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Research Article

The Synthesis of Optically Active Antipyrylmethyl-Amine Derivatives

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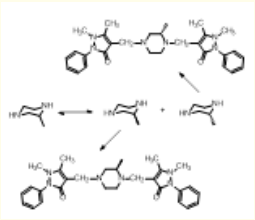
Abstract

The antipyrylmethyl substitution of primary and secondary achiral and chiral amines as well as bis amines was studied. Enantiomer selective Mannich condensation and the optical resolution of racemic Mannich bases were also attempted in order to synthesize antipyrine-containing Mannich bases in an enantiomeric pure form.

Keywords: Antipyrine; Mannich Reaction; Optical Resolution; One Pot; Parallel Synthesis



Graphical Abstract

Introduction

Antipyrine – the first drug with fever and pain release effect – and its derivatives are well known of their antibacterial and anti-inflammatory properties [1]. In search of new antipyretic agents, Mannich and Kather synthesized ligands containing antipyrine moieties, among them, N,N'-bis(antipyrylmethyl)-piperazine (BAMP) [2]. Metal complexes of such ligands have been proved to have antitumor [3-5], antibacterial activity [6,7] or they have found other applications [8,9].

Mannich reaction has been successfully applied for the bis antipyrylmethyl substitution of primary and secondary amines. The cobalt(II) and copper(I) complexes of the bis(antipyrylmethyl)-amines so-obtained were also synthesized [10] and were found to be of potential pharmaceutical interest due to their beneficial physiological effects [5]. Therefore, we aimed at studying the antipyrylmethyl substitution of primary and secondary achiral and chiral amino groups. In case of primary amines, the bis-antipyrylmethyl substitution is preceded by the formation of the corresponding secondary amine. Thus we studied the substitution of secondary bis amines as well.

The optical resolution of the resulting racemic Mannich bases was also attempted, however the synthesis of the pure enantiomers appears to be more beneficial by the antipyrylmethyl substitution of the enantiomers of the base applied. Nevertheless, if these enantiomers are considerably more expensive as compared to the racemic compounds, the resolution of racemic amines followed by their antipyrylmethyl substitution appears to be more efficient for the synthesis of chiral bis(antipyrylmethyl)-amines. A coupled method may be particularly advantageous applying the "branched parallel one pot" resolution and subsequent Mannich condensation of the racemic bases.

Materials and Methods

General procedure for the synthesis of BAMMP: To 1.40 mmol (0.14 g) racemic methylpiperazine (MP) was added 0.25 mL ccHCl in 5 mL of water and stirred at 0°C till the MP has completely dissolved. To this mixture, 2.80 mmol (0.52 g) antipyrine and 0.37 mL formaldehyde (as a 35% aqueous solution) was added. The reaction mixture was stirred at 0-5 °C for 6 hours. After completion of the reaction, the mixture was extracted by 15 mL of dichloromethane. After separation of the phases, 1.5 ml 30% V/V% KOH/aq was added to the aqueous phase. The opal solution obtained was extracted by 15 mL of dichloromethane. The organic phase was dried over Na_2SO_4. The product so-obtained was crystallized from diethyl ether. All other derivatives were synthesized following the same protocol.

