The Wittig Reaction of Benzosfuran-2,3-diones

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The Wittig reaction of benzosfuran-2,3-diones (2), cyclic α-ketoesters, was examined. The reaction of 2 having an electron-donating substituent on the aromatic ring with a stable ylide afforded not 3-alkylidene-2(3H)-benzosfuranones (4) but 2-alkylidene-3(2H)-benzosfuranones (1) with high regioselectivity.

Keywords α-ketoester; benzosfuran-2,3-dione; Wittig reaction; regioselectivity

For studies of the structure–activity relationships of griseofulvin, an antifungal antibiotic, we required 2-ethoxy carbonylmethylene-(1g) and 2-cyanomethylene-(1h) 7-chloro-4,6-dimethoxy-3(2H)-benzosfuranones as intermediates for the synthesis of the griseofulvin congeners.

It is generally known that the Wittig reaction of an α-ketoester1) involving an α-keto-γ-lactone2) with an ylide occurs at the ketone carbonyl group to produce (E)-α-alkenyl esters. Furukawa and Watanabe also reported that the Wittig reaction of benzosfuran-2,3-dione (2a), which corresponds to a cyclic α-ketoester, with ethoxycarbonylmethyleneetriphenylphosphorane (3a)3) gave only 3-ethoxycarbonylmethylene-2(3H)-benzosfuranone (4a).4) These results suggested that the Wittig reagents selectively attack the ketone carbonyl group of α-ketoesters and that our desired 2-alkylidenebenzosfuranones (1g, h) might not be obtainable by the Wittig reaction of benzosfuran-2,3-diones (2).

However, we thought that an electron-donating substituent on the benzene ring of 2 might cause a change in the electron density of the ketone carbonyl group of 2, so that a Wittig reagent might attack the lactone carbonyl group of 2. Consequently, we attempted the Wittig reaction of 7-chloro-4,6-dimethoxybenzosfuran-2,3-dione (2d) with 3a. As we expected, only 2-ethoxycarbonylmethylene-3(2H)-benzosfuranone (1g) was obtained, implying that the substituents affected the regioselectivity of the Wittig reaction of 2. In the present study, we examined how the substituents of 2 and the type of ylide affect the regioselectivity of the Wittig reaction of 2.

First, the Wittig reaction of 2d with 3a or benzyldenedetriphenylphosphorane (3e)5) was examined (Chart 1). Stirring of a mixture of 2d and 3a at room temperature in benzene gave a single product (1g) showing a peak at 1705 cm⁻¹ in its infrared (IR) spectrum in 94% yield. It was expected to be 2- or 3-ethoxycarbonylmethylene-7-chloro-4,6-dimethoxybenzosfuranone. On the other hand, a similar reaction of 2d with 3c afforded two products, assignible as 2- (1i) and 3- (4i) benzyldenedibenzosfuranone derivatives. The 1R spectrum of the major product (1i) (63% yield) showed a peak at 1700 cm⁻¹, whereas that of the minor product (4i) (6% yield) showed a peak at 1775 cm⁻¹. The latter absorption was assignable to the lactone carbonyl group. Moreover, the major product was confirmed to be 2-benzyldene-7-chloro-4,6-dimethoxy-3(2H)-benzosfuranone (1i) by comparison with an authentic sample prepared by the Knoevenagel reaction of 7-chloro-4,6-dimethoxy-3(2H)-benzosfuranone (5)6) with benzaldehyde. Consequently, the product 4g was also established to be 7-chloro-2-ethoxycarbonyl-4,6-dimethoxy-3(2H)-benzosfuranone. These results showed that the Wittig reagents attack the ester carbonyl group of 2d to produce the

Chart 1

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as well as at the ketone carbonyl group, and the regioselective reactivity of the lactone carbonyl group of 2 is increased by the presence of an electron-donating substituent on the benzene ring.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (1H-NMR) spectra were taken on a Hitachi R-24 spectrometer at 60 MHz or on an R-22 FT spectrometer at 90 MHz. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 or VG-70SE, and IR absorption spectra on a JASCO A-102 spectrometer.

