Articles

Synthesis of Highly Functionalized γ-Butyrolactones from Activated Carbonyl Compounds and Dimethyl Acetylenedicarboxylate†

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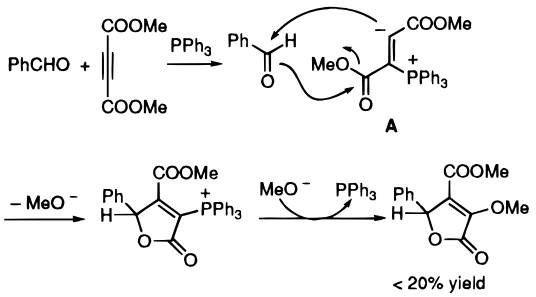
Received October 11, 1995⊗

A triphenylphosphine-catalyzed cyclization of α-keto esters, α-keto nitriles, or α,α,α-trifluoroacetophenone with dimethyl acetylenedicarboxylate is reported to produce highly functionalized α,β-unsaturated γ-butyrolactones in moderate yields. Thus treating a mixture of methyl 4-nitrophenylglyoxylate and dimethyl acetylenedicarboxylate with 20 mol % of triphenylphosphine afforded 5,5′-disubstituted 3-methoxy-4-(methoxycarbonyl)-2(3*H*)-furanone in 94% yield. In the reaction of α-keto esters $R^1COCOOMe$, an electron-withdrawing R^1 substituent is required for satisfactory reactivity. On the other hand, electron-donating R^1 substituents give higher yields with α-keto nitriles R^1COCN. Another electron-deficient carbonyl compound, α,α,α-trifluoroacetophenone, gave the corresponding lactone in good yield. The use of an α-hydroxy ketone as an electrophilic carbonyl compound with more than 1 equiv of triphenylphosphine produced dihydrofuran derivatives. One equivalent of triphenylphosphine oxide was obtained as a major product. An intramolecular Wittig reaction is proposed as a reaction mechanism.

Introduction

Organophosphorus compounds are widely used in organic synthesis.[1] When they act as a catalyst, "soft" nucleophilicity is one of their most characteristic features, as shown in the Michael addition,[2] aldol condensation,[3] isomerization of C−C mutiple bonds,[4] silylcyanation of aldehydes,[5] alcohol addition to methyl propiolate,[6] carbonate formation from propargyl alcohol and carbon dioxide,[7] and cycloaddition of 2,3-butadienotes or 2-butynoates with electron-deficient olefins.[8] In 1966, Winsterfeldt reported a triphenylphosphine-catalyzed lactone formation from benzaldehyde and dimethyl acetylenedicarboxylate in less than 20% yield.[9] The proposed mechanism is shown in Scheme 1, which includes zwitterionic intermediate **A**.[10] A number of organic transformations of intermediate **A** were demonstrated by Tebby,[11] but its use in a catalytic cycle has as yet been limited.

Scheme 1



α-Keto esters and α-keto nitriles have electron-withdrawing groups directly bound to their ketonic carbonyl groups. The strong electrophilic nature of these ketonic groups is expected to facilitate various kinds of nucleophilic additions.[12] We became interested in the use of these activated carbonyl compounds as trapping reagents for the zwitterionic intermediate **A**. In this paper, we report a triphenylphosphine-catalyzed cyclization of α-keto esters, α-keto nitriles, or α,α,α-trifluoroacetophenone with dimethyl acetylenedicarboxylate (**2**) to produce highly functionalized α,β-unsaturated γ-butyrolactones **3** in moderate to good yields. A related cyclization of α-hydroxy ketones **4** with acetylenedicarboxylate **2** is also described. The latter reaction is proposed to proceed *via* an intramolecular Wittig reaction.

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

‡ Deceased Oct 4, 1995.

⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1996.

