Pergamon

Tetrahedron Letters 42 (2001) 4281–4283

TETRAHEDRON
LETTERS

A study of conjugate addition to a γ,δ-dioxolanyl-α,β-unsaturated ester[†]

Guoxia Han and Victor J. Hruby*

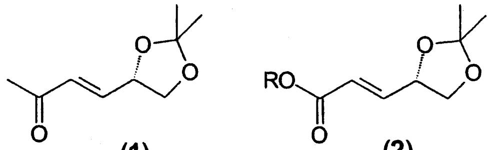
Department of Chemistry, University of Arizona, Tucson, AZ 85721, USA

Received 23 January 2001; revised 27 April 2001; accepted 30 April 2001

Abstract—Diastereoselective phenylcuprate addition to (*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-*trans*-2-propenoate has been achieved in the presence of lithium bromide, copper(I) cyanide, trimethylsilyl chloride and dimethylsulfide cocatalysts. © 2001 Elsevier Science Ltd. All rights reserved.

In the past, relatively few γ-oxygen substituted α,β-unsaturated compounds have been utilized as substrates for conjugate addition reactions. Perhaps the most studied substrates are **1** and **2** (Fig. 1) which are derived from glyceraldehyde acetonide.

Oxygen at the γ-position makes the β-carbon much less electrophilic, and thus these molecules are poor substrates for conjugate additions.[1] A number of modified structures have been studied, such as γ-oxygen substituted α,β-unsaturated ketones,[2] which work well for these conjugate addition reactions. However, when γ-oxygen substituted α,β-unsaturated esters are used as substrates, only limited success has been realized, and the reaction completely failed with a phenyl nucleophile.[1,3] Since these compounds could be useful precursors in further synthetic transformations such as amino acid synthesis, we decided to find condition(s) which can be applied to conjugate addition reactions with poor substrates such as methyl (*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-*trans*-2-propenoate (**3**)—a γ,δ-oxygen substituted α,β-unsaturated ester.



(1) **(2)**

Figure 1. Substrates with γ,δ-oxygen used for conjugate addition reactions.

All of our initial attempts to solve the problem (Eq. (1)) using known techniques and/or additives, such as dimethyl sulfide,[4,5] TMSCl,[6–9] and TMEDA[10,11] were unsuccessful (entries 1–6, Table 1).

After all these failed attempts, we went back to examine other copper reagents which might promote the conjugate addition. It was decided to evaluate relatively stable copper reagents made from copper(I) bromide complexed with dimethyl sulfide. If these copper reagents could promote the reaction, we postulated that the addition of TMSCl should make the substrate **3** (entry 7, Table 1) more reactive toward conjugate addition.[11] At −78°C, the conjugate addition did take place and, the substrate was completely consumed and converted almost quantitatively to the desired conjugate addition adduct based on gas chromatography–mass spectrometry (GC–MS) results. However, the de of the major product **4** was only 74% (Table 1).

To improve the de, we investigated the use of lithium bromide[12–14] (entry 10, Table 1) with the substrate (**3**). Interestingly, the yield (80% estimated by GC–MS, 73.7% after flash column purification) was lower compared to the reaction without LiBr. However, the diastereoselectivity was improved dramatically to >92% by GC–MS. Only one diastereoisomer, **4**, could be isolated. We then decided to evaluate whether any additive could be eliminated and still allow the conjugate addition to take place. When using LiBr with

---

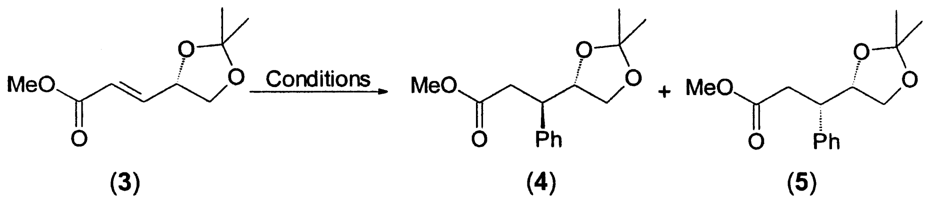
Keywords: conjugate addition; difficult reactions; copper reagents; copper(I) bromide dimethylsulfide complex; copper(I) cyanide (CuCN); trimethylsilyl chloride (TMSCl); α,β-unsaturated substrates with oxygen substitution at γ,δ-positions.

* Corresponding author. Tel.: (520) 621-6332; fax: (520) 621-8407; e-mail: hruby@u.arizona.edu

[†] Preliminary results were presented at the 1998 Fall ACS meeting.

