Pergamon

Tetrahedron Letters 41 (2000) 5583–5587

TETRAHEDRON LETTERS

Intermolecular [3+2] MIRC reactions with alkynoates. Asymmetric Michael addition leading to a nonracemic cyclopentene-annulated α,β-butenolide†[1]

Philippe Nakache, Eugene Ghera* and Alfred Hassner*

Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel

Received 27 March 2000; accepted 23 May 2000

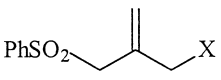
Abstract

A novel Michael-initiated ring closure reaction involving allylic chlorosulfone (**2**) and γ-alkoxy-α,β-ynoates to afford 4-methylenecyclopentenecarboxylates is reported, while with γ-alkylynoates no reaction occurred. With chiral phenyl ynoates **4**, the reaction proceeds by 1,3-asymmetric induction and leads further to a nonracemic annulated α,β-butenolide (**7**). © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Michael reactions; cyclopentenecarboxylates; butenolides; asymmetric induction; lithium ion chelation.

The emergence of widespread targets containing five-membered carbon rings, such as quinane terpenes, has led to continuous interest in new pentannulation strategies. Among the [3+2] disconnections leading to cyclopentanes, utilization of trimethylenemethane (TMM) equivalents as the three-carbon units have been extensively used.[2] Within this context, the intermolecular Michael-initiated ring closure (MIRC) reaction was effectively utilized for the regio- and stereoselective synthesis[3] as well as the asymmetric synthesis[4] of methylenecyclopentanes.

Limited success, however, was achieved in the application of intermolecular [3+2] schemes involving acetylenic acceptors to obtain 4-methylenecyclopentenes. Using mainly methylenecyclopropanes as the TMM synthons, such routes were of limited scope[5] or presented experimental restrictions.[6] The Pd-complexed TMM species, successful in cycloadditions with olefins, failed when applied to acetylene acceptors.[7]



1: X = H; **2**: X = Cl; **3**: X = Br

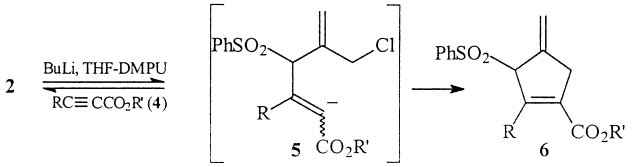
* Corresponding authors. Fax: +972-3-5351250; e-mail: hassna@mail.biu.ac.il

† Dedicated to Professor Richard Neidlein on the occasion of his 70th birthday.

PII: S0040-4039(00)00867-4

We report herein the synthesis of 4-methylenecyclopentenes by a simple MIRC route from 2-(chloromethyl)-3-phenylsulfonyl-1-propene (**2**)[8] (as the TMM synthon) and readily available γ-alkoxy-α,β-alkynoates **4**. The results are summarized in Table 1.[9] By contrast, we found that in the absence of oxygen substitution at C-4, the γ-alkylated or arylated ynoates do not undergo addition of lithiated allylic sulfones **1**–**3**.[10,11] Formation of open-chain adducts, via protonation of the reversible intermediate **5**, was not observed. The use of phenyl instead of ethyl ynoates resulted mostly in improved yields and better diastereoselectivity (entries 7 and 8, Table 1). Moreover, the nonracemic (*S*)-ethyl ynoate **4j**,[12] afforded with **2** a 1:1 stereomeric mixture of cyclopentenecarboxylates (**6j**), whereas the corresponding phenyl ester **4k** gave under the same conditions a single diastereoisomer **6k** (entries 10 and 11).[13] This 1,3-asymmetric induction resulting from conjugate addition to a chiral ynoate may be attributed to a preferred facial approach due to additional chelation between the Li cation and the aryl group of the ester. The effect of aryl–Li ion chelation on remote asymmetric induction has recently been reported by us.[14] Utilization of a bulky, nonaromatic ester (**4l**) resulted in a 1:1 stereomeric mixture of cyclopentenes (**6l**, entry 12), thus eliminating the steric factor as accounting for the stereoselective formation of **6k**.