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S0022-3263(95)01828-7 CCC: $12.00

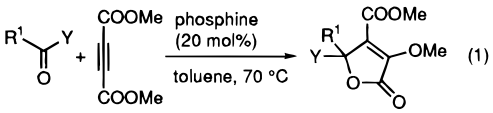
Table 1. Tertiary Phosphine-Catalyzed Lactone Formation from Electron-Deficient Carbonyl Compounds 1 and Dimethyl Acetylenedicarboxylate (2)

run	substrate **1**	R^1	R^2	phosphines	time (h)	yield of **3** (%)[a,b]
1	**1a**	4-$NO_2C_6H_4$	COOMe	PPh_3	22	94
2	**1b**	Ph	COOMe	PPh_3	8	11[c–e]
3	**1c**	4-ClC_6H_4	COOMe	PPh_3	22	*c*
4	**1d**	Ph	CN	PPh_3	8	58
5	**1e**	4-MeC_6H_4	CN	PPh_3	19	58
6	**1f**	4-$MeOC_6H_4$	CN	PPh_3	19	67
7	**1g**	4-ClC_6H_4	CN	PPh_3	22	30[d]
8	**1h**	4-$NO_2C_6H_4$	CN	PPh_3	22	<30[d,e]
9	**1i**	c-C_6H_{11}	CN	PPh_3	22	38
10	**1j**	Ph	CH_3	PPh_3	22	*c*
11	**1k**	Ph	CF_3	PPh_3	17	75
12	**1a**	4-$NO_2C_6H_4$	COOMe	(*S*)-BINAP[f]	49	6[c] (8)
13	**1a**	4-$NO_2C_6H_4$	COOMe	(*R*)-MeO-MOP[g]	47	41[c] (10)
14	**1a**	4-$NO_2C_6H_4$	COOMe	(+)-NMDPP[h]	48	5[c] (5)

[a] Isolated yield. [b] %*ee* for **3** are shown in parentheses. The absolute configuration of the major isomer has not been determined. [c] The unreacted starting materials were recovered. [d] A complex mixture was obtained. [e] The product was not obtained in pure form. [f] (*S*)-BINAP = (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [g] (*R*)-MeO-MOP = (*R*)-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl. [h] (+)-NMDPP = (1*S*,2*S*,5*R*)-neomenthyldiphenylphosphine.

Results and Discussion

Synthesis of 3-Methoxy-4-(methoxycarbonyl)-2(3*H*)-furanones from α-Keto Esters and α-Keto Nitriles. Treatment of a mixture of α-keto ester **1a** and dimethyl acetylenedicarboxylate (**2**) with 20 mol % of triphenylphosphine afforded 5,5′-disubstituted 3-methoxy-4-(methoxycarbonyl)-2(3*H*)-furanone (**3a**) in 94% yield as shown in eq 1. Other electron-deficient carbonyl



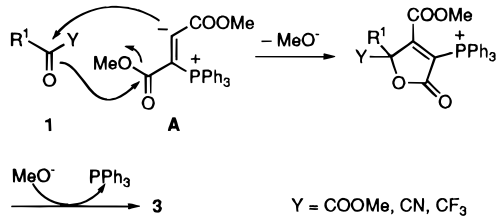
1 **2** **3**

compounds were also examined under similar conditions, and the results are summarized in Table 1. In the reaction of α-keto esters, an electron-withdrawing substituent such as R^1 is required for satisfactory reactivity (runs 1−3). On the other hand, electron-donating substituents give a better yield of **3** in the α-keto nitrile series (runs 4−8). The aliphatic α-keto nitrile **1i** also gave a similar product (run 9). An electron-withdrawing substituent attached to the carbonyl group is essential for the reaction. For example, acetophenone (**1j**) was recovered unchanged under the same reaction condition (run 10). Another electron-deficient carbonyl compound, α,α,α-trifluoroacetophenone, afforded the corresponding lactone **3k** in good yield (run 11). The structure of the product **3d** was determined by single-crystal X-ray analysis.[13]

When other phosphines or phosphites were used in place of triphenylphosphine, the yield of **3d** from **1d** dropped. Reactions with diphenylmethylphosphine and triphenyl phosphite gave complex mixtures, while those with tris(2-methylphenyl)phosphine and tricyclohexylphosphine produced **3d** in 35% and 0% yields, respectively, along with recovered starting materials. α-Keto ester **1a** was the substrate of choice because it gave the highest yield when triphenylphosphine was used as a catalyst. The results are also shown in Table 1. Chiral phosphines such as (*S*)-BINAP, (*R*)-MeO-MOP, and (+)-NMDPP were also used as catalysts for the present

(13) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Scheme 2

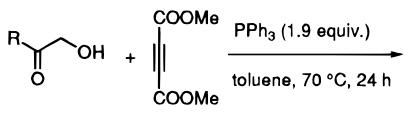


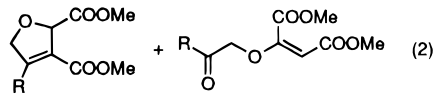
cyclization. No remarkable asymmetric induction, however, was observed. In addition, solvent effects were also examined. The use of 1,4-dioxane and tetrahydrofuran gave **3d** from **1d** in moderate yields (60% and 56%), while acetonitrile and 1,2-dichloroethane afforded it in lower yields (15% and 30%).

