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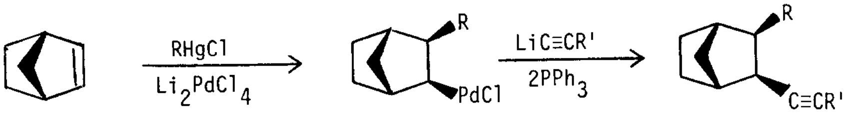
ORGANOPALLADIUM APPROACHES TO PROSTAGLANDINS. 4.
SYNTHESIS OF THE FIRST INTERPHENYLENE PGH_2 ANALOGS VIA BENZYLPALLADATION

Richard C. Larock* and Srinivasan Babu

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

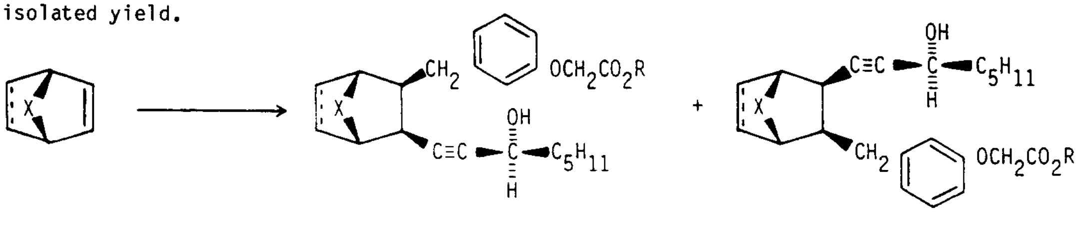
Summary: The reaction of norbornene, norbornadiene and 7-oxanorbornene with methyl 3-(chloromethyl)phenoxyacetate, (S)-1-octyn-3-ol and 8% $Pd(PPh_3)_4$ affords in one step satisfactory yields of the corresponding, first interphenylene PGH_2 analogs.

There has been considerable recent interest in the synthesis of interphenylene analogs of prostaglandins A,[1] E,[2-9] F[2,8,10-15] and I.[7,16-23] We have recently prepared a variety of PGH analogs by organopalladium additions to bicyclic olefins and subsequent acetylide displacement (eq. 1).[24-26] Some of these compounds have proven to be potent inhibitors of blood platelet aggregation.[25] More recently, Chiusoli reported that aryl and vinyl halides react with bicyclic olefins, acetylenes and catalytic amounts of $Pd(PPh_3)_4$ to undergo an analogous transformation.[27,28] We have observed that benzylic chlorides undergo similar chemistry, and now wish to report a convenient, palladium-catalyzed, one-step synthesis of the first interphenylene PGH_2 analogs using this chemistry.



(1)

The reaction of equimolar amounts of methyl 3-(chloromethyl)phenoxyacetate,[2] optically active (S)-1-octyn-3-ol[29] and anhydrous sodium acetate, plus 4 equiv. of norbornene and 8% $Pd(PPh_3)_4$, when heated to 70°C for 1 day in anisole provided a 58% isolated yield of an inseparable mixture of the two possible diastereomers of compound **1** ($R=CH_3$) (eq. 2). Saponification (1M KOH/MeOH, 2 hr. reflux) afforded the corresponding acids **1** (R=H) in 95% isolated yield.



(2)

X = CH_2, O   X = CH_2 **1** (alkane), **2** (alkene)
(alkene and diene)   O **3** (alkane)

This chemistry has been extended to norbornadiene. In this case, 8 equivalents of the diene was employed to avoid double addition to the diene. A diastereomeric mixture of **2**

($R=CH_3$) was obtained in 37% isolated yield. Saponification afforded the corresponding acids **2** (R=H) in 88% yield.

The current interest in oxygen derivatives of PGH,[26] encouraged us to examine this approach using 7-oxabicyclo[2.2.1]heptene.[30] The anticipated oxygen diastereomers **3** ($R=CH_3$) were obtained in 34% isolated yield. A significant amount of a product derived from insertion of two bicyclic olefin units was also observed. Saponification to compounds **3** (R=H) proceeded in 85% yield.

All new compounds gave correct ^{13}C and ^{1}H (300 MHz) NMR, IR, exact mass and combustion analysis data. We have thus far been unable, however, to separate by HPLC or column chromatography any of the diastereomic mixtures of esters or acids though our efforts continue. Biological testing of these compounds is presently underway. We anticipate that this basic approach should prove applicable to the synthesis of a number of other PGH analogs and we are presently examining this possibility.

