Selective Reduction of $\alpha,\beta$-Unsaturated Weinreb Amides in the Presence of $\alpha,\beta$-Unsaturated Esters

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Introduction

Weinreb amides$^{1–3}$ are well known as the synthetic equivalents of aldehydes and ketones and are commonly used in synthetic organic chemistry. Therefore, the selective conversions of $\alpha,\beta$-unsaturated Weinreb amides in the presence of similarly reactive $\alpha,\beta$-unsaturated esters provide a useful approach. However, no such conversion has been reported. As an extension of our efforts to develop in situ protection methods for carbonyl derivatives,$^{4–11}$ we attempted to apply this method to a combination of $\alpha,\beta$-unsaturated Weinreb amides and $\alpha,\beta$-unsaturated esters.

First, the relative reactivities of $\alpha,\beta$-unsaturated ester 1 and $\alpha,\beta$-unsaturated Weinreb amide 2 were investigated (Chart 1). That is, 1 equiv (equiv) of disobutylaluminium hydride (DIBAL-H) (the same mole as 1) was added to a 1:1 mixture of 1 and 2 in CH$_2$Cl$_2$ at −78°C, and the mixture was stirred for 3 h at the same temperature. As a result, 7% of $\alpha,\beta$-unsaturated aldehyde 3, 24% of allyl alcohol 4, and 33% of $\alpha,\beta$-unsaturated aldehyde 5 were obtained along with 56% of recovered 1 and 61% of 2. This result indicated that selective reduction of one in the presence of the other was difficult, although the reactivity of the $\alpha,\beta$-unsaturated Weinreb amide was slightly lower than that of the $\alpha,\beta$-unsaturated ester.

Next, the generality of substrates for the selective reduction reaction of $\alpha,\beta$-unsaturated Weinreb amides in the presence of $\alpha,\beta$-unsaturated esters was examined (Table 2). In this reaction, not only $\alpha,\beta$-unsaturated ester 1 with an aromatic ring at the $\beta$-position, but also $\alpha,\beta$-unsaturated ester 6 with aliphatic chains (Entries 1–4, 6) and a cyclic $\alpha,\beta$-unsaturated ester, coumarin (9) (Entry 5), were available to form selectively the corresponding phosphonium salts. The coexisting $\alpha,\beta$-unsaturated Weinreb amides having an aromatic ring (2) and an aliphatic chain (7) at the $\beta$-position were reduced selectively to give the corresponding $\alpha,\beta$-unsaturated aldehydes in good yields (Entries 1–5). Furthermore, after salt formation, a methyl group could be introduced into Weinreb amide 2 by using a Grignard reagent instead of DIBAL-H to afford the $\alpha,\beta$-unsaturated ketone 10 (Entry 6).

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In conclusion, we have developed an easy, selective conversion of $\alpha,\beta$-unsaturated Weinreb amides in the presence of $\alpha,\beta$-unsaturated esters. To achieve this selective conversion, new conditions for \textit{in situ} protection have been developed. Since Weinreb amides are synthetic equivalents of aldehydes and ketones, the method here would provide a useful tool in synthetic organic chemistry.  

### Experimental

#### General Information
All reagents were purchased from commercial sources. Reactions were performed under a nitrogen atmosphere using purchased anhydrous solvent. All reactions were monitored by TLC using Merck silica gel 60 F254. The products were purified by column chromatography over silica gel Kieselgel 60 (70–230 mesh ASTM) purchased from Merck or Silica Gel 60N (40–50 $\mu$m, spherical neutral).
The substrates 1, 3, 6, 9 are commercially available.

Weinreb amide 2^{25}: To a solution of benzaldehyde (1.0 g, 9.4 mmol) in CH₂Cl₂ (19 mL, 0.50 M) was slowly added N-methoxy-N-methyl-2-(triphenylphosphoranylidene) acetamide (4.1 g, 11.3 mmol, 1.2 equiv) at r.t. After being stirred for 5 h at r.t., the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (n-hexane/AcOEt = 1/1) to afford 2 (1.7 g, 9.0 mmol, 96%) as a colorless oil.

1H-NMR (500 MHz, CDCl₃) δ: 7.73 (1H, d, J = 15.7 Hz), 7.55 (2H, m), 7.35 (3H, m), 7.04 (1H, d, J = 15.7 Hz), 3.74 (3H, s), 3.29 (3H, s).

