CARBON-CARBON BOND FORMATION BY INTERMOLECULAR RADICAL REACTION. Smi2-PROMOTED CARBONYL-ALKYNE REDUCTIVE COUPLING

Junji Inanaga,* Junko Katsuki,† Osamu Ujikawa,† and Masaru Yamaguchi† Institute for Molecular Science, Myodaiji, Okazaki 444, Japan and †Department of Chemistry, Kyushu University 33, Hakozaki, Fukuoka 812, Japan

Summary: An efficient intermolecular carbonyl-alkyne reductive coupling reaction was realized for the first time by using the system, Sml₂-HMPA-hydrogen donor, to give the corresponding allylic alcohols in good yields.

Carbon-carbon bond-forming reactions via radical process are of intense current interest because of their great potential in organic synthesis.¹ Ketone-olefin and ketone-alkyne reductive coupling reactions, which proceed through the addition of ketyl radicals, have often been effectively used instead of conventional Barbier- or Grignard-type reaction in the preparation of tertially alcohols.¹⁻⁴ However, most of them are restricted to entropically favored intramolecular reactions and there has been little precedents of intermolecular carbonyl-alkyne reductive coupling reaction.⁵ We found that such a reaction could be efficiently promoted by the reduction system, Sml₂-HMPA-hydrogen donor, to give the corresponding allylic alcohols under mild conditions (Eq 1).⁶



The reactions were carried out by using carbonyl compounds (1 eq), alkynes (1.5 eq), *t*-BuOH (2.5 eq), and a Sml₂-THF solution (0.1 mol dm⁻³, 2.5 molar eq) in the presence of HMPA (8~10 vol%) at room temperature for 5 min under argon. The results are summarized in Table 1.

A variety of alkynes were found to be good acceptors for ketyl radicals thus affording the addition products in modest to high yields although it has been reported that alkynes are generally less reactive than alkenes for alkyl radicals.⁷⁻⁹ Terminal alkynes were always attacked on their terminal carbons exclusively and in the case of internal alkynes, C-C bond formation occurred at more electropositive site. Another notable feature is that allylic alcohols with *E*-configuration were obtained as sole or major products, which is different from the case reported for the addition of alkyl radicals to terminal acetylenes, where *Z*-alkenes became major.¹⁰ Aldehydes could also be coupled with activated acetylenes, but the yields were generally not high because of the simple reduction of aldehydes to the corresponding primary alcohols.

Entry	Carbonyl compound	Alkyne	Product	%Yield ^{b)}
1	Ph~	<u></u> — C ₆ H ₁₃	Ph C ₆ H ₁₃	21
2	n	🚍 — Ph	Ph OH c)	93
3	11	≡— CH ₂ OAc	Ph CH ₂ OAc	90
4	11	≡— TMS	Ph	84
5	11	—≡Ph	Ph OH o	70
6	·· T	™S — ═ — Ph	Ph TMS	73
7		<u></u>		78
8	Π	≡-TMS	┎┎┎┍╩┈᠉ ┖╻┎┍╩┈	82
9		₩-TMS	CH h)	69 ⁰
10	+~~~~°	≅—TMS	тмз	87
11	O ↓ CO₂Et	≡—⊺MS	0= ⁰ ∕∕∽™s	75
12	()-сно	≡ — Ph		49

Table 1. Sml₂-Promoted Carbonyl-Alkyne Reductive Coupling^{a)}

a) The reactions were conducted at 0.2 mmol scale. b) Isolated yield. c) E/Z=86/14. d) E/Z=78/22. e) The product is very sensitive to acid and the corresponding desilylation product was also isolated in ca. 20 % yield. f) E/Z=85/15. g) The desilylation took place partially under the reaction conditions or work-up stage to give the desilylated derivative (X=H) as the major product in 62 % yield. h) E/Z=63/37. i) The corresponding dehydration product (indene derivative) was also isolated in 14 % yield. j) ax-OH/eq-OH=14/86. k) E/Z=56/44.

_



Scheme 1.

