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Preparation and Use of Chiral (Z)-Enol Ethers in Asymmetric Bradsher Cycloaddition

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Abstract: Chiral (Z)-enol ethers 7a-7p have been prepared in two steps. Bradsher cycloaddition between such compounds and 2,7-naphthyridinium salt 4b in water or in ter-butanol-water afforded, in some cases with good yield and diastereoselectivity, highly functionalized isoquinoline derivatives, potential intermediates in Manzamine A 1 total synthesis. X-Ray analysis secured the direction of asymmetric induction with enol ether 71. Copyright © 1996 Published by Elsevier Science Ltd

During the course of preliminary studies toward the total synthesis of cytotoxic alkaloid Manzamine A 1^1 , we recently demonstrated² the synthetic potential of a Bradsher cycloaddition³ strategy. An extension of this reaction to its asymmetric counter part could give rise in few steps to highly functionalized isoquinoline derivative 3, potential precursor of Manzamine A 1 according to the retrosynthetic scheme (Scheme 1).



Asymmetric Bradsher cycloadditions between unsubstituted enol ethers and an isoquinolinium salt have already been reported in literature⁴. In the present communication, we describe a versatile preparation of enantiomerically pure (Z)-enol ethers from the corresponding allylic ethers and their use in asymmetric Bradsher cycloaddition with 2,7-naphthyridinium salt **4b** as diene.

Chiral (Z)-1,2-disubstituted enol ethers were prepared in two steps starting from alcohols 5a-51. Classical O-alkylation with allyl bromide gave rise to the corresponding allylic ethers 6a-61 (Scheme 2, table 1). Isomerisation of the double bond in the presence of potassium *ter*-butylate in DMSO⁵ at 60°C afforded geometrically pure (Z)-enol ethers **7a-7l** generally in good yields⁶. However, deprotonation of allylic ether **6f** induced a β -elimination producing phenyl cyclohexene. This side reaction was partially supressed by using THF and *sec*-butyl lithium as the base at -78°C⁷. Under these conditions, (Z)-enol ether **7f** was obtained in 20% yield, with 21% of starting allylic alcohol **6f**, and 10% of phenyl cyclohexene. Moreover, this inconvenience has been overcome using the 4-methoxyphenyl cycohexanol **5g**. For further synthetic elaborations, a tandem isomerisation-alkylation sequence of reactions has also been studied with the *sec*-BuLi-THF system and methyl iodide or allyl bromide as electrophiles. Alkylated (Z)-enol ethers **7m-7p** were thus obtained in moderate to good yields.



Cahama	4
Scheme	4

Entry	1	2	3	4	5	6	7	8	9	10	11	12
Starting material	5a	5 b	5 c	5d	5 e	5 f	5 g	5 h	5 i	5 j	5 k	51
Alkylation												
Yield %	95	68	40	60	99	90	85	54	68	93	98	90
Isomerisation				00	-		00		70	05	00	65
Yield %	90	40	15	90	/0	20	90	90	/0	95	98	00

Table 1

Bradsher cycloadditions between enol ethers 7a-7n and naphthyridinium salt 4b were studied, the most significant results are reported in table 2. The use of the Bradsher cycloaddition conditions developed in our preliminary study² (dichloromethane-methanol 9:1, CaCO₃) gave rather poor results with dienophile 7a and naphthyridinium salt 4b. Adduct 8a as a mixture of diastereomers was isolated in 15% yield after 48 hours at room temperature. Only starting materials were recovered with other solvents such as ter-butanol, N.N-dimethylformamide or 1.4-dioxan. Fortunately, when the reaction was performed in water⁸, a faster cycloaddition was observed and adduct 8a was isolated in 55% yield after 9 hours at room temperature with a diastereoselectivity of 20% (Table 2, entry 1). Other cycloadditions with dienophiles 7b-7i were performed under the same conditions with or whithout cobalt (II) nitrate as an additive⁹. Finally the best results were obtained with isosorbide enol ether derivative 7j and isomannide derivatives 7k and 71¹⁰ in a mixture of terbutanol-water as solvent (entries 8, 9 and 10). These compounds gave interesting results for both yield and diastereoselectivity¹¹. As previously observed with Bradsher cycloadditions³, these reactions were highly exo selective¹². Diastereoselectivities were measured by ¹H NMR¹². However, the direction of the asymmetric induction could not be easily deduced from the examination of the NMR spectra and a crystal of adduct 81 (or 91) has been submitted to an X-ray analysis¹³. As shown in figure 1, the absolute configuration does agree with structure 81 which fit well for further use of such adduct in asymmetric synthesis of Manzamine A1.