7-Chloro-4,6-dimethoxybenzofuran-2,3-dione (2d) Oxalyl chloride (19 g, 150 mmol) was added dropwise to a solution of 2-chloro-3,5-dimethylpyridine (14 g, 75 mmol) in 1,2,2,4-tetrachloroethane (70 ml) at 0°C. The mixture was heated at 60°C for 2 h. Then the solvent was removed under reduced pressure and the residue was crystallized from CH₂Cl₂ to give 2d (15 g, 82%) as yellow prisms, mp 198–200°C. Anal. Calcd for C₁₀H₈Cl₂O₂: C, 49.51; H, 2.91. Found: C, 49.40; H, 2.75. IR (Nujol): 1715 cm⁻¹. 1H-NMR (DMSO-d₆): δ: 4.05, 4.10 (each 3H, each s, OCH₃ x 2), 6.62 (1H, s, =CH), MS (EI) m/z (%): 244 (2), 242 (M⁺, 5), 214 (100), 171 (30).

Reaction of 2d with Ethoxybenzylideneethylidenephosphonite (3a) A mixture of 3a (320 mg, 0.99 mmol) and 2d (200 mg, 0.88 mmol) in dry benzene (8 ml) was refluxed for 30 min. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (15 g, EtOAc : hexane = 1:3) to give 1g (240 mg, 94%) as pale yellow prisms, mp 186–188°C (EtOAc-hexane). Anal. Calcd for C₂₁H₁₇O₃P: C, 59.77; H, 4.19. Found: C, 59.63; H, 4.11. IR (Nujol): 1705 cm⁻¹. 1H-NMR (CDCl₃): δ: 1.41 (3H, t, J = 7 Hz, OCH₂CH₃), 4.10 (6H, s, OCH₃ x 2), 4.40 (2H, q, J = 7 Hz, OCH₂), 6.17 (1H, s, C-H), 6.34 (1H, s, =CH), MS (EI) m/z (%): 314 (2), 312 (M⁺, 3), 277 (10), 86 (100).

Reaction of 2d with Benzyldienemethanephosphonite (3c) A 1.28 M solution of n-butyllithium in hexane (1.42 ml, 1.88 mmol) was added dropwise to a solution of benzylideneethylidenephosphonium chloride (0.77 g, 2.9 mmol) in dry tetrahydrofuran (THF) (25 ml) at 0°C. The mixture was stirred at 0°C for 30 min, then a solution of 2d (0.46 g, 1.77 mmol) in dry THF (15 ml) was added. The mixture was stirred at 0°C for 30 min and refluxed for 5 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with water, dried (MgSO₄), and evaporated. The residue was column-chromatographed on silica gel (30 g, EtOAc : hexane = 2:3). The first fractions gave 4i (0.03 g, 6%) as pale yellow prisms, mp 243–246°C (CH₂Cl₂-ether). Anal. Calcd for C₁₅H₁₇O₃P: C, 64.47; H, 4.14. Found: C, 64.19; H, 4.14. IR (Nujol): 1780 cm⁻¹. 1H-NMR (CDCl₃): δ: 3.94, 4.00 (each 3H, each s, OCH₃ x 2),
A mixture of 3b (1.1 g, 3.7 mmol) and 2d (0.74 g, 3.1 mmol) in dry benzene (30 mL) was refluxed for 30 min. Then the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (35% EtOAc:hexane = 1:19) to give 2e (0.63 g, 78%) as yellow prisms, mp 218–220°C (EtOAc-hexane). Anal. Calc'd for C_{8}H_{14}ClO_{3}C: C, 54.26; H, 3.04; N, 5.27. Found: C, 54.55; H, 3.00; N, 5.01. IR (Nujol): 2225, 1700 cm\(^{-1}\). 1\(^{1}H\)-NMR (CDCl\(_{3}\)) \(\delta\): 4.02 (2H, s, OCH\(_{2}\)X), 3.63 (2H, m, aromatic H), 1.74 (1H, d, J = 8 Hz, C\(_{5}\)H\(_{4}\)). MS (EI m/z): (M\(^{+}\), 236), 208 (27), 81 (22).

