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Stereoselective Synthesis of *Z*-α-Aryl-α,*β*-unsaturated Esters

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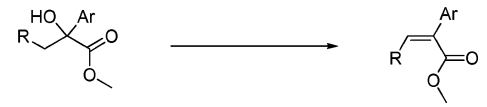
An efficient method for the stereoselective synthesis of (*Z*)-α-arylacrylates is described. Treatment of α-hydroxyesters with triflic anhydride and pyridine at 0 °C followed by warming to room temperature afforded the corresponding (*Z*)-α-aryl-α,*β*-unsaturated esters in very good yields and excellent stereoselectivity.

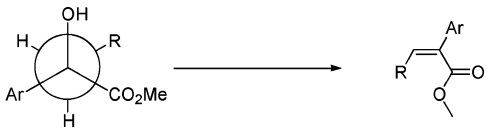
Stereoselective synthesis of *Z*-α,*β*-unsaturated acid derivatives remains one of the enduring, classic problems in organic synthesis. The Corey−Winter[1] olefination of 1,2-diols, carbodiimide-assisted syn elimination of *erythro*-aldols,[2] Peterson olefination,[3] Wittig reaction,[4] and *Z*-selective modifications of the Horner−Wadsworth−Emmons reaction developed by Seyden-Penne et al.,[5] Breuer and Bannet,[6] Still and Gennari,[7] and Ando[8] are some of the notable solutions developed over the years to address the problem of controlling olefin geometry. Among these methods, the Still−Gennari protocol has clearly emerged as the method of choice in most applications. However, even this method is not without some limitations, particularly in the synthesis of α,*β*-disubstituted acrylate derivatives, wherein Marshall et al. and others have observed diminished *Z*-selectivity.[9] Perhaps the most serious disadvantage to this method is the difficulty of accessing the required phosphonocarboxylate precursors with substituents in the α-position.[10] In connection with our work aimed at the synthesis of a (*Z*)-1,2-diarylacrylate intermediate for a drug discovery program, we too observed diminished *Z*-selectivity in the Still−Gennari reaction, particularly in large-scale (10−20 g) reactions, prompting us to explore alternate approaches. One of the approaches we examined was the possibility of stereoselective dehydration of an α-hydroxy ester. Herein we report our results, which show that carefully controlled dehydration of α-aryl-α-hydroxyesters can proceed with remarkable *Z*-selectivity, efficiently providing the desired *Z*-α-arylacrylates.

Aldol condensation and subsequent dehydration of a *β*-hydroxy ester is a classical method for the synthesis of α,*β*-unsaturated acid derivatives.[11] High stereoselectivities were observed in the E2 elimination of *erythro*-aldols to form *E*-acrylates. However, in the case of corresponding *threo*-aldols, a clean E2 elimination to form Z-acrylates remains elusive.[12] Stereoselective dehydration of an α-aryl-α-hydroxy ester (eq 1) was devised based on the hypothesis that the aryl group being larger than the ester group, a trans E2 elimination should give the desired *Z*-acrylate, as suggested by the corresponding Newman projection (eq 2).

Equation 1



Equation 2



Disubstituted α-hydroxy esters are easily prepared either by addition of a Grignard reagent to an α-keto ester[13] or more efficiently by the alkylation of an α-hydroxyester.[14]

Initial attempts at dehydration according to conventional methods were disappointing. In this regard, heating the hydroxyester **1** with acetic anhydride in the presence of catalytic amounts of sodium acetate[15] favored formation of the *E*-isomer. Treatment with methanesulfonyl chloride and triethylamine gave

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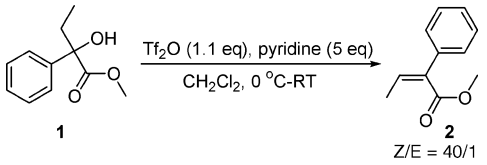
SCHEME 1. Stereoselective Dehydration



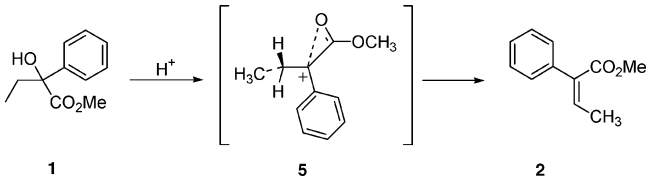
only trace amounts of elimination product. In contrast, clean elimination according to our method was achieved by treating a cold (0 °C) solution of the α-hydroxyester in dichloromethane (~0.2 M) with triflic anhydride and pyridine. After warming to room temperature and an aqueous workup, the *Z*-acrylate was obtained in very good yields and excellent stereoselectivity (Scheme 1).

