Pergamon

Tetrahedron Letters 40 (1999) 3367–3370

TETRAHEDRON
LETTERS

γ-1,4 Addition of Substituted Methoxyallylcopper Reagents to Methylvinylketone

Jean-François Berrien, Marie-Noëlle Raymond, Fatima Zaari,
Henri Moskowitz and Joëlle Mayrargue*

Laboratoire de Chimie Organique UPRES-A CNRS, Biocis 8076, Faculté de Pharmacie,
Université Paris-Sud, 5 rue J.-B. Clément, 92296 Châtenay-Malabry Cedex, France.

Received 9 February 1999; accepted 2 March 1999

Abstract: Methoxyallylcopper reagents substituted in α and/or β position of methoxy group reacted regiospecifically with MVK to give γ-1,4 adducts, i.e. ketoenolethers. γ substituted methoxyallylcopper reagents gave mixtures of γ-1,4 and α-1,4 adducts © 1999 Elsevier Science Ltd. All rights reserved.

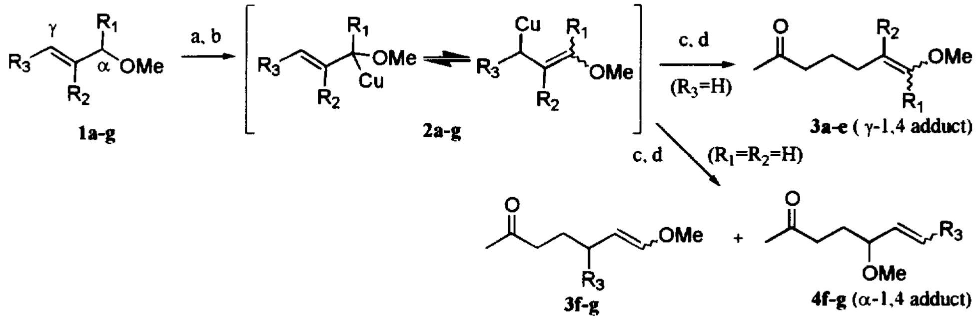
Metal homoenolates are important intermediates in synthetic organic chemistry since they offer the possibility to introduce an electrophilic moiety in β position of a carbonyl function[1]. Use of masked carbonyl functions is a general solution to avoid nucleophilic attack of the too reactive metal carbanion to the carbonyl function. Metalated allylic methylethers are known as homoenolate equivalents[2] and various solutions have been reported to control nucleophilic attack regiospecifically either from the α or γ position of oxygen[2,3]. In a recent paper[4], we reported the preparation of methoxyallylcopper reagent **2a** (Scheme 1) by transmetallation of known methoxyallyllithium[2] and its total γ-1,4 selective addition to several enones, affording ketoenolethers in good yields. In order to check the influence of any substitution on allylic moiety of the methylallylether and explore the scope of the methodology, a series of methylallylethers **1a-i** substituted in α, β and/or γ position of the methoxy group, were submitted to reaction with methylvinylketone (MVK). In a similar reaction of silyloxyallylcuprate reagents on enones developed by Kuwajima[5], substitution in α position of the silyloxy substituent did not affect the excellent γ-1,4 selectivity. To our knowledge, the influence of a substitution in β and γ position on the selectivity has not been reported yet for this kind of reaction.

Thus, methylallylethers **1a-g** (Table 1) were deprotonated by *sec*-BuLi within 30 mn in THF at -78°C. Their corresponding methoxyallylcopper species **2a-g** (Scheme 1) were formed as previously reported[4] and underwent 1,4 addition on MVK in the presence of TMSCl[6]. Desilylation with TBAF afforded the recovered ketone adducts **3a-g** and **4f-g**. As shown in table I, α- and/or β-substituted allylethers **1b-e** gave only γ-1,4 adducts **3b-e** as for the unsubstituted one **1a**, whilst γ-substituted allylethers **1f** and **1g** afforded a mixture of γ-1,4 and α-1,4 adducts (respectively **3f-g** and **4f-g**). Enhancement of steric hindrance in γ position seemed to favor γ-1,4 adducts. However, in the case of methyl cinnamylether **1g**, dimerization of the corresponding methoxyallylcopper reagent **2g** was observed in these experimental conditions, without any γ/α selectivity, yet lowering the yields of γ-1,4 and α-1,4 adducts.