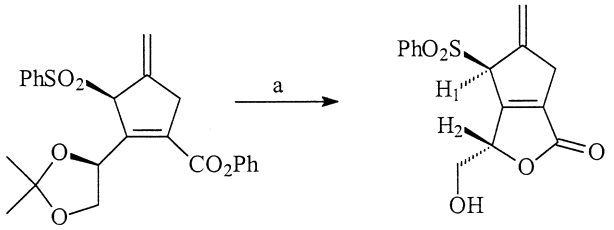
Table 1
[3+2] MIRC reaction of chlorosulfone **2** with ynoates **4**



entry		alkynoates	product	% yield[a]	dr[b]
1	**4a**	R=CH_2OTBS; R'=Et	**6a**	48	
2	**4b**	R=CH_2OTBS; R'=Ph	**6b**	58	
3	**4c**	R=CH_2OCH_2OEt; R'=Et	**6c**	60	
4	**4d**	R=CH_2OCH_2OEt; R'=Ph	**6d**	67	
5	**4e**	R=CH_2OMe; R'=Et	**6e**	53	
6	**4f**	R=CH_2OMe; R'=Ph	**6f**	64	
7	**4g**	R=$CH(CH_3)OTBS$; R'=Et	**6g**	47	50:50
8	**4h**	R=$CH(CH_3)OTBS$; R'=Ph	**6h**	57	80:20
9	**4i**	R=$CH(OTBS)CH_2CH_2OTBS$; R'=Et	**6i**	30	
10	**4j**	R=  ; R'=Et	**6j**	42	50:50
11	**4k**	R=  ; R'=Ph	**6k**	44	>99:1
12	**4l**	R=  ; R'=$CH(CH_3)_2$	**6l**	41	45:55

[a]isolated products which were characterized by ^1H, ^{13}C NMR spectroscopy and by HRMS.
[b]diastereomeric ratio

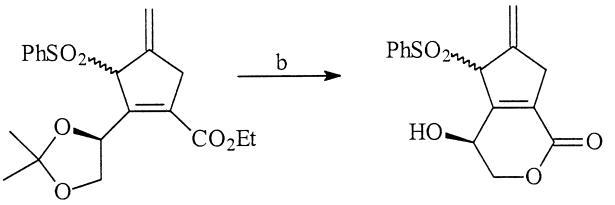
Acid treatment of phenyl ester **6k** afforded the α,β-butenolide **7** in which the given stereochemistry is based on NOE measurements (Eq. (1)).[15] By contrast, the less strained unsaturated δ-lactones **8** were obtained from the diastereomeric ethyl esters **6j** (Eq. (2)).[16] The kinetic preference for the formation of **7** rather than of δ-lactones **8** may be due to the better leaving (phenoxy) group in **6k**.



(1)

6k **7**

(a) TFA cat, MeOH, rt, 5h, 85%; utilization of p-TSA-MeOH gave **7** containing 10% of **8**

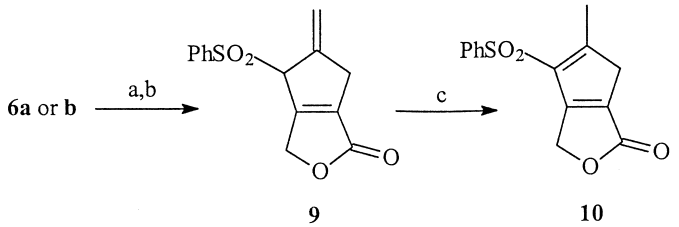


(2)

6j **8**

(b) p-TSA, MeOH, rt, 3h, 89%

The cyclopentenation route provides an entry to annulated α,β-butenolides such as **9**, which, on exposure to an aqueous base, can be converted to an annulated cyclopentadiene **10** (Eq. (3)).[17]



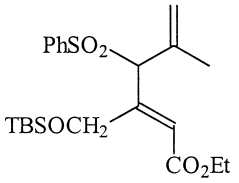
(3)

9 **10**

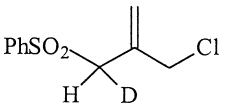
(a) 2N HCl, THF, rt, 4h; (b) p-TSA cat, benzene, reflux, 2h, 89% yield over two steps.
(c) Na_2CO_3 aq, THF, rt, 1h, >95%.

