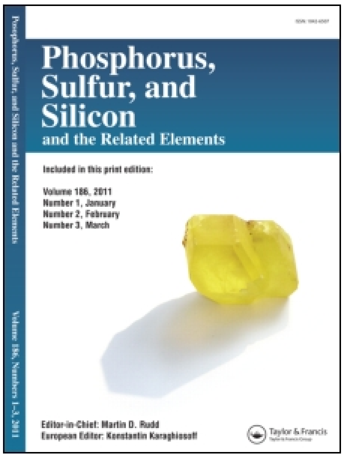

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THE PREPARATION OF TWO NOVEL HOMOALLYLIC ALCOHOLS VIA THE REACTION OF EPOXIDE WITH PHOSPHONIUM YLIDE

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Two novel homoallylic alcohols, *E*-4-(4-methoxyphenyl)-1-phenyl-3-buten-1-ol and *E*-4-(3,4,5-trimethoxyphenyl)-1-phenyl-3-buten-1-ol, were synthesised by the reaction of methelentriphenylphosphonium ylide with epoxide. The reaction first gave an initial betaine which upon treatment with butyl lithium gave a new ylide. When this new ylide reacted with the proper aldehyde, gave the corresponding homoallylic alcohol. Preliminary biological screening showed that the former alcohol possesses a significant estrogenic activity in rats. The latter alcohol was found to have partial antiestrogenic activity.

Keywords: homoallylic alcohol; phosphonium ylide; epoxide; estrogenic; antiestrogenic

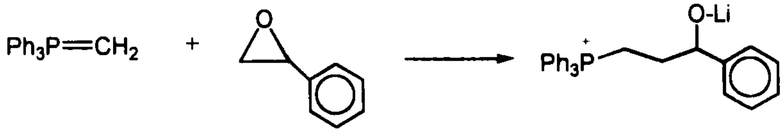
The study of the reaction of phosphonium ylides with epoxides was developed through three historical stages. The first stage is the reaction of phosphonium ylides with epoxides which gave phosphonium betaines. Thermal decomposition of these betaines at high temperature (200°C) gave several products such as: alkenes, ketones, and cyclopropanes.[1–6] The uncontrolled reaction may be attributed to the free radical formation at elevated temperature. The second stage of the study was running the reaction in the presence of lithium bromide to increase the activity of the epoxide this gave, after hydrolysis, hydroxyalkyltriphenyl-phosphonium chloride as stable product.[7–9] An interesting modification of this reaction is reacting the methylphosphonium chloride with two equivalents of an organolithium to form α-lithomethylene triphenylphosphorane.[10–11] The reaction of this activated α-lithio ylide with epoxide gave a new ylide. The reaction of the new ylide with carbonyl compounds gave olefins. Another interesting work is the reaction of Wittig-Horner reagent with epoxides to give, after estreification, esters of 3-hydroxypropylphosphine oxides, which rearranged in base to hydroxy ketones. Selective reduction of these hydroxy ketones gave *E*-homoallylic alcohols.[12]

In this work, the methelene triphenylphosphonium ylide was prepared by the addition of one equivalent of butyllithium to the methylphosphonium bromide. The reaction of this ylide with epoxide gave a betaine, which when treated with one equivalent of butyllithium gave a new ylide. The reaction of this ylide with carbonyl compounds gave new betaines, which decomposed to form homoallylic alcohols.

