Tetrahedron Letters, Vol. 33, No. 20, pp. 2863-2866, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Divergent Stereoselective Synthesis of *(E)* and *(Z) O*-Alkyl Enol Ethers

Lluís Solà, Jaume Castro, Albert Moyano*, Miquel A. Pericàs* and Antoni Riera.

Departament de Química Orgànica, Universitat de Barcelona, Martí i Franquès 1-11, 08028 Barcelona, Spain.

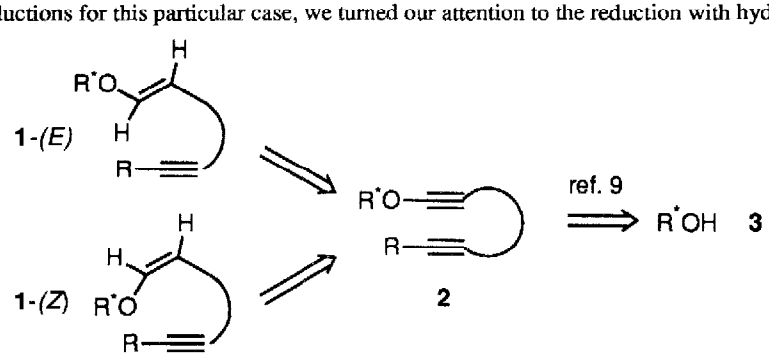
Key Words: Acetylenic Ethers, *O*-Alkyl Enol Ethers, Stereoselective Reduction.

Abstract: *While the reduction of alkynyl ethers with lithium aluminum hydride (or with sodium bis(2-methoxyethoxy) aluminum hydride) gives almost exclusively O-alkyl enol ethers with (E) configuration, the reaction with sodium bis(2-methoxyethoxy) aluminum hydride pretreated with one equivalent of a free alcohol leads stereoselectively to enol ethers with (Z) configuration.*

Enantiopure *O*-alkyl enol ethers are evolving as very promising chiral educts for asymmetric synthesis and have been employed in asymmetric versions of Diels-Alder reactions,[1] ketene[2] and isocyanate[3] [2+2] cycloadditions, Bradsher cycloadditions,[4] 1,3-dipolar cycloadditions[5] and tandem [4+2]/[3+2] cycloadditions.[6] Two characteristics are in general required for these applications: satisfactory enantiofacial discrimination provided by appropriate chiral *O*-alkyl groups and strict control of double bond geometry. Despite their promise, there are very few generally applicable methods for the *stereoselective synthesis* of acyclic enol ethers,[7,8] in particular for those bearing chiral *O*-alkyl groups.[7a]

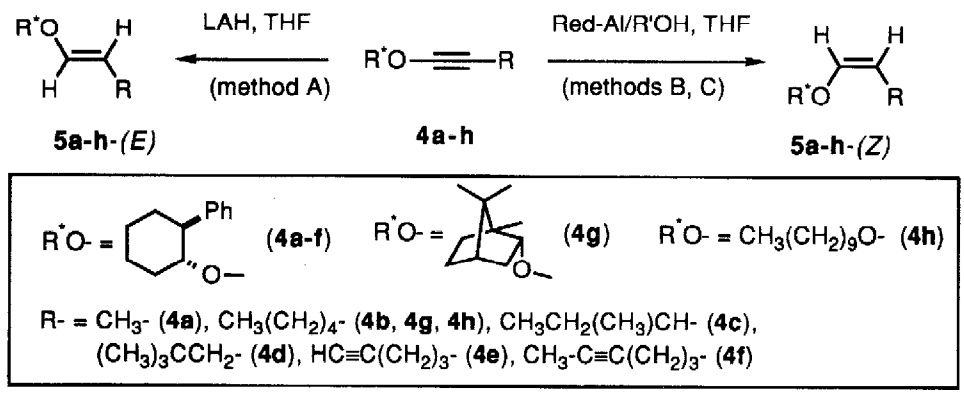
The present general availability[9] of chiral acetylenic ethers renders these substances excellent starting materials for the preparation of chiral enol ethers through reduction protocols. Common methodology for partial stereoselective reduction of triple bonds (*i. e.*, Birch-type reduction for (*E*)-stereoisomers or Lindlar hydrogenation for (*Z*)-stereoisomers)[10] should prove applicable in many instances, but none of these methods would allow the chemoselective reduction of an acetylenic ether in the presence of another electron-rich triple bond.

