

HETEROCYCLES, Vol. 66, 2005, pp. 147 – 151. © The Japan Institute of Heterocyclic Chemistry
Received, 14th September, 2005, Accepted, 28th October, 2005, Published online, 1st November, 2005. COM-05-S(K)57

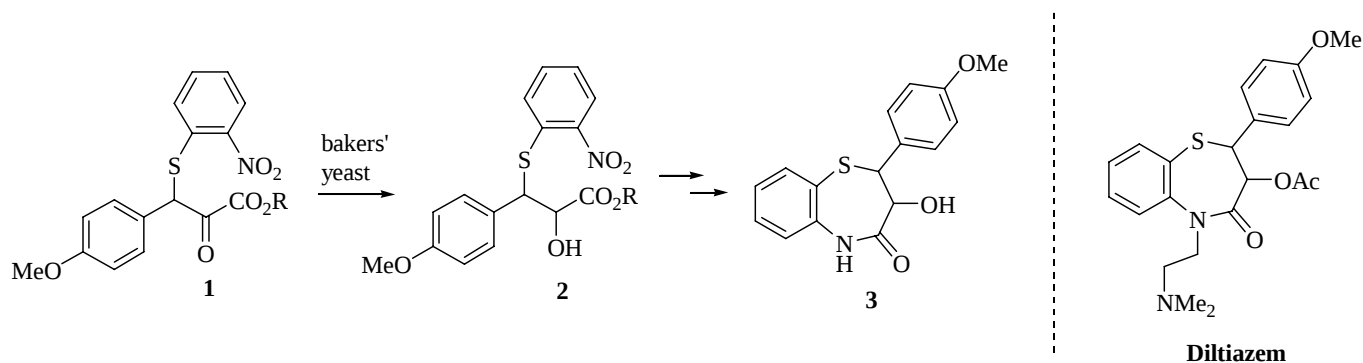
NOVEL PROTOCOL FOR THE ASYMMETRIC SYNTHESIS OF 3-HYDROXY-2-(4-METHOXYPHENYL)-2,3-DIHYDRO-1,5- BENZOTHIAZEPIN-4(5H)-ONE VIA BAKERS' YEAST REDUCTION

Takuzo Komiyama, Yutaka Takaguchi, and Sadao Tsuboi*

Department of Material and Energy Science, Graduate School of Environmental
Science, Okayama University, Okayama 700-8530, Japan
E-mail address: stsuboi6@cc.okayama-u.ac.jp

Abstract – A novel protocol for the asymmetric synthesis of 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one is reported. Darzens condensation reactions of anisaldehyde with dichloroacetates, followed substitution reaction of sodium *o*-nitrophenylthiolate and bakers' yeast reduction furnished 2-hydroxy-3-(4-methoxyphenyl)-3-(2-nitrophenylsulfanyl)-propionates. Further reduction of a nitro group and cyclization gave the title compound.

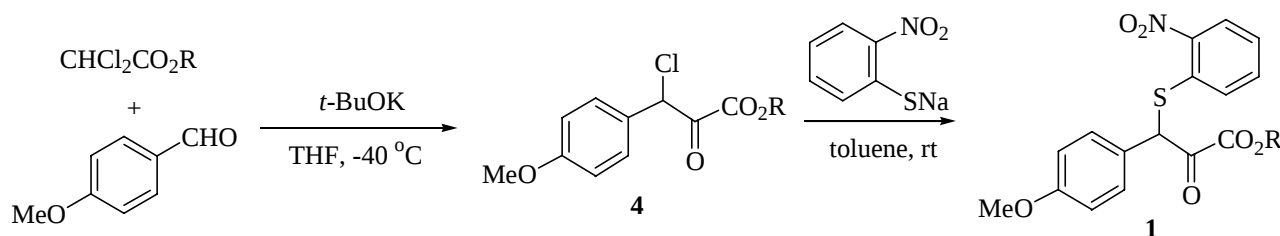
Derivatives of 1,5-benzothiazepin are well known calcium channel blockers and represented by diltiazem [(2*S*,3*S*)-3-acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one]. Diltiazem is one of the most potent calcium antagonist and used as a remedy for hypertension and angina.¹ In contrast, its enantiomer, (2*R*,3*R*)-form compound, has a weak activity as an antihypertensive agent. However it has more brain-waves awakening activity.² Because of their potent biological activity, various synthetic approaches have been reported toward to the asymmetric synthesis of diltiazem and its isomer.³



Scheme 1.