PII: S0040-4039(01)00719-5

Table 1. Conjugate addition from PhMgBr



(1)

Entry	Reagent	Additives[a]	Temp. (°C)	de[b] (%)	Yield[b] (%)
1	PhMgBr	CuI	−78		0[b]
2	PhMgBr	CuI/TMSCl (1:1)	−78		0[b]
3	PhMgBr	CuBr·Me$_2$S/Me$_2$S (1:1)	−78 or −100		0[b]
4	PhMgBr	CuBr·Me$_2$S/Me$_2$S (1:1)	−23		0[b]
5	PhMgBr	TMSCl	−78		0[b]
6	PhMgBr	TMEDA	−78		0[b]
7	PhMgBr	CuBr·Me$_2$S/Me$_2$S/TMSCl (1:1:1)	−78	74	100[b]
8	PhMgBr	CuCN/TMSCl (1:1)	−23 to rt	78 (85[c])	100[b] (80[c])
9	PhMgBr	CuCN/TMEDA (1:1)	−78		0[b]
10	PhMgBr	CuBr·Me$_2$S/Me$_2$S/TMSCl/LiBr (1:1:1:1)	−78	92 (>95[c])	80[b] (73.7[c])
11	PhMgBr	TMEDA/TMSCl (1:1)	−78		0[b]

[a] Results were almost the same when additives were used in 0.1, 1 or 1.2 equiv.

[b] Estimated results from GC–MS (based on the integration of GC peaks for **3**, **4** and **5**).

[c] Results from RP–HPLC (Vydac C18 column) or separation.

PhMgBr (Fig. 2) the 1,2-adduct **7** was obtained when the reaction was run at higher temperatures (–40°C to rt). On the other hand, when using CuBr·Me$_2$S/TMSCl/LiBr without Me$_2$S as a coadditive, a Claisen condensation accompanied the conjugate addition, and gave compound **6** as the only product. Further study is needed to understand this reaction.

It has been reported that copper cyanide (CuCN)[5,16–20] can improve conjugate addition reactions. When CuCN was used alone, there was none of the desired product even after a long extension of the reaction time. However, when a catalytic amount of TMSCl was used in conjunction with CuCN (entry 8, Table 1), the reaction went to completion rapidly. All of the starting material **3** was converted to the desired products with a small improvement in the de (78–85%) compared with the de (74%) when CuBr·Me$_2$S/Me$_2$S/TMSCl was used Eq. (1). On the other hand, by adding a Lewis base, TMEDA, along with CuCN, we were not able to detect any of the desired products (entry 9, Table 1).

The diastereoselectivity of the major product **4** was analyzed by ^{1}H NMR. By bubbling pure HCl gas into the methanolic solution of compound **4**, the lactone bridge was formed rapidly, and the cyclic compound **8** was obtained in quantitative yield (Scheme 1). Rotary evaporation of all the solvents gave the product. The large coupling constant ($J_{4,5}=12.81$ Hz) between the protons at positions 4 and 5 indicate that they are in *anti* positions.[21] Hence, phenyl copper reagents in our study attack the less sterically hindered side of the substrate **3**. Consequently, an *R* chiral center in position 3 of the product **4** was obtained (for experimental procedure, see Ref. 22). When LiBr was used as a coadditive, the significant increase in diastereoselectivity might be attributed to chelation between the γ-position substituted oxygen and the oxygen at the ester functional group. Such chelation would enhance the diastereofacial bias of the substrate, resulting in a more selective attack of the nucleophile from the less hindered side. Consequently, a higher diastereoselectivity (de 92%) was achieved. Further study is necessary to

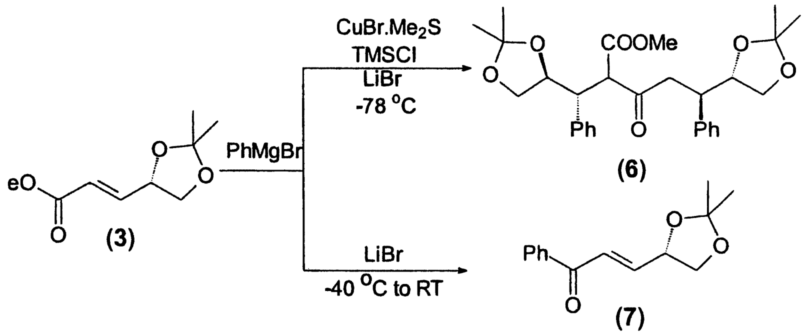
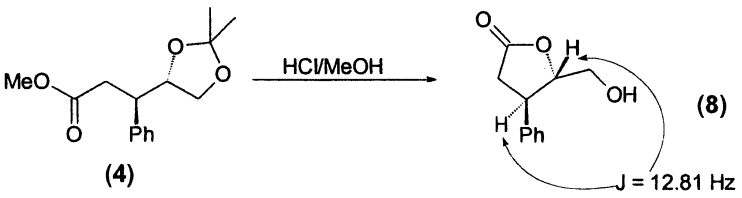


Figure 2. Conjugate addition followed by Claisen condensation.



