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Cyclic Ketones in Spiroannulation

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Abstract: Conversion of a cyclic carbonyl carbon into a quaternary carbon has been effected by a Wittig–Horner reaction with diethyl (*N*-benzyliden)-aminomethylphosphonate and a subsequent alkylation with a protected vinyl ketone. The product was a substrate for spiroannulation after initial hydrolysis. The reaction sequence was carried out as a one-pot reaction.

Keywords: Addition reactions, carbonyl quaternization, lithiation, spiroannulation, Wittig–Horner reaction

INTRODUCTION

For some time, we have been interested in developing synthetic routes for ready preparation of spiranes.[1–6] The two rings in a spirane are interconnected through a common ring atom and have an orthogonal relationship. Spiranes constructed from small- to medium-sized rings possess a rigid skeleton and confer stiffness onto the structures in which they are embedded, thereby providing a potentially useful structural unit for attachment of configurationally highly oriented functional substituents, especially in the α,α'-positions next to the spiro center. This report describes a method for the conversion of a carbonyl carbon in a cyclic ketone into a quaternary carbon appropriately functionalized for spiroannulation.

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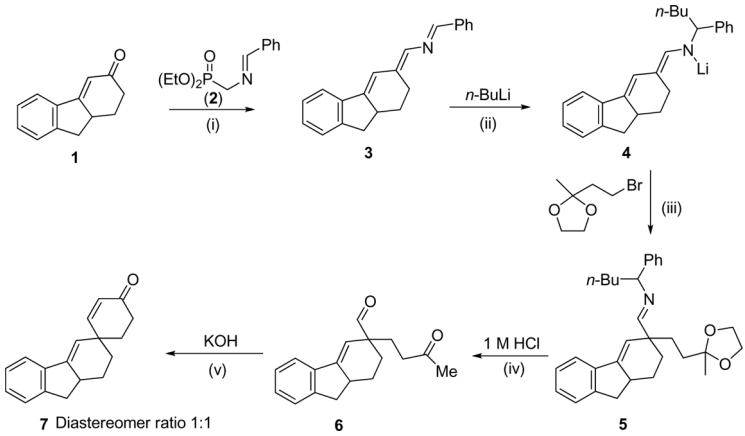
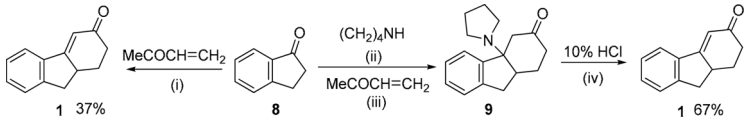
RESULTS AND DISCUSSION

The starting material for the ketone spiroannulation reaction was 1,2,3,9a-tetrahydro-*9H*-fluoren-3-one (**1**; Scheme 1). The initial conversion of carbonyl carbon into a quaternary carbon was based on methodology developed by Martin et al., who in 1980 reported an effective procedure for geminal disubstitution at the carbonyl carbon atom of aldehydes and ketones.[7] The carbon–oxygen double bond of the carbonyl function is replaced by an acyl group and an alkyl group.[8] Surprisingly, few subsequent reports have appeared in the literature utilizing this methodology.[9,10]

To effect quaternization of the ketone **1**, the latter was initially reacted with diethyl (*N*-benzyliden)aminomethylphosphonate (**2**). The phosphonate was prepared as shown in Scheme 3. The reagent **2** was deprotonated in the cold with *n*-butyllithium and reacted with the 3-fluorenone **1** to yield the imine **3** in a Wittig–Horner reaction (Scheme 1), and subsequently treated in situ with an excess of *n*-butyllithium, which resulted in imine alkylation and the formation of a metalloenamine **4**. The solution of the lithiated enamine **4** in tetrahydrofuran (THF) was subsequently treated with 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1H)-one (DMPU) to favor C-alkylation and reacted with a β-bromoketone, 2-(2-bromoethyl)-2-methyl-1,3-dioxolane,[11] to form the alkylated product **5**. The latter was hydrolyzed in situ with aqueous hydrochloric acid to provide the deprotected dicarbonyl product **6**, which in methanolic potassium hydroxide was directly transferred by



Scheme 1. Reagents and conditions: (i) (a) *n*-BuLi, THF, −78°C, 1 h, (b) reflux, 2 h; (ii) THF, −78°C, 1 h; (iii) DMPU, rt, 20 h; (iv) rt, 6 h; and (v) MeOH, rt, 1 h.