---

* Email : Joelle.mayrargue@chimorg.u-psud.fr ; Fax : 01 46 83 53 23.

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00485-2



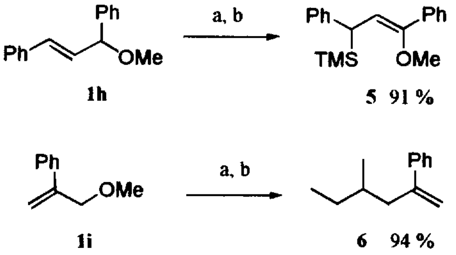
a) *sec*-BuLi, THF, -78°C. b) CuI, DMS. c) TMSCl, then MVK, -78°C. d) TBAF.3H_2O, THF, rt.

Scheme 1

When the reaction was performed with substituted methylallylethers **1h-i** (Scheme 2), the formation of expected γ-1,4 or α-1,4 adducts was not observed with MVK. In order to understand this lack of reactivity, the efficiency of deprotonation with *sec*-BuLi in THF was first checked, by quenching the allyllithium species with TMSCl.

Methylallylether **1h** gave allylsilane **5** in 91% yield with no detectable starting material **1h** after 10 mn of reaction with *sec*-BuLi at -78°C. One can note that silylation occured exclusively at the γ position of the methoxyl function, leading to the corresponding *Z* enolether as sole isomer, as previously reported for other alkylallylethers[11]. So, even if deprotonation of **1h** leading to the corresponding allylcopper **2h** was efficient, subsequent nucleophilic attack to MVK did not occur, even at -30°C.

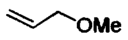
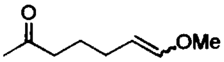
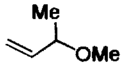
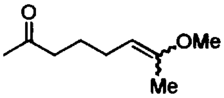
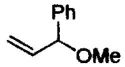
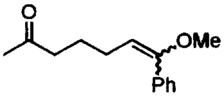
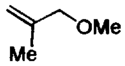
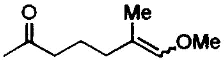
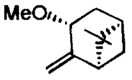
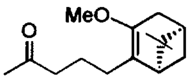
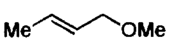
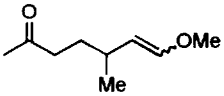
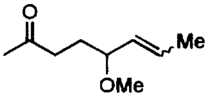
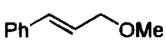
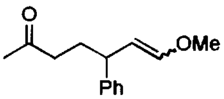
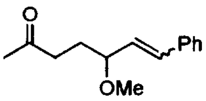
2-phenylallylether **1i** subjected to *sec*-BuLi in THF gave, in less than 5mn at -78°C, formal S_N2' product **6** in 94% yield. A similar behaviour was observed with 3-ethoxy-2-(4-methoxyphenyl)-1-propene when performed with *n*BuLi at 0°C in THF[12], or with other allylethers with organolithium reagents[13]. Change of either the lithiated bases, or the solvents and cosolvents didn't give any satisfactory results on deprotonation.



a) *sec*-BuLi, THF, -78°C. b) TMSCl, -78°C to rt.

