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Synthesis of 3-(1-phenyl-vinyl)-1, 2, 5-trioxa-spiro undecane and its derivatives

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ABSTRACT

3-(1-Phenyl-vinyl)-1, 2, 5-trioxa-spiro undecane is synthetic derivative of Artemisinin. Artemisinin is a well known antimalarial drug from leaves of *Artemisia annua* find in china. Five different derivatives of 3-(1-Phenyl-vinyl)-1, 2, 5-trioxa-spiro undecane were synthesized using well standardized method. These compounds were purified by simple column chromatography and successfully analysed using H^1NMR, IR and FAB-MS techniques.

Key words: 1, 2, 4-trioxane, Artemisinin, NMR, IR, FAB-MS

INTRODUCTION

Malaria is a major parasitic disease, affecting over 100 countries of the tropical and subtropical regions of the world. Around 300-500 million clinical cases of malaria are reported every year, of which more than a million die of severe and complicated cases of malaria.[1]. The increasing resistance of causal parasite, *Plasmodium* to the contemporary antimalarial drugs, including chloroquine, has further complicated the malaria problem. Against this scenario, isolation of artemisinin 1 as the antimalarial principle of Chinese traditional herb, *Artemisia annua*, is a major milestone in the history of malaria chemotherapy. Artemisinin is very effective and safe against chloroquine (CQ) sensitive and chloroquine (CQ) resistant strains of *P. falciparum* but has certain limitations like poor oil and water solubility and high rate of recrudescence. Hence a lot of efforts have been put to develop semi synthetic derivatives of artemisinin. Ether derivatives of artemisinin[2-5] have the advantage of better oil solubility and are prepared by treating dihydroartemisinin with an appropriate alcohol in the presence of an acid catalyst. Artemether 2 and arteether 3 (Fig. 1) are the two most important derivatives of artemisinin. Both of them show better oil solubility and improved activity and are currently in clinical use.

The antimalarial activity of artemesinin and its clinically useful derivatives such as artemether 2, arteether 3, and artesunic acid 4 (Fig. 1) is due to the presence of 1,2,4- trioxane moiety in their molecular structure. Because of the limited availability of artemisinin, currently the focus is on the synthesis and antimalarial assessment of structurally simplified 1,2,4-trioxanes and a variety of methods of their synthesis has been reported in resent years[6,7]. In contrast, 1,2,4-trioxepanes, the next higher homologs of 1,2,4-trioxanes and the

next obvious candidates for structure activity relationship (SAR) studies in this area, have received only limited attention. Only a few methods of their synthesis have been reported,[8-11] the number of compounds synthesized is small.

A well standardized method by photooxygenation route for the preparation of 1,2,4-trioxepanes has been used for the preparation of 3-(1-Phenyl-vinyl)-1, 2, 5-trioxa-spiro undecane and it's four derivatives. The key steps of this method are (i) preparation of c-hydroxyhydroperoxides by photooxygenation of homoallylic alcohols and (ii) acid catalyzed condensation of these hydroxyhydroperoxides with various ketones to furnish 1,2,4-trioxepanes (Scheme 1).[9]

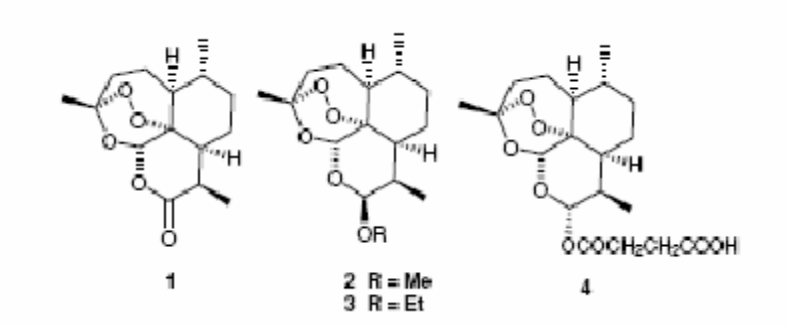
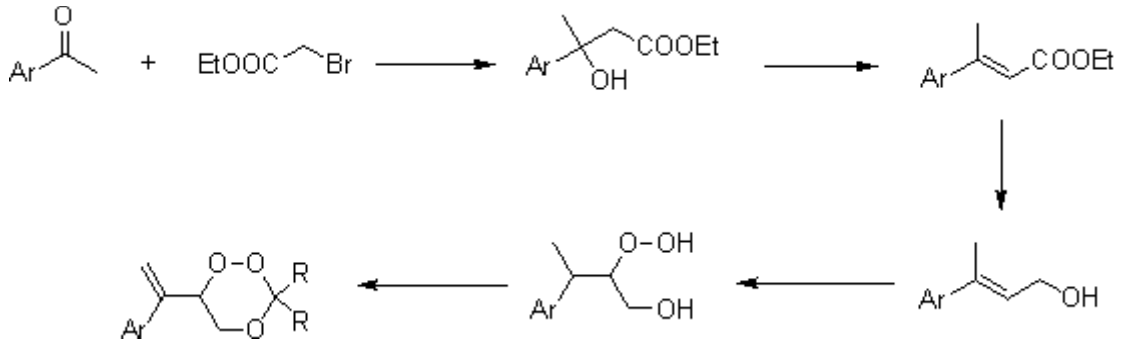