Weinreb amide 7^{23}: To a solution of decanal (1.0 g, 6.4 mmol) in CH₂Cl₂ (13 mL, 0.50 M) was slowly added N-methoxy-N-methyl-2-(triphenylphosphoranylidene) acetamide (2.8 g, 7.7 mmol, 1.2 equiv) at r.t. After being stirred for 5 h at r.t., the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (n-hexane/AcOEt = 1/1) to afford 7 (1.4 g, 5.8 mmol, 90%) as a colorless oil.

1H-NMR (500 MHz, CDCl₃) δ: 6.97 (1H, dt, J = 15.7, 5.0 Hz), 6.38 (1H, d, J = 15.7 Hz), 3.70 (3H, s), 3.23 (3H, s), 2.22 (2H, dt, J = 5.0, 1.6 Hz), 1.46 (2H, m) 1.29 (12H, m), 0.88 (3H, m).

Experimental Details for Chart 1: A solution of 1 (240.0 mg, 1.00 mmol) and 2 (191.1 mg, 1.00 mmol) in CH₂Cl₂ (10 mL, 0.1 M) was cooled to −78 °C. DIBAL-H (2.0 mL, 1.0 M) was added dropwise to the reaction mixture, and the reaction mixture was stirred for 2 h. After the reaction mixture was quenched with 1N HCl and the solvent volume was reduced under vacuum. The residue left behind was extracted with ethyl acetate (EtOAc) (3 × 30 mL). The organic layer was separated and dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (n-hexane/EtOAc = 2/1) to afford the recovered 1 (134.4 mg, 0.56 mmol, 56%) and 2 (116.6 mg, 0.61 mmol, 61%), and the reduced products 3 (14.7 mg, 0.07 mmol, 7%), 4 (50.9 mg, 0.24 mmol, 24%) and 5 (43.6 mg, 0.33 mmol, 33%).

3: 1H-NMR (400 MHz, CDCl₃) δ: 9.69 (1H, d, J = 7.4 Hz), 7.57 (2H, d, J = 6.4 Hz), 7.42 (2H, d, J = 6.4 Hz), 7.41 (1H, d, J = 16.0 Hz), 6.69 (1H, dd, J = 16.0, 7.4 Hz), 7.69 (2H, d, J = 15.9 Hz), 6.56 (1H, d, J = 15.9 Hz), 6.35 (1H, dt, J = 5.6, 15.6 Hz), 4.32 (2H, d, J = 5.6 Hz), 1.59 (1H, brs, OH).

Experimental Details for Chart 3, Table 2: General procedure: To a solution of α,β-unsaturated Weinreb amide (1.00 mmol, 1.0 equiv), α,β-unsaturated ester (1.00 mmol, 1.0 equiv) and P(1,4) (1.0 M in toluene solution, 1.5 mL, 1.50 mmol, 1.5 equiv) in toluene (10 mL) was added dropwise TMSOTf (272 µL, 1.50 mmol, 1.5 equiv) at r.t. After being stirred for 5 h at 110 °C, the reaction mixture was then cooled to −78 °C. DIBAL-H (2.0 mL, 1.0 M n-hexane solution, 2.0 equiv) was added to the reaction mixture. After the starting α,β-unsaturated Weinreb amide was consumed, suspension of TBAf (1.0 M in THF, 3.0 mL, 3.0 equiv) was added, then the resulting solution was stirred for 30 min. After adding H₂O, the mixture was extracted with CH₂Cl₂. The extract was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (n-hexane/AcOEt = 6/1).

Cinnamaldehyde (5)^{35} (Charts 1 and 3, Table 2, Entries 1, 2, and 5): Entry 1: According to the general procedure, 1 (240.0 mg, 1.00 mmol), 2 (191.1 mg, 1.00 mmol), P(1,4) (1.0 M in toluene solution, 1.5 mL, 1.50 mmol, 1.5 equiv), TMSOTf (272 µL, 1.50 mmol, 1.5 equiv), DIBAL-H (2.0 mL, 1.0 M n-hexane solution, 2.0 equiv), and suspension of TBAF (1.0 M, 3.0 mL, 3.0 equiv) gave recovered 1 (218.4 mg, 0.91 mmol, 91%) and 5 (118.9 mg, 0.90 mmol, 90%) as a colorless oil after purification by flash column chromatography (n-hexane/AcOEt = 6/1).

