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Ni(0)-Catalyzed Conjugate Addition of Me_3SiCN to Ynones: α-Bromo-β-cyano Tetrasubstituted Enones

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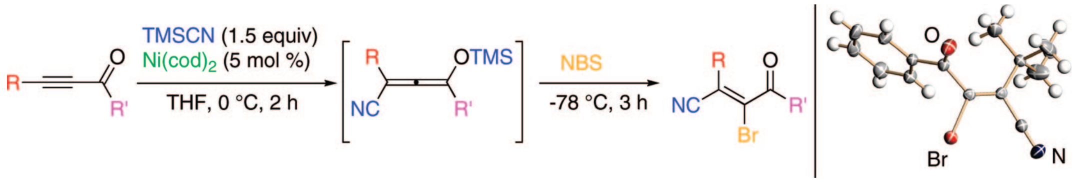
ABSTRACT



Conjugate addition of Me_3SiCN to ynones is smoothly catalyzed by $Ni(cod)_2$ to give the β-cyanosilyloxyallene quantitatively. Further reaction of the silyloxyallenes with NBS provides the tetrasubstituted α-bromo-β-cyano enones in high yields (up to 95%) with excellent *Z*-selectivity (E/Z = up to >1/99). X-ray crystallographic analysis showed a bent structure of the α-bromo-β-cyano enone due to a deconjugation of the π-bond and carbonyl group.

Due to the great importance of conjugate addition reactions (i.e., 1,4-addition) in organic synthesis, α,β-unsaturated carbonyl compounds have been extensively utilized.[1] Horner−Emmons reactions, Claisen−Schmidt condensations, and eliminations of phenylselenium groups via oxidation have been employed widely for preparing such α,β-unsaturated carbonyl compounds.[2] While these conventional methods are quite useful, a general method for the synthesis of highly functionalized tetrasubstituted α,β-unsaturated carbonyl compounds is still needed.[3] Because tetrasubstituted olefins are also of interest for the development of light- and/or electron-responsive materials such as liquid crystals and molecular devices including sensors, switches, and motors,[4] the efficient regio- and stereoselective synthesis of the tetrasubstituted olefins having four different functional groups becomes an important task in organic synthesis. We report herein the nickel(0)-catalyzed conjugate addition of trimethylsilyl cyanide (Me_3SiCN) to ynones to provide silyloxyallenes, and further transformation to the α-bromo-β-cyano tetrasubstituted enones.[5,6]

Regarding the Ni(0)-catalyzed conjugate addition of Me_3SiCN, Shibasaki et al. reported one elegant example in the synthesis of Tamiflu, in which the reaction proceeded on the cyclohexenone derivative.[7] This Ni(0)-catalyzed conjugate addition is quite efficient for cyclic enones; however, the simple application of the Ni(0)-catalyst to acyclic substrates were unsuccessful (Scheme 1).[8]

One possibility for the obstacle in the reaction using acyclic enones might be explained by the formation of a stable Ni−enone complex (**A**). These examinations led us to experiment further on ynones, which would avoid formation of a tight Ni−substrate complex such as **A**.[9]

To our delight, the reaction of diphenyl ynone[10] with Me_3SiCN was smoothly catalyzed by $Ni(cod)_2$ in THF, and the corresponding β-cyano enone was obtained in 90% yield

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(2) Takeda, T., Ed. *Modern Carbonyl Olefination*; Wiley-VCH: Weinheim, Germany, 2004.

(3) Flynn, A. B.; Ogilvie, W. W. A Review for the synthesis of tetrasubstituted olefins. *Chem. Rev.* **2007**, *107*, 4698.

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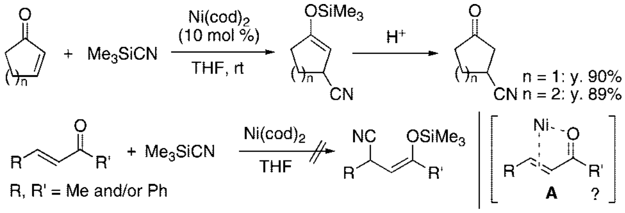
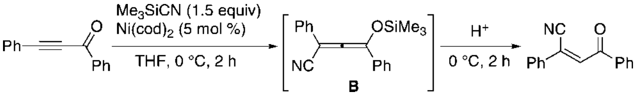
Scheme 1. $Ni(cod)_2$-Catalyzed Conjugate Addition of Enones



after treatment with 1 N HCl (Table 1, entry 1).[11] Though the *E*/*Z* selectivities of the obtained *β*-cyano enones are low when the reactions were quenched by strong acids, quenching with AcOH improved the *Z*-selectivity in the ratio of 11:89 (Table 1, entry 2).

