HETEROCYCLES, Vol. 57, No. 1, 2002, pp. 1 - 4, Received, 15th October, 2001

SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDROISOQUINOLINE-1-CARBOXYLATES BY PICTET-SPENGLER CONDENSATION USING PHENYLIODINE(III) BIS(TRIFLUOROACETATE)

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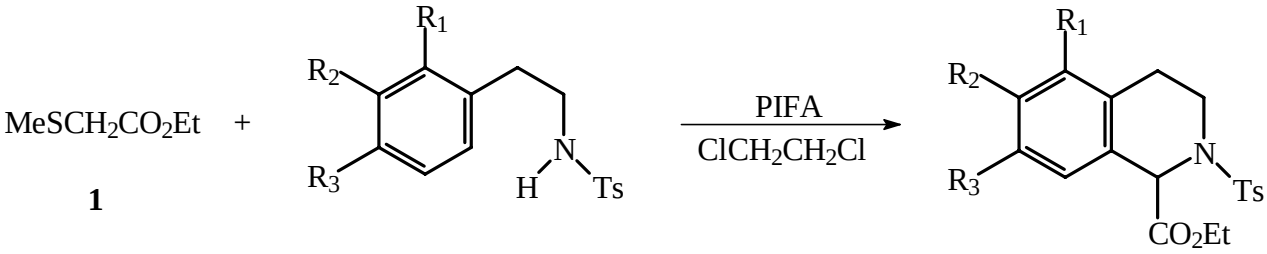
Abstract—The reaction of *N*-sulfonyl-β-phenethylamines with ethyl methylthioacetate using phenyliodine(III) bis(trifluoroacetate) gives moderate to good yields of the corresponding ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylates.

Pictet-Spengler condensation is one of the fundamental reaction for the preparation of 1,2,3,4-tetrahydroisoquinolines.[1] This cyclization occurs only when the ring-closure position is activated by electron donating substituents. However, β-phenethylamines bearing an electron withdrawing substituent on the benzene ring afford 1,2,3,4-tetrahydroisoquinoline derivatives in poor yields or do not give any cyclized product. Modifications of the original strategy to increase the electrophilicity of the iminium intermediate, which employ electron withdrawing groups on the nitrogen such as acyl [2] or sulfonyl [3] moieties are known.

Hypervalent iodine(III) reagents have generated considerable interest in the recent years due to their applications in the synthesis of heterocyclic compounds.[4] As a continuation of our studies concerning hypervalent iodine(III) chemistry, we have reported a Pummerer-type reaction that provides a very simple and convenient procedure for the preparation of 4*H*-pyrrolo[2,1-*c*][1,4]benzothiazines by treatment of α-acyl sulfides with phenyliodine(III) bis(trifluoroacetate) (PIFA).[5] We reported here a modified Pictet-Spengler cyclization of *N*-sulfonyl-β-phenethylamines with ethyl methylthioacetate using PIFA to prepare ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylates.

As shown in Table 1, the reaction of ethyl methylthioacetate (**1**) with *N*-sulfonyl-β-phenethylamine (**2a**) gave **3a** in high yield (Entry 1). On the other hand, reaction of the electron rich **2b** gave a mixture of the cyclized product (**3b**) and Friedel-Crafts product (**4b**) in moderate yields (Entry 2). The 3,4-dimethoxy derivative (**2c**), carrying activating substituent *para* to the ring closure position afforded good yield of

the expected product (**3c**, 76%) along with the Friedel-Crafts product (**4c**, 21%) (Entry 3). However, *N*-sulfonyl-β-phenethylamines such as **2d**, **2e**, **2f** and **2g** containing deactivated aromatic rings also furnished the corresponding cyclized products in reasonable yields. (Entries 4, 5, 6 and 7).

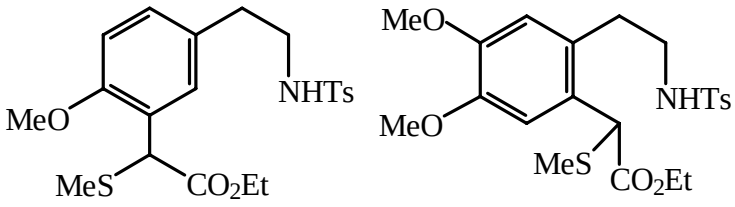


2 a-g **3 a-g**

Table 1. The reaction of *N*-sulfonyl-β-phenethylamines (**2a-g**) with ethyl methylthioacetate **(1)** using PIFA.