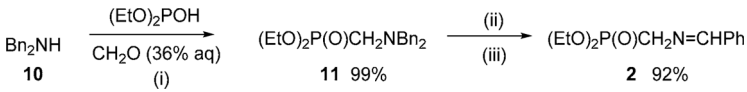


Scheme 2. Reagents and conditions: (i) KOH, EtOH, 40°C, 15 min; (ii) benzene, reflux, 10 h; and (iii) THF, rt ≥reflux, 8 h; (iv) rt, 5 h.

an intramolecular condensation to the spiroannulated target compound 7, which was a 1:1 mixture of the two diastereomers in 43% overall yield. It should be emphasized that the whole set of reactions was performed as a one-pot reaction, which renders the methodology very convenient and attractive. In the alkylation step in the tandem acylation–alkylation methodology, carcinogenic hexamethylphosphoramide (HMPA) was originally used as a cosolvent.[7] According to our experience, HMPA can be replaced by DMPU as a solvent in this reaction in accord with the general recommendation to replace HMPA with DMPU.[12]

The fluorenone substrate **1** is reported to be available in 58% yield from a Robinson annulation reaction with methyl vinyl ketone using a large excess of melted 1-indanone.[13] Although the original report describes recovery of excess 1-indanone, we observed mainly self-condensation, with formation of the *cis* and *trans* isomers of 2-(1-indanyliden)indan-1-one,[14] which complicated isolation of the fluorenone **1** (Scheme 2). A more effective enamine approach, however, has been developed for the synthesis of the ketone **1**. In this procedure, pyrrolidine enamine was prepared from 1-indanone and treated with methyl vinyl ketone in THF. A ready C-alkylation of the enamine was evident followed by a spontaneous cyclization, which furnished the product **9**. Hydrolysis of the latter under acidic conditions provided the desired ketone **1** in good yield.

The reagent **2** for the acylation–alkylation protocol was prepared by Schiff base formation from diethyl aminomethylphosponate and benzaldehyde (Scheme 3). Dibenzylamine, diethyl phosphite, and aqueous formaldehyde were heated together in THF to furnish the aminomethylated product **11** (Scheme 3) in close to quantitative yield. Hydrogenolysis of **11**, as a hydrochloride in ethanol, produced the pure debenzylated product, which could be transformed directly into the Schiff base **2**. Alternative, but less efficient, methods have been described in the literature.[8,15]



Scheme 3. Reagents and conditions: (i) THF, 50°C, 20 h; (ii) [H_2], Pd-C (10%), EtOH; and (iii) PhCHO, 0°C.

CONCLUSION

Methodology has been developed for the preparation of spiranes from cyclic ketones. The carbonyl carbon is initially converted into a quaternary carbon by a tandem acylation–alkylation reaction and a subsequent spiroannulation.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 MHz and 50 MHz, respectively, with a Bruker DPX 200 instrument. Chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (7.24 ppm) and $CDCl_3$(77 ppm). The mass spectra were recorded at 70 eV ionizing potential. Infrared (IR) spectra were measured on a Nicolet Magma 550 spectrometer using attenuated total reflection (ATR).

THF was dried by distillation from sodium benzophenone under nitrogen. Reactions requiring dry and/or oxygen-free conditions were run under the slight positive pressure of argon.

1,2,3,9a-Tetrahydro-9*H*-fluoren-3-one (1)

Method (A)

