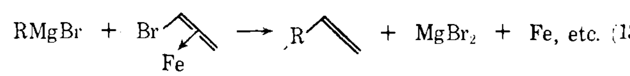
2 or propylene. The latter certainly would have resulted if a propenyliron species (for example, from reactions 5 and 6, R = propenyl) were involved in the catalytic process. Moreover, the ethyliron species which were involved (eq 4–7) in the disproportionation reaction 11a could not have participated in the alkenylation reaction.

$$CH_3CH_2Fe + CH_3CH{=}CHBr \not\rightarrow CH_3CH{=}CHCH_2CH_3 + FeBr, \text{etc.} \quad (12)$$

The conclusion that the mechanism of the reaction of alkenyl halides differs from alkyl halides is based on the following observations: (a) the high yields and stereospecificity of the cross-coupled products, (b) the inverse dependence of the rate on the concentration of the Grignard reagent, (c) the effect of styrene, and (d) the one and one-half times greater reactivity of propenyl bromide compared to ethyl bromide despite the higher bond dissociation energy of the former.

We propose that the alkenylation reaction proceeds *via* an Fe-assisted displacement of the alkenyl halide by the Grignard reagent (eq 13). Retention of con-



(13)

figuration during substitution implies an intramolecular delivery of the Grignard reagent, a process which may be possible *via* a ternary complex. The retardation by the Grignard reagent or added triphenylphosphine is consistent with coordination of the active Fe species in competition with the alkenyl halide.

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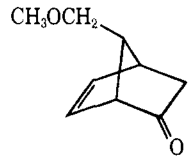
Methoxymethylation of Thallous Cyclopentadienide. A Simplified Preparation of a Key Intermediate for the Synthesis of Prostaglandins

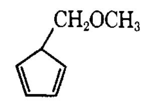
Sir:

The bicyclic ketone I has been used as a key intermediate for the synthesis of all *six* of the primary prostaglandins[1] in naturally occurring form.[2-4] The synthetic approach to prostaglandins *via* I or its 7-benzyloxymethyl analog is currently being utilized on a substantial scale in several industrial laboratories and appears to be the most effective route for the production of these medically important substances. This communication describes a new preparation of I which involves novel chemistry and has several advantages over the procedure outlined earlier, most important of which is its operational simplicity and suitability for use on a large scale.

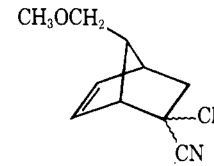
The first step in the synthesis of I as originally described[2a] was the alkylation of sodium cyclopentadienide with chloromethyl methyl ether in tetrahydrofuran at $-55°$ to give after evaporation, addition of cold ether, and washing with pH 7 phosphate buffer (all operations $<0°$) the alkylated cyclopentadiene II. The diene II was utilized without delay in a diene addition to 2-chloroacrylonitrile at 0° in the presence of cupric tetrafluoroborate to generate the adduct III, from which the ketone I could be derived by alkaline hydrolysis. The preparation of II and III in this way, though acceptable as a research operation, left much to be desired for several reasons. Most importantly, isom-



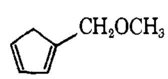
I



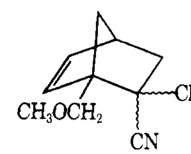
II



III



IV



V

erization of II to form the undesired IV occurs readily in the presence of acidic or basic substances even below 0°, and for this reason experimental results vary widely. As the scale of the alkylation reaction is increased, isolation requires more time, and isomerization becomes a serious side reaction so that chromatographic purification of the adduct III is required to separate the isomeric adduct V and other by-products in the bicyclo[3.2.0]heptane series.[5] Definite improvement in the alkylation process was effected by the use of the less basic lithium cyclopentadienide and the more reactive bromomethyl methyl ether as reactants in ether as solvent at $-45°$, followed by the usual low-temperature washing with a small amount of concentrated pH 7 buffer to remove inorganic salts. However, an outstanding and clearly superior procedure could be developed based on thallous cyclopentadienide rather than the conventionally employed alkali metal salts. One considerable advantage of the thallium derivative is its ready availability from aqueous thallous sulfate, potassium hydroxide, and cyclopentadiene (nitrogen atmosphere, $>97\%$ yield).[6] Another advantage is ease of handling and storage, since thallous cyclopentadienide is relatively stable in air.

