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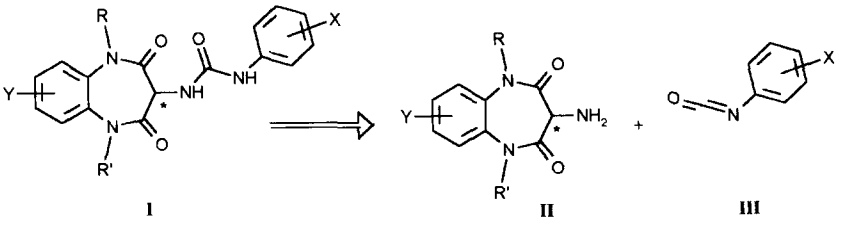
A New Method for the Resolution of Amines and its Application to 3-Amino-1,5-Benzodiazepines

Giovanni Curotto*, Daniele Donati, Gabriella Finizia, Antonella Ursini
Glaxo Research Laboratories, Via A. Fleming 4, 37153 Verona, Italy

Abstract: A new method for the resolution of racemic amines and its application to 3-amino-1,5-benzodiazepines is reported. The method is based upon the reaction of the amines with a chiral auxiliary, namely the tosyl derivative of (S)-(+)-methyl mandelate, followed by the separation of the two diastereomers formed and the subsequent hydrogenation of the separated compounds to give the free chiral amines with good enantiomeric excesses.

Benzodiazepines are very important templates in pharmaceutical research. In the course of our studies on non-peptidic antagonists of cholecystokinin at the CCK-B receptor we synthesized a series of N-(1,5-benzodiazepin-3-yl)-N'-arylureas of general formula **I** shown below (*Scheme 1*).

Scheme 1



I **II** **III**

The possibility for such compounds to exist in two enantiomeric forms, due to the presence of a stereogenic center at C3, and the consideration that the two enantiomers could exhibit different pharmacological activities prompted us to search for a method by which we could obtain the pure enantiomers.

The precursors of the ureidic bond are the free amine **II** and the arylisocyanate **III**, as illustrated. Since the reaction between the amines and the arylisocyanates is unlikely to cause racemization at C3, it is clear that it would be possible to obtain the enantiomerically pure ureas after separation of the corresponding amines.

Several methods for the resolution of 3-amino-1,4-benzodiazepines are reported in the literature; among them the most common is the formation and preferential crystallization of diastereomeric salts with chiral acids

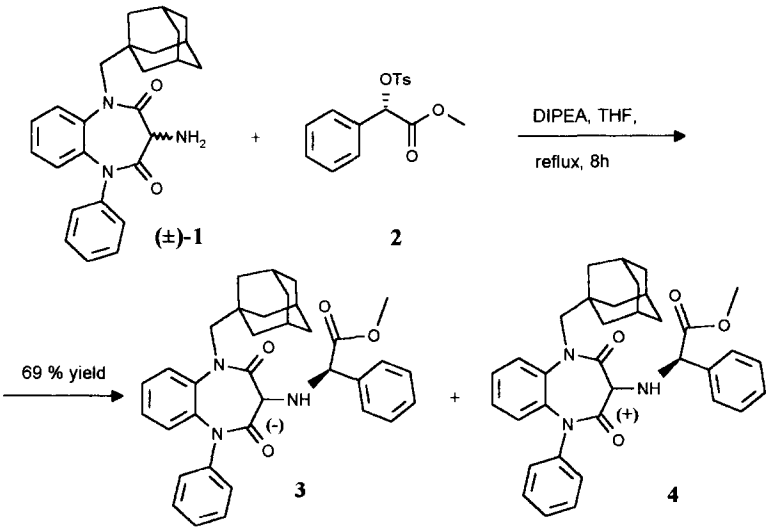
(e.g. camphorsulphonic acid[1]). The use of covalent diastereomeric derivatives (e.g. amides) is generally precluded by the strong conditions required for their cleavage to obtain the resolved amines. Recently the resolution of 3-amino-1,4-benzodiazepines was achieved by means of the preparation and separation of diastereomeric phenylalanyl amides followed by removal of phenylalanine *via* the Edman degradation[2]. This procedure was also applied to the 1,5-benzodiazepine series[3].

We wish to report the development of a new method of resolution involving the formation of two diastereomeric phenylglycine derivatives by the reaction between the racemic amines and (S)-(+)-2-(4-toluenesulfonyloxy)-phenylacetic acid methyl ester, **2**, as the chiral auxiliary. The procedure is illustrated by the resolution of compound **(±)-1**, a key intermediate in our recent studies on CCK-B antagonists[4].

The choice of **2** as chiral auxiliary has several advantages: a) it can be easily synthesized[5], b) it is readily available in both enantiomeric forms, c) it is relatively inexpensive and, above all, d) it can be easily removed without affecting the optical purity of the substrates.