Our group has studied about the utilization of bakers' yeast for the synthesis of optically active compounds.⁴ So, in this report, we demonstrate the mild and inexpensive protocol for the synthesis of 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**3**), which is a precursor of *cis* or *trans* isomer of diltiazem *via* bakers' yeast reduction of prepared β -arylthio- α -keto esters (**1**) (Scheme 1).

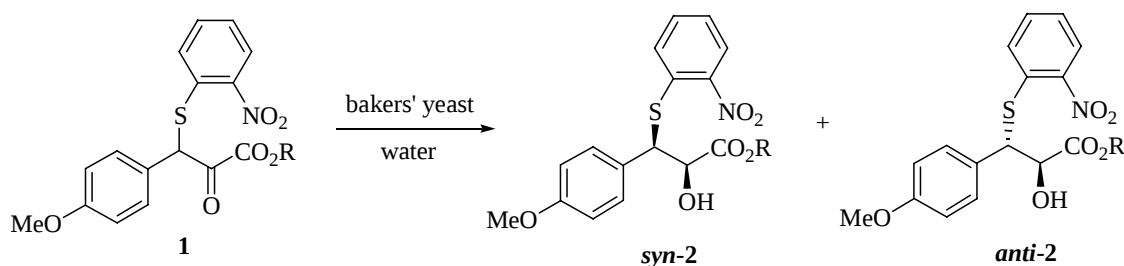
Substrates of bakers' yeast reaction, β -arylthio- α -keto esters (**1**) were prepared easily as shown in Scheme 2. Darzens condensation reaction of anisaldehyde with dichloroacetates gave β -chloro- α -keto esters (**4**)⁵ and further treatment with sodium *o*-nitrophenylthiolate furnished the β -arylthio- α -keto esters (**1**).



Scheme 2.

Then, we attempted to bakers' yeast reduction of prepared compound β -arylthio- α -keto esters (**1**). Treatment of β -arylthio- α -keto esters (**1a-e**) with bakers' yeast furnished corresponding 2-hydroxy-3-(4-methoxyphenyl)-3-(2-nitrophenylsulfanyl)propionates (**2a-e**) (Table 1).⁶ Treatment of glycidic ester (**1a**) with bakers' yeast in water for 5 days provided reduced product (**1a**) in 41% yield after purification by silica gel flash chromatography (Entry 1). And an *anti*-form product was obtained selectively (*syn/anti* = 20: 80) with the reasonable stereoselectivity (*syn*: 76% ee, *anti*: 71% ee). Then we tried to change the ester group of substrates (Entries 2-4). We found that a *syn*-form product ratio increased by employing the substrate having the bulky ester group. Furthermore, the *syn*-form product was obtained in good selectivity with good stereoselectivity (96% ee) by the use of *tert*-butyl ester (Entry 5). Although there is no report about the bakers' yeast reduction of β -arylthio- α -keto ester, this change of diastereoselectivity depending on the ester group has reported in the case of β -keto- α -sulfenyl esters. As for the change of diastereoselectivity, our case exhibited more conspicuously.⁸

Then the obtained *anti*-form of β -arylthio- α -hydroxy ester (**anti-2a**) was converted to *trans*-form benzothiazepine (**trans-3**) by the reduction of the nitro group and cyclization (Scheme 3). The absolute configuration of **trans-3** was confirmed by comparison of its specific rotation with authentic data.^{3g}