It is noteworthy that lithiated methallyl sulfone **1** reacted more effectively than chlorosulfone **2** with γ-oxygenated ynoates and afforded 82% of 1:1 conjugate adducts (30 min, –60°C), including an isolated 53% of **11** arising from *cis* addition of the organometallic to the double bond. Though lithiated **1** underwent chloride displacement with methallyl chloride, it led solely to proton transfer when exposed to chloroallylsulfone **2**, to afford **12** and **1** upon D_2O quenching. The

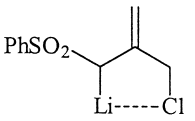
higher stability of the lithio derivative of **2** is attributed to Li–Cl coordination (**A**), hence its lower reactivity in conjugate additions.[18]



11



12



(A)

In conclusion, the coordination between the γ-alkoxy group of ynoates **4** and the Li cation has proven critical for successful MIRC reaction utilizing the lithiated allyl sulfone **2**, presumably by displacement of the equilibrium toward **5**, thus promoting the ring closure. Additional coordination of the lithium cation with the aromatic group of the ester in **4** contributes to the stereoselectivity of the conjugate additions.

Acknowledgements

The authors wish to thank the US–Israel Science Foundation and the Marcus Center for Pharmaceutical and Medicinal Chemistry at Bar-Ilan University for financial support, and Dr. Hugo E. Gottlieb for his valuable help in NMR analysis.

References

1. Stereochemistry. Part 91. For part 90 see: Gottlieb, L.; Hassner, A. *Synth. Commun.* **2000**, in press.
2. For reviews, see: Chan, D. M. T. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp. 287–313; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 1457.
3. Ghera, E.; Yechezkel, Y.; Hassner, A. *J. Org. Chem.* **1996**, *61*, 4959, and references cited therein.
4. Yechezkel, T.; Ghera, E.; Hassner, A. *Tetrahedron: Asymmetry* **1996**, 2422.
5. Binger, P.; Buch, H. M. *Top Curr. Chem.* **1987**, *135*, 77; Binger, P.; Lu, Q.-H.; Wedemann, P. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 316.
6. Yamago, S.; Ejiri, S.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2154; see also: van der Louw, J.; van der Baan, F.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Lett.* **1987**, *28*, 2889.
7. Trost, B. M.; Balkovek, J. M.; Angle, S. R. *Tetrahedron Lett.* **1986**, *27*, 1445.
8. Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1987**, *28*, 6053.
9. In a typical experiment, BuLi in hexane (1.2 mmol) was added to a stirred solution of **2** (1.3 mmol) in anhydrous THF (4 ml) and DMPU (1 ml) under argon, at –78°C; After 15 min the alkynoate (**4**, 1 mmol in 1 ml THF) was added and stirring of the mixture continued at –60°C for about 4 h and the reaction was quenched (aqueous NH_4Cl) after all the alkynoate reacted (TLC). The crude product, after extraction with ether, was rapidly filtered via a short silica column (ethyl acetate–ether) to separate unreacted **2** and the polymerized polar material and then purified by silica gel (flash) chromatography (petroleum ether–ethyl acetate).
10. Reaction of **2** with unsubstituted ethyl propiolate afforded, however, the open-chain adduct; see also: Alonso, D. A.; Flavello, L. R.; Mancheno, B.; Najera, C.; Tomas, M. *J. Org. Chem.* **1996**, *61*, 5004.
11. Stabilized carbanions are poor donors for intermolecular Michael reactions with γ-alkyl or aryl ynoates unless the adduct intermediate is trapped by strong electrophiles: see, e.g.: Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p. 41; Bury, A.; Joay, S. D.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1986**, 124.