A possible mechanism for the present reaction is shown in Scheme 2, which is analogous to Scheme 1. The first step is the formation of zwitterionic intermediate **A**. We consider that the strongly electrophilic carbonyl compounds accelerate the nucleophilic addition of **A**. This also explains the fact that the electron-deficient α-keto esters afford the products in better yields. In the case of α-keto nitriles, however, the electron-rich carbonyl compounds were better substrates for the cyclization reaction. For example, nitro-substituted **1h** gave the desired product in lower yield along with complex mixtures. A possible explanation is as follows. For α-keto nitriles, the nitrile is a good electron-withdrawing group, but at the same time, it is also a good leaving group. Undesired side reactions may also occur where the nitrile behaves as a leaving group. The nucleophilic addition seems to be retarded in the case of less activated carbonyl compounds, such as acetophenone.

Reductive Formation of a Dihydrofuran Derivative from α-Hydroxy Ketones and Dimethyl Acetylenedicarboxylate: Intramolecular Wittig Reaction. The use of α-hydroxy ketone **4** in place of activated carbonyl compounds **1** produced the dihydrofuran derivative **5** in the presence of more than 1 equiv of triphenylphosphine as shown in eq 2. One equivalent of triphenylphosphine oxide was obtained, and olefin **6** was a minor product. Both toluene and acetone were used as solvents. In the reaction of **4a**, when the amount of the phosphine was reduced to 20 mol %, only 8% of **5a** was obtained and most of the starting material was recovered. The spectral data for **5b** were identical with those of an

authentic sample.[14] The structure of **6a** has been determined by X-ray diffraction.[13]



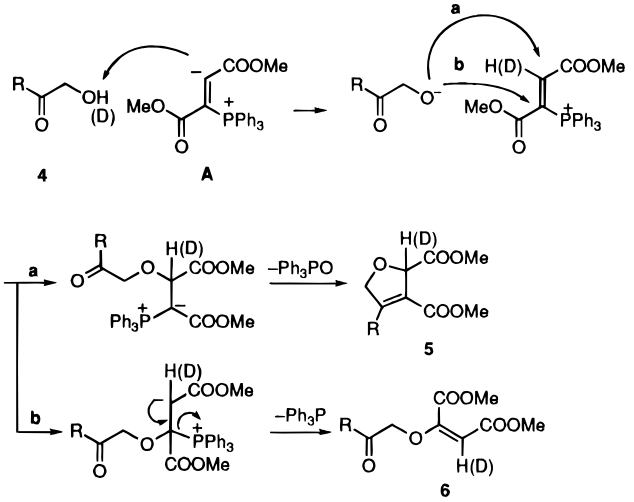


5a 80% yield
5b 73%

6a 10% yield
6b trace

A proposed mechanism for this reaction is shown in Scheme 3. The zwitterion **A** is readily protonated by the alcoholic proton. At that stage, the resulting alkoxide anion may partition itself between two pathways in a nucleophilic 1,4 addition to the cationic diester. In path **a**, the alkoxide oxygen binds to the carbon β to the phosphorus atom, affording a phosphorus ylide. The following intramolecular Wittig reaction gives the dihydrofuran derivative **5**. In path **b**, the alkoxide attacks the position α to the cationic phosphorus. In this case, triphenylphosphine will be produced to give olefinic compound **6**. When the alcoholic proton of **4** was replaced by deuterium, the deuterium was transferred to the corresponding positions in **5** and **6** as shown in Scheme 3.

Scheme 3



Conclusion

We have developed a new synthetic route to highly functionalized α,β-unsaturated γ-butyrolactones. A reductive cyclization to a dihydrofuran derivative has also been studied. The present work provides new extentions of phosphine-catalyzed organic syntheses.

Experimental Section

General Method. All manipulations of oxygen- and moisture-sensitive materials were conducted under a purified argon atmosphere (BASF-Catalyst R3-11) by use of standard Schlenck techniques. Silica-gel chromatography was performed using Wakogel C-200.

