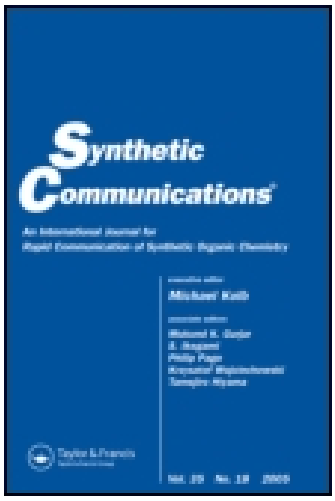

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A HIGH YIELDING PROCEDURE FOR PREPARATION OF MONO-CARBOXYLATE SURROGATES OF ALLENIC DICARBOXYLATES AND DIESTERS

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A HIGH YIELDING PROCEDURE FOR PREPARATION OF MONO-CARBOXYLATE SURROGATES OF ALLENIC DICARBOXYLATES AND DIESTERS

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ABSTRACT

A high yielding procedure for preparation of various allenyl mono-carboxylates is presented.

Key Words: Allene; Thioester; Silylester; Mitsunobu

Allenyl dicarboxylates[1] and their corresponding diesters[2] are readily accessible five carbon synthons that have proven tremendously versatile.[3] These systems undergo a myriad of reactions including [4+2],[4] [3+2],[5] and [2+2]-cycloadditions,[6] additions with radicals[7] and soft nucleophiles,[8] and

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†Professor Schlessinger had been a member of the department of chemistry at the University of Rochester for more than three decades. He passed away on December 11, 1998 at the age of 62 and will be remembered by his students as a colorful teacher and demanding mentor.

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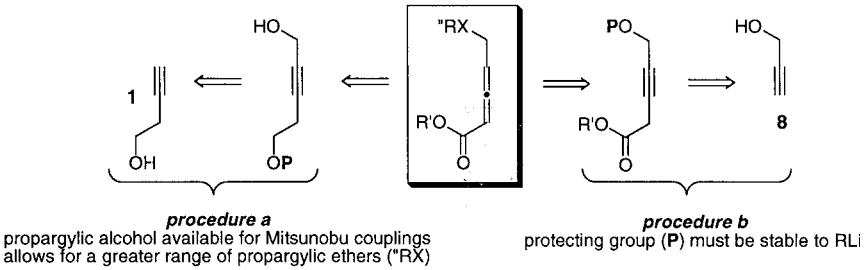


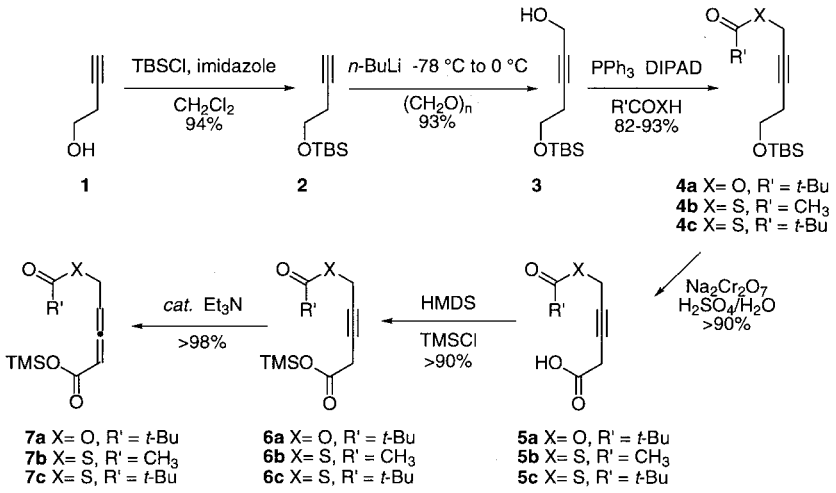
Figure 1.

sundry metal mediated couplings.[9] Recent reports of procedures for dynamic kinetic resolution of allenyl carboxylates should significantly increase their applications in enantioselective syntheses as well.[10] However, differentiating the 1,3-dicarboxylate moieties in the adducts often proves challenging. An obvious solution, using a mono-carboxylate surrogate in these processes, has been largely ignored because of the difficulty associated with preparation of a non-symmetric allenyl system.

