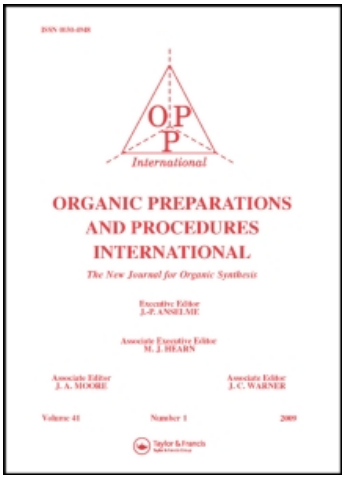

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED PROCEDURE FOR SYNTHESIS OF α-ASARONE

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To cite this Article Xu, Guangyu , Zhouf, Yi , Zuo, Gaolei and Jiang, Yongjun(2007) 'AN IMPROVED PROCEDURE FOR SYNTHESIS OF α-ASARONE', Organic Preparations and Procedures International, 39: 5, 514 — 517
To link to this Article: DOI: 10.1080/00304940709458604
URL: http://dx.doi.org/10.1080/00304940709458604

AN IMPROVED PROCEDURE FOR SYNTHESIS OF α-ASARONE

Submitted by (10/06/06)

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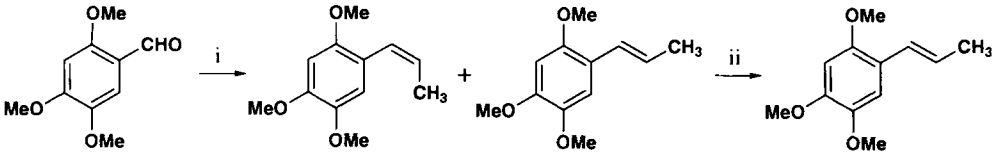
α-Asarone, (*E*)-1-(2,4,5-trimethoxyphenyl)-1-propene (**1**), occurring in nature in the common asarabacca root *Asarum europaeum* L. and calamus *Acorus calamus* L. root, is reported to be an active hypolipidemic agent.[1] In addition, it is known to have sedating, neuroleptic, spasmolytic, antiulcerogenic and antiatherogenic activity.[2] Due to its difficult availability from natural sources, various synthetic methods have been reported for α-asarone which involve Friedel-Crafts (88%),[3] Grignard (53%) [4] and Wittig reactions (50%).[5] However, these methods always give the unwanted toxic *cis*-isomer which is difficult to separate by column purification because of the similarity in R_f values of the two isomers. It was therefore thought desirable to develop a reliable and mild method for the conversion of β-asarone to α-asarone.

This paper reports a more practical synthesis of α-asarone *via* palladium(II)-catalyzed isomerization[6] of the α-and β-asarone mixture obtained from 2,4,5-trimethoxybenzaldehyde and ethyltriphenylphosphonium bromide (*Scheme 1*). The isomeric mixture of asarone was prepared according to the published procedure[5] with minor modification from 2,4,5-trimethoxybenzaldehyde (**3**) to give 78% yield of an isomeric mixture of asarone (*cis/trans* = 57/43) by using K_2CO_3 instead of *n*-BuLi or NaH. In the next step, the crude mixture was isomerized to *E* and *Z* asarone in 94.6/5.4 ratio with $(MeCN)_2PdCl_2$ as catalyst. After crystallization pure α-asarone was obtained in 71% yield. In addition to $(MeCN)_2PdCl_2$, we investigated other catalysts such as $PdCl_2$, $Pd(OAc)_2$, $Pd(NO_3)_2(PPh_3)_2$ and $PdCl_2(PPh_3)_2$, but none effected isomerization.