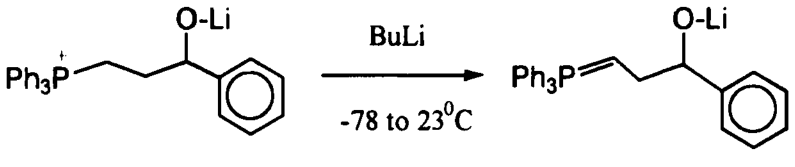
DISCUSSION

As shown by the following equations when methelentriphenylphosphonium bromide was treated with one equivalent of butyle lithium at –78°C under nitrogen, methelentriphenylphosphonium ylid was formed. The reaction of this phosphonium ylid with styrene epoxide gave the betaine-lithium complex **1**.

$$Br^{-}\ Ph_3\overset{+}{P}{-}CH_3 + BuLi \xrightarrow{-78^0C,\ THF} Ph_3P{=}CH_2$$

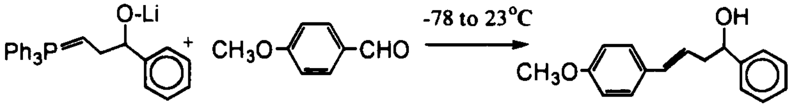


Addition of another equivalent of butyl lithium gave a new ylide (**2**).



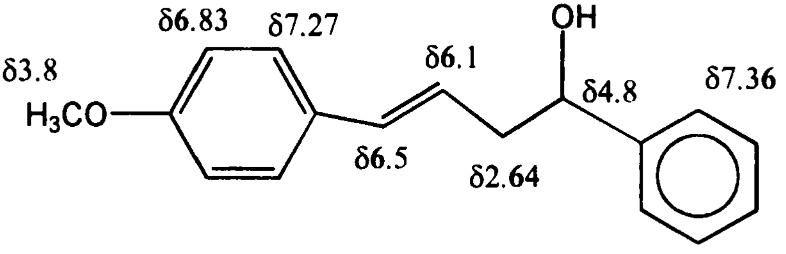
(1) **(2)**

Wittig reaction of ylide **2** with p-methoxybenzaldehyde (**3**) gave a new betaine, which then decomposed to form E-4-(4-methoxyphenyl)-1-phenyl-3-buten-1-ol (**4**), 3.47 g (68%), and triphenylphosphine oxide.



(2) **(3)** **(4)**

The mass spectrum for product **4** shows the molecular ion M$^+$, *m/z* 254 (100%), 146 (30%), 121 (57%), 115 (100%), ArCHOH 107 ((37%).

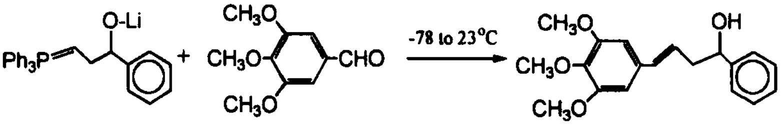


(4)

The ^{1}H NMR in $CDCl_3$ for product **4** showed a multiplet of two protons at δ2.64, a singlet of three protons at δ3.80, and a mulitplet of one proton at δ4.80 which due to the allylic protons, the methoxy protons, and the C<u>H</u>OH proton respectively. The spectrum also showed a multiplet of one proton at δ6.10 and a doublet of one proton at δ6.50 (J_{trans} 16Hz) which are attributed to the presence of 2 *trans* vinylic protons. Also it showed a doublet of two protons at δ6.00, another doublet of two protons at δ7.27, and a multiplet of five protons at δ7.36 which due to 2 phenyls protons.

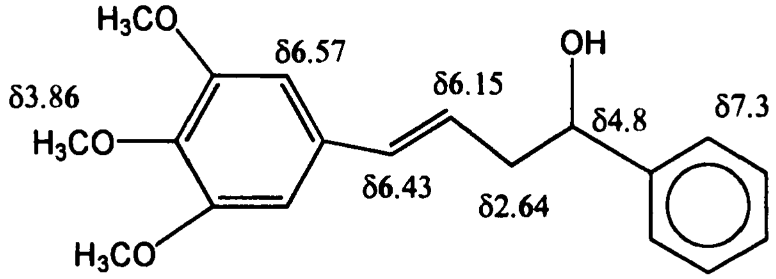
The MS for triphenylphosphine oxide shows the molecular ion M$^+$, *m/z* 277 (100%), 183 (50%), and 77 (50%). The ^{1}H NMR in $CDCl_3$ for triphenylphosphine oxide shows multiplet at δ7.4 – 7.7 due to the phenyl protons.