The previous method (**b**, Fig. 1) for syntheses of mono-carboxylate allene derivatives begins with a propargylic alcohol **8**, which is converted to a robust propargylic ether and then coupled as the corresponding acetylide with a two-carbon fragment such as an epoxide[2a] or α-diazoester.[11] The coupling usually proceeds in less than 50% yield and examples employing epoxides also require oxidation to an acid and conversion to an ester. The resulting deconjugated ynoate is then isomerized into an allenyl system upon treatment with a catalytic quantity of Et_3N.

Our method (**a**, Fig. 1) begins instead with the homo-propargylic alcohol **1**. This is protected as an acid-labile ether. Formation of the lithium acetylide and coupling with aldehydes, in this instance formaldehyde, proceeds in a far greater yield (>80%), than the umpolung couplings of procedure **b**. The resulting propargylic alcohol can be displaced with a variety of nucleophiles via a modified Mitsunobu reaction in good yields. Jones oxidation of the labile homo-propargylic ether furnishes a deconjugated ynoate that can be esterified and isomerized into the allenyl system.

The differences between these processes may seem inconsequential, however, allenes **7a–c** (Sch. 1) illuminate the benefits of process (**a**). Compounds **7a–c** are not accessible by type (**b**) processes. The route to these materials begins with **1**, which is converted to the silyl ether **2** (94%) by treatment with TBSCl and imidazole in CH_2Cl_2. Next, alkyne **2** is



Scheme 1. Procedure **a**.

deprotonated with *n*-BuLi. The corresponding lithium acetylide smoothly adds to formaldehyde bubbled into the pot by cracking *para*-formaldehyde in a separate flask under a nitrogen stream.[12] This combination results in the formation of the propargylic alcohol **3** (93%), which is displaced in good yields (82–93%) using a modified Mitsunobu procedure.[13] Trimethylacetic acid, as well as the thio-acids CH_3COSH and *t*-BuCOSH,[14] all smoothly couple under these conditions affording **4a–c**, respectively. Submitting the respective products, which contain an acid-labile ether, to Jones conditions causes both deprotection and oxidation. The resulting carboxylic acids **5a–c** are readily purified by base extraction into an aqueous phase followed by acidification and extraction into an organic phase. Each acid is produced in >90% yield. The acids are poised for conversion to any number of ester derivatives. However, we had a need for a very labile ester derivative and chose to silylate **5a–c**. Treatment of each with a 1 : 1 equiv admixture of TMSCl–HMDS provides **6a–c**, each respectively in >90% after Kugelrohr distillation (10^{-4} torr). Submission of the pertinent silyl ester (0.05 M in CH_2Cl_2) to a catalytic quantity of Et_3N (0.2 equiv) affords the desired allene monoester (*cf.* **7a–c**) in essentially quantitative yield. These allenes can be stored indefinitely at −78°C. It is hoped that the procedure developed for the synthesis of **7a–c** may expand the future prospects for allene mono-carboxylates in synthesis.

EXPERIMENTAL

Compound 2: To a solution of alcohol (1 equiv 1 M in CH_2Cl_2) at 0°C under nitrogen was added imidazole (1.1 equiv) and *t*-butyldimethylsilyl chloride (1.1 equiv) and a catalytic quantity of DMAP. The reaction was stirred at 0°C for 1 h and slowly warmed to r.t. After stirring at 25°C for 4 h, the reaction was diluted with ether/hexanes (4 : 1) and filtered through celite. The solvent was evaporated and the material was purified by distillation (45°C, 2 torr, 94%) to give the TBS ether as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.76 (m, 2H), 2.42 (m, 2H), 1.98 (m, 1H), 0.92 (s, 9H), 0.08 (s, 6H).

Compound 3: To a solution of alkyne (1 equiv, 1 M in Et_2O) at −78°C under nitrogen was added *n*-BuLi (1.1 equiv, 1.54 M). The contents were warmed to 0°C and stirred for 1 h. A nitrogen stream was passed through a separate round bottom flask containing excess solid $(CH_2O)_n$ heated to 150°C, through a clean glass tube, and bubbled into the Et_2O solution of the lithium acetylide at 0°C until the Et_2O solution turned cloudy. The reaction was diluted with ether and quenched with 5% aqueous citric acid solution. The organic layer was separated, dried over Na_2SO_4 and filtered through celite. After removal of solvent, the material was purified by distillation (110°C, 0.2 torr, 87%) to give the propargyl alcohol as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.23 (m, 2H), 3.75 (m, 2H), 2.47 (m, 2H), 1.7 (br m, 1H), 0.97 (s, 9H), 0.07 (s, 6H).