(1) S. Bergström, *Science*, **157**, 382 (1967).
(2) Prostaglandins $F_{2\alpha}$ and E_2: (a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969); (b) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970).
(3) Prostaglandins $F_{1\alpha}$ and E_1: E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, **92**, 2586 (1970).
(4) Prostaglandins $F_{3\alpha}$ and E_3: E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971).
(5) The reaction of 2-chloroacrylonitrile with cyclopentadienes under catalysis by cupric fluoroborate produces in addition to the expected norbornene adducts smaller amounts (10–40% depending on medium and temperature) of 2 + 2 cycloadducts of the bicyclo[3.2.0]heptane type; *cf.* (a) W. L. Dilling, R. D. Kroening, and J. C. Little, *ibid.*, **92**, 928 (1970), and (b) H. W. Thompson and D. G. Mellilo, *ibid.*, **92**, 3219 (1970).
(6) (a) H. Meister, *Angew. Chem.*, **69**, 533 (1957); (b) F. A. Cotton and L. T. Reynolds, *J. Amer. Chem. Soc.*, **80**, 272 (1958).

A typical alkylation experiment was performed as follows. A suspension of 1 mol of thallous cyclopentadienide in 400 ml of dry ether at −20° (N_2) was treated gradually with 1 mol of chloromethyl methyl ether with stirring. After 5 hr the insoluble thallous chloride was removed by rapid filtration from the precooled (to −40°) mixture and washed with a small amount of pentane.[7] Concentration of the ether solution under reduced pressure (<0°) afforded the monoalkylated cyclopentadiene II containing 0–3% of the isomer IV by nmr analysis. Reaction of the cyclopentadiene II so obtained with 2-chloroacrylonitrile (4 equiv) and cupric fluoroborate[8] (0.3 equiv) at 0° for 18 hr followed by addition of brine containing some sodium tartrate, extraction with ether, and concentration *in vacuo* afforded an oily product (80–90% yield) containing 75–85% of the desired adduct III by vpc analysis.[9] Alkaline hydrolysis of this crude product dissolved in 1 l. of dimethyl sulfoxide was accomplished by addition of a hot solution of 2.5 mol of potassium hydroxide in 45 ml of water and maintenance at 30–35° for 1.5 hr. Addition of water to the reaction mixture, extraction with ether, and distillation of the organic extract through a spinning band column afforded pure ketone I,[2a] bp 68° (0.5 mm), in 50–55% yield based on thallium cyclopentadiene and overall for three steps.[10,11]

The procedure outlined here for the methoxymethylation of cyclopentadiene without prototropic rearrangement is advantageous for the following reasons: (1) availability of the reagent, (2) simple isolation of the monoalkylated cyclopentadiene II without the need for aqueous treatment, (3) suitability for large-scale synthesis. The benzyloxy analogs of II and I have been obtained similarly starting from chloromethyl benzyl ether and thallous cyclopentadienide. To our knowledge these are the first carbon-substituted cyclopentadienes to be prepared from the thallium derivative. Further studies on the utility of thallous cyclopentadienide for the synthesis of alkylated cyclopentadienes and 7-substituted bicyclo[2.2.1]heptane derivatives are in progress.

Caution. Certain hazards are associated with the above procedures.[12,13]

(7) The thallous chloride (>97% recovery) was readily converted to thallous sulfate by treatment with sulfuric acid, thereby permitting efficient recycling of thallium.

(8) Commercial cupric fluoroborate was powdered (exclusion of moisture) and dried over KOH at 25° for 1 day and then over P_2O_5 at 25° for >5 days.

(9) The analysis was performed using a 10 ft × 0.125-in. column containing 5% silicone (SE-30) at 135°.

(10) The conversion of III to I in 80% yield by alkaline hydrolysis described previously[2a] refers to chromatographically purified III.

(11) The higher boiling fraction contains chloronitrile(s) in the bicyclo[3.2.0]heptane series. These are resistant to the hydrolysis conditions which convert III to I.

(12) Thallium and its compounds are highly toxic and must be handled with great care; see, for example, E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, 3, 338 (1970). 2-Chloroacrylonitrile is also an unusually hazardous substance, and inhalation of vapors or contact with the skin must be avoided. Severe skin irritation and blistering have been experienced with this substance in a number of laboratories.