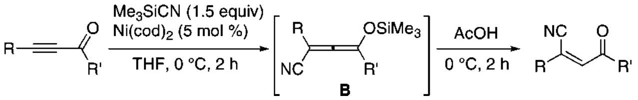
Table 1. $Ni(cod)_2$-Catalyzed Conjugate Addition of Me_3SiCN to Ynones



entry	H^+ source	yield (%)	*E*/*Z*
1	1 N HCl (aq)	90	58/42
2	AcOH	94	11/89
3	TFA	92	25/75
4	$PhCO_2H$	85	30/70
5	PhOH	88	59/41

The current procedure is useful not only for aromatic ynones, but aliphatic ynones as well, which give *β*-cyano trisubstituted enones efficiently (Table 2). The introduction of electron donating or withdrawing group on the aromatic substrates couldn't improve the *E*/*Z* selectivities of the products.

Table 2. Catalytic Synthesis of *β*-Cyano Trisubstituted Enones



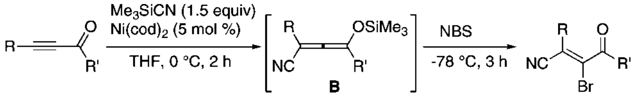
entry	R	R′	yield (%)	*E*/*Z*
1	Ph	Ph	94	11/89
2	Ph	Me	68	24/76
3	*n*-Bu	Ph	92	24/76
4[a]	*t*-Bu	Ph	84	31/69
5	Ph	$4\text{-MeOC}_6\text{H}_4$	84	27/73
6	Ph	$4\text{-BrC}_6\text{H}_4$	71	46/54
7	$4\text{-MeOC}_6\text{H}_4$	Ph	94	35/65

[a] Conjugate addition was carried out at rt.

The predominant formation of the silyloxyallene (**B**) was confirmed by ^1H NMR analysis of the reaction mixture. Actually, in the Ni(0)-catalyzed reaction of diphenyl ynone and $t\text{-BuMe}_2SiCN$, the corresponding silyloxyallene was isolated in 64% yield (rt, 3 h). The mild reaction conditions would be an alternative way for the synthesis of silyloxyallenes without use of the 1,2-Brook rearrangement.[12]

Next, we tried to trap the silyloxyallene with a halogen ion to obtain α-halo-*β*-cyano enones.[13] After completion of the Ni-catalyzed conjugate addition, 1.0 mol equiv of *N*-bromosuccinimide (NBS) was added to the reaction mixture. Bromination at the α-position occurred smoothly at −78 °C to give α-bromo-*β*-cyano enones with high isolated yields (Table 3).

Table 3. Catalytic Synthesis of α-Bromo-*β*-cyano Tetrasubstituted Enones

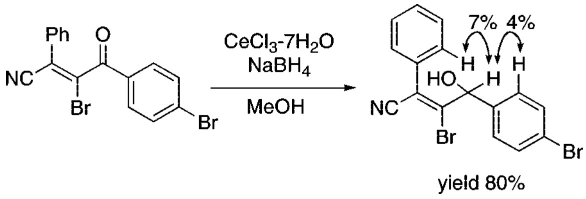


entry	R	R′	yield (%)	*E*/*Z*
1	Ph	Ph	94	>1/99
2	Ph	Me	44	>1/99
3[a]	*t*-Bu	Ph	90	>1/99
4	Ph	$4\text{-MeOC}_6\text{H}_4$	89	>1/99
5	Ph	$4\text{-BrC}_6\text{H}_4$	84	>1/99
6	$4\text{-MeOC}_6\text{H}_4$	Ph	95	>1/99

[a] Conjugate addition was carried out at rt.