12. For the preparation of a similar ester, see: Boeckman, R. K.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1991**, *113*, 5337.
13. Data for **6k**: mp = 117°C; $[\alpha]_D = -69.3$ ($c = 1.5$, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) $\delta = 1.41$ (s, 3H), 1.63 (s, 3H), 3.19 (dq, $J = 18.2$, 2.4 Hz, 1H), 3.29 (d, $J = 19.3$ Hz, 1H), 4.26 (dd, $J = 7.20$, 7.10 Hz, 1H), 4.47 (t, $J = 7.19$ Hz, 1H), 4.71 (s, 1H), 5.12 (s, 2H), 5.52 (t, $J = 7.1$ Hz, 1H), 7.05–7.13 (m, 2H), 7.26 (m, 1H), 7.42 (m, 2H), 7.57 (m, 2H), 7.66–7.71 (m, 1H), 7.86–7.89 (m, 2H).
14. Ghera, E.; Kleiman, V.; Hassner, A. *J. Org. Chem.* **1999**, *64*, 8; for subsequent similar observations, see: Juaristi, E.; Leon-Romo, J. L.; Ramirez-Quiros, Y. *J. Org. Chem.* **1999**, *64*, 2914; Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 7050.
15. Data for **7**: mp = 81°C; $[\alpha]_D^{20} = -70$ ($CHCl_3$); IR (film): 1636, 1756 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.68 (d, $J = 20$ Hz, 1H), 3.07 (dq, $J = 20$, 2 Hz, 1H), 3.98 (dd, $J = 12.5$, 3.8 Hz, 1H), 4.07 (dd, $J = 12.5$, 3.8 Hz, 1H), 5.02 (m, 1H), 5.39 (m, 1H), 5.43 (m, 1H), 5.50 (m, 1H), 7.56 (m, 2H), 7.71 (m, 1H), 7.79 (m, 2H); ^{13}C NMR: δ 31.68, 61.20, 73.09, 81.07, 118.96, 129.17, 129.72, 134.73, 134.87, 135.30, 142.94, 143.21, 163.21; NOE: strong interaction for H_1–CH_2OH, very weak for H_1–H_2.
16. Data for **8**: IR: 1722 cm^{-1}; The ^{13}C NMR spectrum (600 MHz, $CDCl_3$) exhibits a long range interaction between the C=O group (δ 161.1) and one of the protons of the oxymethylene group (δ 4.56) which is missing in the spectrum of **7**; other spectral data agree with the given structure.
17. Data for **9**: ^1H NMR (300 MHz, $CDCl_3$: δ 2.60 (d, $J = 10$ Hz, 1H), 3.10 (d, $J = 10$ Hz, 1H), 5.02 (m, 2H), 5.16 (d, $J = 9$ Hz, 1H), 5.44 (s, 1H), 5.53 (s, 1H), 7.52–7.57 (m, 2H), 7.68–7.78 (m, 3H); ^{13}C NMR: δ 31.80, 69.37, 73.52, 77.00, 118.98, 128.28, 128.43, 134.72, 135.07, 142.06, 143.09, 162.96. MS: 294 (MNH_4^+, 227 (MH^+). Compound **10**: ^1H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H), 3.44 (t, $J = 3.1$ Hz, 2H), 5.10 (t, $J = 3.1$ Hz, 2H), 7.58–7.94 (m, 5H).
18. In contrast with the well-known effects of Li cation coordination with heteroatoms, the influence of Li–Cl coordination was not sufficiently explored; see, however: Gschwend, H. W.; Rodriguez, H. R. In *Org. Reactions*; Vol. 26, 1979; pp. 74–75; Najera, C.; Sansano, J. M. *Tetrahedron Lett.* **1992**, *33*, 6543. For an example of F–Li coordination effects, see: Gilday, J. P.; Widdowson, D. A. *Tetrahedron Lett.* **1986**, *27*, 5525. We are indebted to Prof. G. H. Posner for valuable comments.