Apparatus. ^{1}H NMR spectra were recorded at 270 MHz, ^{13}C NMR were recorded at 67.8 MHz, and ^{19}F NMR were recorded at 254 MHz. ^{1}H and ^{13}C NMR spectra are referenced against internal tetramethylsilane and ^{19}F NMR apectra against external trifluoroacetic acid. All melting points were not corrected.

Chemicals. Toluene and 1,2-dichloroethane were purified by distillation under argon after drying over calcium hydride. 1,4-Dioxane and tetrahydrofuran were dried by sodium benzophenone ketyl and distilled under argon. Acetonitrile was purified by distillation under argon after drying over phosphorus pentoxide. Acetone was dried over 3A molecular sieves and distilled under argon.

Triphenylphosphine-Catalyzed Addition of Methyl *p*-Nitrobenzoate (1a) to Dimethyl Acetylenedicarboxylate (3a). A solution of dimethyl acetylenedicarboxylate (189 mg, 1.33 mmol) and methyl *p*-nitrobenzoate (225 mg, 1.08 mmol) in toluene (4.00 mL) was degassed by three cycles of freeze−thaw. To the yellow solution was added triphenylphosphine (57.4 mg, 0.220 mmol), and the resulting orange solution was heated at 70 °C for 8 h. The solvent was removed *in vacuo*. The crude product obtained was purified by column chromatography on silica gel (hexane:EtOAc = 5:1) to give lactone **3a** (353 mg, 94% yield): mp 73.4−74.6 °C (hexane−EtOAc); R_f = 0.13 (hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.86 (s, 3H), 4.32 (s, 3H), 7.66 (d, 2H, J = 8.58 Hz), 8.22 (d, 2H, J = 8.58 Hz); ^{13}C NMR ($CDCl_3$) δ 52.6, 54.1, 60.1, 84.4, 123.3, 127.4, 128.3, 131.5, 141.0, 148.2, 161.4, 164.5, 166.3; IR (Nujol) 1793, 1749, 1708 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO_9$: C, 51.29; H, 3.73; N, 3.99. Found: C, 51.07; H, 3.55; N, 4.01.

5-Cyano-3-methoxy-4-(methoxycarbonyl)-5-phenyl-2(3*H*)-furanone (3d): mp 110.8−111.1 °C (benzene); R_f = 0.17 (hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 4.31 (s, 3H), 7.35−7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 52.6, 60.9, 78.2, 114.6, 119.7, 126.0, 129.2, 130.9, 131.9, 149.3, 159.7, 163.4; IR (Nujol) 2232, 1794, 1702, 1648 cm^{-1}; mass spectrum m/z 273 ($M^+ - C_{14}H_{11}NO_5$). Anal. Calcd for $C_{14}H_{11}NO_5$: C, 61.53; H, 4.06; N, 5.13. Found: C, 61.42; H, 4.16; N, 4.95.

5-Cyano-3-methoxy-4-(methoxycarbonyl)-5-(4-methylphenyl)-2(3*H*)-furanone (3e): mp 106.4−110.3 °C (hexane−dichloromethane); R_f = 0.21 (hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.69 (s, 3H), 4.39 (s, 3H), 7.24 (d, 2H, J = 8.24 Hz), 7.37 (d, 2H, J = 8.24 Hz); ^{13}C NMR ($CDCl_3$) δ 21.2, 52.6, 60.8, 77.9, 114.8, 119.6, 126.0, 129.0, 129.8, 141.2, 149.3, 159.8, 163.5; IR (Nujol) 1794, 1699, 1657 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.51; H, 4.58; N, 4.90.

5-Cyano-3-methoxy-4-(methoxycarbonyl)-5-(4-methoxylphenyl)-2(3*H*)-furanone (3f): mp 110.2−113.6 °C (hexane−dichloromethane); R_f = 0.13 (hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.84 (s, 3H), 4.39 (s, 3H), 6.94 (d, 2H, J = 8.91 Hz), 7.43 (d, 2H, J = 8.91 Hz); ^{13}C NMR ($CDCl_3$) δ 52.6, 55.4, 60.8, 77.7, 114.5, 114.8, 119.4, 126.7, 127.7, 149.3, 159.8, 161.4, 163.5; IR (Nujol) 2222, 1788, 1708, 1655, 1608 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.30; H, 4.09; N, 4.34.