We were, in fact, faced with this problem in connection with a program on asymmetric Pauson-Khand bicyclizations,[11] for which the preparation of a number of chiral alkoxyenynes with general structures **1**-*(E)* and **1**-*(Z)* was required (Scheme 1). A most direct entry to these systems would involve the chemo- and stereoselective reduction of the readily available[9] alkoxydiynes **2**. In view of the unsuitability of usual triple to double bond reductions for this particular case, we turned our attention to the reduction with hydridoaluminates.



Scheme 1

We report in the present communication the results of a systematic study on the reduction of alkynyl ethers with hydridoaluminates (See Scheme 2 and Table I), showing that either (*E*)- or (*Z*)-enol ethers can be stereoselectively obtained by appropriate selection of reaction conditions.



Scheme 2

TABLE I. DIASTEREOSELECTIVE REDUCTION OF ALKOXYACETYLENES WITH HYDRIDOALUMINATES.

Alkoxyacetylene[a]	Method[b]	Enol Ether	Yield[c,d]	*(E)* / *(Z)* [d]
4a	A	**5a**	75%(83%)	94:6(94:6)
4a	B	**5a**	70%	50:50
4a	C	**5a**	84%	<5:95[e]
4b	A	**5b**	70%(72%)	>95:5[e](>95:5[e])
4b	B	**5b**	68%	20:80
4b	C	**5b**	62%	<5:95[e]
4c	A	**5c**	71%	>95:5[e]
4c	B	**5c**	83%	5:95
4c	C	**5c**	80%	7:93
4d	A	**5d**	80%	>95:5[e]
4d	B	**5d**	43%	<5:95[e]
4d	C	**5d**	72%	<5:95[e]
4e	A	**5e**	40%(77%)	>95:5[e](91:9)
4e	B	**5e**	93%	<5:95[e]
4f	A	**5f**	55%	>95:5[e]
4f	B	**5f**	70%	<5:95[e]
4g	A	**5g**	92%	>95:5[e]
4g	B	**5g**	78%	13:87
4g	C	**5g**	72%	62:38
4h	A	**5h**	79%	>95:5[e]
4h	B	**5h**	76%	8:92
4h	C	**5h**	86%	66:34

[a]The acetylenic ethers were prepared according to the procedures described in ref. 9, except for **4d**, which was obtained by the method outlined in ref. 17a. [b]Method A: 4eq. LAH, THF, reflux, 4h. Method B: 8eq. Red-Al®, 8eq. *trans*-2-phenylcyclohexanol or *t*-butyl alcohol, THF, reflux, 6h. Method C: 8eq. Red-Al®, 8eq. MeOH, THF, reflux, 6h.[c]Yield of product isolated after chromatographic purification. [d]The values in parenthesis refer to results obtained when Red-Al® was used instead of LAH. [e]A single diastereomer was detected by NMR.

The reduction of simple acetylenic ethers with lithium aluminum hydride has received little attention in the literature. It is known, however, that ethoxyacetylene is reduced by this reagent much more easily than simple alkynes and in a stereoselective fashion.[12] The results summarized in the Table represent the first systematic investigation of this process, and clearly demonstrate its generality. Irrespectively of the steric bulk of either the alkoxy group or the alkyl substituent of the triple bond, *(E)*-*O*-alkyl enol ethers **5** are always produced with good to excellent yields and with essentially complete diastereoselectivity (method A in the Table) when the corresponding acetylenic ether **4** is heated to reflux in a THF suspension of 4 equivalents of lithium aluminum hydride.[13] As shown in the Table, essentially the same results can be achieved by using sodium bis(2-methoxyethoxy) aluminum hydride (Red-Al®) in refluxing THF.

On the other hand, and most gratifyingly, we subsequently discovered that when the reduction is effected with a complex hydride reagent generated by the prior addition of one equivalent of a hindered alcohol (*tert*-butyl alcohol or (±)-*trans*-2-phenylcyclohexanol) to a refluxing THF solution of Red-Al® (method B in the Table), we obtained stereoselectively in most instances (the only exception being the propynyl ether **4a** and to a lesser extent the heptynyl ether **4b**) *O*-alkyl enol ethers of *(Z)*-configuration with stereochemical purity greater than 90:10. It is interesting to observe that the steric bulk of the added alcohol is not a primary factor in the stereoselectivity of the reduction, since the use of one equivalent of methanol (method C in the Table), while leading in some cases (**4g**, **4h**) to increasing amounts of *(E)*-isomers, in others (**4a**, **4b**) has a beneficial effect on the stereoselectivity of the process. In fact, by judicious choice of the added alcohol all of the alkynyl ethers **4a-h** can be reduced to the *(Z)*-enol ether.[14]

