

Synthesis of β -Disubstituted Enones from Yrones. An Alternative Route to 1,4-Addition of Cuprate to the Ynone System

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A one-pot reaction of 4-phenyl-3-butyne-2-one with hydrogen iodide generated *in situ* gave a hydroiodinated product that underwent cross coupling with organozinc compounds in the presence of palladium catalyst to provide a simple preparation of 4-disubstituted-3-alken-2-ones in fair to good yields.

INTRODUCTION

The stereoselective synthesis of di- or tri-substituted alkenes remains synthetically challenging in organic chemistry. The constant discovery of new olefinic compounds in natural products, e.g. insect pheromones and terpenoids,^{1,2} stimulated development of methodologies in alkene synthesis.

Although many methods for the synthesis of substituted olefins are known, a widely applied method for preparation of tri-substituted enones is addition of organocuprates, e.g. lithium dialkylcuprates, to ynones.^{3,4} Even though vinylcuprate species undergo conjugate addition to ynones,⁵ there was no report of addition of alkynyl groups to ynones in the conjugate addition manner. Although the addition of hexynyl organocuprate in a 1,2-addition manner to an ynone⁶ is known, the corresponding 1,4-addition of cuprates to the ynone to form a 4-disubstituted-3-alken-2-one system needs further development.



We reported use of the NaI/TMSCl/H₂O system for hydroiodination of alkynes, in turn cross-coupled with organozinc compounds in the presence of palladium catalyst to give *gem*-disubstituted alkenes in fair to good yields.^{7,8} We also observed that treatment of 3-decyn-2-one with NaI/TMSCl/H₂O in acetonitrile at 25 °C gave (*Z*)-4-iodo-4-decen-2-one in good yield.⁹ In continuing work, we undertook reaction of 4-phenyl-3-butyne-2-one with NaI/TMSCl/H₂O, the resulting hydroiodinated product underwent cross-coupling with organozinc compound in the presence of palladium catalyst to give 4-disubstituted-3-alken-2-ones in reasonable yields.

RESULTS AND DISCUSSION

As representative alkyl, 2-furyl, 2-thienyl, and sily-

lated alkynylzinc compounds were chosen. The results obtained in this one-pot reaction are shown in Table 1. The yields were fair and the reaction worked for both alkyl and heteroaryl groups. The yields of alkylzinc chlorides were better than those of heteroarylzinc chloride. Even when using alkylzinc chlorides it was noticed that the yields decreased when the size of the alkyl group increases from methyl to hexyl group. The stereoselectivities in the reaction were also noted. As expected on the basis of complete retention of alkenyl stereochemistry in palladium-catalyzed cross-coupling reaction of alkenyl iodide with organozinc complexes,⁸ the stereoselectivity of **3** arose from the stereoselectivity of **2**. The *E/Z* ratio of **2** obtained from **1** is 1 to 3 according to its crude ¹H NMR spectral analysis. The

Table 1. Conversion of 4-Phenyl-3-butyne-2-one into 4-Disubstituted-3-buten-2-ones

Entry	R in RZnCl	Yield %	Z/E ratio ^a
1	CH ₃ -	83	1:3
2	n-Bu-	74	E only
3	n-C ₆ H ₁₃ -	70	1:3
4		58	Z only
5		63	Z only
6	Me ₃ Si-C≡C-	67	3:1

^a The ratio was determined by the ¹H NMR spectral analysis of the crude reaction mixture. The stereochemistry of the products were confirmed by 2D NOESY ¹H NMR spectra.

predominant product was one in which the incoming alkyl or heteroaryl group is *cis* to the ketone functionality. For three reactions (entries 2, 4 and 5) only a single isomer was observed and isolated.

Interestingly, an alkynyl group (entry 6) can add to 4-phenyl-3-butyne-2-one with a reasonable yield. Such kind of 1,4-addition of alkynyl group to the ynone system has not been previously achieved, as far as we know, by use of cuprate reagents.

Mechanistically, this hydrocarbonation involves hydroiodination of **1** in the first step to form the vinylic iodide **2** that undergoes cross-coupling with organozinc compound in the presence of palladium catalyst to give addition product **3**.

The scope and synthetic utility of this reaction are being investigated in our laboratory at present.

CONCLUSION

The one-pot reaction of 4-phenyl-3-butyne-2-one with hydrogen iodide generated *in situ*, followed by cross-coupling with organozinc compounds in the presence of palladium catalyst provides a simple method for the formation of 4-disubstituted-3-buten-2-ones with good stereoselectivities. An advantage of this methodology over other previously reported ones are, that, even alkynyl groups can be added to alkynone systems.

