Nickel-Catalyzed Tandem Coupling of Enones, Alkynes, Alkynylzincs, and Chlorotrimethylsilane

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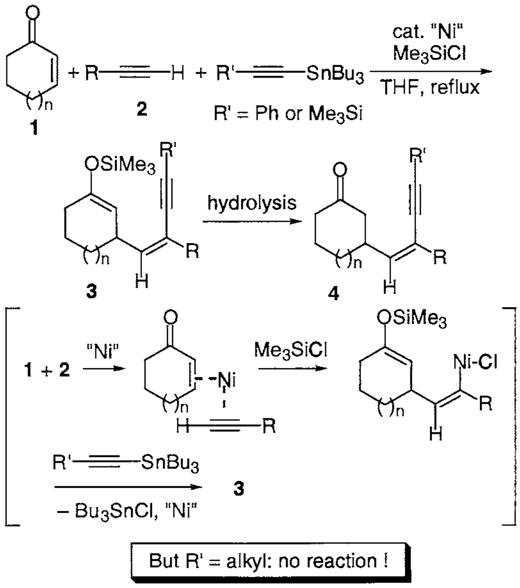
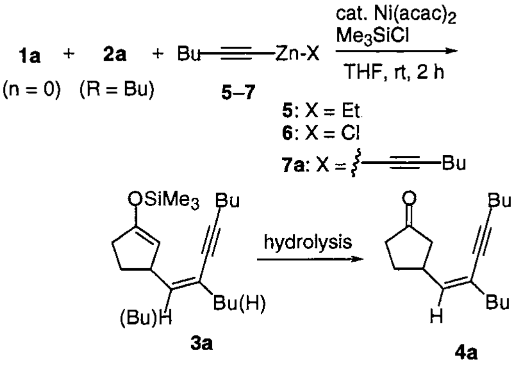
A nickel complex catalyzes a new tandem coupling of chlorotrimethylsilane (Me_3SiCl), α,β-enones **1**, alkynes **2**, and di(alkynyl)zincs **7** (R' = Bu, *t*-Bu, Me_3Si, and Ph) to give the coupling products **3**. This procedure was complementary to the reaction with alkynyltins.

Tandem reactions, which permit complex molecules to be reasonably well constructed in a few steps, are an important topic in organic synthesis.[1-3] We have investigated the successive introduction of carbon units into an alkyne based on a nickel-catalyzed coupling reaction with organometallics and found a nickel-catalyzed tandem coupling of α,β-enones **1**, 1-alkynes **2**, (phenylethynyl)tin (R' = Ph) or [(trimethylsilyl)ethynyl]tin (R' = Me_3Si), and chlorotrimethylsilane (Me_3SiCl) to give regio- and stereoselective conjugated enyne compounds **3** (hydrolysis product **4**) in high yields (Scheme 1).[4] However, the reaction with an alkynyltin derivative such as (1-hexynyl)tin (R' = Bu) failed to give a corresponding tandem coupling product. Herein we report an investigation of the tandem reaction of the more reactive alkynylzinc derivatives with **1**, **2**, and Me_3SiCl in the presence of a nickel catalyst.[5]

Scheme 1.



When the reaction of alkynylzinc **5**, which was prepared from diethylzinc (Et_2Zn, 1 mmol) and 1-hexyne (**2a**, 1 mmol),[6] was carried out with 2-cyclopenten-1-one (**1a**, 1 mmol), **2a** (1.2 mmol), and Me_3SiCl (1.2 mmol) in the presence of $Ni(acac)_2$ (0.05 mmol) in THF at room temperature, the expected tandem coupling product was not obtained (Eq. 1 and Run 1 in Table 1). The same result was obtained for the reaction with [(hex-1-yn)yl]zinc chloride (**6**), prepared from zinc chloride ($ZnCl_2$, 1 mmol) and 1-hexynyllithium (1 mmol) (Run 2 in Table 1). On the other hand, when di[(hex-1-yn)yl]zinc (**7a**), prepared from $ZnCl_2$ (1 mmol) and 2 equivalents of 1-hexynyllithium, was treated with the reaction mixture, **4a** (after the hydrolysis of **3a**) was obtained in 67% isolated yield and 88% regioselectivity (based on ^1H NMR spectra) (Run 3 in Table 1).[7] In this reaction, a product arising from the conjugated addition of alkynyl unit to **1a** was not detected. The use of a ligand (0.1 mmol) such as triphenylphosphine (PPh_3) or pyridine led to a reduction in regioselectivity (Runs 4 and 5 in Table 1).



(1)

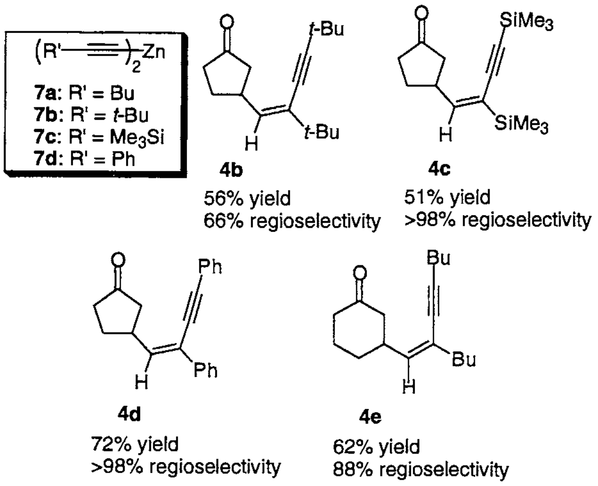
Table 1. The nickel-catalyzed tandem coupling of **1a**, **2a**, alkynylzinc, and Me_3SiCl[a]

Run	Alkynylzinc	Additive	Yield /%[b]	Ratio of **4a**/isomer[c]
1	**5**	no	trace	–
2	**6**	no	trace	–
3	**7a**	no	67	88:12
4	**7a**	PPh_3	64	80:20
5	**7a**	pyridine	62	80:20

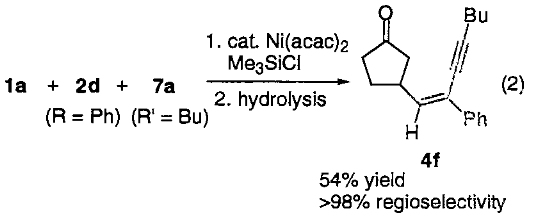
[a]The reaction was done as described in the text. [b]Combined yield of **4a** and its regioisomer. [c]Determined by ^1H NMR spectra.

