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CLAISEN ORTHO ESTER REARRANGEMENT WITH TRIMETHYL 3-(PHENYLSELENO)ORTHOPROPIONATE: A SYNTHON FOR THE PREPARATION OF 2-SUBSTITUTED ACRYLATES AND α-METHYLENE-γ-BUTYROLACTONES[1]

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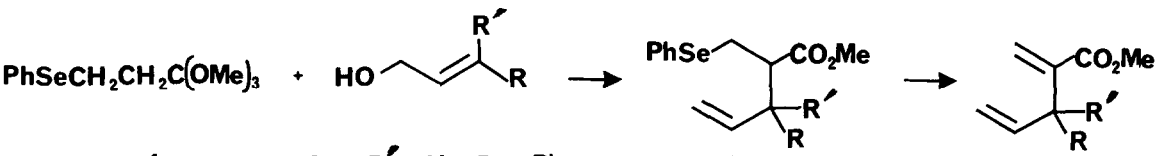
Summary: Trimethyl 3-(phenylseleno)orthopropionate may be utilized as a synthon for the preparation of either 2-substituted acrylates or α-methylene-γ-butyrolactones via Claisen ortho ester rearrangement with allylic alcohols followed by oxidative-elimination of PhSeOH.

The 2-substituted acrylate moiety is present in a variety of interesting compounds. Recently, in connection with projects directed toward the synthesis of a number of natural products, we desired to develop a general method for the regio- and stereospecific introduction of a masked 2-substituted acrylic acid moiety via [3,3] sigmatropic rearrangement.[2] Although Still[3] has reported a clever procedure for this transformation based upon the rearrangement of enolates[4] derived from esters of allyl 3-(pyrrolidino)propionates, our requirements necessitated the use of a thermal Claisen ortho ester rearrangement.[5,6]

We now wish to report that trimethyl 3-(phenylseleno)orthopropionate (1)[8] readily undergoes Claisen ortho ester rearrangement with allylic alcohols 2 to give methyl 2-substituted-3-(phenylseleno)propionates 3.[9] It is noteworthy that no β-elimination to the corresponding 2-substituted acrylates 4 occurs under the rearrangement conditions. Generation of the acrylate moiety by oxidative-elimination of PhSeOH may be effected either in the next step, or after other desired transformations have been carried out.

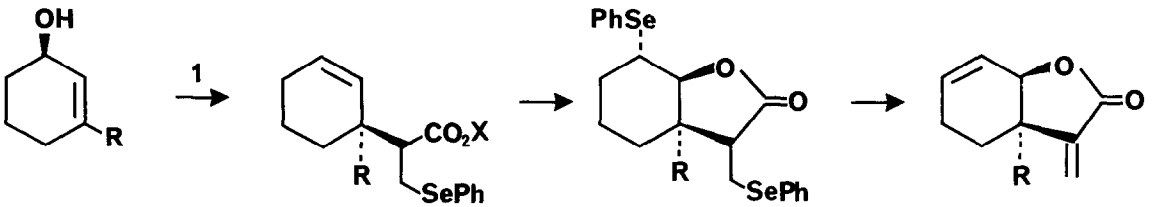
For example, the reaction of cinnamyl alcohol (2a) with 1 (1.5 equiv) and trimethylacetic acid (0.05 equiv) at 170 °C (18 hours, argon atmosphere) gave the Claisen ortho ester rearrangement product 3a as a mixture of diastereomers[11] (84% yield); oxidation of 3a with 30% H_2O_2 (4 equiv) in THF at 25 °C afforded the 2-substituted acrylate 4a in 80% overall yield from 2a. No isomerization to the more stable conjugated isomer could be detected.[9] Likewise, heating geraniol (2b) with 1 (1.3 equiv) and trimethylacetic acid (0.1 equiv) in mesitylene (3 mL per mmol of 2b) at 160 °C (20 hours, argon atmosphere) gave 3b as a mixture of diastereomers[11] (64% yield); oxidation, as above, produced 4b in 61% overall yield from 2b.