Scheme 2

Table 1: Conjugate addition of substituted methoxylallylcopper reagents **2a-g** to methylvinylketone[a]

Entry	allylether **1a-i**[b]	γ-1,4 adduct **3a-f** (*Z* / *E*)[c]	α-1,4 adduct **4a-f**	Selectivity[c,d] γ-1,4 / α-1,4	Yields[e] %
a		 (65/35)	not detected	100 / 0	95
b		 (35/65)[f]	not detected	100 / 0	65
c		 (85/15)[f]	not detected	100 / 0	95 (80)[g]
d		 (65/35)[f]	not detected	100 / 0	66
e			not detected	100 / 0	91 (77)
f		 (20/80)		65 / 35	75[h]
g		 (50/50)		40 / 60	(20)[h]

a) Except for **1a**, all reactions were performed with equimolar quantities of reagents **2b-g** and MVK. b) Prepared from the corresponding allylalcohols using NaH, Me_2SO_4 in xylenes[7] for **1a**, **1b**, **1d** and **1f**, or using NaH, MeI in THF for **1c**, **1e**, **1g**, **1h** and **1i**. Allylic alcohols were either purchased from commercial sources and used without further purification (entry **a**,**f** and **g**), either obtained as 1,2 Grignard adducts on enals[8] (entry **b**,**c** and **h**), either from enone reduction following Luche procedure[9] (entry **e**) or either obtained as Duboudin adducts on propargylalcohol[10] (entry **d** and **i**). c) Determined on crude ^1H NMR. d) 1,2 addition products were not detected. e) Yields determined on crude ^1H NMR ; Yields in parenthesis refer to flash chromatography purified product, as an inseparable mixture of *E* and *Z* isomers. f) *E* and *Z* isomers were identified by NOESY experiment. g) Pure *Z* isomer. h) Yields of γ-1,4 and α-1,4 adducts.

In conclusion, we have shown that methoxyallylcopper reagents substituted in α and/or β position of oxygen added with total γ-1,4 regioselectivity to MVK. The resulting ketoenolethers obtained in good yields (except for volatile ones) were equivalent to disymmetric 1,6-dicarbonyl compounds having one of their two carbonyl functions protected as methylvinylether. In contrast, γ-substituted methoxyallylcopper reagents added on MVK with poor γ-1,4 / α-1,4 regioselectivity.

Acknowledgements

We thank Dr. Jacqueline Mahuteau and Mrs. Sophie Mairesse-Lebrun for valuable assistance on NMR study and elemental analysis.

References

1. For reviews, see: (a) Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205-268. (b) Crimmins, M. T.; Nantermet, P. G. *Org. Prep. Proced. Int.* **1993**, *25*, 41-81.
2. Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560-5561.
3. (a) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242-2244. (b) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1982**, *47*, 2498-2500. (c) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535-1538. (d) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263-5266. (e) Fukuzawa, S.-I.; Sakai, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3308-3314. (f) Marshall, J. A.; Jablonowski, J. A.; Welmaker, G. S. *J. Org. Chem.* **1996**, *61*, 2904-2907.
4. Berrien, J.-F.; Raymond, M.-N.; Moskowitz, H.; Mayrargue, J. *Tetrahedron Lett.* **1999**, *40*, 1313-1314.
5. Schlosser, M.; Strunk, S. *Tetrahedron* **1989**, *45*, 2649-2664.
6. (a) Enda, J.; Matsutani, T.; Kuwajima, I. *Tetrahedron Lett.* **1984**, *25*, 5307-5310. (b) Enda, J.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 5495-5501.
7. Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349-362.
8. Tzeng, D.; Weber, W. P. *J. Org. Chem.* **1981**, *46*, 693-696.
9. Georgoulis, C.; Smadja, W.; Ville, G. *Bull. Soc. Chim. Fr.* **1984**, *7-8*, 269-270.
10. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.
11. Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1-11.
12. Gupton, J. T.; DiCesare, J.; Brown, J. *Synth. Commun.* **1989**, *19*, 1413-1422.
13. (a) Whitham, G. H.; Wright, M. *J. Chem. Soc. (C)* **1971**, 891-896. (b) Still, W. C. *Tetrahedron Lett.* **1976**, *25*, 2115-2118. (c) Bailey, W. F.; Jiang, X.-L. *J. Org. Chem.* **1994**, *59*, 6528-6533.