Compounds 4a–c: To a stirred solution of PPh_3 (2 equiv) 0.5 M in THF at 0°C was added DIPAD (2 equiv). A white precipitate resulted after stirring for 1 h at 0°C. The propargyl alcohol was added neat (1 equiv) and followed by the addition of the appropriate acid (2 equiv). After stirring for 4 h, the volatiles were removed and the residue was taken up in (hexanes : Et_2O, 4 : 1), washed with aqueous $NaHCO_3$, filtered through celite and the volatiles were removed. This process was continued until no solids remained. Drying and evaporation gives the respective ester as a yellow oil. The S or O ester could be used directly in subsequent Jones oxidation without purification. **Compound 4a:** 87% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.61 (t, 2H), 3.73 (t, 2H), 2.45 (m, 2H), 1.22 (s, 9H), 0.97 (s, 9H), 0.09 (s, 6H). **Compound 4b:** 82% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.72 (m, 2H), 3.68 (t, 2H), 2.47 (m, 2H), 2.42 (s, 3H), 0.97 (s, 9H), 0.08 (s, 6H). **Compound 4c:** 93% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.72 (m, 2H), 3.63 (m, 2H), 2.41 (m, 2H), 1.32 (s, 9H), 0.97 (s, 9H), 0.08 (s, 6H).

Compounds 5a–c: To a stirred solution of the TBS–ether (1 equiv) in acetone (0.25 M solution) at −78°C was added Jones reagent (4 equiv of an 8 M solution). The reaction was permitted to warm to 25°C and stirring

was continued for 2 h. Upon completion by TLC analysis, isopropyl alcohol (1 equiv) was added slowly. After stirring for an additional 20 min, the reaction was diluted with ether and solids were removed by filtration through celite. Volatiles were removed at reduced pressure and the residue was dissolved in ether. After basification with saturated aqueous $NaHCO_3$, the organic phase was separated and discarded. The aqueous solution was acidified with solid citric acid. After extraction with ether, the organic layer was dried and the volatiles removed to give a crystalline white solid. **Compound 5a:** 93% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.5–5.0 (br, 1H), 4.71 (s, 2H), 3.48 (s, 2H), 1.22 (s, 9H). **Compound 5b:** 95% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.5–6.5 (br, 1H), 3.70 (s, 2H), 3.59 (s, 2H), 2.39 (s, 3H). **Compound 5c:** 94% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.5–4.0 (br, 1H), 3.70 (s, 2H), 3.65 (s, 2H), 1.22 (s, 9H).

Compounds 6a–c: To a stirred solution of the acid (1 equiv 1 M in CH_2Cl_2) at 0°C was added HMDS (1.1 equiv); followed by the slow addition of TMSCl (1.1 equiv). The reaction was permitted to warm to 25°C and stirring was continued for 6 h. The reaction was then diluted with ether and the solids were removed by filtration through celite. Once the volatiles were removed, the cloudy material was purified by distillation (0.01 torr) affording colorless oils. **Compound 6a:** 92% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.77 (s, 2H), 3.36 (s, 2H), 1.43 (s, 9H), 0.42 (s, 9H). **Compound 6b:** 94% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 2H), 3.33 (s, 2H), 2.46 (s, 3H), 0.42 (s, 9H). **Compound 6c:** 92% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 2H), 3.38 (s, 2H), 1.28 (s, 9H), 0.42 (s, 9H).

Compounds 7a–c: To a stirred solution of the TMS-ester 0.5 M in CH_2Cl_2 at 0°C was added Et_3N (0.2 equiv) and the reaction stirred at 0°C for 6 h. The volatiles (Et_3N) were removed, a crystal of Rose Bengal was added for stabilization and the material was stored at −78°C for use in subsequent reactions. **Compound 7a:** >98% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 2H), 4.65 (m, 2H), 1.25 (s, 3H), 0.38 (s, 9H). **Compound 7b:** >98% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 2H), 3.61 (m, 2H), 2.44 (s, 3H), 0.41 (s, 9H). **Compound 7c:** >98% ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 2H), 3.54 (m, 2H), 1.27 (s, 9H), 0.41 (s, 9H).

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