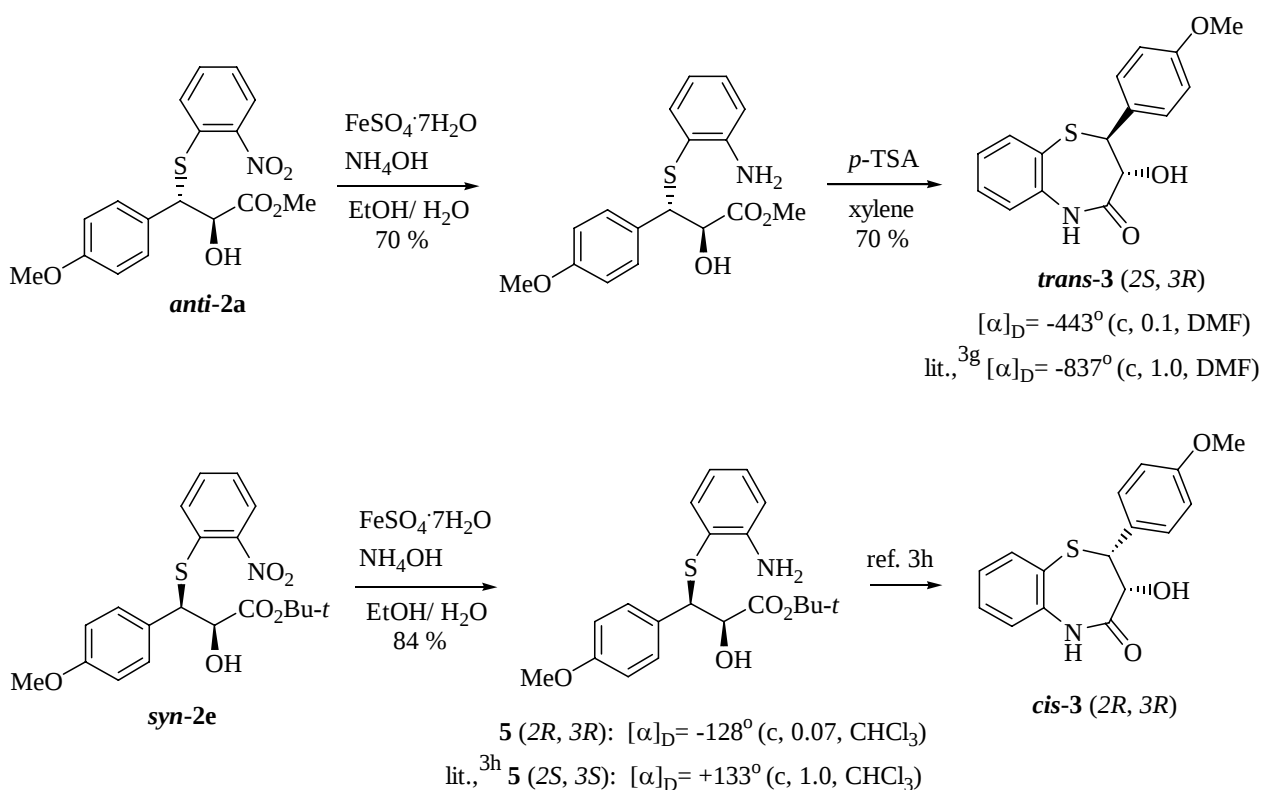
Table 1. Bakers' yeast reduction of β -arylthio- α -keto esters (**1**)

Entry	Conditions			Product/ Yield ^a (%)	Syn: anti ^b	Ee (%) ^c
	Substrate/ R	Temp. (°C)	Time (day)			
1	1a / Me	35	5	2a / 41 (48)	20:80	syn : 76 anti : 71
2	1b / <i>n</i> -Bu	35	6	2b / 61 (65)	35:65	syn : 92 anti : 91
3	1c / <i>i</i> -Pr	38	4	2c / 43 (59)	37:63	syn : 92 anti : 87
4	1d / <i>i</i> -Bu	38	4	2d / 45 (59)	46:54	syn : 96 anti : 93
5	1e / <i>t</i> -Bu	35	6	2e / 28 (36)	85:15	syn : 96 anti : 60

a) Yield which calculated based on recovery is given in a parenthesis.

b) Diastereo ratio was determined by the 300MHz NMR analysis.

c) Ee was determined by the 500MHz NMR analysis after converted to MTPA ester.



Scheme 3.

The obtained *syn*-form of β -arylthio- α -hydroxy ester (**syn-2e**) was also reduced to a compound (**5**) and confirmed its absolute configuration by comparison of its specific rotation with authentic data.^{3h} Further cyclization of the compound (**5**) can be prepared *cis*-form benzothiazepine (**cis-3**).^{3h}

In conclusion, we have developed the novel method for the synthesis of 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one *via* bakers' yeast reduction. The important and new discovering in this report is the efficiency of bakers' yeast reduction of β -arylthio- α -keto esters for the preparation of optically active β -arylthio- α -hydroxy esters. Each diastereomer of β -arylthio- α -hydroxy ester can be prepared selectively by changing its ester group. Other features and advantage of our method against previously reported one for the preparation of 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one is ease of experimental operations, using inexpensive reagents and mild reaction conditions.

