyl cinnamate with NMR and IR spectra identical with those of an authentic sample. The aqueous layer was acidified to pH 4 with concentrated hydrochloric acid and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated in vacuo to yield 0.98 g (50%) of (*E*)-cinnamic acid with an NMR spectrum identical with that obtained above.

Registry No. 1b, 3095-95-2; **4**, 762-04-9; (*E*)-**5**, 140-10-3; **7**, 79-08-3; **8**, 598-72-1; **9**, 80-58-0; **10**, 584-93-0; **11**, 616-05-7; **12**, 18263-25-7; **13**, 4870-65-9; **14**, 565-74-2; **15**, 50364-40-4; **16**, 49628-52-6; **17**, 2052-01-9; **18**, 923-06-8; **19**, 600-05-5; (*E*)-**20**, 1895-97-2; (*E*)-**21**, 26197-64-8; (*E*)-**22**, 77124-15-3; (*E*)-**23**, 77136-32-4; (*E*)-**24**, 77124-16-4; (*E*)-**25**, 91-48-5; (*E*)-**26**, 77124-17-5; **27**, 541-47-9; **28**, 1070-83-3; (*E*)-**29**, 77124-18-6; **30**, 77124-19-7; (*E*)-**31**, 110-17-8; **32**, 10443-65-9; bromoacetic acid, 79-08-3; benzaldehyde, 100-52-7; dimethyl phosphite, 868-85-9; chloroacetic acid, 79-11-8; 3′,4′-dichloro-(*E*)-cinnamic acid, 7312-27-8; 3′,4′-dimethoxy-(*E*)-cinnamic acid, 14737-89-4; 3′-phenoxy-(*E*)-cinnamic acid, 77124-20-0; 2′-bromo-(*E*)-cinnamic acid, 7345-79-1; 3,4-dichlorobenzaldehyde, 6287-38-3; 3,4-dimethoxybenzaldehyde, 120-14-9; 3-phenoxybenzaldehyde, 39515-51-0; 2-bromobenzaldehyde, 6630-33-7; cyclohexanone, 108-94-1; **6**, 1552-91-6; **33**, 30094-28-1; 2-ethylacrylic acid, 3586-58-1; formaldehyde, 50-00-0; (*E*)-2-propyl-2-hexenoic acid, 77124-21-1; butyraldehyde, 123-72-8; (*E*)-2-methyl-2-dodecenoic acid, 53663-29-9; decanaldehyde, 112-31-

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2; (*E,E*)-2-methyl-5-phenyl-2,4-pentadienoic acid, 20414-94-2; (*E*)-cinnamaldehyde, 14371-10-9; (*E,E*)-2,5-diphenyl-2,4-pentadienoic acid, 23848-94-4; 2-cyclohexylidenepropionic acid, 77124-22-2; 3,3-diphenylacrylic acid, 606-84-8; benzophenone, 119-61-9; 2-methylpropionaldehyde, 78-84-2; (*E*)-2,4-dimethyl-2-pentenoic acid, 3876-52-6; (*Z*)-2,4-dimethyl-2-pentenoic acid, 3876-51-5; (*E*)-2-ethyl-4-methyl-2-pentenoic acid, 77124-23-3; (*Z*)-2-ethyl-4-methyl-2-pentenoic acid, 77124-24-4; (*E*)-ethyl cinnamate, 4192-77-2; **1a**, 53243-58-6.

Aromatic Fluorinations Suitable for Fluorine-18 Labeling of Estrogens

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Received February 3, 1981

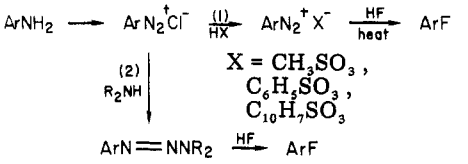
Two aromatic fluorination methods, the decomposition of aryl azides and the decomposition of aryltriazenes, were investigated as methods potentially suitable for fluorine-18 labeling of estrogens. The aryltriazene method gives moderate yields in many systems but fails with *o*-methoxy or (methanesulfonyl)oxy groups. The aryl azide method gives good yields of *p*-fluoroanilines, which can be deaminated readily, but oxygen or large alkyl groups ortho to the azide interfere with the fluorination. The synthesis of *m*-fluorohexestrol via the aryltriazene decomposition approach is reported.

Introduction

The changes in physical and chemical properties resulting from the introduction of fluorine into organic compounds have long been recognized by organic chemists, and fluorinated substituents have been used as labels, probes, and controlling substituents for mechanistic studies.[1] The isosteric replacement of hydrogen by fluorine has been used by pharmacologists to elevate hydrophobicity and to retard metabolism.[1d] Recently, interest in the preparation of radiopharmaceuticals labeled with short-lived isotopes as imaging agents and physiological probes has rekindled an interest in developing methods for the introduction of fluorine that would be suitable for isotope incorporation.[2]

Fluorine-18 is a 110-min half-life positron emitter that can be produced readily and in large quantities by medical cyclotrons and is an excellent radionuclide for studies by positron-emission transaxial tomography.[3] Methods for the introduction of fluorine-18 into organic molecules need to be convenient and rapid and should also be of reasonably high yield. In addition, the preparation of radiopharmaceuticals whose distribution is based on uptake by high-affinity, limited capacity binding systems (receptor binding) requires labeling methods that will operate without added carrier fluorine and will produce agents of high specific activity.[4] For the preparation of aliphatic fluorine-containing compounds, the modification of methods based on displacements by fluoride ion appear to be suitable,[2f,5] but the preparation of high specific activity fluorine-labeled aromatic compounds presents additional challenges.

Scheme I



While there are a number of methods for aromatic fluorination, the traditional Balz–Schiemann reaction[6] is the only commonly used method in the syntheses of fluorine-18 labeled aromatic compounds.[2c,7] This reaction is very inefficient from a radiochemical point of view, because the maximum radiochemical yield is only 25%. But, more importantly, since fluorine is introduced by exchange labeling of an aryldiazonium tetrafluoroborate precursor, the dilution of specific activity by the unlabeled fluorine in the counterion is enormous. In fact, the low specific activity of some radiopharmaceuticals synthesized by this method can account for their failure to localize in target organs.[7b]

In conjunction with studies toward the development of γ-emitting estrogen analogues as receptor-based agents for imaging breast tumors,[8] we realized the need for new methods for the synthesis of fluorine-18 labeled aromatic compounds of high specific activity, particularly methods that would be suitable for the preparation of fluoroaromatics containing phenolic oxygen functions, as are found in estrogens. Here, we report two methods for aromatic fluorination: fluoride trapping of arylnitrenium

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