Fig. 1:



Scheme 1: In this article, we report the preparation of 3-(1-Phenyl-vinyl)-1, 2, 5-trioxa-spiro undecane 5 and its four derivatives 5a-d.

EXPERIMENTAL

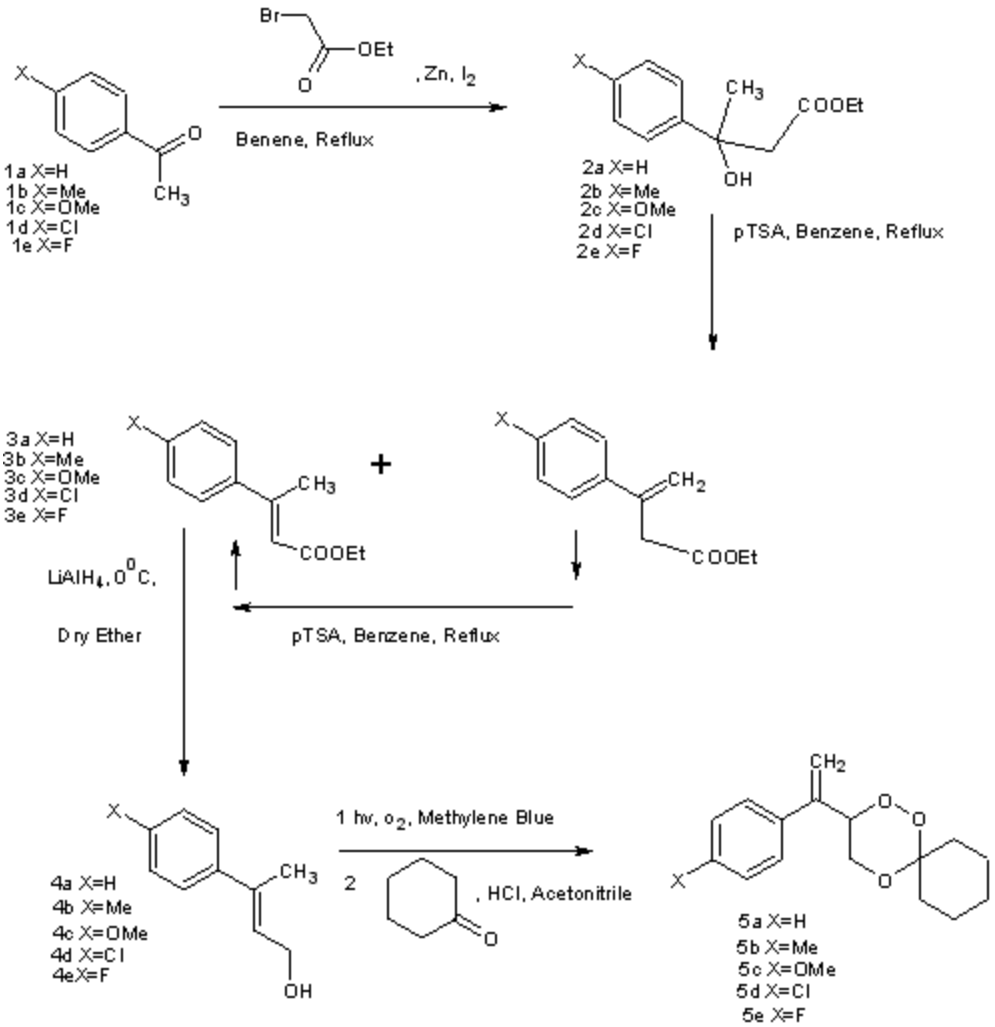
Procedure

Aromatic ketones 1a-e were taken, which were subjected to Reformatsky reaction using ethylbromoacetate, zinc and iodine crystals in benzene to furnish β-hydroxy ester, which on dehydration using pTSA furnish α-β and β-γ isomers of unsaturated esters (2a-e and 3a-e), α-β unsaturated esters were isomerized 3a-e to α-β unsaturated ester 2a-e. β-γ unsaturated esters were then reduced using LAH, to furnish allyl alcohols, these allyl alcohols 4a-e were then photooxygenated using methylene blue, oxygen and visible light furnished respective β-hydroxy-hydroperoxides which were condensed with cyclohexanone, cyclopentanone and 2-adamantanone using conc. HCl as catalyst to furnish, after column