DMAP also gave clean elimination product. Strong tertiary amine bases, triethylamine, and Hünig's base also gave the *Z*-acrylate, but the reactions were messy and incomplete. Other strong organic bases such as DBU, *N*-methylpiperidine, quinoline, and 2,6-lutidine or inorganic bases such as sodium acetylide and K_2CO_3 gave only trace amounts of the elimination product. When a mixture of Et_3N (5 eq) and pyridine (0.1 eq) was used, it gave lower yields and diminished stereoselectivity. Nonpolar solvents, such as toluene and dichloromethane, gave very good results. In polar solvents, such as acetonitrile and DMF, and in ethereal solvents, such as THF, diethyl ether, and DME, very little or no reaction was observed.

The effectiveness of pyridine and DMAP toward dehydration piqued our curiosity about the actual mechanism of dehydration, that is, whether base-induced elimination of a triflate intermediate occurred by an E2 pathway or through the formation of an acylcarbenium ion by an E1 pathway. Although formation of species having positively charged carbon attached to strongly electron-withdrawing groups are expected to be highly unfavorable, electron-withdrawing groups such as cyano, acyl, and alkynyl substituents have indeed been shown to *stabilize* the carbenium ion through resonance. Thus, Gassman et al.[16] and Olah et al.[17] have shown that the surprising stability of cyano-substituted carbocations arose from the mesomeric acylnitrenium ions. In the case of α-acylcarbenium ions, Morize and Begue[18] have postulated that mesomeric stabilization can occur through an overlap with the lone pair p orbital of the oxygen or the pi orbital of the carbonyl group. Solvolytic studies by Richard et al.[19] have shown that the lifetime of α-carboxyethyl-4-methoxybenzylcarbocation is indeed 14-fold longer than that for the unsubstituted carbocation. To test these possibilities, a number of NMR time course experiments were carried out using **1** as the substrate.

In the first experiment, a solution of **1** in CD_2Cl_2 taken up in an NMR tube was cooled to 0 °C, and triflic anhydride and pyridine-d_5 were added. The NMR tube was then transferred to the NMR instrument, and a time-course experiment was started immediately, while allowing the reaction to warm to room temperature. This experiment indicated slow formation of the elimination product from the starting material. The triflate intermediate **3** was not observable in the NMR time scale, indicating that it may be highly reactive. Interestingly, formation of small amounts (~20%) of a polar product, which did not undergo further elimination, was observed in this experiment. Isolation of this side product by thin-layer chromatography, followed by NMR and mass spectral analysis, revealed it to be the pyridinium triflate **4** (Scheme 2).

SCHEME 3. Mechanism of Dehydration



The pyridinium salt **4** was quite stable at room temperature. Treating **4** with various bases, such as triethylamine, DBU, or pyridine, to induce elimination were unsuccessful, and heating **4** in pyridine led to decomposition. Solution and vapor-phase elimination of alkylpyridinium salts to form alkenes has been reported,[20] however, from the above experiments it is clear that this pathway does not operate to form alkenes in our experiments. Next, in a similar experiment we used only triflic anhydride without any added pyridine. This experiment also showed slow conversion of the starting alcohol to the alkene, a clear indication that the elimination possibly takes place through an acylcarbenium ion. In a third time-course experiment, we used triflic acid to see if protonation can lead to the carbocation, with water as a leaving group. In this case, stereoselective elimination to form the *Z*-alkene was also observed, strongly suggesting an acylcarbenium ion intermediate **5** (Scheme 3).