REFERENCES AND NOTES

1. (a) H. Kugita, H. Inoue, M. Ikezaki, M. Konda, and S. Takeo, *Chem. Pharm. Bull.*, 1971, **19**, 595; (b) T. Nagao, M. Sato, H. Nakajima, and A. Kiyomoto, *Chem. Pharm. Bull.*, 1973, **21**, 92.
2. H. Inoue, S. Takeo, M. Kawatsu, A. Kiyomoto, H. Nakajima, H. Kugita, and M. Ikesaki, JP-53018038, 1978 (*Chem. Abstr.*, 1978, **90**, 6431).
3. (a) K. G. Wtson, Y. M. Fung, M. Gredley, G. J. Bird, W. R. Jackson, H. Gountzos, and B. R. Matthews, *J. Chem. Soc., Chem. Commun.*, 1990, 1018; (b) H. Akita, I. Umezawa, H. Matsukura, and T. Oishi, *Chem. Pharm. Bull.*, 1991, **39**, 1632; (c) A. Schwartz, P. B. Madan, E. Mohacsi, J. P. O'Brien, L. J. Todaro, and D. L. Coffen, *J. Org. Chem.*, 1992, **57**, 851; (d) L. T. Kanerva and O. Sundholm, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1385; (e) K. Matsuki, M. Sobukawa, A. Kawai, H. Inoue, and M. Takeda, *Chem. Pharm. Bull.*, 1993, **41**, 643; (f) B. B. Lohray, B. Jayachandran, V. Bhushan, E. Nandan, and T. Ravindranathan, *J. Org. Chem.*, 1995, **60**, 5983; (g) S. Yamada, Y. Mori, K. Morimatsu, Y. Ishizu, Y. Ozaki, R. Yoshioka, T. Nakatani, and H. Seko, *J. Org. Chem.*, 1996, **61**, 8586; (h) B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. McCague, T. C. Nugent, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3501; (i) R. Imashiro and T. Kuroda, *Tetrahedron Lett.*, 2001, **42**, 1313.
4. S. Tsuboi, H. Furutani, M. H. Ansari, T. Sakai, M. Utaka, and A. Takeda, *J. Org. Chem.*, 1993, **58**, 486.
5. (a) A. Takeda, S. Tsuboi, S. Wada, and H. Kato, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 1217; (b) S. Tsuboi, H. Furutani, A. Takeda, K. Kawazoe, and S. Sato, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2475.
6. Typical procedure (synthesis of **2e** from **1e**): To a stirring mixture of KH_2PO_4 (40 mg), $\text{NH}_4\text{H}_2\text{PO}_4$

(40 mg), MgSO_4 (20 mg), CaCO_3 (12 mg), glucose (1.0 g), and water (24 ml) was added bakers' yeast (1.0 g) at 35 °C. After stirring for 30 min, α -keto- β -arylthio ester (**1e**) (60 mg, 0.15 mmol) was added and the reaction mixture was stirred at 35 °C. And bakers' yeast (1.0 g) and glucose (1.0 g) were added every 24 h during after 2 days. After 6 day stirring, the reaction mixture was treated with celite for 1 h and filtrated. Then the filtrate was extracted four times with EtOAc and washed with brine. The combined organic extracts were dried over MgSO_4 and evaporated. The residual crude products were purified by column-chromatography (hexane: EtOAc= 15: 1) to give β -arylthio- α -hydroxy ester (**2e**) (17 mg, 28%).

7. Compound (**syn-2e**): $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.42 (s, 9H), 3.29 (br, 1H), 3.79 (s, 3H), 4.46 (d, 1H, $J=3.6$ Hz), 4.68 (d, 1H, $J=3.6$ Hz), 6.85-6.87 (m, 2H), 7.17-7.24 (m, 1H), 7.26-7.49 (m, 4H), 8.01-8.04 (m, 1H); IR (neat, cm^{-1}) 3475, 2977, 1728, 1511, 1251 cm^{-1} . Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_6\text{S}$: C, 59.24; H, 5.72; N, 3.45. Found: C, 59.39; H, 5.66; N, 3.72.
8. T. Fujisawa, T. Ito, and T. Sato, *Tetrahedron Lett.*, 1984, **25**, 5083.