Entry 2: According to the general procedure, 6 (156.1 mg, 1.00 mmol), 2 (191.1 mg, 1.00 mmol), P(1,4) (1.0 M in toluene solution, 1.5 mL, 1.50 mmol, 1.5 equiv), TMSOTf (272 µL, 1.50 mmol, 1.5 equiv), DIBAL-H (2.0 mL, 1.0 M n-hexane solution, 2.0 equiv), and suspension of TBAF (1.0 M, 3.0 mL, 3.0 equiv) gave recovered 1 (134.6 mg, 0.89 mmol, 90%) and 5 (121.5 mg, 0.92 mmol, 92%) as a colorless oil after purification by flash column chromatography (n-hexane/AcOEt = 6/1).

Entry 5: According to the general procedure, 9 (146.0 mg, 1.00 mmol), 2 (191.1 mg, 1.00 mmol), P(1,4) (1.0 M in toluene solution, 1.5 mL, 1.50 mmol, 1.5 equiv), TMSOTf (272 µL, 1.50 mmol, 1.5 equiv), DIBAL-H (2.0 mL, 1.0 M n-hexane solution, 2.0 equiv), and suspension of TBAF (1.0 M, 3.0 mL, 3.0 equiv) gave recovered 9 (134.0 mg, 0.89 mmol, 90%) and 5 (116.3 mg, 0.88 mmol, 88%) as a colorless oil after purification by flash column chromatography (n-hexane/AcOEt = 3/1).

1H-NMR (400 MHz, CDCl₃) δ: 9.70 (1H, d, J = 7.6 Hz), 7.56 (2H, m), 7.50 (3H, m), 7.46–7.44 (3H, m), 6.75–6.70 (m, 7H).

(E)-Dodec-2-enal (8)^{40} (Table 2, Entries 3 and 4): Entry 3: According to the general procedure, 1 (240.0 mg, 1.00 mmol), 7 (241.2 mg, 1.00 mmol), P(1,4) (1.0 M in toluene solution, 1.5 mL, 1.50 mmol, 1.5 equiv), TMSOTf (272 µL, 1.50 mmol, 1.5 equiv), DIBAL-H (2.0 mL, 1.0 M n-hexane solution, 2.0 equiv), and suspension of TBAF (1.0 M, 3.0 mL, 3.0 equiv) gave recovered 7 (191.5 mg, 0.90 mmol, 90%) and 8 (153.0 mg, 0.84 mmol, 84%) as a colorless oil after purification by flash column chromatography (n-hexane/AcOEt = 6/1).

Entry 4: According to the general procedure, 6 (156.1 mg, 1.00 mmol), 7 (241.2 mg, 1.00 mmol), P(1,4) (1.0 M in toluene solution, 1.5 mL, 1.50 mmol, 1.5 equiv), TMSOTf (272 µL, 1.50 mmol, 1.5 equiv), DIBAL-H (2.0 mL, 1.0 M n-hexane solution, 2.0 equiv), and suspension of TBAF (1.0 M, 3.0 mL, 3.0 equiv) gave recovered 6 (132.7 mg, 0.85 mmol, 85%) and 8 (156.7 mg, 0.86 mmol, 86%) as a colorless oil after purification by flash column chromatography (n-hexane/AcOEt = 6/1).
1H-NMR (400 MHz, CDCl₃): δ = 9.43 (1H, d, J = 7.5 Hz), 6.68 (1H, dt, J = 15, 7.5 Hz), 6.04 (1H, dd, J = 15, 7.5 Hz), 2.49–2.12 (2H, m), 2.02–1.06 (14H, m), 1.01–0.73 (3H, m).

(E)-4-Phenylbut-3-en-2-one (10) (Table 2, Entry 6)

Entry 6: According to the general procedure, 1 (240.0 mg, 1.00 mmol), 2 (191.1 mg, 1.00 mmol), PEt₃ (1.0 M in toluene solution, 1.5 mL, 1.50 mmol, 1.5 equiv), TESOTf (389 µL, 1.50 mmol, 1.5 equiv), MeMgBr (2.0 mL, 1.0 M THF solution, 2.0 equiv), and suspension of TBAF (1.0 M, 3.0 mL, 3.0 equiv) gave recovered 1 (199.2 mg, 0.83 mmol, 83%) and 10 (119.8 mg, 0.82 mmol, 82%) as a colorless oil after purification by flash column chromatography (n-hexane/AcOEt = 7/1).

1H-NMR (500 MHz, CDCl₃) δ: 7.58–7.48 (m, 3H), 7.43–7.37 (3H, m), 6.71 (1H, d, J = 16.1 Hz), 2.39 (s, 3H).

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Conflict of Interest The authors declare no conflict of interest.

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