(13) This work was assisted financially by a grant from the National Institutes of Health.

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Stereospecific Total Synthesis of Prostaglandins E_3 and $F_{3\alpha}$

Sir:

This communication reports the first synthesis of prostaglandins E_3 and $F_{3\alpha}$ in optically active, naturally occurring form.[1] The optically active hydroxy lactone I (oil, $[\alpha]^{25}D$ −10° in $CHCl_3$), readily available from previously described intermediates,[2] was converted to the tetrahydropyranyl (THP) derivative II[3a] (1.5 equiv of dihydropyran and *ca.* 1 mol % *p*-toluenesulfonic acid in methylene chloride at 25°) and thence to the primary alcohol III[3] (hydrogen at 1 atm with 5% palladium/carbon in 20:1 ethanol–acetic acid at 25°) and the aldehyde V[3] (Collins oxidation[4]) (85–90% of V overall from I).[5] The aldehyde V was converted stereospecifically to the unsaturated alcohol VI by means of the β-oxido ylide reagent[6,7] derived from the hydroxy phosphonium salt (*S*)-(+)-XII as follows. The (*S*)-(+)-phosphonium salt XII was treated at −78° in tetrahydrofuran solution under nitrogen with 2 equiv of methyllithium, and the mixture was brought to and maintained at −25° for 30 min, cooled to −78°, and treated with the aldehyde V. After 5 min at −78° the reaction mixture was brought to 0° for 30 min, and the product was separated by addition of pH 4 citrate buffer and extraction. The desired alcohol VI[3a] was then isolated in 35% yield by chromatography on silica gel (R_f 0.60 using ethyl acetate). As expected from the fact that optically pure phosphonium salt XII was used, none of the epimeric allylic alcohol was present in the reaction product.

The synthesis of the (*S*)-(+)-phosphonium iodide was carried out starting from readily available and inexpensive natural (*S*)-(−)-malic acid *via* (*S*)-(−)-1,2,4-butanetriol[8] and the corresponding acetonide VII,[3] $[\alpha]^{25}D$ −1.29° (*c* 4.6, CH_3OH). Collins oxidation[4] of VII gave the aldehyde VIII[3] in 99% yield further transformed into the *cis*-olefin IX[3] in 70% yield by reaction with propylidenetriphenylphosphorane in tetrahydrofuran (−78° for 30 min, 0° for 30 min, and 25° for 30 min); $[\alpha]^{25}D$ +25.7° (*c* 1.0, $CHCl_3$). *Anal.* Found for IX: C, 70.75; H, 10.64. Hydrolysis of IX in 2 *N* hydrogen chloride in methanol at reflux for 4 hr gave 96% yield of the diol X,[3] $[\alpha]^{25}D$ +9.0° (*c* 1.0,C HCl_3), which was converted to a primary monotosylate[3] (80% yield) with 1 equiv of *p*-toluenesulfonyl

(1) A synthesis of racemic prostaglandin E_3 methyl ester has been outlined by U. Axen, J. L. Thompson, and J. E. Pike, *Chem. Commun.*, 602 (1970).

(2) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, 93, 1491 (1971).

(3) Satisfactory (a) nuclear magnetic resonance and infrared spectra and (b) mass spectra were obtained for this oily intermediate after chromatographic purification; only one component could be detected by thin-layer chromatography using several solvent systems.

(4) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(5) The intermediate III was also obtained from the methyl ether corresponding to the benzyl ether I [E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, 92, 397 (1970); 91, 5675 (1969)] by the sequence (1) acetylation, (2) methyl ether cleavage with boron tribromide, (3) acetate saponification, (4) selective trichloroacetylation of the primary alcohol function in IV, (5) etherification of the secondary alcohol function with dihydropyran, and (6) saponification of trichloroacetate. The intermediate diol IV was crystalline, mp 115.5–116°, $[\alpha]^{25}D$ −43.8° (*c* 1.04, CH_3OH). *Anal.* Found: C, 55.66; H, 7.02.

(6) E. J. Corey and H. Yamamoto, *ibid.*, 92, 226, 3523 (1970).

(7) E. J. Corey and H. Yamamoto, *ibid.*, 92, 6636 (1970).

(8) P. W. Feit and O. T. Nielsen, *J. Med. Chem.*, 9, 416 (1966).