The bromination proceeded in a highly (*Z*)-selective manner, which was confirmed by NOE experiments after conversion to the allylic alcohols by reduction of the enones. In the α-bromination, the substituent on the aromatic ring did not reduce the high (*Z*)-selectivity of the products.

Scheme 2. Reduction of α-Bromo-*β*-cyano Tetrasubstituted Enones and NOE Experiments



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(5) Selected catalytic conjugate additions of cyanide (non asymmetric): (a) Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822. (b) Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 3389. (c) Higuchi, K.; Onaka, M.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1035.

(6) Selected catalytic conjugate additions of cyanide (asymmetric): (a) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (b) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928. (c) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514. (d) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 5820. (e) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 6072.

Furthermore, the structures of the compounds obtained in entry 3 of Table 3 were confirmed by X-ray crystallographic analysis as shown in Figure 1.

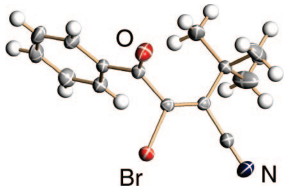


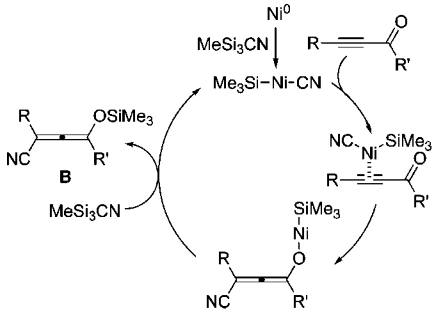
Figure 1. ORTEP diagram of α-bromo-β-cyano tetrasubstituted enones (Table 3, entry 3).

Interestingly, the X-ray structure depicted in Figure 1 suggests an extremely bent enone structure caused by a deconjugation of the π-bond and carbonyl group due to significant steric repulsion between the carbonyl group and the *t*-Bu substituent (θ O=C−C=C = 81.1°).

Typically, when α,β-unsaturated carbonyl compounds are mixed with Ni(cod)$_2$ in THF, the solution has a dark brown color. We originally thought the dark brown color suggested the formation of a Ni-π-bond complex, and the coordination resulted in activation of the π-bond to promote the subsequent conjugate addition of cyanide ion.[14,15] The addition of Me$_3$SiCN into the mixture of Ni(cod)$_2$ and ynone, however, caused the dark brown color to disappear spontaneously. In the infrared (IR) spectrum, the mixture of the Ni(cod)$_2$ and Me$_3$SiCN showed a CN absorption at 2146 cm^{-1}, though the Me$_3$SiCN itself has a CN absorption at 2188 cm^{-1}. The DFT simulation of the IR spectrum using the Gaussian program for Me$_3$Si−Ni−CN, which is generated by an oxidative addition of Ni(0) to Me$_3$SiCN, suggested a CN absorption at 2137 cm^{-1}.[16]

Based on these experimental observations and the theoretical study, the possible mechanism for the current Ni(0)-catalyzed conjugate addition of Me$_3$SiCN to ynones is proposed as shown in Scheme 3. Ni(cod)$_2$ would smoothly cause oxidative addition to Me$_3$SiCN to give the Me$_3$Si−Ni−CN complex. The more Lewis acidic Ni(II) intermediate would form a π-complex with the ynones to promote the conjugate addition of cyanide. Further reductive elimination from the nickel enolate intermediate would provide the silyloxyallene (**B**), and the Me$_3$Si−Ni−CN catalyst would be regenerated by the reaction with Me$_3$SiCN.

Scheme 3. Plausible Reaction Mechanism of Ni(0)-Catalyzed Conjugate Addition of Me$_3$SiCN to Ynones



In conclusion, a facile conjugate addition of Me$_3$SiCN to ynones is presented using the simple Ni(cod)$_2$ catalyst. The reaction of the silyloxyallenes with NBS provides tetrasubstituted α-bromo-β-cyano enones in a *Z*-selective manner. Further applications of silyloxyallenes and α-bromo-β-cyano enones are in progress, including a mechanistic study on the Ni(0) catalysis.

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Supporting Information Available: Detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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