Pyrrolidine (14.2 g, 0.200 mol) was added to 1-indanone (13.2 g, 0.100 mol) in benzene (100 mL). The mixture was heated under reflux overnight with water trapping. The solvent and excess pyrrolidine were removed in vacuo, and dry THF (40 mL) was added. After cooling to 0°C, neat methyl vinyl ketone (7.71 g, 0.110 mmol) was introduced dropwise with stirring. Hydrochloric acid (3 M, 50 mL) was added after 10 h, and the mixture was vigorously stirred overnight. Saturated brine (50 mL) was added, the layers were separated, and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were dried ($MgSO_4$), the solvents were distilled off, and the residual matter was subjected to flash chromatography on silica gel 60 using EtOAc–hexane 1:3; yield 12.4 g (67%). The product was a solid with mp 128–130°C (cyclohexane). HRMS (EI, 70 eV): $[M]^+$ calcd. for $C_{13}H_{12}O$: 184.0888; found: 184.0894; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.7–1.9 (m, 1H), 2.2–2.8 (m, 4H), 3.0–3.3 (m, 2H, H9), 6.24 (s, 1H, H4), 7.2–7.6 (m, 4H, H-Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.1 (C1), 36.9 (C9), 38.0 (C2), 41.7 (C9a), 117.0 (C4), 122.6 (CH-Ar), 125.3 (CH-Ar), 126.6 (CH-Ar), 131.5 (C4), 137.9 (C-Ar), 148.2 (C-Ar), 168.8 (C4a), 199.4 (C3); MS (EI, 70 eV): m/z (%) = 184 (100) $[M]^+$, 156 (95), 128 (88), 115 (7).

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Method B

Methyl vinyl ketone (2.1 g, 30 mmol) was added to molten 1-indanone (10.0 g, 76 mmol) at 40°C, and 2 M potassium hydroxide in ethanol (2 mL) was added. The exothermic reaction was controlled by a water bath at room temperature. The reaction mixture was stirred for 15 min and subsequently poured into a 5% solution of NH_4Cl (100 mL) with stirring. The resultant mixture was extracted with chloroform (3×30 mL). The chloroform solution was dried ($MgSO_4$) and concentrated on a rotatory evaporator. Most of the excess 1-indanone was recovered by vacuum distillation. The residue was subjected to flash chromatography on silica gel 60 using EtOAc–hexane–chloroform 1:3:4. 1,2,3,9a-tetrahydro-*9H*-fluoren-3-one (**1**) was the slower moving compound; yield 37%. ^1H and ^{13}C NMR were in accordance with previously collected data. The faster moving product was *E*-2,3-dihydro-3′H-[1,2′]biindenyliden-1′-one.[14]

Diethyl (Benzyliden)aminomethylphosphonate (2)

To a solution of diethyl dibenzylaminomethylphosphonate (**11**) (68.0 g, 0.195 mol) in ethanol (300 mL), 37% aqueous hydrochloric acid (19.2 g, 0.195 mol) and 10% palladium on charcoal (10.4 g, 9.78 mmol Pd) were added. The catalyst was slightly wetted with water to avoid ignition of the ethanol. The reaction mixture was subjected to vigorous stirring under a slight positive pressure of hydrogen until no more gas was absorbed. NaOH–H_2O (11.31 g, 0.195 mol) was added, and the reaction mixture was filtered through a bed of Celite. The volatiles were distilled off at reduced pressure, and the residue was dissolved in diethyl ether. The solution was dried ($MgSO_4$) and concentrated at reduced pressure to give a colorless oil; yield 30.3 g (92%). ^1H NMR data were in accordance with data from the literature.

1′,2′,3′,9a′-Tetrahydro-9*H*-spiro[cyclohex-2-en-1,3′-fluoren]-4-one (7)

n-Butyllithium in heptane (2.7 M, 4.4 mL, 12 mmol) was added to dry THF (50 mL) at −78°C under the slight positive pressure of argon. Diethyl (*N*-benzyliden)aminomethylphosphonate (**2**) (3.1 g, 12 mmol) in THF (5 mL) was slowly introduced, and the mixture was stirred at −78°C for 1 h. 1,2,3,9a-Tetrahydrofluoren-3-one (**1**) (1.8 g, 10 mmol) in THF (10 mL) was added, and the reaction mixture was heated under gentle reflux for 2 h. The product was benzylidene-(1,2,3,9a)-tetrahydro-9*H*-fluoren-3-ylidenemethyl)amine (**3**). The reaction mixture was cooled to