chromatography over silica gel (60-120 mesh), respecting trioxanes 5a-5e.

Gerneral section

All apparatus were oven-dried prior to use. The progress of all the reaction was monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC plates were developed by the following developing agents: iodine vapours, spraying with an aqueous solution of vanillin in 10% sulphuric acid followed by heating at 150 ÚC. Chromatographic purification was performed over Merck and Spectrochem Pvt. Ltd, silica gel (60-120mesh). Infrared spectra (cm^{-1}) were recorded on Perkin-Elmer FT-IR RX-1 spectrophotometer. H^1 NMR spectra were recorded on Bruker DPX-200 spectrometers. Tetra methyl silane was used as an internal standard. Chemical shifts are reported in ppm relative to TMS. Coupling constants are reported in Hertz (Hz). Splitting patterns are designated as (s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quadrate; dd, doublet of doublet; m, multiplet). FAB-MS were recorded on JEOL SX 102 spectrometer using argon/xenon (6kV, 10mA) as the FAB gas. Glycerol or m-nitrobenzyl alcohol was used as matrix. Melting points of the compounds were recoded on Complab melting point apparatus and were uncorrected. All chemicals and reagents were obtained from Aldrich (USA), Spectrochem Pvt. Ltd. (India) and Lancater Pvt. Ltd (UK). Unless otherwise stated, room temperature was approximately 30°C.



General procedure and characterization data

General procedure for the preparation of α-β unsaturated esters (preparation of 3a as representative). A mixture of 37.7gm crude 2a and 2gm of pTSA in benzene (300ml) was refluxed on oil bath fitted with a condenser and Deen stark apparatus initially for 2hrs till no more reactant left and then for an additional 1hr to isomerize β-α unsaturated ester to α-β unsaturated ester. Reaction mixture was cooled and washed with saturated $NaHCO_3$ solution. Organic layer was decanted and aqueous layer was extracted with 3×50 ml of ether, combined organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography over silica gel (60-120 mesh) using EtOAc:Hexane (5:95) as eluant furnished 21.77gm (55% yield) of product [3a] an oil. IR (Neat, cm^{-1}) 1628.7, 1713.8; H^1 NMR (200MHz, $CDCl_3$), δ 1.31 (t,3H,=7.1Hz), 2.57 (d, 3H, J=1.2Hz), 4.21 (q, 2H, J=7.1Hz), 6.13 (d, 1H, J=1.2Hz), 7.33-7.49 (m, 5H, Ar-H).

Compound 3b-e were prepared by the same procedure

1.1. Compound 3b (3-p-Tolyl-but-2-enoic acid ethyl ester). Yield 59%, oil, IR (KBr, cm^{-1})1628,1716.7; H^1 NMR (200MHz, $CDCl_3$) δ 1.31 (t, 3H, J= 7Hz), 2.36 (s, 3H), 2.56 (d, 3H, J=1Hz), 4.21 (q, 2H, J=7Hz), 6.12 (d, 1H, J=1Hz), 7.12-7.74 (m, 4H).

1.2. Compound 3c (3-(4-Methoxy-phenyl)-but-2-enoic acid ethyl ester). Yield 56%, oil, IR (KBr, cm^{-1})1605.2, 1706.2; H^1 NMR (200MHz, $CDCl_3$), δ 1.22 (t, 3H, J=7Hz), 2.48 (d, 3H, J=0.7Hz), 3.73 (s, 3H), 4.12 (q, 2H, J=7Hz), 6.02 (d, 1H, J=0.8Hz), 6.80 (d, 2H, J=8.6Hz, Ar-H), 7.34-7.39 (d, 2H), (s, 1H).