To examine the scope of this reaction, a diverse set of α-aryl-α-hydroxy esters (Table 1) was subjected to dehydration conditions. Although use of triflic acid as the dehydrating agent did result in elimination to form the alkene in our NMR experiments, in large-scale experiments, diminished yields and isomerizations were observed in many instances. Dehydration using triflic anhydride and pyridine, however, gave a cleaner reaction profile and only very small amounts (1−2%) of the pyridine adduct **4** were observed. Triflic anhydride−pyridine was thus chosen as the preferred reagent system for the preparation of alkenes. Excellent Z selectivity was observed, typically $Z/E > 40/1$ in most cases. Particularly striking was the good *Z*-selectivity observed even in cases with sterically less-demanding, β-carbon substituents such as methyl, vinyl, and alkynyl groups (entries 4, 7, and 8). The stereochemistry of the olefins obtained was easily ascertained, mostly by ^{1}H NMR spectroscopy, based on the considerable downfield shift of the olefinic proton in the case of *E*-acrylates. Typically, the olefinic proton of *Z*-acrylates appears at δ 6−6.5 ppm, and for the corresponding *E*-isomers, the olefinic proton appears at δ 7−8 ppm.

SCHEME 2. Study of Dehydration by ^{1}H NMR

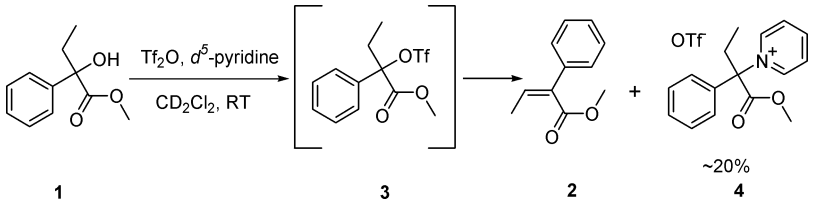
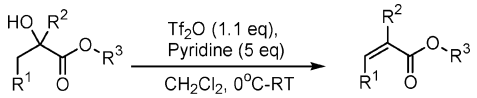


TABLE 1. Stereoselective Dehydration of α-Hydroxyesters



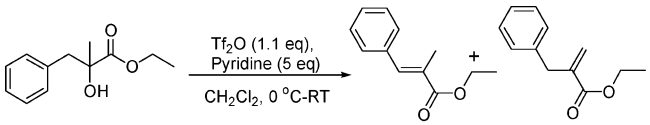
6 7

entry	R^1	R^2	R^3	Z/E^a	yield (%)
1	Ph	Ph	Me	40/1	88
2	2-$CH_3OC_6H_4$	Ph	Me	20/1	93
3	4-PhC_6H_4	Ph	Me	40/1	86
4	Me	Ph	Me	40/1	90
5	Me_2CH	Ph	Me	40/1	93
6	CO_2Me	Ph	Me	99/1	92
7	HC≡C	3-ClC_6H_4	Me	8/1	91
8	H_2C═CH	Ph	Me	10/1	81
9	Ph	Ph	Me_2CH	70/1	86

[a] *Z*/*E* ratios were determined by ^{1}H NMR from the integration of the olefinic protons of *Z*- and *E*-isomers.

Because the mechanistically derived preference for the *Z*-isomer is dependent on the relative size of the α-substituent and the ester group, a smaller α-substituent should exhibit the opposite preference, thus leading to the *E*-isomer. Application of the dehydration procedure to substrate **8** in which the α-substituent is methyl (smaller in size than the ethoxycarbonyl) gave two isomeric products in a 3:1 ratio (Scheme 4). The major product was the expected *E*-cinnamate **9** with an *E*/*Z* ratio of 40/1. The minor product was the isomeric α-benzyl acrylate **10**.[21]

SCHEME 4



8 9 10

In conclusion, we have developed an efficient method for the synthesis of *Z*-α-arylacrylates on the basis of the stereoselective dehydration of the corresponding α-hydroxyester. Excellent *Z*-selectivity was observed with a diverse set of α-aryl-α-hydroxyesters. Our studies coupled with reported investigations on resonance stabilized carbocations strongly suggest that the mechanism involves the intermediacy of an acylcarbenium ion, and the remarkable stereochemical preference likely results from the larger size of the aryl substituent vis-à-vis the alkoxy carbonyl group favoring the *Z*-isomer. A vast number of α-arylacrylates and α-heteroarylacrylates have been reported in the literature,[22] and the methodology outlined here should be suitable to a considerable number of this important class of compounds. The successful application of this methodology toward large-scale synthesis of pharmaceutical target molecules from our laboratories will be reported in due course.