EXPERIMENTAL SECTION

Reaction of organometallic compounds was undertaken in oven- and/or flame-dried glassware equipped with a side arm, gas outlet adapter and mercury bubbler to maintain an inert atmosphere. Tetrakis(triphenylphosphine)palladium was prepared by published procedures.¹⁰ Zinc chloride was dried before use at >50 °C and at <1 mm Hg for 2 h. All other materials were used without further purification unless otherwise stated. IR spectra were recorded in CHCl₃ solution unless otherwise mentioned on a Perkin-Elmer 882 infrared spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Bruker AC 200 or AC 300 NMR spectrometer; chemical shifts are reported in ppm downfield from Me₄Si. Mass spectra were obtained on a HP 5971 GC/MS spectrometer. High resolution MS were obtained on VG 70-250S spectrometer. GLC analyses were performed on a Shimadzu GC-14A gas chromatograph, equipped with a 2 m × 3 mm column packed with SE-30 (5% on Chromosorb W). GLC peak integrals were recorded by using a Shimadzu

Chromatopac C-R3A integrator.

General procedure for the reaction of 4-phenyl-3-butyne-2-one

Into oven- flame-dried flask was taken NaI (0.75 g, 5 mmol) in CH₃CN (5 ml), to this mixture under nitrogen atmosphere was added sequentially TMSCl (0.55 g, 5 mmol), water (0.09 g, 5 mmol) and 4-phenyl-3-butyne-2-one (0.72 g, 5 mmol). The mixture was stirred at 25 °C for 10 min and then allowed to react with the respective organozinc chloride (1.1 equivalents), prepared from the corresponding organolithium compound and zinc chloride in THF, in the presence of Pd(PPh₃)₄ (0.29 g, 0.25 mmol) at 25 °C for another 6 h. The reaction mixture was quenched with water and extracted with ether; the ether extract was washed with water and dried over anhydrous MgSO₄. Solvent removal and purification on a column chromatograph (silica gel, hexane/ether = 4/1) gave the respective 4-disubstituted-3-buten-2-ones.

(*E*)-4-Phenyl-3-penten-2-one: IR 1666, 1628 cm⁻¹; ¹H NMR (CDCl₃, TMS) δ 2.3 (s, 3 H), 2.54 (s, 3 H), 6.5 (s, 1 H), 7.3-7.51 (m, 5 H) ppm; ¹³C NMR (CDCl₃, TMS) δ 18.21, 32.09, 124.40, 126.34, 128.40, 128.94, 142.40, 153.75, 198.77 ppm; MS *m/z* 160 (M⁺), 159, 145, 118, 115, 102, 91; HRMS calcd for C₁₁H₁₂O 160.0888, found 160.0890; Anal. Calcd for C₁₁H₁₂O: C, 82.46; H, 7.55. Found: C, 82.51; H, 7.58.

(*Z*)-4-Phenyl-3-penten-2-one: IR 1666, 1628 cm⁻¹; ¹H NMR (CDCl₃, TMS) δ 1.73 (s, 3 H), 2.11 (s, 3 H), 6.05 (s, 1 H), 7.1-7.19 (m, 2 H), 7.27-7.31 (m, 3 H) ppm; ¹³C NMR (CDCl₃, TMS) δ 27.23, 30.07, 127.02, 128.16, 128.38, 140.80, 152.83, 200.20 ppm; MS *m/z* 159, 145, 115, 102, 91, 77, 63, 51, 43, 49; HRMS calcd for C₁₁H₁₂O 160.0888, found 160.0891.

(*E*)-4-Phenyl-3-octen-2-one: IR 1650, 1204 cm⁻¹; ¹H NMR (CDCl₃, TMS) δ 0.83 (t, *J* = 6.8 Hz, 3 H), 1.3-1.4 (m, 4 H), 2.28 (s, 3 H), 3.00 (t, *J* = 8 Hz, 2 H), 6.39 (s, 1 H), 7.35-7.45 (m, 5 H) ppm; ¹³C NMR (CDCl₃, TMS) δ 13.74, 22.74, 30.75, 31.03, 32.17, 124.49, 126.64, 128.40, 128.77, 141.62, 159.20, 198.36 ppm. MS *m/z* 202 (M⁺), 187, 173, 159, 145, 131, 129, 115, 105, 91; HRMS calcd for C₁₄H₁₈O 202.1358, found 202.1364.