1.3. Compound 3d (3-(4-Chloro-phenyl)-but-2-enoic acid ethyl ester). Yield 60%, oil, IR (KBr, cm^{-1}), 1629.7, 1712.7; H^1 NMR (200MHz, $CDCl_3$), ä 1.31 (t, 3H, J=7Hz), δ2.54 (d, 3H, J= 0.6Hz), 4.21 (q, 2H, J=7Hz), 6.10 (d, 1H, J=0.7Hz), 7.31-7.43 (m, 5H, Ar-H).

1.4. Compound 3e (3-(4-Fluoro-phenyl)-but-2-enoic acid ethyl ester). Yield 66%, oil, IR (KBr, cm^{-1}), 1631.7, 1712.7; H^1 NMR (200MHz, $CDCl_3$), δ1.31 (t, 3H, J= 7.1Hz), 2.55 (d, 3H, J= 1Hz), 4.21 (q, 2H, J= 7.1Hz), 6.09 (d, 1H, J=1Hz), 7.01-7.09 (m, 2H), 7.42-7.49 (m, 2H).

General procedure for the preparation of allyl alcohol (preparation of 4a as representative)

To an ice cooled slurry of LAH (6gm, 0.15mol) in dry ether (300ml), taken in a 1L R.B.flask, kept at 0-10°C, under nitrogen atmosphere with continuous stirring, 20gm(0.11mol) of compound 3a was added via dropping funnel. The reaction mixture was stirred, till no more reactant was left. Reaction mixture was quenched by gradual addition of water, then finally with 10% NaOH, till a sludge settled at the bottom. The ether layer was decanted and the sludge was washed with 3X50 ml of ether, combined organic layer was concentrated and purified by column chromatography over silica gel (60-120 mesh) using EtOAc:Hexane (10:90) as eluant furnished 11.06gm (71% yield) of product [4a] as oil. IR (Neat, cm^{-1}) 1648.1, 3359.5; H^1 NMR (200MHz, $CDCl_3$), 2.06 (s, 3H), 2.37 (s, 1H, -OH, replaceable with D_2O), 4.34 (d, 2H, J=6.6Hz), 5.95 (dt, 1H, J=6.6Hz, J=1.2Hz), 7.24-7.52 (m, 5H).

Compound 4b-4e were prepared by the same procedure

Compound 4b (3-p-Tolyl-but-2-en-1-ol). Yield 73%, oil, IR (KBr, cm) 1647.1, 3359.8; H^1 NMR (200MHz, $CDCl_3$), δ 1.45-1.46 (d,1H, -OH replaceable with D_2O), 2.06 (s, 3H), 2.34 (s, 3H), 4.35 (d, 2H, J=6.7Hz), 5.93 (t, 1H, J6.6Hz), 7.08-7.33 (m,4H, Ar-H).

Compound 4c (3-(4-Methoxy-phenyl)-but-2-en-1-ol). Yield 78%, oil, IR (KBr, cm^{-1}) 1604.8, 3345.4 (broad); H^1 NMR (200MHz, $CDCl_3$), δ 1.6-1.7 (s, 1H, -OH replaceable with D_2O), 2.05 (s, 3H), 3.80 (s, 3H), 4.34 (d, 2H, J=6.7Hz), 5.91 (t, 1H, J=6.7Hz), 6.86 (dd, 2H, J=6.7, 2Hz), 7.35 (dd, 2H, J=6.7, 2Hz).

Compound 4d (3-(4-Chloro-phenyl)-but-2-en-1-ol). Yield 62%, oil, IR (KBr, cm^{-1}), 1646.2, 3337(broad), H^1 NMR (200MHz, $CDCl_3$), δ 1.49 (s, 1H, -0H replaceable with D_2O), 2.05 (s, 3H), 4.34-4.37 (d, 2H, J= 6.2Hz), 5.95 (dt, 1H, J=1Hz, 7Hz), 7.26-7.36 (m, 5H, Ar-H).

Compound 4e (3-(4-Fluoro-phenyl)-but-2-en-1-ol). Yield 78%, oil, IR (KBr, cm^{-1}), 1646.8, 3278.1(broad); H^1 NMR (200MHz, $CDCl_3$), δ 1.49 (s, 1H, -OH replaceble with D_2O), 2.05 (s, 3H), 4.35 (d, 2H J= 6.1Hz), 5.92 (t, 1H, J= 6Hz), 6.96-7.04 (m, 2H), 7.33-7.40 (m, 2H).