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Experimental Section

General Procedure for the Dehydration of α-Hydroxy Esters (Entries 1−9). To a solution of the hydroxyl ester (1.0 mmol) in anhydrous CH_2Cl_2 (10 mL) cooled to 0 °C using an ice bath was added triflic anhydride (0.31 g, 1.1 mmol). After 10 min, anhydrous pyridine (0.4 mL, 5.0 mmol) was added dropwise. The reaction mixture was stirred for 10−12 h, while allowing the mixture to slowly warm to room temperature. The reaction was then quenched by the addition of water (20 mL), and the mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). All organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude unsaturated ester thus obtained was purified by flash column silica gel chromatography (eluting with a gradient of 10−25% EtOAc/hexanes).

(*Z*)-2,3-Diphenylacrylic acid methyl ester (7, Entry 1): colorless oil; yield 88%; *Z*/*E* = 40/1; IR (film) 2921, 1724, 1433, 1264, 1250, 1211, 1195, 1172, 1037, 1007, 751, 734, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 7.05 (s, 1H), 7.29−7.40 (m, 8H), 7.46−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.3, 126.4, 128.1, 128.3, 128.5, 128.7, 131.5, 134.8, 135.6, 136.8, 170.1; HRMS (EI) *m*/*z* calcd for $C_{16}H_{15}O_2$ [M + H]$^+$, 239.1067; found, 239.1072.

(*Z*)-3-(2-Methoxyphenyl)-2-phenylacrylic Acid Methyl Ester (7, Entry 2): white crystalline solid; yield 93%; *Z*/*E* = 20/1; mp 50−51 °C; IR (film) 2948, 2920, 2839, 1722, 1596, 1578, 1494, 1486, 1462, 1433, 1359, 1308, 1275, 1248, 1207, 1194, 1172, 1111, 1077, 1051, 1025, 1007, 971, 847, 779, 751, 736, 694, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.73 (s, 3H), 3.84 (s, 3H), 6.89−6.94 (m, 2H), 7.27 (s, 1H), 7.29−7.33 (m, 3H), 7.35−7.39 (m, 3H), 7.45−7.47 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.9, 55.4, 110.5, 120.4, 125.1, 126.8, 128.1, 128.3, 128.5, 128.6, 129.8, 134.7, 137.4; HRMS (EI) *m*/*z* calcd for $C_{17}H_{17}O_3$ [M + H]$^+$, 269.1172; found, 269.1180.

(*Z*)-3-Biphenyl-4-yl-2-phenylacrylic Acid Methyl Ester (7, Entry 3): white crystalline solid; yield 86%; *Z*/*E* = 40/1; mp 115−116 °C; IR (film) 3029, 1724, 1598, 1486, 1434, 1361, 1218, 1198, 1171, 1004, 892, 836, 763, 695 cm^{-1}; ^{1}H NMR δ 3.81 (s, 3H), 7.06 (s, 1H), 7.23−7.61 (m, 14H); ^{13}C NMR δ 52.2, 126.3, 126.9, 127.1, 127.5, 128.3, 128.6, 128.7, 128.8, 128.9, 131.0, 134.5, 134.6, 136.8, 140.3, 141.0, 170.1; HRMS (EI) *m*/*z* calcd for $C_{22}H_{19}O_2$ [M + H]$^+$, 315.1381; found, 315.1371.

(*Z*)-2-Phenylbut-2-enoic Acid Methyl Ester (7, Entry 4): colorless oil; yield 90%; *Z*/E = 40/1; IR (film) 2950, 1718, 1494, 1434, 1352, 1202, 1114, 1005, 753, 696 cm^{-1}; ^{1}H NMR δ 2.03 (d, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 6.25 (q, *J* = 7.2 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR δ 15.9, 51.5, 127.2, 127.4, 128.1, 135.3, 135.4, 138.1, 168.4; HRMS (EI) *m*/*z* calcd for $C_{11}H_{13}O_2$ [M + H]$^+$, 177.0912; found, 177.0905.