Wittig reaction of ylide **2** with 3,4,5-trimethoxybenzaldehyde (**5**) gave a new betaine, which then decomposed to form E-4-(3,4,5-trimethoxyphenyl)-1-phenyle-3-buten-1-ol (**6**), 1 g (48%).



(2) **(5)** **(6)**

The mass spectrum for product **6** shows the molecular ion M$^+$. *m/z* 254 (100%), 146 (30%), 121 (57%), 115 (100%), ArCHOH 107 ((37%).



(6)

The ^{1}H NMR in $CDCl_3$ for product **6** showed a multiplet of two protons at δ2.64 due to the allylic protons and a singlet of nine protons at δ3.86, and a multiplet of one proton at δ4.80 due to the methoxy protons and the C<u>H</u>OH proton. Also it showed a multiplet of one proton at δ6.15, a doublet of one proton at δ6.43 (J_{trans} 16Hz) which are attributed to the presence of

2 *trans* vinylic protons. Also it showed a singlet of two protons at δ6.57, and a multiplet of five protons at δ7.3 which due to two phenyls protons.

PRELIMINARY BIOLOGICAL SCREENING

Preliminary biological screening for compound **4** showed that it possesses a significant estrogenic activity in rats. Immature female rats treated with 1.14mg/kg (0.2ml) of compound **4** for three consecutive days showed 20% higher uterus weights than that of control and no mortality was seen among rats. Mixing compound **4**with diethylstilbestrol increases the uterotrophic effects of the diethylstilbestrol by 14%. However, compound **6** showed partial estrogen antagonist. Rats injected with 4.57 mg/kg (0.2ml) of compound **6** for the same period showed only 6 % higher uterus weights than that of control and no mortality was seen among rats. Mixing compound **6** with diethylstilbestrol decreases the estrogenic effect of the diethylstilbestrol on rats uterus by 17.7%.

EXPERIMENTS

The flash chromatography was performed using silica gel, Merck, grade 9385, 230–400 mesh, 60°A. The NMR experiments were performed on a Bruker DPX-400 instrument. The mass spectra were obtained on a Shimadzu MS QP-5000 mass spectrometer.

E-4-(4-methoxyphenyl)-1-phenyl-3-buten-1-ol (4)

In a three-necked round-bottomed flask 20 mmol (7.155g) of methyltriphenylphosphonum bromide were dissolved in 40 ml of dry tetrahydrofuran. Nitrogen gas was bubbled in this solution for about 20 minutes while maintaining the temperature at –78°C (using a mixture of dry ice/ acetone). The reaction mixture was kept under nitrogen for another 15 minutes in order to ensure an inert atmosphere. The whole reaction assembly was kept airtight. To this solution 22 mmol of n-butyl lithium (2.2 ml of 10M solution in n-hexane) was added carefully dropwise in a period of 15 minutes. A yellow solution was obtained. The stirring was continued for another 10 minutes at −78°C and then the temperature was slowly raised to 23°C and the stirring was continued for 2.5 hour at 23 °C. The yellow solution turned into orange suspension. The resulting suspension was cooled to 0°C and to this was added 22 mmol (2.64 g) of styrene epoxide. The reaction mixture was left overnight while stirring at 23°C. The orange suspension turned to a yellow suspension. To this resulting reaction mixture, which was once again cooled to -78°C, 22 mmol (2.2 ml of 10M solution) of n-butyl lithium was added dropwise with help of a syringe. The temperature slowly raised to 23°C, and then the reaction mixture was stirred for 2.5 hours at 23°C. This gave orange suspension which was once again cooled to −78°C. To this cooled suspension was added with help of a dropping funnel a solution of 4-methoxybenzaldehyde in dry tetrahydrofuran (20 mmol; 2.72 g dissolved in 15 ml of dry THF). The reaction was kept stirring for 6 hours at 23°C. The reaction was worked up by adding it to crushed ice in a beaker. The resulting mixture was extracted with diethyl ether (3 × 40 ml). The resulting extract was evaporated in vacuo. The thin layer chromatography was done in various solvents and it showed the presence of multiple spots on TLC. Therefore the reaction extract (7.256 g) was subjected to flash column chromatography over silica gel (~ 200 g). Starting with 10% ethyl acetate/n-hexane and then subsequently increasing the polarity by increasing the proportion of ethyl acetate. The final elution was done in 5% methanol/ethyl acetate.