−78°C, and 2.7 M *n*-butyllithium (5.6 mL, 15 mmol) was added dropwise. The *n*-BuLi adduct **4** was formed. Dry DMPU (35 mL) was added after stirring for 1 h, followed by 2-(2-bromoethyl)-2-methyl-1,3-dioxalane[11] (2.9 g, 15 mmol) in THF (5 mL). The alkylated product was the enamine **5**. The reaction mixture was brought to room temperature and stirred for 20 h. Hydrochloric acid (1 M, 50 mL) was added, and the stirring continued for 6 h. Saturated brine (100 mL) was added, and the phases were separated. The water phase was extracted with diethyl ether (3 × 150 mL), and the combined extracts were washed with saturated $NaHCO_3$ (200 mL) and saturated brine (200 mL). The solvents were distilled off, and the residue was dissolved in methanol (60 mL) to yield the dicarbonyl product **6**. Potassium hydroxide (KOH) (3.0 g, 53 mmol) in water (30 mL) was added, and the mixture was stirred vigorously for 1 h. The methanol was distilled off under reduced pressure. Saturated brine (50 mL) was added, and the mixture was extracted with diethyl ether (3 × 20 mL). The dried ($MgSO_4$) ether solution was concentrated at reduced pressure, and the residue was subjected to flash chromatography on silica gel 60 using EtOAc–hexane 1:3; yield 1.2 g (43%) of a yellow oil. The product was a 1:1 mixture of the diastereomers of the spirane **7**. HRMS (EI, 70 eV): $[M]^+$ calcd. for $C_{18}H_{18}O$: 250.1358; found: 250.1368; IR (film): ν cm^{-1} 3310 (w), 3038 (w), 2994 (m), 2911 (s), 2837 (s), 2237 (w), 1662 (s), 1591 (m); ^1H NMR (200 MHz, $CDCl_3$): δ 1.4–1.8 (m, 2H, CH_2), 1.9–2.2 (m, 4H, CH_2), 2.4–2.6 (m, 3H, H9a′ and CH_2), 2.7–2.9 (m, 1H, H9′), 3.1–3.2 (m, 1H, H9′), 5.76 (s, 0.5H, H4′), 5.88 (s, 0.5H, H4′), 5.90 (d, 0.5H, $J = 10.4$ Hz, H2), 6.00 (d, 0.5H, $J = 10.4$ Hz, H2), 6.63 (d, 0.5H, $J = 10.4$ Hz, H3), 6.78 (d, 0.5H, $J = 10.4$ Hz, H3), 7.0–7.6 (m, 4H, H-Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3 (2 × CH_2), 33.1 (2 × CH_2), 34.6 (2 × CH_2), 34.7 (CH_2), 36.9 (CH_2), 37.7 (C1), 38.1 (2 × CH_2), 38.4 (C1), 42.5 (C9a′), 43.0 (C9a′), 118.1 (C4′), 121.1 (C4′), 121.2 (2 × CH-Ar), 125.8 (2 × CH-Ar), 126.2 (C3), 127.9 (2 × CH-Ar), 128.5 (C3), 129.0 (2 × CH-Ar), 141.1 (2 × C-Ar), 145.3 (2 × C-Ar), 147.0 (C4a′), 147.2 (C4a′), 158.6 (C2), 159.1 (C2), 199.8 (C4), 200.1 (C4); MS (EI, 70 eV): m/z (%) = 250 (80) $[M]^+$, 222 (100), 208 (18), 194 (52), 179 (37).

Diethyl Dibenzylaminomethylphosphonate (11)

Diethyl phosphite (33.1 g, 0.24 mol) and dibenzylamine (39.5 g, 0.20 mol) were dissolved in THF (100 mL), and 36% aqueous formaldehyde (20 g, 0.24 mol) was added. The reaction mixture was left stirring for 1 h and subsequently heated at 50°C for 20 h. The solvents were distilled off on a rotatory evaporator, and the residual oil was dissolved in hexane (300 mL). The solution was washed with water (3 × 100 mL) and dried

($MgSO_4$). Concentration under vacuum yielded the pure title compound as a colorless oil; yield 68.6 g (99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, $J = 7.1$ Hz, 6H, CH_3), 2.86 (d, $J = 10.2$ Hz, 2H, PCH_2), 3.76 (s, 4H, CH_2-Ph), 4.04 (quin, 4H, 7.1 Hz, OCH_2), 7.1–7.4 (m, 10H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4 (d, 5.9 Hz, CH_3), 48.3 (d, $J = 157.3$ Hz, PCH_2), 59.2 (d, 8.2 Hz, CH_2Ph), 61.6 (d, 6.7 Hz, OCH_2CH_3), 127.2 (CH-Ar), 128.1 (CH-Ar), 128.9 (CH-Ar), 138.6 (C-Ar).

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