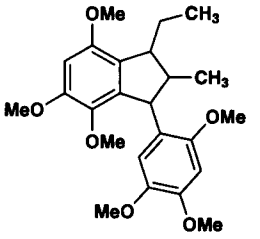


i) $CH_3CH_2\overset{\oplus}{P}Ph_3\overset{\ominus}{Br}$, dioxane, K_2CO_3, reflux, 24 h, 78.4%; ii) $PdCl_2(CH_3CN)_2$, CH_2Cl_2, r.t. 24 h, 71.2%

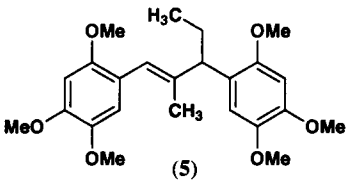
Scheme 1

Furthermore, two impurities **4** and **5** were isolated from the residual mother liquor of asarone. The enriched mother liquor from repeated crystallizations of asarone was evaporated

and chromatographyed over silica gel to give three compounds, one of which was characterized as recovered 2,4,5-trimethoxybenzaldehyde (**3**) by gas chromatography compared with reference sample. The two impurities, dimmers of asarone, were identified as 2,3-dihydro-4,5,7-trimethoxy-1-ethyl-2-methyl-3- (2,4,5-trimethoxyphenyl)indene (**4**) and 3-ethyl-2-methyl-3-(2",4",5"-trimethoxy)phenyl-1-(2',4',5'-trimethoxy)phenyl-1- propene (**5**, Neolasa-I) from their spectra and comparison with literature data.[7-9] The dimmers may have arisen from the reaction of asarone with trimethoxybenzylcarbonium generated through the interaction of asarone with the palladium (II) catalyst.[10]



(4)



(5)

EXPERIMENTAL SECTION

Mps were determined on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker-300 NMR spectrometer. The GC purities were determined on Agilent 6890N with a capillary column (0.32mm x 32m) immobile with liquid SE-30 (column flow rate 1.3 mL/min, vaporizer temperature 240°C, column temperature 170°C, detector temperature 250°C). MS were determined with Shimadzu GC-MS-QP2010. $(MeCN)_2PdCl_2$ was purchased from Acros Organics.

Preparation of (*Z*/*E*) 1-(2,4,5-Trimethoxyphenyl)-1-propene.- To a solution of 70.0 g (0.359 mol) of 2,4,5-trimethoxybenzaldehyde (**3**) in dioxane (500 mL) was added ethyltriphenylphosphonium bromide (172 g, 0.464 mol) and K_2CO_3 (77 g, 0.558 mol). The mixture was refluxed for 24 h. then filtered. The filter cake was washed with an additional 250 mL of dioxane. Evaporation of the combined filtrate gave a faint yellow oily mixture which was stirred vigorously for 30 minutes with 600 mL of petroleum ether and the precipitate triphenylphosphine oxide was collected and washed twice with 400 mL of petroleum ether. The combined filtrate was washed twice with 150mL of methanol/water (3:7 parts by volume), dried with Na_2SO_4 and evaporated to afford 58.6 g (yield 78%, *lit.*[5] 58%) of an isomeric mixture as a pale yellow oil. GC: t_R (β-asarone) = 5.8 min, 54.3%, t_R (α-asarone) = 7.0 min, 40.6%, t_R (2,4,5-trimethoxybenzaldehyde) = 7.9 min, 1.22%.

Preparation of (*E*) 1-(2,4,5-Trimethoxyphenyl)-1-propene (α-Asarone).- To a solution of the above mixture (50.0 g, 0.24 mol) in 250 mL dichloromethane was added 1.84 g (4.80 mmol) of $(MeCN)_2PdCl_2$ (2% mol). The mixture was stirred at room temperature for 24 h under N_2 when GC showed the reaction had reached thermodynamic equilibrium (β-/a-=5.4/94.6). The solvent

was evaporated, 250 mL of diisopropyl ether was added and the mixture was stirred for 5 minutes. Then the ethereal mixture was filtered to remove Pd catalyst and the filtrate was evaporated under reduced pressure to afford an pale yellow oil (GC: t_R (β-asarone) = 5.8 min, 5.3%, t_R (α-asarone) = 7.0 min, 92.2%, t_R (2,4,5-trimethoxybenzaldehyde) = 7.9 min, 2.1%), which was dissolved in hexane (40 mL) then cooled to 0°C to afford **1** (35.6 g, 71%) as a white solid, mp. 59.1-59.4°C, *lit.*[3] 62-63°C. ^{1}H NMR ($CDCl_3$): δ 1.88 (dd, 3H, J = 1.8, 6.8 Hz, -CH_3), 3.82 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3), 3.88 (s, 3H, -OCH_3), 6.09 (q, 1H, J = 6.8, 15.7 Hz, =CH), 6.49 (s, 1H, PhH), 6.65 (d, 1H, J = 15.7 Hz, -CH=), 6.94 (s, 1H, PhH).