Scheme 1. Determination of diastereoselectivity for product **4**.

rationalize the role of LiBr in this conjugate addition and to investigate the mechanism of the reaction, the diastereoselectivity and further applications.

Acknowledgements

We would like to thank Dr Steven H. Bertz and Dr Jon Rainier for helpful discussions. This research was supported in part by grants from the USPHS DK17420 and DA06284. Views expressed are those of the authors and are not necessary those of the USPHS.

References

1. Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Swain, P. A. *Tetrahedron* **1995**, *51*, 12843–12858.
2. Raczko, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3821–3828.
3. Yechezkel, T.; Ghera, E.; Ramesh, N. G.; Hassner, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2423–2436.
4. Hon, Y. S.; Chen, F. L.; Huang, Y. P.; Lu, T. J. *Tetrahedron: Asymmetry* **1991**, *2*, 879–882.
5. Wipf, P.; Xu, W.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1994**, *50*, 1935–1954.
6. Afarinkia, K.; Binch, H. M.; Modi, C. *Tetrahedron Lett.* **1998**, *39*, 7419–7422.
7. Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023–11024.
8. Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288–3295.
9. Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087–7090.
10. Van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Steenkamp, J. A.; Ferreira, D. *Tetrahedron Lett.* **1992**, *33*, 2383–2386.
11. Taylor, R. J. K. *Organocopper Reagents–A Practical Approach*; Oxford University Press, 1994; p. 362.
12. Zhao, S. K.; Helquist, P. *Tetrahedron Lett.* **1991**, *32*, 447–448.
13. Bertz, S. H.; Dabbagh, G.; Cook, J. M.; Honkan, V. *J. Org. Chem.* **1984**, *49*, 1739–1743.
14. Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411–4417.
15. Tamura, R.; Watabe, K.; Ono, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 4895–4903.
16. Tamaru, Y.; Tanigawa, H.; Yamamoto, T.; Yoshida, Z. *Angew. Chem.* **1989**, *101*, 358–360.
17. Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5425–5431.
18. Bhatt, R. K.; Ye, J.; Falck, J. R. *Tetrahedron Lett.* **1996**, *37*, 3811–3814.
19. Dieter, R. K.; Velu, S. E. *J. Org. Chem.* **1997**, *62*, 3798–3799.
20. Wendisch, V.; Sewald, N. *Tetrahedron: Asymmetry* **1997**, *8*, 1253–1257.
21. Costa, J. S.; Dias, A. G.; Anholeto, A. L.; Monteiro, M. D.; Patrocinio, V. L.; Costa, R. R. *J. Org. Chem.* **1997**, *62*, 4002–4006.
22. A representative experimental procedure is summarized here for the preparation of **4** by conjugate addition: Freshly distilled THF (15 mL) was added to a 100 mL round bottom flask under Ar. After the flask was cooled by an ethylene glycol–dry ice bath, CuCN (0.25 g, 2.8 mmol, 0.1 equiv.) and **3** (5.0 mL, 5.4 g, 29.0 mmol) were added sequentially. The mixture was stirred for 10 min before TMSCl (0.35 mL, 0.30 g, 2.8 mmol, 0.1 equiv.) was added via a syringe under Ar. After 25 min stirring, PhMgBr (12 mL, 3.0 M in Et_2O from Aldrich, 36 mmol, 1.2 equiv.) was added dropwise over a period of 30 min. Upon the completion of the addition of PhMgBr, the cooling bath was removed and the reaction mixture was stirred for another 3 h at rt. Gas chromatograph (GC) results indicated that the starting material **3** completely disappeared. Then the reaction was quenched by the addition of aqueous saturated NH_4Cl solution (10 mL). After workup, the product **4** was obtained by flash chromatograph as a thick colorless oil, which became a waxy solid after a long stand at rt, yield: 80%. Spectra of **4**: ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.36–7.14 (5H, m), 4.28–4.18 (1H, m), 3.78–3.70 (1H, dd), 3.62–3.50 (4H, m), 3.30–3.16 (1H, m), 3.10–3.00 (1H, dd), 2.74–2.60 (1H, dd), 1.46 (3H, s), 1.34 (1H, s). FAB-MS: calcd for $C_{15}H_{20}O_4$, 264.1; found: *m*/*e* 265.1 [$M+H^+$].