Scheme 3

Entry	1	2	3	4	5	6	7	8	9	10
Dienophile Solvent	7a	7a	7 b	7 b	7 c	7f	7 g	7j	7 k	71
+ Additive Time	a	b	a	c	c	c	c	b	b	b
(Hour or day))9h	5 d	4 h	5 h	5 h	6 h	5 h	4 d	2 d	3 d
Yield %	55	62	40	70	58	52	48	90	90	63
d. e. %	20	20	37		20	69	80	80	80	80

 Table 2 : Reaction condition : 4b (1 equiv.), 20°C, CaCO3 (1.5 equiv.), 7a-7f (10 equiv.), 7j-7l: (5 equiv.).

 a: H₂O. b: H₂O-tert butanol = 2:1. c: H₂O, Co(NO3)2 (0.025 equiv.)



Figure 1 X-Ray structure of 81

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References and notes:

1) a) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. J. Am. Chem. Soc., 1986, 108, 6404-6405. b) Sakai, R.; Kohmoto, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. Tetrahedron Lett., 1987, 28, 5493-5496. c) Nakamura, H.; Deng, S.; Kobayachi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T. Tetrahedron Lett., 1987, 28, 621-624. d) Ichiba, T.; Sakai, R.; Kotmoto, S.; Saucy, G.; Higa, T. Tetrahedron Lett., 1988, 29, 3083-3086. e) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sakai, T; Kobayashi, J; J. Org. Chem., 1992, 57, 2480-2483. f) Ichiba, I.; Corgiat, J. M.; Scheuer, P. J.; Borges, M. K. J. Nat. Prod., 1994, 57, 168-170. g) Tsuda, M.; Kawasaki, N.; Kobayashi, J. Tetrahedron Lett., 1994, 35, 4387-4388. h) Kobayashi, M.; Chen Y.-J.; Aoki, S.; In, Y.; Ishida, T.; Kitagawa, I. Tetrahedron, 1995, 51, 3727-3736.

2) Magnier, E.; Langlois, Y.; Merienne, C. Tetrahedron Lett., 1995, 36, 9475-9478.

3) Chen, T.-K.; Bradsher, C. K. J. Org. Chem., 1979, 44, 4680-4683. b) Manna, S.; Falk, J. R.; Mioskowski; C. J. Org. Chem., 1982, 47, 5021-5023. C) Falk, J. R.; Manna, S.; Mioskowski, C. J. Am. Chem. Soc., 1982, 105, 631-633. d) Gupta, R. B.; Frank, R. W. J. Am. Chem. Soc., 1987, 109, 5393-5403. e) Gupta, R. B.; Franck, R. W.; Onan, K. D.; Soll, C. E. J. Org. Chem., 1989, 54, 1097-1101. f) Bolitt, V.; Mioskowski, C.; Kollah, R. O.; Manna, S.; Rajapaksa, D.; Falk, J. R. J. Am. Chem. Soc., 1991, 113, 6320-6321. g) Yin, H.; Frank, R. W.; Chen, S.-L.; Quigley, G. J.; Todaro, L. J. Org. Chem., 1992, 57, 644-651.