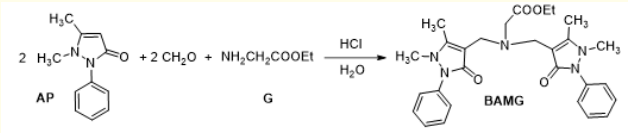
BAMMP: ^{1}H NMR (499.9 MHz, $CDCl_3$) δ (ppm) 1.25 (d, J = 6.1 Hz, 3H, C_2-CH_3), 2.09–2.15 (m, 1H, C_3-H_{ax}), 2.266 (s, 3H), 2.272 (s, 3H): $C_{5'}$-CH_3, $C_{5''}$-CH_3, 2.31–2.37 (m, 1H, C_5-H_{ax}), 2.37–2.44 (m, 1H, C_6-H_{ax}), 2.50–2.70 (br m, 1H, C_2-H_{ax}), 2.76–2.83 (m, 2H, C_3-H_{eq}, C_5-H_{eq}), 2.83–2.88 (m, 1H, C_6-H_{eq}), 3.052 (s, 3H), 3.053 (s, 3H): $N_{1'}$-CH_3, $N_{1''}$-CH_3), 3.19 (d, J = 13.6 Hz, 1H, C_7-H_x), 3.28 & 3.33 (AB, J = 13.5 Hz, 2H, C_8-H_2), 3.67 (d, J = 13.6 Hz, 1H, C_7-H_y), 7.23–7.27 (m, 2H, 2xPh: H_{para}), 7.36–7.39 (m, 4H, 2xPh: H_{ortho}), 7.41–7.45 (m, 4H, 2xPh: H_{meta}). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm) 11.6 ($C_{5'}$-CH_3, $C_{5''}$-CH_3), 17.5 (C_2-CH_3), 36.0 ($N_{1'}$-CH_3, $N_{1''}$-CH_3), 45.0 (C_7), 49.7 (C_8), 51.1 (C_6), 52.5 (C_5), 55.1 (C_2), 60.2 (C_3), 106.0 ($C_{4''}$), 106.7 ($C_{4'}$), 123.7 (2xPh: C_{ortho}), 126.2 (2xPh: C_{para}), 129.0 (2xPh: C_{meta}), 135.4 (2xPh: C_{ipso}), 155.6 ($C_{5'}$, $C_{5''}$), 166.3 ($C_{3''}$), 166.4 ($C_{3'}$). HRMS: M+H=501.29690 (delta=-1.8 ppm; $C_{29}H_{37}O_2N_6$). ESI-HR-MS-MS (CID=35%; rel. int. %): 389(100); 313(26); 299(27); 201(60); 189(8).

Results and Discussion

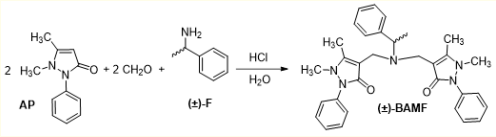
Bis Antipyrylmethyl substitution of primary amines

As the first model, primary amines, such as glycine ethyl ester (G) and racemic phenylethylamine (F) were used as the amine component. Following the method known from the literature 2,10 starting from antipyrine, formaldehyde, and the chlorohydrate of the primary amine (G or F) in a 2:2:1 ratio, at a low temperature (0–5°C), the desired bis antipyril adducts (BAMG or BAMF) were obtained in yields of 76% and 84%, respectively (Schemes 1 and 2). Starting from racemic phenylethylamine, racemic BAMF was obtained.

It is worth mentioning, that combining separate pharmacophoric groups into one compound may generate novel molecular templates which are likely to exhibit interesting biological properties.



Scheme 1: Synthesis of BAMG.



Scheme 2: Synthesis of BAMF.

Bis Antipyrylmethyl substitution of secondary amines

The metal complexes of N,N'-bis(antipyrylmethyl)-piperazine (BAMP) are known and were also proved to have beneficial physiological effects [5].

We investigated the synthesis of the methyl-substituted derivative of BAMP, named as BAMMP (Figure 1), where the methyl substituent is located on the piperazine ring, introducing a new asymmetry center into the molecule. The synthesis of BAMMP was carried out starting from racemic methylpiperazine ((±)-MP) as well as from its enantiomers ((*R*)-(-)-MP and (*S*)-(+)-MP), with particular regard to the significant deviation of their prices.

Racemic BAMMP could be obtained in a yield of 77%, although 8% of the mono-substituted MMAMP was formed as a by-product (Scheme 3).

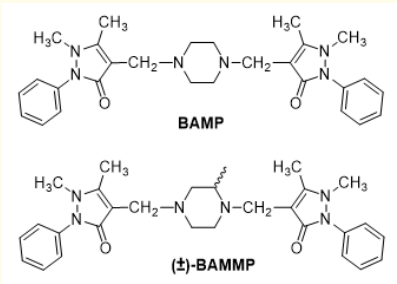
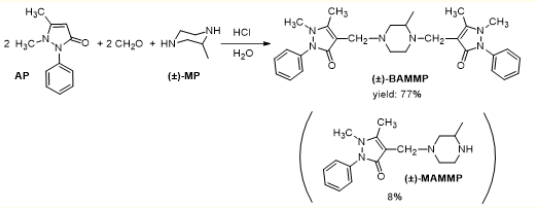


Figure 1: The structures of BAMP and BAMMP.

