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Synthesis of Enantiomerically Pure 4-Amino-tetrahydroindazoles

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Keywords **– Tetrahydroindazoles, Chiral resolution, Tartaric acid, Camphoric acid**

I. Introduction

Tetrahydroindazoles play important role in medicinal chemistry. There has been considerable interest in the development of various molecular scaffolds for this field of chemistry. The term Fsp^3 has been suggested which stands for the ratio of sp^3 hybridized carbon atoms to the total carbon count.[1] It was demonstrated that for a successful drug candidate Fsp^3 approaches 0.5 and that the structure probably contains at least one chiral center. In this context tetrahydroindazoles (THIs) have proved to be particularly attractive due to the presence of both the planar pyrazole moiety and a C_4-tether which points the substituents in distinct spatial directions. This concept in the tetrahydroindazole series has resulted in many distinct biological activities [1]. In the light of these facts, many groups, including ours [2], have worked on functionalization of the tetrahydroindazole core.

II. Results and Discussion

Here we report a straightforward method for synthesis of racemic 4-aminotetrahydroindazoles and their resolution into enantiomerically pure forms (+)-**1** and (-)-**1**, (+)-**2** and (-)-**2**, (+)-**3** and (-)-**3** (Fig. 1).

The synthesis starts from well known tetrahydroindazolones **4-6** [3], which are transformed into corresponding oximes. The following reduction provides racemic amines **1-3**. In the case of amine **3** better results in its synthesis are achieved *via* the Ritter reaction [2c] (Fig. 2).

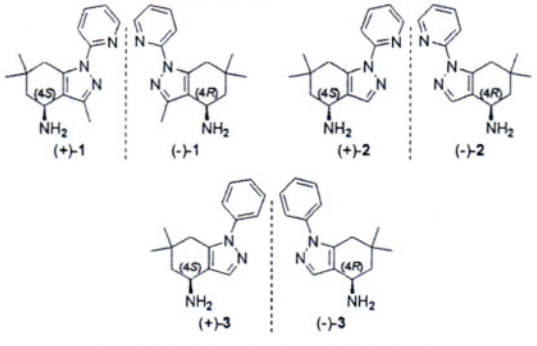

Fig.1. Obtained chiral 4-amino-tetrahydroindazoles

Chiral resolution of racemic amines **1-3** can be performed by following enantiomerically pure acids: tartaric acid, di-*O*,*O*'-benzoyl-tartaric acid, camphoric acid. It is interesting to note that in the case of *N*(1)-substituted 4-amino-tetrahydroindazoles **1** and **2** (+)-(1*R*,3*S*)-camphoric acid and (-)-(2*R*,3*R*)-*O*,*O*'-dibenzoyl tartaric acid (L-form) produce the precipitate with the same amine enantiomer. Thus, they are exchangeable. This allows to exchange also (-)-(1*S*,3*R*)-camphoric acid with (+)-(2*S*,3*S*)-*O*,*O*'-dibenzoyl tartaric acid (D-form). The latter observation is important form economical viewpoint as (-)-camporic acid is much more expensive then (+)-dibenzoyl tartaric acid. The absolute configuration of obtained amines was unambiguously established by single crystal X-ray analysis in one case (Fig. 3).

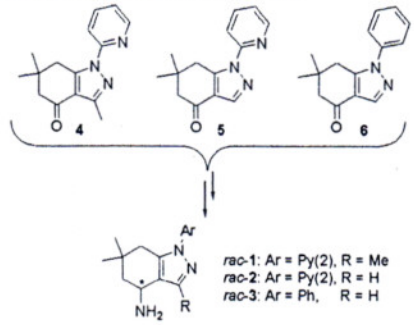

Fig.2. Synthesis of racemic amines **4-6**.

With the developed experimental conditions amines **1-3** can be obtained with good isolated yields and excellent ee's (up to 98%).

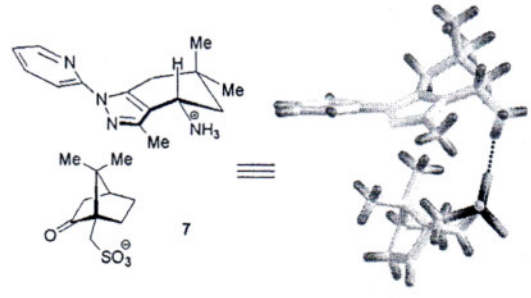

Fig.3 Molecular structure of salt **7** between (4*S*)-4-amino-3,6,6-trimethyl-1-(pyrid-2-yl)-4,5,6,7-tetrahydro-1*H*-indazole and (-)-(*R*)-camphor-10-sulfonic acid.

III. References

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