Reaction of 2b with 3c: A 1.36 mol solution of n-butylthiophosphonic acid (1.80 mL, 2.5 mmol) was added dropwise to a solution of benzyltriphenylphosphonium chloride (1.05 g, 2.7 mmol) in dry THF (25 mL) at 0°C. The mixture was stirred at 0°C for 30 min, then a solution of 2b (0.36 g, 2.2 mmol) in dry THF (15 mL) was added. The mixture was stirred at 0°C for 30 min, refluxed for 8 h, poured into water and extracted with EtOAc. The organic layer was washed with water, dried (MgSO\(_{4}\)), and evaporated. The residue was column chromatographed on silica gel (40 g, EtOAc:hexane = 1:19). The first fractions gave 4d (0.13 g, 24%) as pale yellow prisms. IR (Nujol): 1780 cm\(^{-1}\). 1\(^{1}H\)-NMR (CDCl\(_{3}\)) \(\delta\): 2.35 (3H, s, CH\(_{3}\)), 6.62–7.04 (2H, m, aromatic H), 7.20–7.85 (7H, m, aromatic H and C\(_{13}\)–CH\(_{3}\)). MS (EI m/z): (M\(^{+}\), 236), 208 (27), 81 (22).

The last fractions gave 1d (0.03 g, 5%) as pale yellow prisms. IR (Nujol): 1700 cm\(^{-1}\). 1\(^{1}H\)-NMR (CDCl\(_{3}\)) \(\delta\): 2.49 (3H, s, CH\(_{3}\)), 6.84 (1H, s, C\(_{13}\)–CH), 6.95–7.20 (2H, m, aromatic H), 7.30–8.09 (6H, m, aromatic H). MS (EI m/z): (M\(^{+}\), 236), 134 (5).

Reaction of 2c with 3c: A 1.28 mol solution of n-butyllithium in hexane (2.03 mL, 2.6 mmol) was added dropwise to a solution of benzyltriphenylphosphonium chloride (1.10 g, 2.8 mmol) in dry THF (25 mL) at 0°C. The mixture was stirred at 0°C for 30 min, then a solution of 2c (0.42 g, 2.4 mmol) in dry THF (15 mL) was added. The reaction mixture was stirred at 0°C for 30 min, refluxed for 15 h, poured into water and extracted with EtOAc. The organic layer was washed with water, dried (MgSO\(_{4}\)), and evaporated. The residue was chromatographed on silica gel (40 g, EtOAc:hexane = 1:19). The first fractions gave 4f (0.09 g, 16%) as pale yellow prisms, mp 107–109°C (lit.\(^{11}\) 115°C). Anal. Calc'd for C\(_{13}\)H\(_{17}\)O\(_{2}\)C: C, 76.18; H, 4.79. Found: C, 76.56; H, 4.73. IR (Nujol): 1775 cm\(^{-1}\). 1\(^{1}H\)-NMR (CDCl\(_{3}\)) \(\delta\): 3.81 (3H, s, OCH\(_{3}\)), 6.37–6.72 (2H, m, aromatic H), 7.25–7.73 (7H, m, aromatic H and C\(_{13}\)–CH). MS (FAB m/z): 253 (M\(^{+}\), 1). The last fractions gave H (0.10 g, 17%) as pale yellow prisms, mp 147–148°C (lit.\(^{11}\) 147–148°C). Anal. Calc'd for C\(_{13}\)H\(_{17}\)O\(_{2}\)C: C, 76.18; H, 4.79. Found: C, 76.18; H, 4.78. IR (Nujol): 1700 cm\(^{-1}\). 1\(^{1}H\)-NMR (CDCl\(_{3}\)) \(\delta\): 3.87 (3H, s, OCH\(_{3}\)), 6.52–6.84 (3H, s, aromatic H and C\(_{13}\)–CH), 7.22–7.97 (6H, m, aromatic H). MS (FAB m/z): 253 (M\(^{+}\), 1).

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