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References and Notes:

(1) D. R. Morton and J. L. Thompson, J. Org. Chem., **43**, 2102 (1978).
(2) N. A. Nelson, R. W. Jackson, A. T. Au, D. J. Wynalda and E. E. Nishizawa, Prostaglandins, **10**, 795 (1975).
(3) D. R. Morton and J. L. Thompson, J. Org. Chem., **43**, 2093 (1978).
(4) R. T. Buckler, U. S. Pat. 4,096,336 (1978); Chem. Abstr., **90**, 38582n (1979).
(5) W. Morozowich, U. S. Pat. 4,100,192 (1978); Chem. Abstr., **90**, 38589v (1979).
(6) T. Honohan, F. A. Fitzpatrick, D. G. Booth, J. P. McGrath, D. R. Morton and E. E. Nishizawa, Prostaglandins, **19**, 123 (1980).
(7) P. A. Aristoff and A. W. Harrison, Tetrahedron Lett., **23**, 2067 (1982).
(8) Z. Cai, B. Nassim and P. Crabbé, J. Chem. Soc., Perkin Trans. I, 1573 (1983).
(9) G. A. Tolstikov, M. S. Miftakhov, N. N. Sidorov and A. A. Volkov, Zh. Org. Khim., **19**, 220 (1983); J. Org. Chem. USSR, **19**, 203 (1983).
(10) H. W. Smith, U. S. Pat. 4,018,803 (1977); Chem. Abstr., **87**, 134036w (1977).
(11) W. Morozowich, U. S. Pat. 4,136,115 (1979); Chem. Abstr., **91**, 19978a (1979).
(12) W. Morozowich, U. S. Pat. 4,138,549 (1979); Chem. Abstr., **90**, 203545n (1979).
(13) W. Morozowich, U. S. Pat. 4,154,926 (1979); Chem. Abstr., **91**, 157339u (1979).
(14) W. Morozowich, U. S. Pat. 4,205,011 (1980); Chem. Abstr., **93**, 204152f (1980).
(15) W. Morozowich, U. S. Pat. 4,207,257 (1980); Chem. Abstr., **93**, 204153g (1980).
(16) S. Katsuichi and H. Masaki, Tetrahedron Lett., **21**, 1255 (1980).
(17) Toray Industries, Inc., Japan Pat. 82 32, 77 (1982); Chem. Abstr., **96**, 217562b (1982).
(18) K. Ohno, H. Nagase, M. Ishikawa, K. Matsumoto and S. Nishio, Eur. Pat. Appl. EP 60,640 (1982); Chem. Abstr., **98**, 107061w (1983).
(19) U. Seipp, Ger. Pat. DE 3,317,159 (1983); Chem. Abstr., **100**, 120766j (1984).
(20) K. Ohno, H. Nagase, K. Matsumoto, S. Nishio, Eur. Pat. Appl. EP 84,856 (1983); Chem. Abstr., **100**, 51356m (1984).
(21) P. A. Aristoff, Eur. Pat. Appl. EP 88,619 (1983); Chem. Abstr., **100**, 22502a (1984).
(22) L. Flohe, H. Boehlke, E. Frankus, S. M. A. Kim, W. Lintz, G. Loschen, G. Michel, B. Mueller and J. Schneider, Arzneim - Forsch. (English), **33**, 1240 (1983).
(23) P. A. Aristoff, A. W. Harrison and A. M. Huber, Tetrahedron Lett., **25**, 3955 (1984).
(24) R. C. Larock, D. R. Leach and S. M. Bjorge, Tetrahedron Lett., **23**, 715 (1982).
(25) R. C. Larock, J. P. Burkhart and K. Oertle, Tetrahedron Lett., **23**, 1071 (1982).
(26) R. C. Larock and D. R. Leach, J. Org. Chem., **49**, 2144 (1984) and references therein.
(27) M. Catellani and G. P. Chiusoli, Tetrahedron Lett., **23**, 4517 (1982).
(28) M. Catellani, G. P. Chiusoli and A. Mari, J. Organometal. Chem., **275**, 129 (1984).
(29) J. Fried, C. H. Lin, M. M. Mehra and P. Dalven, Ann. N. Y. Acad. Sci., **180**, 38 (1971).
(30) L. W. Butz and W. Nudenberg, J. Am. Chem. Soc., **66**, 307 (1944).

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