1 2a R' = H, R = Ph 3 4

2b R' = Me, R = $(CH_2)_2CH{=}CMe_2$

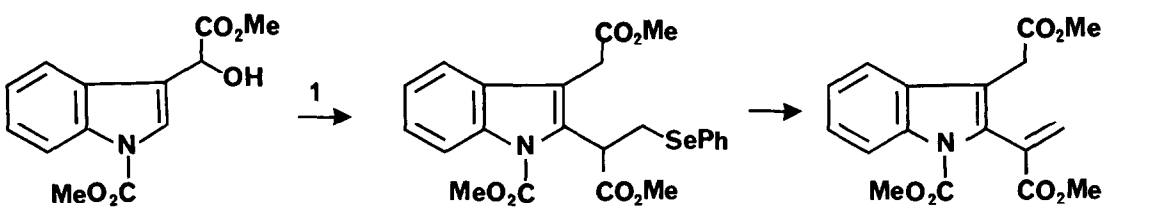
We have also utilized the ortho ester 1 for the synthesis of α-methylene-γ-butyrolactones[12] as an example of a procedure in which oxidative-elimination of PhSeOH is deferred until after other transformations have been effected. Reaction of 2-cyclohexen-1-ol (5a) with 1 (1.5 equiv) and trimethylacetic acid (0.1 equiv) in mesitylene (3 mL per mmol of 5a) at 160 °C (24 hours, argon atmosphere) gave 6a as a mixture of diastereomers (55% yield). Treatment of 6a with LiI (5 equiv) in 2,6-dimethylpyridine (reflux, 2 hours, argon atmosphere) afforded the carboxylic acid 7a (75% yield) after normal work-up.[13] Selenolactonization[14] of 7a to 8a (70% yield) followed by oxidative-elimination of both phenylseleno groups (8 equiv 30% H_2O_2 in THF at 25 °C) gave the known[15] cis-fused α-methylene-γ-butyrolactone 9a (90% yield). In an identical manner, 3-methyl-2-cyclohexen-1-ol (5b) was converted to 6b (40% yield), then to 7b (93% yield), 8b (61% yield) and 9b (60% yield).



5a R = H 6 X = Me 8 9

5b R = Me 7 X = H

Finally, we have also effected Claisen ortho ester rearrangement of 1 with methyl N-carbomethoxy-3-indoleglycolate (10) to give the 2,3-disubstituted indole 11;[16] oxidative-elimination afforded the acrylate 12. This compound is of potential utility for the preparation of the iboga alkaloid catharanthine via a [4+2] cycloaddition with an appropriate 1,2-dihydropyridine.[17] Futhermore, 2-(2-indolyl)-acrylates have been utilized for the preparation of aspidosperma alkaloids,[18] and have been postulated to be key intermediates in the biosynthesis of indole alkaloids.[19]



10 11 12

We are currently investigating the use of 1 for the total synthesis of a number of natural products.

Trimethyl 3-(phenyseleno)orthopropionate (1) was prepared by the following procedure. A suspension of PhSeSePh (50.0 mmol) in EtOH (150 mL) was reduced with $NaBH_4$ (~6 g) at 0 °C until the yellow color was discharged; 3-bromopropionitrile (100 mmol) was added dropwise at 0 °C, the mixture was stirred for 30 min, the EtOH was removed in vacuo, and the residue was extracted with ether, dried ($MgSO_4$) and distilled (bp 101-103 °C, 0.04 mm) to give 3-(phenylseleno)propionitrile (97% yield). Anhydrous HCl (44 mmol) was added to a solution of 3-(phenylseleno)propionitrile (40.0 mmol), absolute MeOH (44 mmol) and anhydrous ether (40 mL) at -20 °C. The mixture was stored in a freezer at -20 °C for 4 days during which time a large amount of imidate hydrochloride crystallized from the solution. These crystals were filtered under argon, washed with ether, and dried in vacuo to give methyl 3-(phenylseleno)propionimidate hydrochloride (65% yield). The imidate hydrochloride (26 mmol) was suspended in dry hexane (25 mL), absolute MeOH (65 mmol) was added and the mixture was stirred at 20 °C for 4 days. Triethylamine (0.5 mL) was added, the mixture was filtered, the hexane solution was dried (K_2CO_3), the hexane was removed in vacuo, and the residue was distilled (bp 140 °C, 0.02 mm) to give 3-(phenylseleno)orthopropionate (92% yield): ^{1}H HMR (CCl_4) δ 1.95 (m, 2H), 2.80 (m, 2H), 3.10 (s, 9H), 7.25 (m, 5H).

