Pergamon

Tetrahedron Letters 40 (1999) 7109–7112

TETRAHEDRON
LETTERS

# Preparation of Unsymmetrical Dialkenyl Ketones from the Reactions of Alkenyl Alkynyl Ketones with Gilman Reagents

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Received 17 June 1999; revised 26 July 1999; accepted 30 July 1999

***Abstract:*** Unsymmetrical dialkenyl ketones were prepared from the reactions of alkenyl alkynyl ketones with 0.55 equiv of lithium dialkylcuprates.

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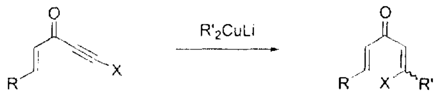
Keyword; *alkenyl alkynyl ketones, unsymmetrical dialkenyl ketones, Michael reaction*

In connection with our research program toward the development of synthetic methods for the preparation of cyclic compounds *via* Michael and Nazarov reactions, we have studied the preparation of unsymmetrical dialkenyl ketones, which are important building blocks for organic syntheses.[1-7] Generally, unsymmetrical dialkenyl ketones can be prepared from vinyl organometallic addition to 2-propenal derivatives,[8-13] Pd-catalyzed carbonylation/coupling of vinyl stannane derivatives,[14-16] acylation of vinyl copper reagents[12] and aldol condensation.[17] However, each method suffers from operational problems and the use of rather expensive reagents. Although a number of different synthetic methods have been developed for this purpose,[18-25] one of the most promising methods is the Michael reaction of alkenyl alkynyl ketones with Gilman reagents. In this respect, we reported that unsymmetrical dialkenyl ketones could be easily prepared *via* ring opening reactions of 2-alkenyl-2-methoxycyclopropyl phenyl sulfones.[26] As part of our continuing effort to expand the synthetic utility of alkenyl alkynyl ketones, we now report a convenient procedure for preparing unsymmetrical dialkenyl ketones from the regioselective Michael reaction of alkenyl alkynyl ketones with Gilman reagents (Scheme 1).



X = H, SiMe$_3$

**Scheme 1**

Initial studies were performed with (*E*)-6-trimethylsilyl-2-hexen-5-yn-4-one **4** (entry a, Table 1), which could be prepared from Friedel-Crafts acylation of crotonyl chloride (Scheme 2).[27] When ketone **4** was treated with lithium dibutylcuprate (1.05 equiv) in THF, the *n*-butyl group was added chemoselectively to the double bond due

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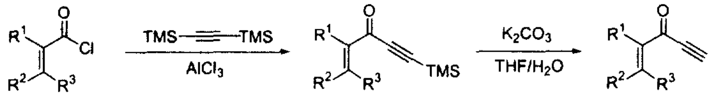
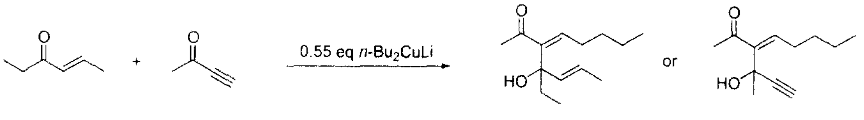
*PII:* S0040-4039(99)01490-2

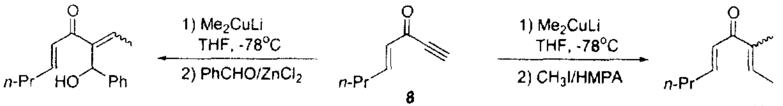


Scheme 2

to the steric effect of trimethylsilyl group to yield **1a** in 74% yield. In addition, the same result was obtained in spite of using 0.55 equiv of lithium dibutylcuprate. $\alpha,\beta$-Ynone **1a** wasn't obtained when using *n*-butyl copper (entry b). When ketone **5** reacted with 0.55 equiv of cuprate, the *n*-butyl group was added regioselectively to the triple bond to produce **2c** in 72% yield in contrast with **4**. Because the major limitations involving the use of organocuprates in synthetic applications have been the need of a large excess of the reagent, the special synthetic significance is essentially complete utilization of both the *n*-butyl groups of organocuprates reagents.[28] This observation is in marked contrast to the results obtained from the reaction of organocuprate reagents with 4-hexen-3-one where 1 equiv of $R_2CuLi$(2 equiv of R) are required for optimal yields of ketones.[29] Presumably the intermediate complex also reacts with alkenyl alkynyl ketones to afford ketones. Ketone **7**, which lacks the trimethylsilyl group, was treated with 0.55 equiv of cuprate to give **2i** in 80% yield. Table 1 summarizes the experimental results and illustrates the efficiency and scope of the present method. An equimolar mixture of 4-hexen-3-one and 3-butyn-2-one in THF was added to 0.55 equiv of lithium dibutylcuprate in THF at -78 $^{\circ}$C to yield **12** in 48% yield to compare the reactivity of double and triple bonds of ketones to cuprates. However, when 0.55 equiv of lithium dibutylcuprate was added to an equimolar mixture of 4-hexen-3-one and 3-butyn-2-one, $\alpha,\beta$-enone **13** was obtained in 40% yield.[30] These results indicate that the conjugated triple bond is more reactive to cuprate than a double bond.



