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CLAISEN ORTHO ESTER REARRANGEMENT WITH TRIMETHYL β-(METHOXY)ORTHOPROPIONATE: A THERMALLY STABLE SYNTHON FOR THE PREPARATION OF METHYL α-SUBSTITUTED ACRYLATES[1]

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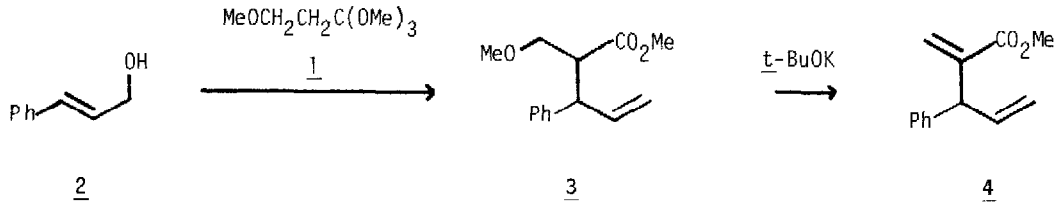
Summary: Trimethyl β-(methoxy)orthopropionate, a compound which is thermally stable at 190 °C for prolonged times, may be utilized as a synthon for the preparation of methyl α-substituted acrylates via Claisen ortho ester rearrangement with allylic alcohols followed by β-elimination of methanol with base.

The Claisen ortho ester rearrangement[2] provides a versatile method for the construction of new carbon to carbon bonds with high regio- and stereospecificity.[3] We recently reported that Claisen ortho ester rearrangement of allylic alcohols with trimethyl β-(phenylseleno)-orthopropionate, followed by oxidative-elimination of PhSeOH from the resulting methyl α-substituted-β-(phenylseleno)propionates, provided a convenient procedure for the preparation of methyl α-substituted acrylates.[4] Unfortunately, this procedure is limited by the thermal stability of the trimethyl β-(phenylseleno)orthopropionate, which undergoes rapid decomposition at temperatures greater than 170 °C. Hence, it is not feasible to employ the seleno ortho ester for rearrangements which require high temperatures for extended periods of time.

We now wish to report that trimethyl β-(methoxy)orthopropionate (1) may be utilized for the preparation of methyl α-substituted acrylates in an analogous strategy. Claisen ortho ester rearrangement of cinnamyl alcohol (2) with 1 (3 equiv) and 2,4,6-trimethylbenzoic acid (0.05 equiv) at 185-190 °C (2 hours, argon atmosphere) gave 3 as a mixture of diastereomers[5] (78% yield); β-elimination of methanol with t-BuOK (1 equiv) in THF (-78 °C, 10 min) gave 4 in 70% yield. In the same manner, geraniol (5) with 1 (3 equiv) and 2,4,6-trimethylbenzoic acid (0.05) at 185-190 °C (2 hours, argon atmosphere) gave 6 in 92% yield. Reaction of 6 with t-BuOK (1 equiv) in THF (0 °C, 10 min) gave 7 in 90% yield. Likewise, trans-pinocarveol (8)[7] with 1 (3 equiv) and 2,4,6-trimethylbenzoic acid (0.05 equiv) at 185-190 °C (2 hours, argon atmosphere) gave 9 in 70% yield; treatment of 9 with t-BuOK (1 equiv) in THF (0 °C, 10 min) gave 10 in 88% yield.

The Claisen ortho ester rearrangement of 1-tosyl-N,N-dimethyl-3-indolegylcolamide (11)[8] requires both a larger amount of acid catalyst and longer reaction times, and in this instance both rearrangement and thermal elimination of methanol take place concurrently. Thus, reaction of 11 with 1 (20 equiv) and 2,4,6-trimethylbenzoic acid (0.5 equiv) at 185-190 °C (4 hours, argon atmosphere) gave 12 (mp 172-173 °C) in 80% overall yield from 11.



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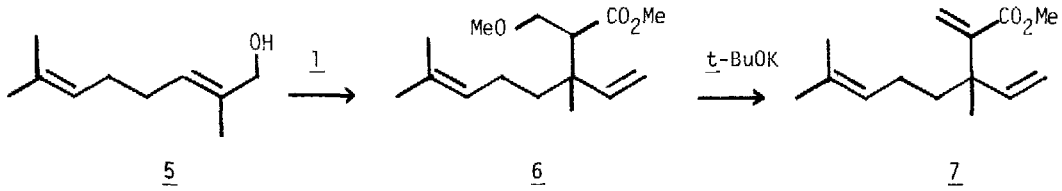

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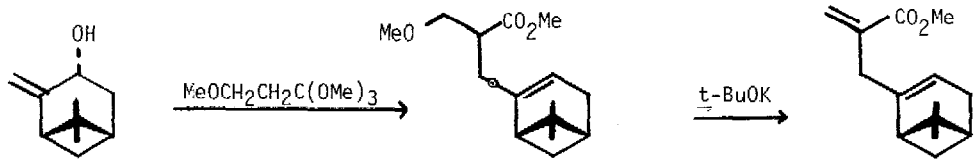

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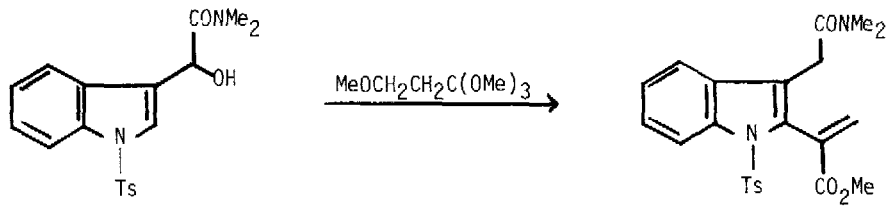

11 12

The ortho ester 1 has a number of attractive features for the above strategy. First, and most important, 1 is thermally stable at its atmospheric boiling point (185 °C) for periods in excess of 48 hours. Second, 1 is readily prepared in good yields on a large scale from inexpensive starting materials.[9] Third, with the exception of 11, Claisen ortho ester rearrangement of allylic alcohols with 1 occurs without concomitent β-elimination of methanol. And finally, conversion of the α-substituted-β-methoxypropionates to the α-substituted acrylates occurs under mild conditions.

