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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

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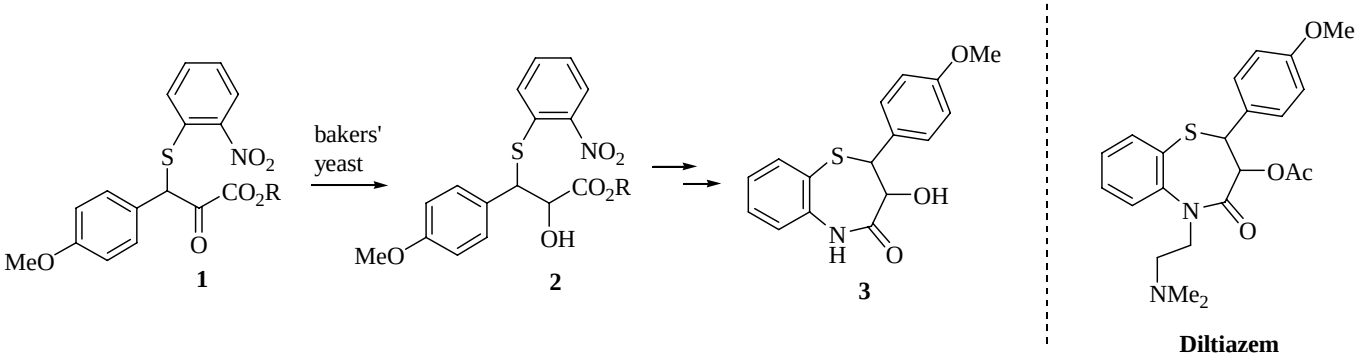
Abstract – A novel protocol for the asymmetric synthesis of 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one is reported. Darzens condensation reactions of anisaldehyde with dichloroacetates, followed substitution reaction of sodium *o*-nitrophenylthiolate and bakers' yeast reduction 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]

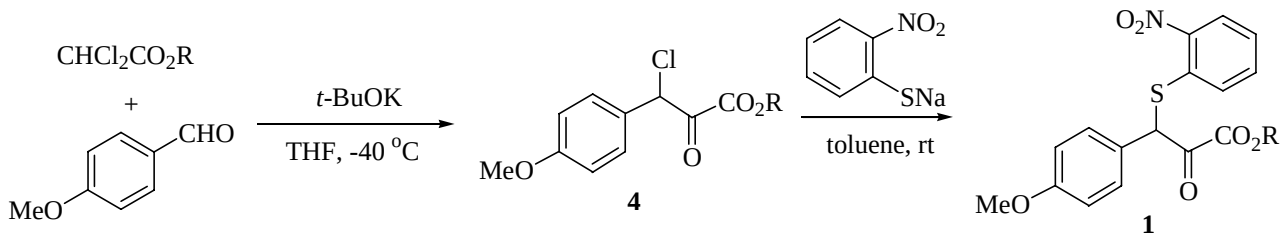


Scheme 1.

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

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**).

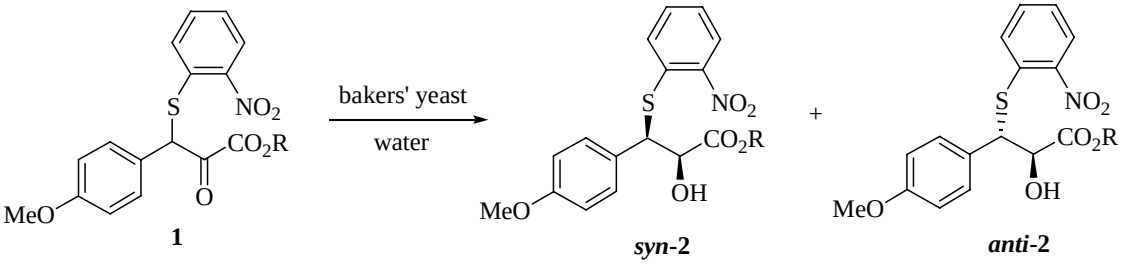


Scheme 2.