**12** 48% **13** 40%

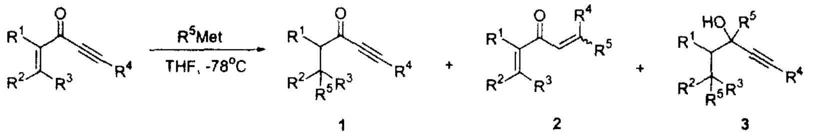


**14** 44% **8** **15** 63%

The conjugate addition of cuprates (0.55 eqiuv) to alkenyl alkynyl ketones **8** followed by enolate trapping with benzaldehyde or methyl iodide gave unsymmetrical dialkenyl ketones **14** and **15** in 44% and 63% yield, respectively.[30]

In summary, regioselective addition of homocuprates to alkenyl alkynyl ketones is a new, useful route to prepare various unsymmetrical dialkenyl ketones. Although various preparative methods are available for unsymmetrical dialkenyl ketone synthesis, the present method is noteworthy in terms of its simplicity.

Table 1. Preparation of Unsymmetrical Dialkenyl Ketones from the Reaction of Alkenyl Alkynyl Ketones with Organocopper Reagents



| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | compound number | $R^5$Met | isolated yield,% 1 | 2(*cis*:*trans*) | 3 |
|---|---|---|---|---|---|---|---|---|---|
| a | H | $CH_3$ | H | $SiMe_3$ | **4** | *n*-$Bu_2CuLi$[a or b] | 74 | 0 | 0 |
| b | | | | | | *n*-BuCu[b] | 0 | 0 | 0 |
| c | H | $CH_3$ | $CH_3$ | $SiMe_3$ | **5** | *n*-$Bu_2CuLi$[a] | 0 | 72(1.9:1)[e] | 0 |
| d | H | Ph | H | $SiMe_3$ | **6** | *n*-$Bu_2CuLi$[a] | 0 | 0 | 0 |
| e | | | | | | *n*-$Bu_2CuLi$[b] | 15 | 45 | 0 |
| f | | | | | | *n*-$Bu_2CuLi$[b] | 17 | 43 | 0 |
| g | | | | | | *n*-$Bu_2CuLi$[c] | 19 | 34 | 0 |
| h | | | | | | *n*-BuCu[b] | 0 | 0 | 0 |
| i | H | $CH_3$ | H | H | **7** | *n*-$Bu_2CuLi$[a] | 0 | 80(1:1.2) | 0 |
| j | | | | | | *n*-$Bu_2CuLi$[a,d] | 0 | 16(1:1.8) | 44 |
| k | | | | | | *n*-$Bu_2CuCNLi_2$[b] | 0 | 18(1:1.7) | 19 |
| l | | | | | | *n*-$Bu_2CuCNLi_2$[a] | 0 | 0 | 40 |
| m | | | | | | $Me_2CuLi$[a] | 0 | 82(1.2:1) | 0 |
| n | H | *n*-Pr | H | H | **8** | *n*-$Bu_2CuLi$[a] | | 84(1:1.1) | |
| o | | | | | | $Me_2CuLi$[a] | | 84(1:1.1) | |
| p | H | Ph | H | H | **9** | *n*-$Bu_2CuLi$[a] | | 70(1:1.2) | |
| q | | | | | | $Me_2CuLi$[a] | | 81(1.3:1) | |
| r | | | | | | *n*-BuCu[b] | | 38(1:1)[f] | |
| s | H | $CH_3$ | $CH_3$ | H | **10** | *n*-$Bu_2CuLi$[a] | | 80(1:1.4) | |
| t | | | | | | $Me_2CuLi$[a] | | 82(1:1) | |
| u | $CH_3$ | Ph | H | H | **11** | *n*-$Bu_2CuLi$[a] | | 83(1:1) | |
| v | | | | | | $Me_2CuLi$[a] | | 82(1.1:1) | |

[a] 0.55 equiv was used. [b] 1.05 equiv was used. [c] CuBr·$SMe_2$ was used. [d] $Et_2O$ was used. [e] Isomer ratio. [f] Starting material was recovered in 11% yield.

**Acknowledgement:** We thank the Korea Research Foundation (F00014) for financial support and Research Center for Advanced Mineral Aggregate Composite Products for gas chromatograph and Professor T. Livinghouse of Montana State University for helpful discussions and proof of the manuscript.

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[29] 4-Hexen-3-one was treated with 1.05 equiv of $n$-$Bu_2CuLi$ to give 5-methyl-3-nonanone in 80% yield. However, this compound was produced only in 38% yield when using 0.55 equiv of $n$-$Bu_2CuLi$.

[30] Satisfactory spectral data and high-resolution mass spectra were obtained for the $\alpha,\beta$-enones **12**, **13**, **14** and **15**.