The reaction to form the diastereomers was carried out in conditions not affecting the enantiomeric purity of the chiral auxiliary. Such conditions were found to be refluxing in THF for 8 hours with diisopropylethylamine (DIPEA) as the base needed to neutralize the p-toluenesulfonic acid formed. The diastereomeric compounds **3** and **4** were obtained in a 69% overall yield and were easily separated by flash-chromatography (eluting with mixtures 1:2 and 1:3 of ethyl acetate and cyclohexane)[6] (*Scheme 2*).

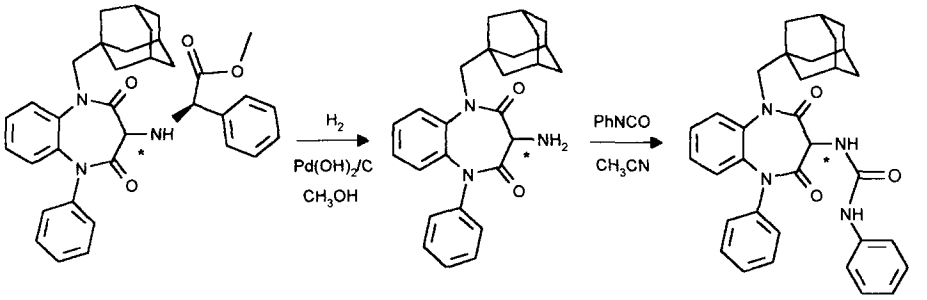
Scheme 2



Hydrogenation[7,8] of the separated diastereomers **3** and **4**, afforded the corresponding amines **(-)-1** and **(+)-1** in 85% and 69% yield respectively. These were then reacted with phenylisocyanate to give the desired ureas **(-)-5** and **(+)-5** in 92% and 68% yield respectively[9] and in good enantiomeric excesses[10]. The

enantiomeric excesses of the ureas **(-)-5** and **(+)-5** reflect those of amines **(-)-1** and **(+)-1** and thus are an indication of the efficiency of the method[11] (*Scheme 3*).

Scheme 3



* =(-) **3** **(-)-1** **(-)-5**
* =(+) **4** **(+)-1** **(+)-5**

The enantiomeric excesses of compounds **(-)-5** and **(+)-5** were high enough to allow for pharmacological evaluation. The results obtained will be reported elsewhere.

In conclusion, a new chemical method was established to resolve racemic 3-amino-1,5-benzodiazepines. All the reactions used are of proven generality, the chiral auxiliary is readily available in both enantiomeric forms and the auxiliary moiety can be easily applied and removed.

Acknowledgements

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References and Notes

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5. Tosyl chloride was slowly added to a cooled solution (0 °C) of (S)-(+)-methyl mandelate and triethylamine in dichloromethane. The mixture was stirred between 0 and 5 °C (in order to avoid

racemization of **2**) for 7-8 hours. The mixture was then washed with 10% aqueous hydrochloric acid and brine, dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by flash chromatography (eluting with CH/EA 5:1 then 2:1) to give compound **2** as a white wax in a 60% yield. TLC: R_f=0.54 (cyclohexane/ethyl acetate 2:1), HPLC: e.e.=98%, M.p.: 57-58 C, $[\alpha]_D$=+61.7 (c=1.085, $CHCl_3$).

6. Compound **3**: TLC: R_f=0.24 (cyclohexane/ethyl acetate 3:1), HPLC: d.e.=100%, $[\alpha]_D$=-109.5 (c=0.795, $CHCl_3$) M.p.: 170-173 °C. Compound **4**: R_f=0.20, d.e.=90%, $[\alpha]_D$=-25.9 (c=0.755, $CHCl_3$) M.p.: 135-140 °C
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8. In a typical experiment 20% palladium (II) hydroxide on charcoal was added to a methanol solution of the phenylglycine derivative. The mixture was hydrogenated at atmospheric pressure for 6 hours. The mixture was then filtered on a Celite® pad and the crude was purified by flash chromatography eluting with mixtures of ethyl acetate/cyclohexane then ethyl acetate/methanol.
9. In a typical experiment phenyl isocyanate was added to a solution of the amine in acetonitrile. The mixture was kept at room temperature for 10 minutes and then purified by flash chromatography eluting with mixtures of ethyl acetate and cyclohexane.
10. Compound **(-)-5**: TLC: R_f=0.38 (cyclohexane/ethyl acetate 2:1) HPLC: e.e.=94%, $[\alpha]_D$=-34.8 (c=0.870, $CHCl_3$) M.p.: 262-265 °C. Compound **(+)-5**: R_f=0.38, e.e=88%, $[\alpha]_D$=+35.5 (c=0.933, $CHCl_3$) M.p.: 263-265 °C
11. All the new compounds were characterized by means of NMR, MS, IR and HPLC.

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