Isolation and Spectral Data of Compounds 4 and 5.- Chromatography of the mother liquor from two crystallizations on a silical gel column using hexane/ethyl acetate 5/1 as eluent gave analytical samples of **4** and **5**.

2,3-Dihydro-4,5,7-trimethoxy-1-ethyl-2-methyl-3-(2,4,5-trimethoxyphenyl)indene (4) white solid, mp. 99.1-100.1°C, *lit.*[7] 101°C. R_f = 0.32. ^{1}H NMR($CDCl_3$): d 0.86 (t, 3H, J = 7.6 Hz, -CH_3), 1.17 (d, 3H, J = 7.2 Hz, -CH_3), 1.45, 1.83 (m, m, 2H, -CH_2-), 2.07 (m, 1H, CH), 2.68 (m, 1H, CH), 3.39 (s, 3H, -OCH_3), 3.64 (s, 3H, -OCH_3), 3.84 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 4.29 (d, J = 4.0 Hz, 1H, CH), 6.37 (s, 1H, ArH), 6.43 (s, 1H, ArH), 6.55 (s, 1H, ArH); ^{13}C NMR($CDCl_3$): d 11.78, 21.99, 26.70, 47.75, 49.92, 52.46, 55.51, 56.13, 56.62, 56.77, 56.81, 59.91, 97.19, 98.12, 113.23, 127.16, 127.71, 139.26, 139.85, 142.80, 147.62, 151.33, 152.08,152.22; *m/z* (rel. int.): 416.30 ([M]$^+$, 47.70), 385.30 (4.70), 219.15 (100.00).

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.13; H, 8.05.

(*E*)-ethyl-2-methyl-3-(2'',4'',5''-trimethoxy)phenyl-1-(2',4',5'-trimethoxy)phenylpropene (5) white solid, mp. 94.7-95.9°C, *lit.*[9a] 96-97°C. R_f = 0.18. ^{1}H NMR ($CDCl_3$): d 0.91 (t, 3H, J = 7.2 Hz, -CH_3), 1.65 (d, 2H, J = 1.2 Hz, -CH_3), 1.71, 1.95 (m, m, 2H, -CH_2-), 3.74 (t, 1H, J = 7.2 Hz), 3.79 (s, 3H, -OCH_3), 3.81 (s, 3H, -OCH_3), 3.83 (s, 6H, 2x-OCH_3), 3.89 (s, 3H, -OCH_3), 6.46 (s, 1H, =CH-), 6.53 (s, 1H, ArH), 6.55 (s, 1H, ArH), 6.74 (s, 1H, ArH), 6.84 (s, 1H, ArH); ^{13}C NMR($CDCl_3$): δ 12.43, 17.40, 26.31, 46.96, 56.05, 56.13, 56.52, 56.65, 56.67, 56.95, 97.95, 98.06, 111.73, 114.47, 119.70, 119.75, 124.46, 139.99, 142.47, 143.16, 147.52, 148.06, 151.60, 152.06; *m/z*: 416.20 ([M]$^+$, 32.23), 220.05 (14.11), 219.05 (100.00), 181.10 (4.72).

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.04; H, 7.94.

Acknowlegment.- We thank the National Natural Science Foundation of China (No. 20602010) and Hunan Provincial Natural Science Foundation of China (No. 06JJ50024) for financial support.

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SYNTHESIS OF INDAZOLE DERIVATIVES FROM 3,5-DIARYL-6-ETHOXYCARBONYL-2-CYCLOHEXEN-1-ONES

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Increasing attention is being paid to the synthesis of heterocyclic compounds bearing a 1,2-diazole ring system such as indazoles because of their broad pharmacological activities. Indazole derivatives exhibit anti-inflammatory,[1] antidepressant,[2] antiarthritic,[3] antitumor[4] and analgesic[1] activities. Different pathways have been devised to generate these compounds. Most of these methods proceed from benzene derivatives on which the pyrazole moiety was attached by ring closure.[5] Other methods starting from the pyrazole ring include cycloaddition reactions[6] and Baraldi's[7] methodology of Stobbe condensation of 4-formylpyrazoles with diethyl succinate in the