5-Cyano-3-methoxy-4-(methoxycarbonyl)-5-(4-chlorophenyl)-2(3*H*)-furanone (3g): mp 116.8−117.7 °C (hexane−ethyl acetate); R_f = 0.30 (hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H), 4.38 (s, 3H), 7.42 (s(br), 4H); ^{13}C NMR (CD_2Cl_2) δ 54.6, 61.4, 77.7, 114.8, 119.6, 128.0, 129.8, 131.2, 137.3, 149.7, 160.1, 163.7; IR (Nujol) 1791, 1709, 1655, 1594 cm^{-1}. Anal. Calcd for $C_{14}H_{10}ClNO_5$: C, 54.65; H, 3.28; N, 4.55. Found: C, 54.72; H, 3.17; N, 4.57.

5-Cyano-5-cyclohexyl-3-methoxy-4-(methoxycarbonyl)-2(3*H*)-furanone (3i): bp 140 °C (0.10 Torr); R_f = 0.43 (hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 0.73−2.50 (m, 11H), 3.88 (s, 3H), 4.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 24.1, 25.2, 25.3, 25.8, 27.4, 43.0, 52.6, 60.3, 79.6, 115.0, 118.6, 149.0, 160.2, 163.5; IR (Nujol) 1793, 1714, 1656 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.08; H, 6.23; N, 5.01.

3-Methoxy-4-(methoxycarbonyl)-5-phenyl-5-(trifluoromethyl)-2(3*H*)-furanone (3k): mp 54.3−55.1 °C; R_f = 0.13 (hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 4.26

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(s, 3H), 7.41−7.46 (m, 3H), 7.53−7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 52.5, 60.0, 116.4, 120.6, 124.8, 126.5, 128.7, 130.0, 131.0, 149.6, 161.0, 164.0; ^{19}F NMR ($CDCl_3$) δ 2.90; IR (Nujol) 1794, 1718, 1645 cm^{-1}. Anal. Calcd for $C_{14}H_{11}F_3O_5$: C, 53.17; H, 3.51. Found: C, 52.89; H, 3.47.

Reductive Synthesis of Dihydrofuran Derivative 4 from α-Hydroxy Ketones and Dimethyl Acetylenedicarboxylate. A solution of dimethyl acetylenedicarboxylate (154 mg, 1.09 mmol) and α-hydroxyacetophenone (140 mg, 1.03 mmol) in toluene (4.00 mL) was degassed by three cycles of freeze−thaw. To the yellow solution was added triphenylphosphine (509 mg, 1.94 mmol), and the resulting orange solution was heated at 70 °C for 24 h. The solvent was removed *in vacuo*, and the resulting crude product was purified by column chromatography on silica gel (hexane:EtOAc = 5:1) to give **5a** and **6a** in 80% and 10% yield. **5a**: bp 120 °C (0.1 mmHg); R_f = 0.34 (hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.80 (s, 3H), 5.11 (dd, 1H, J = 2.64, 14.51 Hz), 5.25 (dd, 1H, J = 5.61, 14.51 Hz), 5.60 (dd, 1H, J = 5.61, 2.64 Hz), 7.38−7.49 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 51.8, 52.5, 80.0, 86.5, 122.9, 128.2, 129.8, 130.4, 151.2, 162.8, 170.7; IR (neat) 1729 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.86; H, 5.45. **6a**: mp 99.1−100.6 °C (hexane−dichloromethane); R_f = 0.17 (hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 3.95 (s, 3H), 5.21 (s, 2H), 5.22 (s, 1H), 7.52−7.70 (m, 3H), 7.94−7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 51.7, 53.1, 71.2, 95.0, 128.0, 129.0, 133.7, 134.3, 160.4, 163.3, 165.7, 190.9; IR (Nujol) 1747, 1700 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.23; H, 5.11.

5b: ^{1}H NMR ($CDCl_3$) δ 2.04 (d, J = 0.99 Hz, 3H), 3.65 (s, 6H), 4.60 (bd, J = 14.8 Hz, 1H), 4.78 (bdd, J = 14.8, 5.28 Hz, 1H), 5.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 11.7, 51.5, 52.3, 80.7, 85.1, 122.8, 153.7, 163.0, 171.0. The ^{1}H NMR data are identical with those of reference.[14]

Acknowledgment. We thank Professor K. Utimoto (Kyoto University) for helpful discussions. One of the authors (N.S.) is grateful to Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists. One of the authors (K.N.) is grateful for a Pfizer Pharmaceutical Inc. Award in Synthetic Organic Chemistry, Japan, and to The Asahi Glass Foundation for partial financial support.

JO951828K