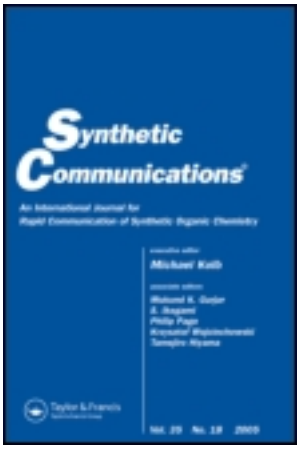

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Improved Process for the Preparation of Tamsulosin Hydrochloride

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Abstract: Ellman's sulfinamide reagent is used in asymmetric synthesis of Tamsulosin hydrochloride. The enantiomeric ratio achieved is 87:13. The crystallization of the same with dibenzoyl tartarate afforded the product **2** with >99.5% ee.

Keywords: Dibenzoyl tartarate, hydrogenation, *t*-butyl sulfinamide (Ellman's sulfinamide)

INTRODUCTION

During the past two decades, many synthetic groups have been engaged in the development of single enantiomeric drug targets that exhibit an amine functionality at the chiral center.[1,2] In spite of the fact that these chiral amines are regarded as an important class of compounds, their practical synthesis poses significant challenges to organic chemists. Tamsulosin (**1**), an antihypertensive drug also used in the treatment of benign prostatic hyperplasia, was invented by Yamanouchi (now Astellas Pharma) and codeveloped by Boehringer Ingelheim in the United States and CSL Pharma in Australia.

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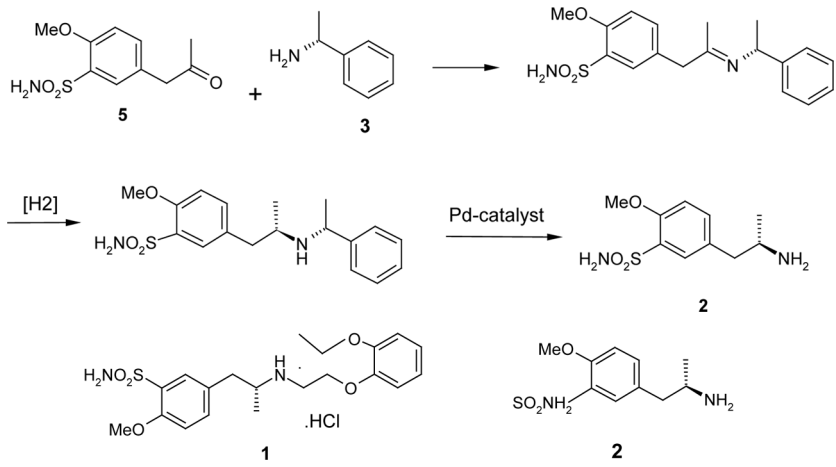
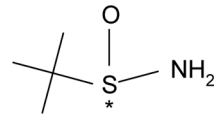


RESULTS AND DISCUSSION

The key intermediate in the preparation of Tamsulosin (**1**) is the amine (**2**), an amphetamine derivative 3-(4-methoxy-3-sulfonamido-phenyl)-2-amino propane or 1-methyl-2-(4-methoxy-3-sulfonamido phenyl) ethyl amine. The known methods of synthesis for this amine are given in Scheme 1.

The innovator[3] prepared the amine (**2**) using asymmetric synthesis with the help of (R)-phenyl ethylamine (**3**). The optical purity they achieved is 94.5%, and they purified it four times to get the optical purity of >99%. The Indian authors[4,5] used the conventional resolution technology of the dl-amine (**2**) with (D)-tartaric acid. They also did the purification two times to get the optically pure (>99%) amine (**2**).

During the past decade, Prof. Ellman developed the *t*-butyl sulfinamide reagents (**4**) (both R/S isomers) as chiral reagents to prepare a variety of amines.[6]



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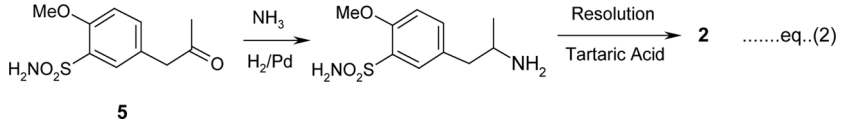
Because these reagents (R and S) have started to be available commercially, we decided to study the preparation of amine (**2**) using this technology.

1-Phenyl (substituted) propan-2-one (**5**) is reacted with (R)-*t*-butyl sulfinamide (**4**) as per Ellman's procedure[7] to give the product with



Scheme 1. Synthesis of **2** by resolution method.

87% optical purity (Scheme 2). Different reaction conditions, such as low temperatures during condensation, and different reducing agents in next step did not improve the optical ratio. The results are given in Table 1.