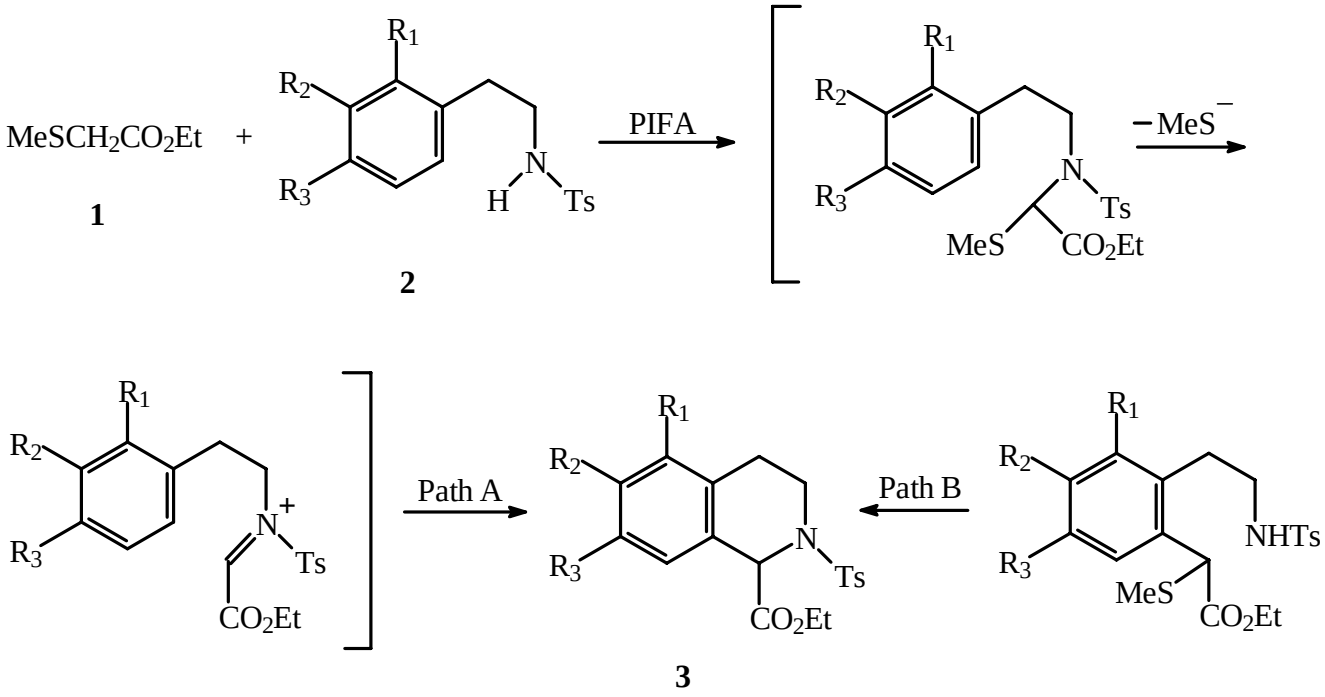
Entry	Compd	R_1	R_2	R_3	Product (Yield %)[a]			
1	**2a**	H	H	H	**3a**	87		
2	**2b**	H	H	OMe	**3b**	42 (15)[b]	**4b**	35
3	**2c**	H	OMe	OMe	**3c**	76	**4c**	21
4	**2d**	H	H	Cl	**3d**	50 (25)[b]		
5	**2e**	Cl	H	H	**3e**	61 (18)[b]		
6	**2f**	H	Cl	H	**3f**	64 (15)[b]		
7	**2g**	Cl	H	Cl	**3g**	25 (30)[b]		

a) All compounds gave the satisfactory spectral data.
b) Yield of recovered starting material.



4b **4c**

Two possible pathways of the cyclization are illustrated in Scheme 1. The cyclization is assumed to proceed through iminium cation which would be formed by Pummerer-type reaction of ethyl methylthioacetate (**1**) with *N*-sulfonyl-β-phenethylamines (**2**) using PIFA (Path A).[6]



Scheme 1

In summary, our results herein that the modified Pictet-Spengler cyclization of *N*-sulfonyl-β-phenethylamines with ethyl methylthioacetate using PIFA provides moderate to good yields of 1,2,3,4-tetrahydroisoquinolines, even when deactivated starting sulfonamides are employed.

ACKNOWLEDGEMENT

We gratefully acknowledge the National Council Science of Republic of China for financial support of this work. (Grant No. 90-2113-M-037-016)

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7. A typical procedure for cyclization of **2a** is as follows: PIFA (516 mg, 1.2 mmol) was added to a solution of ethyl methylthioacetate (**1**) (134 mg, 1.0 mmol) in 1,2-dichloroethane (10 mL) and the mixture was stirred at room temperature for 1 h. Then *N*-sulfonyl-β-phenethylamine (**2a**) (275 mg, 1.0 mmol) was added and the mixture was refluxed for 3 h to complete the reaction. The resultant mixture was quenched with water and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column with hexane-ethyl acetate (5:1) to give **3a**.