(*Z*)-4-Methyl-2-phenylpent-2-enoic Acid Methyl Ester (7, Entry 5): colorless oil; yield 93%; *Z*/*E* = 40/1; IR (film) 2952, 1720, 1615, 1495, 1435, 1331, 1200, 1171, 1093, 1028, 990, 868, 812, 775, 699 cm^{-1}; ^{1}H NMR δ 1.08 (d, *J* = 6.6 Hz, 6H), 2.95 (m, 1H), 3.79 (s, 3H), 5.95 (d, *J* = 10.0 Hz), 7.27 (m, 5H); ^{13}C NMR δ 22.6, 29.4, 51.6, 127.1, 127.4, 128.2, 132.3, 137.8, 146.4, 168.7; HRMS (EI) *m*/*z* calcd for $C_{13}H_{17}O_2$ [M + H]$^+$, 205.1225; found, 205.1228.

(*Z*)-2-Phenylbut-2-enedioic Acid Dimethyl Ester (7, Entry 6): pale tan oil; yield 92%; *Z*/*E* = 99/1; IR (neat) 2951, 2836, 1719, 1625, 1577, 1497, 1450, 1434, 1357, 1291, 1197, 1169, 1024, 1003, 887, 835, 773, 753, 687, 668, 633 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.78 (s, 3H), 3.94 (s, 3H), 6.31 (s, 1H), 7.37−7.42 (m, 3H), 7.46−7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.0,

52.7, 116.9, 126.7, 128.9, 130.6, 133.1, 148.9, 165.4, 168.3; HRMS (EI) *m*/*z* calcd for $C_{12}H_{13}O_4$ $[M + H]^+$, 221.0808; found, 221.0812.

(*Z*)-2-(3-Chlorophenyl)-pent-2-en-4-ynoic Acid Methyl Ester (7, Entry 7): pale yellow oil; yield 91%; *Z*/*E* = 8/1; IR (film) 3289, 2951, 2100,1725, 1592, 1563, 1475, 1435, 1345, 1207, 1178, 1099, 1048, 784, 690, 638 cm^{-1}; ^1H NMR δ 3.48 (d, J = 2.4 Hz, 1H), 3.88 (s, 3H), 6.17 (d, J = 2.4 Hz, 1H), 7.26−7.37 (m, 4H); ^{13}C NMR δ 52.3, 79.6, 87.2, 114.6, 125.2, 127.1, 129.1, 129.7, 134.5, 137.0, 144.2, 166.4; HRMS (EI) *m*/*z* calcd for $C_{12}H_{10}ClO_2$ $[M + H]^+$, 221.0291; found, 221.0293.

(*Z*)-2-Phenylpenta-2,4-dienoic Acid Methyl Ester (7, Entry 8): pale yellow oil; yield 81%; *Z*/*E* = 10/1; IR (film) 2951, 1714, 1484, 1493, 1434, 1345, 1243, 1202, 1171, 1003, 918, 763, 695 cm^{-1}; ^1H NMR δ 3.83 (s, 3H), 5.43 (dd, J = 1.4, 10.4 Hz, 1H), 5.52 (ddd, J = 1.4, 2.1, 16.7 Hz, 1H), 6.66 (d, J = 11.2 Hz, 1H), 7.01 (m, 1H), 7.29−7.35 (m, 5H); ^{13}C NMR δ 51.8, 123.8, 127.4, 127.9, 128.3,133.5,133.7, 137.1, 137.4, 168.0; HRMS (EI) *m*/*z* calcd for $C_{12}H_{13}O_2$ $[M + H]^+$, 189.0912; found, 189.0910.

(*Z*)-2,3-Diphenylacrylic Acid Isopropyl Ester (7, Entry 9): colorless oil; yield 86%; *Z*/*E* = 70/1; IR (film) 2980, 1715, 1495, 1449, 1373, 1215, 1184, 1103, 1078, 1030, 1001, 985, 914, 858, 826, 753, 719, 692, 668, 649 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, J = 6.3 Hz, 6H), 5.19 (septuplet, J = 6.3 Hz, 1H), 7.02 (s, 1H), 7.27−7.40 (m, 8H), 7.46−7.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 68.9, 126.3, 128.1, 128.2, 128.3, 128.6, 130.6, 135.7, 135.8, 136.9, 169.1; HRMS (EI) *m*/*z* calcd for $C_{18}H_{19}O_2$ $[M + H]^+$, 267.1380; found, 267.1373.

Acknowledgment. We thank professor Scott E. Denmark and Dr. James P. Edwards for useful discussions.

Supporting Information Available: Representative experimental procedures, details of NMR time course experiments, and spectroscopic data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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