4) Choudury, A.; Frank, R. W.; Gupta, R. B. Tetrahedron Lett., 1989, 37, 4921-4924.

5) Taskinen, E. Tetrahedron, 1993, 49, 11389-11394 and references there in.

6) For alternative methods for preparation of enantiomerically pure enol ethers, see inter alia : a) Denmark, S. E.; Schnute, M. E.; Marcin, L; R.; Thorarensen, A. J. Org. Chem., 1995, 60, 3205-3220. b) Solà, L.; Castro, J.; Moyano, A.; Pericàs, M.A.; Riera, A. Tetrahedron Lett., 1992, 33, 2863-2866. c) Charbonnier, F.; Moyano, A.; Greene, A. E. J. Org. Chem., 1987, 52, 2303-2306. d) Moyano, A.; Charbonnier, F.;
Greene, A. E. J. Org. Chem., 1987, 52, 2919-2922 and references there in.
7) a) Clark Still, W.; Macdonald, T. L. J. Org. Chem., 1976, 41, 3620-3622. b) Evans, D. A.; Andrews,
G. C.; Buckwalter, B. J. Org. Chem., 1974, 96, 5560-5561. c) Clark Still, W.; Macdonald, T. L. J. Org.

Chem., 1974, 96, 5561-5563.

8) For recent reviews concerning the water promoted organic reactions, see: a) Lubineau, A.; Augé, J.; Queneau, Y. Synthesis, 1994, 741-760. b) Li, C. Chem. Rev. 1993, 93, 2023-2035.

9) The role of this salt is not well understood.

10) For the preparation of isosorbide-isomannide derivatives 5j-5l, see: Abenhaim, D.; Loupy; A.; Munnier, L.; Tamion, R.; Marsais, F.; Queguiner, G. Carbohydrate Res., 1994, 261, 255-266.

11) For the use of isomannide-isosorbide derivatives in normal electron demand asymmetric Diels-Alder reactions, see the following paper, Loupy, A.; Monteux, D.

12) The exo selectivity of these cycloadditions was deduced from nOe experiments showing the spatial proximity between N-CH-O and R*O-CH. Moreover, a cycloaddition performed with (E) 7f afforded a mixture of diastereomeric endo-exo adducts. For further discussion, see ref. 3d. The diastereoselectivity of these cycloadditions was measured by integration of the signal attributed to N-CH-O which appeared as a doublet between 4.8 and 5 ppm.

13) Crystal data: C₂₀ H₂₆ N₂ O₅, M_w = 374.44, crystal of 0.33 x 0.37 x 0.46 mm, monoclinic, space group P 2₁, Z = 2, a = 7.938(5), b = 8.129(7), c = 14.287(8) Å, β = 98.95(2)°, V = 910 (1) Å³, d_{calc} = 1.37 g cm⁻³, F(000) = 400, λ (Cu Kα) = 1.5418 Å, μ = 0.76mm⁻¹. Enraf-Nonius CAD-4 diffractometer, (0-20) scan technique up to $\theta = 65^{\circ}$; 6296 collected reflexions (h: -9 to 9, k: -9 to 9, l: -16 to 16), 3099 unique reflexions (R_{int} = 0.023), 3063 observed having I \geq 3 σ (I). R = 0.037 and R_w = 0.051 (with R_w = { Σ w(Fo-IFcl)² / ΣwFo^2 ^{1/2} and w = 1/[$\sigma^2(Fo)$ + 0.0034 Fo²]. Residual electron density: -0.32 and 0.49 e Å⁻³. The structure was solved by direct methods using *SHELXS86* and refined by full matrix least squares with *SHELX76*, minimizing the function Sw(Fo-IFcl)². The coordinates of the hydrogen atoms were refined with an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Atomic coordinates, bond lengths, bond and torsion angles, and thermal parameters at the Cambridge Crystallographic Data Centre, UK.