General procedure for the preparation of 1,2,4-trioxane (preparation of 3-(1-Phenyl-vinyl)-1, 2, 5-trioxa-spiro [5.5] undecane 5a as representative)

A solution of allyl alcohol 4a (500mg, 0.002mol), methylene blue (5mg) in acetonitrile (25ml) taken in a double jacketed round bottom flask, maintained below 0 to -10°C through ultra cryostat. Oxygen was bubbled into the reaction mixture and mixture was irradiated with visible light by means of tungsten-halogen lamp (500W), till no more reactant was left in reaction mixture. Reaction mixture was poured in a 500ml R.B.flask, 2ml of cyclopentanone, 2-4 drops of conc. HCl was added and reaction mixture stirred at r.t. till no more hydroperoxide was left. Reaction mixture was concentrated under reduce pressure and purified by column chromatography over silica gel (60-120 mesh) using EtOAc: Hexane (1:99) as eluant furnished 351mg (40% yield) of product [5a] as oil. IR (KBr, cm^{-1}) 1597.8, 1112.7; H^1 NMR (200MHz, $CDCl_3$) δ1.97-2.04 (m, 1H), 2.16-2.26 (m, 1H), 3.71-3.78 (dd, 1H, J=12Hz, J=2.8Hz), 3.91-4.02 (m, 1H), 5.22-5.27 (dd, 1H, J=9.5Hz, 2Hz), 5.32 (s, 1H), 5.50 (s, 1H), 7.26-7.37 (m, 5H, Ar-H). FAB-MS (M+H), 261.

Compounds 5b-e were prepared by the same procedure

Compound 5b (3-(1-p-Tolyl-vinyl)-1, 2, 5-trioxa-spiro [5.5] undecane). Yield 40%, oil, IR (KBr, cm^{-1})1629.3, 1093.4; H^1 NMR (200MHz, $CDCl_3$), α 1.46-1.61 (m, 8H), 1.97-2.04 (m, 1H), 2.16-2.26 (m, 1H), 2.34 (s, 3H), 3.74 (dd, 1H, J=11, 2.5Hz), 3.90-4.01 (m, 1H), 5.20-5.27 (m, 2H), 5.46 (s, 1H), 7.14 (d, 2H, J=7.9Hz), 7.28 (d, 2H, J=8.3Hz), FAB-MS (M+H), 275.

Compound 5c (3-[1-(4-Methoxy-phenyl)-vinyl]-1, 2, 5-trioxa-spiro [5.5] undecane). Yield 43%, 0il, IR (KBr, cm^{-1}), H^1 NMR (200MHz, $CDCl_3$), δ 1.47-1.61 (m, 8H), 2.01-2.04 (m, 1H), 2.16-2.22 (m, 1H), 3.81 (s, 3H), 3.70-4.01 (m, 2H), 5.20-5.23 (m, 2H), 5.42 (s, 1H), δ 6.87 (d, 2H, J= 8.4Hz, Ar-H), 7.33 (d, 2H, J= 8.4Hz, Ar-H). FAB-MS (M+H), 290.

Compound 5d (3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undecane). Yield 41%, oil, IR (KBr, cm^{-1}), 1596.4, 1093.3; H^1 NMR (200MHz, $CDCl_3$), δ 1.25-1.61 (m, 8H), 1.93-2.03 (m, 1H, 2.14-2.23 (m, 1H), 3.74 (dd, 1H, J=11.8Hz, 2.8Hz), 3.91-4.02 (m, 1H), 5.19 (dd, 1H, J= 10.1Hz, 1.8Hz), 5.31 (s, 1H), 5.45 (s,1H), 7.02 (t, 2H, J=8.6Hz, Ar-H), 7.32-7.39 (m, 2H). FAB-MS (M+H), 295.

Compound 5e (3-[1-(4-Fluoro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undecane). Yield 44%, oil, IR (KBr, cm^{-1}), 1629.6, 1105.1; H^1 NMR (200MHz, $CDCl_3$), δ1.47-1.62 (m, 8H), 1.93-2.03 (m, 1H), 2.14-2.24 (m, 1H), 3.74 (dd, 1H, J=11.8Hz, 2.7Hz), 3.91-4.02 (m, 1H), 5.19 (dd, 1H, J= 10.1Hz, 1.7Hz), 5.31 (s, 1H), 5.45 (s, 1H), 6.98-7.07 (m, 2H), 7.33-7.40 (m, 2H), FAB-MS (M+H), 279.

RESULT AND DISCUSSION

In this work, five simple 1, 2, 4,-trioxanes were synthesized using readily available and simple starting material in good to moderate yield. Like semisynthetic artemisinin derivatives, many of these synthetic 1, 2, 4-trioxanes are quite stable and can serve as good lead compound for the development of new antimalartal compounds with promising antimalarial activity.

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