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]

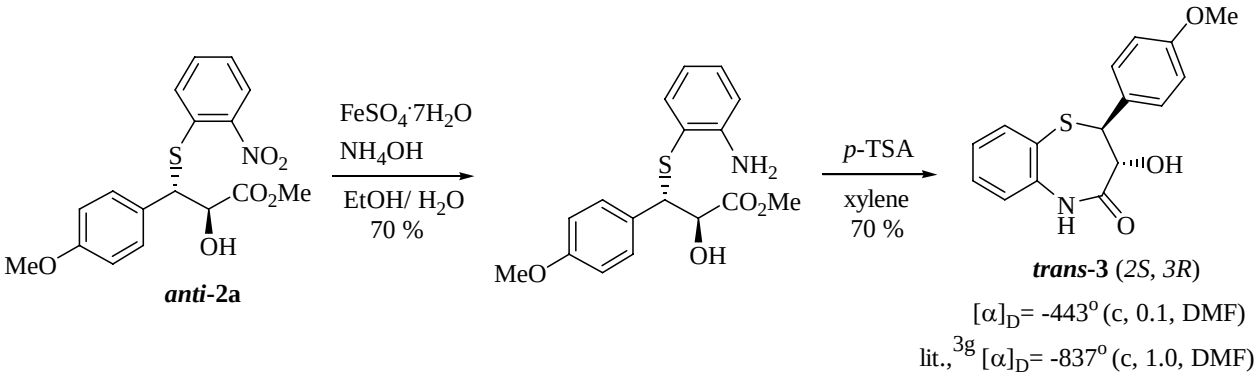
Table 1. Bakers' yeast reduction of β-arylthio-α-keto esters (**1**)



1 ***syn*-2** ***anti*-2**

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**/ *n*-Bu	35	6	**2b**/ 61 (65)	35:65	*syn* : 92 *anti* : 91
3	**1c**/ *i*-Pr	38	4	**2c**/ 43 (59)	37:63	*syn* : 92 *anti* : 87
4	**1d**/ *i*-Bu	38	4	**2d**/ 45 (59)	46:54	*syn* : 96 *anti* : 93
5	**1e**/ *t*-Bu	35	6	**2e**/ 28 (36)	85:15	*syn* : 96 *anti* : 60

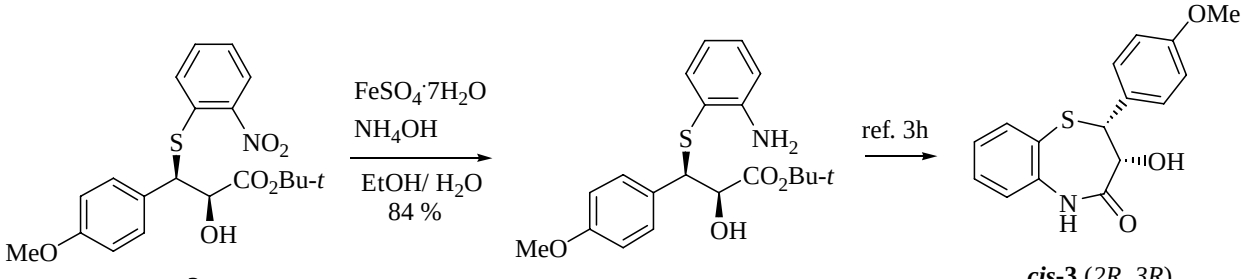
a) Yield which calculated based on recovery is given in a parenthesis.
b) Diastereo ratio was determined by the 300MHz NMR analysis.
c) Ee was determined by the 500MHz NMR analysis after converted to MTPA ester.



***anti*-2a** ***trans*-3** (*2S, 3R*)

$[\alpha]_D$= -443° (c, 0.1, DMF)

lit.,[3g] $[\alpha]_D$= -837° (c, 1.0, DMF)



***syn*-2e** ***cis*-3** (*2R, 3R*)

5 (*2R, 3R*): $[\alpha]_D$= -128° (c, 0.07, $CHCl_3$)

lit.,[3h] **5** (*2S, 3S*): $[\alpha]_D$= +133° (c, 1.0, $CHCl_3$)

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.

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6. Typical procedure (synthesis of **2e** from **1e**): To a stirring mixture of KH_2PO_4 (40 mg), $NH_4H_2PO_4$

(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 ^oC. 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 ^oC. 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}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 $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72; N, 3.45. Found: C, 59.39; H, 5.66; N, 3.72.
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