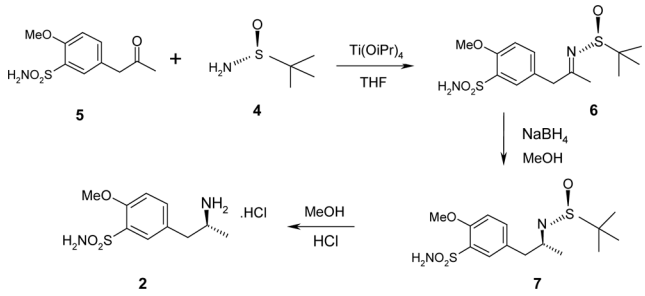
The results are similar with (S) isomer of (**4**). Simple crystallizations of (**2**) as HCl or as a base did not improve the chirality further. Different tartarate salts (see Table 2) were tried to prepare the amine (**2**) with high optical purity. As reported, tartaric acid salt, did not give the best quality even after two crystallizations (98.2% chiral purity). The ditoluoyl tartarate also did not yield the correct quality of product in one crystallization. Only with the dibenzoyl tartaric acid salt and two crystallizations was the optical purity improved to 99.55%. This amine **2** was further converted to tamsulosin and confirmed in all respects.

In conclusion, we have demonstrated the *t*-butyl sulfinamide's usefulness in producing tamsulosin hydrochloride with chiral purity >85%. The chiral purity has been enhanced further to >99.5% with salt formation and recrystallization.

EXPERIMENTAL

General Procedure for the Condensation of Ketone (5) with 4

(R)-*t*-Butyl sulfinamide (**4**) (1 equiv.) was added to a 0.5 M solution of titanium tetraisopropoxide (2 equiv.) and 5-acetonyl-2-methoxybenzene sulfonamide (**5**) (1.2 equiv.) in tetrahydrofuron (THF) under an N_2



Scheme 2. Synthesis of **2** with (R)-*t*-butylsulfinamide.

Table 1. Reduction of imine with different reducing agents

Entry	Temperature	Reducing agent	Optical purity (%)	Comments
6	−48 °C	$NaBH_4$	87	No improvement in optical purity
6	−70 °C	$NaBH_4$	87	Optical purity is low
6	55–60 °C & rt	Raney nickel	—	No reaction
6	rt	$NaBH(OAc)_3$	—	No reaction
6	−40 °C	Vitride	—	No reaction
6	−40 °C	DIBAL	—	No reaction

atmosphere, and the flask was heated (65–75 °C). Upon completion, as determined by thin-layer chromatography (TLC), the mixture was cooled to room temperature first and then to −48 °C with a dry ice/acetone bath. $NaBH_4$ (4 equiv.) was added portionwise at −48 °C, and the reaction mixture was stirred at −48 °C until the reduction was complete. Then methanol was added dropwise until gas no longer evolved. The resulting mixture was poured into an equal volume of brine with rapid stirring. The resulting suspension was filtered through hyflo, and the bed washed with ethyl acetate. The filtrate was extracted with ethyl acetate. The combined organic portions were dried (Na_2SO_4), filtered, and concentrated to obtain the crude product (**2**). The crude product thus obtained was purified by making hydrochloride salt, followed by base preparation using a known procedure.[3] Chiral ratio of the crude product is 85:15.

Preparation of Dibenzoyl-D-tartarate Salt of (R)-5-(2-Aminopropyl)-2-Methoxybenzene Sulfonamide

(R)-5-(2-Aminopropyl)-2-methoxybenzene sulfonamide (25 g) was dissolved in a solvent mixture of alcohol (250 ml) and N,N-dimethyl formamide (50 ml) with heating. Dibenzoyl-D-tartaric acid (40 g) was added at 75–80 °C, and the temperature was maintained for 6 h. The crystals formed were collected by filtration and washed with alcohol,

Table 2. Resolution of **2** with different tartarate derivatives

Tartaric salt	Solvent mixture	HPLC chiral purity (%)
D-(–)-Tartaric acid	MeOH–DMF (10:2)	98.5
Di-p-toluoyl tartarate	Acetone–DMF (6:3)	99.25
Dibenzoyl-D-tartarate	Alcohol–DMF (10:2)	99.55

affording dibenzoyl-D-tartarate salt of (R)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide, dry weight: 26 g and HPLC chiral purity: 97–98%. (Chiral purity was checked on a Daicel chiralpak AD–H, 250×4.6 mm with eluent 1 ml diethyl amine in 1.0 L of ethanol and wavelength at 226 nm. Flow rate was 1.0 ml/min.)

Purification of Dibenzoyl-D-tartarate Salt of (R)-5-(2-aminopropyl)-2-methoxybenzene Sulfonamide

A mixture of dibenzoyl-D-tartarate salt of (R)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide (26 g) and methanol (25 ml) was stirred for 15 min to become a clear solution. Absolute alcohol (260 ml) was added to the clear solution and heated to reflux temperature, which was maintained for 1 h. The reaction mixture was cooled to 28–30 °C, filtered, and washed with alcohol. The solid was dried at 50–55 °C to a constant weight to give dibenzoyl-D-tartarate salt, dry weight: 24 g and HPLC chiral purity: 99.5%.

(R)-5-(2-Aminopropyl)-2-methoxybenzenesulfonamide

K_2CO_3 (16 g) was added to dibenzoyl-D-tartarate salt of (R)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide (24 g) in water (72 ml). The reaction mixture was stirred for 1 h at room temperature. The isolated solid was filtered, washed with water, and dried at 60–65 °C to a constant weight to give pure (R)-5-(2-aminopropyl)-2-methoxy benzene sulfonamide, dry weight: 8 g and HPLC chiral purity: 99.5%.

$[\alpha]_D^{23}$ (C = 1.07, methanol): −17.1° (lit: −17.3°); melting point: 166–167 °C.

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