97 : 3 (E/Z=54/46)

Scheme 2. Ph Smb OSml₂ <path b> (C_1) Sml₂ Ph Ph "H•" OSml₂ OSml₂ <path a> (D₁) (B1) (A1) 11 OSml₂ OSml₂ OH <path a> and/or <path b> (A₂) (B₂) (D₂)

The reaction of 4-tert-butylcyclohexanone with phenylacetylene gave a mixture of stereoisomers in a ratio of 85 (eq-OH) : 15 (ax-OH) (Scheme 1), which is less storeoselective by comparison with the ratio of 98 : 2 obtained in the reaction with styrene.¹¹ However, when Bu₃SnH was used as a hydrogen donor in place of t-BuOH, the axial-attack selectivity increased.

These results may lead to a possible reaction mechanism illustrated in Scheme 2: One electron transfer from Sml2 to the ketone produces the corresponding anion radical, the preferred configuration of which is considered to be A1.11,12 Accordingly, the subsequent C-C bond formation occurs on the axial site to give the intermediate vinyl radical (B1), which then abstracts hydrogen atom from the solvent (THF) (or from Bu₃SnH as an additive) path a> and/or accepts one electron from Sml₂ affording the vinyl anion (C_1) which leads to the final product (D_1) as the major isomer <path b>. The second electron transfer step <path b> seems to compete with hydrogen atom-transfer step <path a> since D atom was incompletely incorporated (deuterated : non-deuterated = 41 : 59) when CD₃OD was employed as the "proton" source.

A rapid equilibrium between A1 and B1 and A1 and A2 may be considered to explain the

experimental results; the addition of Bu₃SnH as an efficient trapping agent for B_1 brought about the kinetic product (D_1) highly selectively whereas the formation of equatorial-attacked product with *E*-configuration (D_2) increased reflecting the thermodynamic stability of the intermediate (B_2) when *t*-BuOH was used as a less effective hydrogen donor.

A reversed stereoselection observed in the following two reactions (Scheme 3) may be explained similarly by considering such an equiliburium between the ketyl and the vinyl radical intermediate described above.

Scheme 3.



It is noteworthy that the present method offers a new way to allylic alcohols under almost neutral conditions in which alkynes can be used as the corresponding vinyl anion equivalents.

References and Notes

- For recent reviews, see a) D. P. Curran, Synthesis, 417 and 489 (1988); b) M. Ramaiah, Tetrahedron, 43, 3541 (1987); c) B. Giese, Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Pergamon Press (1986).
- 2. For a review on electrolytic methods, see H. J. Schafer, Angew. Chem., Int. Ed. Engl., 20, 911 (1981).
- For ketone-olefin reductive coupling, see a) K. Otsubo, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, 27, 5763 (1986); b) O. Ujikawa, J. Inanaga, and M. Yamaguchi, *ibid.*, 30, 2837 (1989) and references cited therein.
- 4. For ketone-alkyne reductive coupling, see, for example, G. A. Molander and C. Kenny, J. Am. Chem. Soc., 111, 8236 (1989) and references cited therein.
- 5. For intermolecular addition of alkyl radicals to alkynes, see reference 1.
- A part of this work was presented at the 57th Meeting of the Chemical Society of Japan, Sendai, September (1988).
- 7. B. Giese, Angew. Chem., Int. Ed. Engl., 22, 753 (1983).
- 8. The LUMO of alkynes lies higher than that of alkenes. See J. C. Giordan, J. Am. Chem. Soc., 105, 6544 (1983).
- 9. Even an unactivated alkyne reacted to give the addition product (Table 1, entry 1) while the corresponding alkenes (e.g., allybenzene) did not react at all under similar conditions; see reference 3b. It is interesting that in the competitive reactions of 4-tert-butylcyclohexanone with styrene vs. phenylacetylene the corresponding coupling products were obtained in equal amount when Bu₃SnH was employed as a hydrogen donor though the adducts with phenylacetylene were produced predominantly when *t*-BuOH was used as a proton source.
- 10. B. Giese and S. Lachhein, Angew. Chem., Int. Ed. Engl., 21, 768 (1982).
- 11. J. Inanaga, O. Ujikawa, and M. Yamaguchi, unpublished result.
- 12. a) R. V. Lloyd and J. G. Causey, J. Chem. Soc., Perkin Trans 2, 1143 (1981); b) S. K. Pradhan, Tetrahedron, 42, 6388 (1986).

(Received in Japan 22 April 1991)