Although the mechanisms of these useful transformations may well be rather complex, the reductions with lithium aluminum hydride or Red-Al® alone could be explained by a *trans*-hydroalumination involving a nucleophilic hydride attack at the α-position of the alkoxyacetylene, while the *cis*-selectivity obtained with the Red-Al®/R'OH reagents could be the result of preferential *cis*-hydroalumination by means of a bis(alkoxy)alane[15] produced by dismutation of the initially formed tris(alkoxy)aluminum hydride.[16]

In summary, alkoxyacetylenes can be efficiently and stereoselectively reduced either to *(E)* or *(Z)* *O*-alkyl enol ethers by appropiate choice of hydridoaluminate reagents. In the case of diynes **2**, the reaction is also completely chemoselective (see entries **4e** and **4f** in the Table), and provides access to the chiral alkoxyenynes **1** with the desired (either *(E)* or *(Z)*) stereochemistry of the double bond[11a]. Due to the easy availability of alkoxyalkynes,[9] the present methodology appears to be the method of choice for the stereoselective synthesis of 2-substituted enol ethers.

Acknowledgments. We thank the DGICYT (Grant PB89-0255) for financial support, and Dr. Andrew E. Greene (Université Joseph Fourier de Grenoble) for helpful discussions. The technical assistance of Dr. Miguel Feliz in the recording of NMR spectra is also gratefully acknowledged.

REFERENCES AND NOTES

1. a) Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett* **1986**, *27*, 667-670. b) Posner, G. H.; Wettlaufer, D. G.*J. Am. Chem. Soc.* **1986**, *108*, 7373-7377 c) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.***1986**, *108*, 7060-7067 d) Bäckvall, J.-E.; Rise, F.. *Tetrahedron Lett* **1989**, *30*, 5247-5348. e) Gupta, R. C.; Slawin, A. M. Z.; Stoodley, R. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1986**, 668-670 f) Thiem, R.; Rotscheidt, K.; Breitmaier, E. *Synthesis* **1989**, 836-843.

2. a) Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525-5529. b) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752-4753.

3. Kaluza, Z.; Fudong, W.; Belzecki, C.; Chmielewski, M. *Tetrahedron Lett.* **1989**, *30*, 5171-5172

4. Choudhury, A.; Franck, R. W.; Gupta, R. B. *Tetrahedron Lett.* **1989**, *30*, 4921-4924.

5. a) RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458-5461. b) Carruthers, W.; Coggins, P.; Weston, J. B. *J. Chem. Soc., Chem. Commun.* **1991**, 117-118.

6. Denmark, S. E.; Senanayake, C. B. W.; Ho, G.-D. *Tetrahedron* **1990**, *46*, 4857-4876.

7. For general references on the synthesis of *O*-alkyl enol ethers, see: a) Charbonnier, F.; Moyano, A.; Greene,

A. E. *J. Org. Chem.* **1987**, *52*, 2303-2306. b) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410-4412. c) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 235-239, and references cited therein.

8. For recent (nonstereoselective) synthesis of acyclic *O*-alkyl enol ethers, see: a) Julia, M.; Uguen, D.; Verpeaux, J.-N.; Zhang, D. *Synlett* **1991**, 505-506. b) Katritzky, A. R.; Bayyuk, S. I.; Rachwal, S. *Synthesis* **1991**, 279-283. c) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757-5761.

9. Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919-2922.

10. For reviews on the reduction of alkynes, see: a) Dickstein, J. J.; Miller, S. I. In *The Chemistry of the Carbon-Carbon Triple Bond.* ; Patai, S., Ed.; John Wiley: Chichester, 1978; pp. 843-853. b) Gutmann, H.; Lindlar, H. In *Chemistry of Acetylenes* ; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp. 355-364.

11. a) Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388-9389. b) Poch, M.; Valentí, E.; Moyano, A.; Pericàs, M. A.; Castro, J.; DeNicola, A.; Greene, A. E. *Tetrahedron Lett.* **1990**, *31*, 7505-7508.