The chromatography yielded two compounds in pure form. These products are: *E*-4-(4-methoxyphenyl)-1-phenyl-3-buten-1-ol (**4**) 3.47gm (68%) as white crystals, the MS: M^+, *m/z*254 (100%), 146 (30%), 121 (57%), 115 (100%), ArCHOH 107 ((37%). The ^1H NMR in $CDCl_3$: δ2.64 (2H, m, CH_2); δ3.80 (3H, s, CH_3O); δ4.8 (1H, m, CHOH); δ6.1 (1H, m, =CH); δ6.5 (1H, d, CH=, J 16Hz); δ6.83 (2H, d, ArH); δ7.27 (2H, d, Ar-H); and δ7.36 (5H, m, Ar-H). The second product is triphenylphosphine oxide, the MS: M^+, *m/z* 277 (100%), 183 (50%), and 77 (50%). ^1H NMR in $CDCl_3$: δ7.4 – 7.7 (m, Ar-H).

E-4-(3,4,5-trimethoxyphenyl)-1-phenyl-3-buten-1-ol (6)

A solution of methyltriphenyl phosphine (7.16 g; 20 mmol) in 20 ml of dry tetrahydrofuran (THF) was stirred under nitrogen and cooled with dry ice/acetone to −78°C. Then 2.2 ml (22 mmol) of a solution of butyl lithium in hexane was added dropwise. This gave a yellow solution which was stirred for 10 minutes at –78°C. Then the temperature was slowly raised to 23°C and stirred for 2.5 hours at 23°C. The yellow solution turned into an orange suspension. This was cooled to 0°C and 2.64 g (22 mmol) of styrene oxide was added. The reaction mixture was stirred overnight, under nitrogen, at 23°C. The orange suspension turned again to a yellow suspension. Then the reaction mixture was cooled again to –78°C and 2.2 ml (22 mmol) of a solution of butyl lithium was added dropwise. The temperature was slowly raised to 23°C and stirred for 2.5 hours at 23°C. The colour of the suspension turned to orange.

One third of this solution (6.64 mmol) was transferred to a three necked round bottom flask and kept under nitrogen. This was cooled to –78 °C and a solution of 1.3g (6.64 mmol) of 3,4,5-trimethoxybenzaldehyde in dry tetrahydrofuran was added. The temperature was slowly raised to 23°C and stirred for 6 hours at 23°C. The reaction was worked up by adding it to crushed ice in a beaker. The resulting mixture was extracted with diethyl ether (3x20ml). The reaction extract was subjected to flash column chromatography over silica gel. Starting with 20% ethyl acetate/n-hexane and then subsequently increasing the polarity by increasing the proportion of ethyl acetate. This gave the major product **6** as yellow oil (1.0 g, 48%). The H^1 NMR: δ2.64 (2H, m, CH_2); δ3.86 (9H, s, CH_3O); δ4.8 (1H, m, CHOH); δ6.15 (1H, m, =CH); δ6.43 (1H, d, CH=, J 16Hz); δ6.57 (2H, s, ArH); δ7.3 (5H, m, Ar-H). The C^{13}NMR: δ43.9 (t, CH_2); δ54.7 (q, CH_3-O): δ61.8(q, CH_3-O); δ74.45 (d, C$\underline{H}$-OH); δ103.95(d, CH=); δ125.9–154.1 (Ar).

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