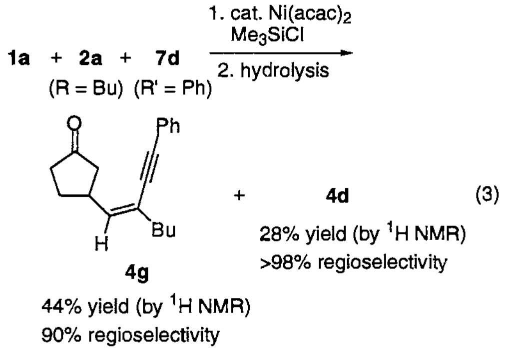
The results of the nickel-catalyzed tandem coupling of **1**, **2**, **7**, and Me_3SiCl are summarized in Chart 1.[7] Di[1-(3,3-dimethylbut-1-yn)yl]zinc (**7b**, R' = *t*-Bu) was reacted with **1a** and *tert*-butylacetylene (**2b**) to give **4b**, although the regioselectivity was decreased to 66%. Products **4c** and **4d** were synthesized via reaction with di(alkynyl)zincs **7c** (R' = Me_3Si) and **7d** (R' = Ph) derived from (trimethylsilyl)acetylene (**2c**, R = Me_3Si) and phenylacetylene (**2d**, R = Ph), respectively, with high regioselectivities. The stereochemistry of **4c** was assigned to an *E*-geometry by NOE experiment. A reaction with six-membered enones **1b** (n = 1) gave a mixture of **4e** and its regioisomer in 62% yield (**4e**/isomer = 88:12).

Chart 1.

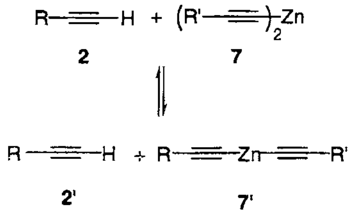


When R^1 in **2** and R^2 in **7** are different ($R^1 \neq R^2$), the interesting behavior was observed in the reaction. Thus, the reaction of **1a** with **2d** (R = Ph) and **7a** (R' = Bu) proceeded to give the corresponding **4f** in 54% isolated yield as the sole product (Eq. 2).[7] On the other hand, when the reaction with **2a** (R = Bu) and **7d** (R' = Ph) was carried out under the same reaction conditions, **4d** (28% yield) was obtained along with the desired product **4g** (44% yield, 90% regioselectivity) (Eq. 3). Although the details are not clear, these results would be dependent on difference of the reactivities of alkynes **2** and **2'** and alkynylzincs **7** and **7'**, which were generated from the equilibrium between **2** and **7** (Scheme 2).[8]





Scheme 2.



In summary, di(alkynyl)zincs **7** allowed to react with enones **1** and alkynes **2** in the presence of a nickel catalyst and Me_3SiCl at room temperature to give tandem coupling products **3** (the hydrolysis products **4**). This procedure is complementary to the reaction with alkynyltins.[4]

References and Notes

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7 **4a**: ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3 H), 1.27–2.36 (m, 18 H), 3.29–3.33 (m, 1 H), 5.48 (d, J = 8.8 Hz, 1 H); IR (neat): 1743 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.57; H, 10.08; **4b**: ^1H NMR (270 MHz, $CDCl_3$) δ 1.00–2.53 (m, 24 H), 3.27–3.48 (m, 1 H), 5.49 (d, J = 8.6 Hz, 1 H); IR (neat): 1743 cm^{-1}. HRMS for $C_{17}H_{26}O$ (M^+): Calcd, 246.1984. Found, 246.1979; **4c**: ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (s, 9 H), 0.18 (s, 9 H), 1.59–2.54 (m, 6 H), 3.41–3.57 (m, 1 H), 5.98 (d, J = 8.6 Hz, 1 H); IR (neat): 1747 cm^{-1}. HRMS for $C_{15}H_{26}OSi_2$ (M^+): Calcd, 278.1522. Found, 278.1520; **4e**: ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3 H), 1.21–2.46 (m, 20 H), 2.97–3.02 (m, 1 H), 5.41 (d, J = 8.9 Hz, 1 H); IR (neat): 1714 cm^{-1}. HRMS for $C_{18}H_{28}O$ (M^+): Calcd, 260.2145. Found, 260.2140; **4f**: ^1H NMR (270 MHz, $CDCl_3$) δ 0.75 (t, J = 7.1 Hz, 3 H), 1.46–2.61 (m, 12 H), 3.51–3.62 (m, 1 H), 6.21 (d, J = 8.8 Hz, 1 H), 7.24–7.60 (m, 5 H); IR (neat): 1743 cm^{-1}. HRMS for $C_{19}H_{22}O$ (M^+): Calcd, 266.1671. Found, 266.1682.

8 In the crossover experiment depicted in Eq. i, **2d** was more reactive than **2a**.