12. Keul, H.; Choi, H.-S.; Kuczkowski, R. L. *J. Org. Chem.* **1985**, *50*, 3365-3371.

13. Typical Experimental Procedure for the Preparation of *trans*-Enol Ethers; Preparation of *(E)*-5a: In a 10 mL round-bottomed flask, under nitrogen atmosphere, a mixture of $LiAlH_4$ (75 mg, 1.87 mmol), anhydrous THF (4 mL, pre-saturated with $LiAlH_4$) and alkoxyacetylene **4a**[9] (100 mg, 0.47 mmol) is heated to reflux during 4 h. The reaction mixture is cooled to room temperature, successively treated with water (0.75 mL), 15% aq. NaOH (0.75 mL) and water (3x0.75 mL), and stirred for 30 min. The greyish-white precipitate is filtered off and washed with diethyl ether (3x10 mL). Evaporation of the solvents gives a crude product (0.12 g) which is purified by filtration through 3 g of triethylamine-pretreated silicagel (2.5% v/v) eluting with hexane, to give pure *(E)*-**5a** (75 mg, 75% yield) as a white solid of m. p. = 43.5-44.5 °C. **IR** (NaCl): 2910. 2825, 1670, 1655, 1645, 1445, 1165, 1120, 750, 695 cm^{-1}. **^{1}H-NMR** (200 MHz, $CDCl_3$): 7.1-7.4 (m, 5H), 5.85 (d of q, J=13.0 Hz, J'=2 Hz, 1H), 4.7 (d of q, J=13.0 Hz, J' =6.8 Hz, 1H), 3.7 (m, 1H), 2.65 (m, 1H), 1.2-2.0 (complex signal, 8H), 1.39 (d of d, J=6.8 Hz, J'=2 Hz, 3H). **^{13}C-NMR** (50 MHz, $CDCl_3$): 145.5 (d), 143.5 (s), 128.2 (d), 127.6 (d), 126.2 (d), 100.2 (d), 82.0 (d), 50.3 (d), 34.2 (t), 32.3 (t), 25.9 (t), 24.9 (t), 12.4 (q). Anal. Calcd. for $C_{15}H_{20}O$: C, 83.29%; H, 9.32%. Found: C, 82.89%; H, 9.51%.

14. Typical Experimental Procedure for the Preparation of *cis*-Enol Ethers; Preparation of *(Z)*-5b: In a 10 mL round-bottomed flask, under N_2, a mixture of Red-Al® (1.7 mL, of a 3.4 M hexane solution, 5.92 mmol), anhydrous THF (2 mL) and dry methanol (0.24 mL, 5.92 mmol) is refluxed for 15 min. Subsequently, a solution of alkoxyacetylene **4b**[9] (200 mg, 0.74 mmol) in dry THF (2 mL) is added and the resulting mixture is maintained at reflux during 6 h. The reaction mixture is cooled to room temperature, stirred for 12 h and successively treated with water (1.5 mL) and 15% aq. NaOH (1.5 mL), and stirred for 1 h. The precipitate is filtered off and washed with diethyl eher (3x15 mL). Evaporation of the solvents gives a crude product (0.79 g) which is purified by column chromatography over 20 g of triethylamine-pretreated silicagel (2.5% v/v) eluting with hexane, to give (Z)-**5b** (0.124 g, 62% yield) as a viscous, colorless oil. **IR** (NaCl): 3130, 2920, 2860, 1660, 1500, 1450, 1360, 1260, 1100, 760, 700 cm^{-1}. **^{1}H-NMR** (200 MHz, $CDCl_3$): 7.1-7.4 (m, 5H), 5.73 (d, J=6.4 Hz, 1H), 4.08 (q, J=6.4 Hz, 1H), 3.6 (m, 1H), 2.62 (m, 1H), 0.9-2.0 (complex signal, 16H), 0.82 (t, 3H). **^{13}C-NMR** (50 MHz, $CDCl_3$): 144.0 (s), 143.6 (d), 128.0 (d), 127.8 (d), 126.1 (d), 106.6 (d), 83.8 (d), 50.5 (d), 33.6 (t), 32.8 (t), 31.4 (t), 29.3 (t), 25.9 (t), 24.9 (t), 23.8 (t), 22.5 (t), 14.1 (q).

15. The reduction of ethoxyacetylene with diisobutylaluminum hydride is highly *cis*-stereoselective. See: Eisch, J. J.; Gopal, H.; Rhee, S.-G. *J. Org. Chem.* **1975**, *40*, 2064-2069.

16. For a discussion of the dismutation reactions of alkoxyaluminum hydrides, see: Málek, J. *Org. React.* **1985**, *34*, 1-317.

17. a) Sörensen, H.; Greene, A. E. *Tetrahedron Lett.* **1990**, *31*, 7597-7598. In our hands, best results were obtained when the requisite active zinc powder was obtained by the procedure described by Rieke: b) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445-1453. c) Rieke, R. D.; Li, P.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4324-4326.

(Received in UK 3 March 1992)