We are currently investigating the application of this strategy to the synthesis of a number of natural products.[11,12]

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(5) Spectral data (^{1}H and ^{13}C NMR, IR, high resolution MS) are in full accord for all new compounds. Yields refer to products purified by flash chromatography[6] and have not been optimized. ^{1}H NMR data: 3 (CCl_4) δ 3.0 (m), 3.10 (s), 3.22 (s), 3.29 (s), 3.5 (m), and 3.60 (s) (total 10 H), 4.9 (m, 1 H), 5.1 (m 1 H), 5.6-6.4 (m, 1 H); 4 see Ref. 4; 6 (CCl_4) δ 1.00 (s) and 1.05 (s) (total 3 H), 1.5 (m), 1.57 (s), 1.65 (s), and 2.1 (m) (total 10H), 2.5 (m, 1 H), 3.20 (s, 3 H), 3.5 (m, 2 H), 3.58 (s) and 3.62 (s) (total 3 H), 5.1 (m, 3H), 5.5-6.2 (m, 1 H); 7 see Ref. 4; 9 (CCl_4) δ 0.83 (s, 3 H), 1.12 (d, J = 8, 1 H), 1.28 (s, 3 H), 2.0-3.0 (m, 8 H), 3.27 (s) and 3.35 (m) (total 5 H), 3.62 (s, 3 H), 5.22 (m, 1 H); 10 (CCl_4) δ 0.81 (s, 3 H), 1.16 (d, J = 8) and 1.26 (s) (total 4 H), 2.0-2.6 (m, 5 H), 2.93 (m, 2 H), 3.69 (s, 3 H), 5.26 (m, 1 H), 5.48 (d, J = 2, 1 H), 6.11 (d, J = 2, 1 H); 12 ($CDCl_3$) δ 2.16 (s, 3 H), 2.85 (s) and 2.90 (s) (total 6 H), 3.60 (br s, 2 H, - CH_2CO), 3.80 (s, 3 H), 5.83 (d, J = 2 , 1 H), 6.72 (d, J = 2, 1 H), 7.0-7.7 (m, 7 H), 8.15 (m, 1 H). ^{13}C NMR data: 12 ($CDCl_3$, 20 MHz) δ 21.23, 30.57, 35.45, 37.20, 52.09, 114.53, 118.05, 119.73, 123.57, 125.23, 126.45 (2 C), 129.43 (2 C), 129.96, 130.85, 132.65, 133.19, 135.22 135.94, 144.56, 165.81, 169.26.

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(9) Trimethyl β-(methoxy)orthopropionate (1) was prepared by the following procedure. To a solution of β-methoxypropionitrile[10](250 mmol) and absolute methanol (270 mmol) in anhydrous ether (50 mL) cooled to 0 °C was added anhydrous HCl (268 mmol). This solution was stored at 0 °C for 3 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-(methoxy)propionimidate hydrochloride (92% yield). The imidate hydrochloride (230 mmol) was suspended in dry hexane (50 mL), absolute MeOH (560 mmol) was added and the mixture was stirred at 20 °C for 3 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 89-90 °C, 20 mm) to give trimethyl β-(methoxy)orthopropionate (179 mmol, 72% overall yield): ^{1}H NMR (CCl_4) δ 1.95 (t, J = 8 Hz, 2 H); 3.17 (s, $C(OCH_3)_3$), 3.25 (s, CH_3OCH_2), and 3.34 (partially obscured t, J = 8 Hz) (total 14 H).

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(11) For an alternative method for the introduction of an α-substituted acrylate moiety via [3,3] sigmatropic rearrangement, see: W. C. Still and M. J. Schneider, J. Am. Chem. Soc., 99, 948 (1977).

(12) A detailed procedure for the synthesis of 12 follows. A mixture of 11[8] (215 mg, 0.577 mmol), 1 (1.89 g, 11.5 mmol), and 2,4,6-trimethylbenzoic acid[13] (47 mg, 0.29 mmol) in a 10-mL flask fitted with a 15-cm Vigreux column topped with a short-path distillation head under an atmosphere of argon was heated in a silicon oil bath at 185-190 °C for 4 hours. The majority of excess ortho ester was removed at reduced pressure (0.1 mm), the residue was dissolved in CH_2Cl_2 (30 mL), 20% aqueous HCl (2 mL) was added and the mixture was stirred at 25 °C for 1 hour in order to hydrolyze any remaining ortho ester. The CH_2Cl_2 layer was separated, the aqueous layer was extracted with additional CH_2Cl_2 (20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and the CH_2Cl_2 was removed in vacuo. The residue (305 mg) was purified by flash chromatography[6] using 40% EtOAc in Et_2O, followed by crystallization from hexane-EtOAc to give 12 (202 mg, 0.46 mmol, 80% yield): mp 172-173 °C.

(13) We have found that 2,4,6-trimethylbenzoic acid is a superior catalyst for Claisen ortho ester rearrangements. Even when a large amount is required, as in the conversion of 11 to 12, there are no complications from esterification of the allylic alcohol with the acid catalyst.

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