(*E*)-4-Phenyl-3-decen-2-one: IR 1673, 1593, 1486 cm⁻¹; ¹H NMR (CDCl₃, TMS) δ 0.84 (t, *J* = 7.0 Hz, 3 H), 1.24-1.38 (m, 8 H), 2.27 (s, 3 H), 3.02 (t, *J* = 7.8 Hz, 2 H), 6.39 (s, 1 H), 7.34-7.43 (m, 5 H) ppm; ¹³C NMR (CDCl₃, TMS) δ 13.92, 22.45, 28.88, 29.30, 31.02, 31.43, 32.16, 124.48, 126.63, 128.39, 128.76, 141.61, 159.23, 198.36 ppm; MS *m/z* 230 (M⁺), 215, 173, 159, 145, 131, 115; HRMS calcd for C₁₆H₂₂O 230.1671, found 230.1663.

(Z)-4-Phenyl-3-decen-2-one: IR 1650 cm^{-1} ; ^1H NMR (CDCl_3 , TMS) δ 0.85 (t, $J = 7.0$ Hz, 3 H), 1.24-1.76 (m, 8 H), 1.76 (s, 3 H), 2.40 (t, $J = 8.0$ Hz, 2 H), 6.08 (s, 1 H), 7.13-7.38 (m, 5 H) ppm; ^{13}C NMR (CDCl_3 , TMS) δ 13.90, 22.39, 27.31, 28.66, 30.10, 31.43, 40.49, 127.36, 127.95, 128.26, 140.19, 157.27, 200.57 ppm; MS m/z 230 (M^+), 215, 173, 159, 145, 131, 115; HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{O}$ 230.1671, found 230.1676.

(Z)-4-Phenyl-4-(2-furyl)-3-buten-2-one: IR 1640, 1583 cm^{-1} ; ^1H NMR (CDCl_3 , TMS) δ 1.87 (s, 3 H), 6.11 (d, $J = 3.2$ Hz, 1 H), 6.40 (m, 1 H), 6.77 (s, 1 H), 7.27-7.25 (m, 6 H) ppm; ^{13}C NMR (CDCl_3 , TMS) δ 30.54, 112.28, 115.58, 122.59, 128.22, 128.64, 128.96, 136.25, 141.93, 144.57, 153.78, 198.99 ppm; MS m/z 212 (M^+), 197, 183, 170, 155, 141, 115, 105; HRMS calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2$ 212.0837, found 212.0920.

(Z)-4-Phenyl-4-(2-thienyl)-3-buten-2-one: IR 1640, 1569, 1204 cm^{-1} ; ^1H NMR (CDCl_3 , TMS) δ 1.80 (s, 3 H), 6.63 (s, 1 H), 6.81 (m, 1 H), 6.95 (m, 1 H), 7.25-7.43 (m, 6 H) ppm; ^{13}C NMR (CDCl_3 , TMS) δ 30.13, 124.89, 127.99, 128.36, 128.43, 128.79, 129.00, 130.32, 138.11, 145.21, 147.50, 198.73 ppm; MS m/z 228 (M^+), 227, 213, 184, 152, 111; HRMS calcd for $\text{C}_{14}\text{H}_{12}\text{OS}$ 228.0609, found 228.0612.

(Z)-4-Phenyl-4-(trimethylsilyl)ethynyl-3-buten-2-one: IR 2339, 1650 cm^{-1} ; ^1H NMR (CDCl_3 , TMS) δ 0.28 (s, 9 H), 2.58 (s, 3 H), 6.72 (s, 1 H), 7.3-7.7 (m, 5 H) ppm; ^{13}C NMR (CDCl_3 , TMS) δ 0.58, 30.36, 101.98, 110.05, 127.12, 128.53, 129.84, 113.50, 136.96, 198.15 ppm; MS m/z 242 (M^+), 227, 212, 197, 183, 169, 153, 129; HRMS calcd $\text{C}_{15}\text{H}_{18}\text{OSi}$ 242.1127, found 242.1131. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{OSi}$: C, 74.33; H, 7.48. Found: C, 74.38; H, 7.52.

(E)-4-Phenyl-4-(trimethylsilyl)ethynyl-3-buten-2-one: IR 2395, 1650 cm^{-1} ; ^1H NMR (CDCl_3 , TMS) δ 0.21 (s, 9 H), 1.96 (s, 3 H), 6.53 (s, 1 H), 7.26-7.38 (bs, 5 H) ppm; ^{13}C NMR (CDCl_3 , TMS) δ 0.58, 30.39, 101.96, 127.13, 128.54, 129.86, 133.50, 136.95, 198.23 ppm; MS m/z 242 (M^+), 227, 212, 197, 183, 169, 153; HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{OSi}$ 242.1127, found 242.1131.

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Key Words

4-Phenyl-3-butyn-2-one; Cross coupling; Organozinc compounds; Palladium catalyst.

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