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(8) This ortho ester is thermally stable at temperatures less than 175 °C.

(9) Spectral data (^{1}H NMR, IR, high resolution MS) are in full accord for all new compounds. Yields refer to products purified by flash chromatography[10] utilizing silica gel 60 (40-63 μm) with hexane-ethyl acetate eluent. Yields have not been optimized. ^{1}H NMR data (CCl_4): 3a δ 2.7 (m) and 3.0 (m) (total 4 H), 3.52 (s) and 3.54 (s) (total 3 H), 4.8 (m) and 5.0 (m) (total 2 H), 5.72 (dd, J = 9, 17 Hz, 1 H), 7.1 (m, 10 H). 3b δ 1.05 (s, 3 H), 1.2 - 2.0 (m) and 1.55 (s) and 1.68 (s) (total 10 H), 2.5 (m) and 2.9 (m) (total 3 H), 3.53 (s) and 3.57 (s) (total 3 H), 5.0 (m, 3 H), 5.80 (dd, J = 10, 16 Hz, 1 H), 7.1 - 7.7 (m, 5 H). 4a δ 3.57 (s, 3 H), 4.6 (m, 2 H), 5.10 (d, J = 10 Hz, 1 H), 5.45 (s, 1 H), 5.9 (m) and 6.12 (s) (total 2 H), 7.2 (m, 5 H). 4b δ 1.30 (s, 3 H), 1.5 - 2.2 (m, 10 H), 3.63 (s, 3 H), 4.9 (m, 3 H), 5.46 (s, 1 H), 5.95 (dd, J = 10, 16 Hz) and 5.98 (s) (total 2 H). 6a δ 0.8 - 2.7 (m, 8 H), 2.95 (m, 2 H, CH_2SePh), 3.59 (s, 3 H), 5.27 (m, 1 H), 5.65 (m, 1 H), 7.0 - 7.5 (m, 5 H). 6b δ 0.97 (s, 3 H), 1.1 - 2.0 (m, 6 H), 2.5 (m, 1 H, CHCO$_2$Me), 2.95 (m, 2 H, CH_2SePh), 3.60 (s, 3 H), 5.10 (d, J = 10 Hz, 1 H), 5.57 (m, 1 H), 7.0 - 7.6 (m, 5 H). 9a δ 1.3 - 2.3 (m, 4 H), 3.62 (m, 1 H), 4.85 (m, 1 H), CHO-), 5.50 (m, 1 H), 5.90 (m) and 6.14 (m) (total 3 H). 9b δ 1.22 (s, 3 H), 1.55 - 2.2 (m, 4 H), 4.30 (m, 1 H, CHO-), 5.35 (1 H), 5.90 (m) and 6.11 (s) (total 3 H). 12 δ 3.73 (s, $CH_2CO_2CH_3$) and 3.78 (s, $=CCO_2CH_3$) (total 8 H), 3.99 (s, 3 H, NCO_2CH_3), 6.05 (d, J = 2 Hz, 1 H), 6.72 (d, J = 2 Hz, 1 H), 7.2 - 7.8 (m, 3 H), 8.25 (dd, J = 6, 2 Hz, 1 H).

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