When the enantiomers are to be produced, the cost of the starting ((*R*)-(-)-MP and (*S*)-(+)-MP) is up to 100-140 times the price of the racemic amine. Thus, when preparing any of the



Scheme 3: Synthesis of BAMMP.

enantiomers of BAMMP, only racemic methylpiperazine ((±)-MP) can be considered as the starting material.

Another option would be the optical resolution of (±)-BAMMP, that was attempted with (*R,R*)-tartaric acid. The specific optical rotation of the base separated from the diastereomeric salt precipitated indicated the reaction of (*R*)-(-)-BAMMP.

We further stated, that the synthesis of (*R*)-(-)-BAMMP starting from optically pure (*R*)-(-)-MP (obtained from MERCK) resulted in a yield of 82% with an optical rotation of [α]20D –5.8° (c = 1, ethanol).

In essence, similar results (82% yield and [α]20D +5.0°) were obtained in the synthesis of (*S*)-(+)-BAMMP (Figure 2) and the same yields were obtained when preparing the racemic BAMMP.

We did not succeed in separating racemic MP enantiomers with either mandelic nor camphorsulfonic acid. At the same time using

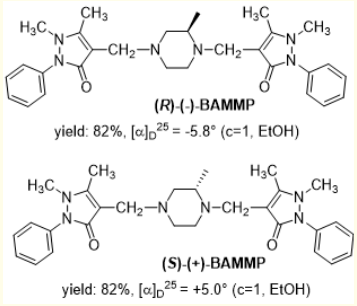
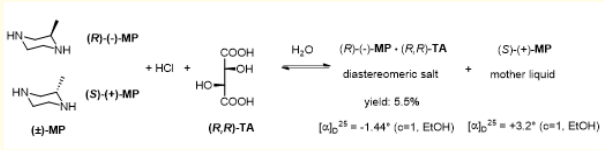


Figure 2: The structures of (*R*)- and (*S*)-BAMMP.

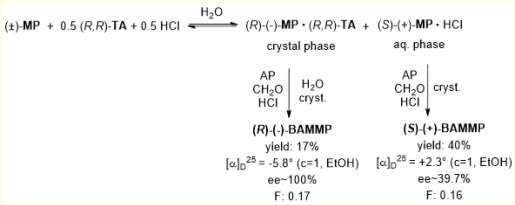
(*R,R*)-tartaric acid both from the aqueous and ethanolic solutions, the (*R*)-(-)-MP containing diastereomeric salt was crystallized (Scheme 4). However, both the yield and enantiomeric purity of the enantiomers isolated from the diastereomeric salt and from the mother liquor are low ((*R*)-(-)-MP yield: 5,5%, ee~25%; (*S*)-(+)-MP yield: 8,5%, ee~50%). The low productivity and the low enantiomeric purity are primarily due to the fact that the solubility of the MP is rather good in water, thus we could not achieve good separation even on the addition of concentrated or solid KOH. This solubility problem is further deteriorated by the higher solubility of the enantiomeric excess of the dissolved base enantiomer mixtures as compared to the racemic ratio [11].

Subsequently, the diastereomeric salt and mother liquor



Scheme 4: Optical resolution of (±)-MP.

obtained by resolving the racemic methyl piperazine by (*R,R*)-tartaric acid were separated, then these phases were individually and directly submitted to "branched parallel one pot" Mannich condensation in reaction with antipyrine, formaldehyde and hydrochloric acid (in a calculated amount, based on the diastereomeric salts) (Scheme 5).



Scheme 5: The synthesis of BAMMP enantiomers.

From the diastereomeric salt (*R*)-(-)-BAMMP was isolated in a yield of 17% and enantiomeric purity of ee ~ 100%. The enantiomeric efficiency (F) was 0.17. From the mother liquor, (*S*)-(+)-BAMMP was obtained in yield of 40% with an ee of 39.7% and efficacy of 0.16.

The overall yield of 17% may arise from 41-41% yields in two steps, and that of 40% final yield may result from 63-63% yields in two steps, both of which are acceptable.

If MP enantiomers are used to produce BAMMP enantiomers, we have to pay 100-140 times the (±)-MP price. On the other hand, starting from (±)-MP applying the "branched parallel one-pot" resolution and subsequent Mannich reaction, we only have to pay 7 times of the racemic (±)-MP price.

Conclusion

In conclusion, the Mannich reaction was successfully applied for the preparation of antipyrinylmethylamine derivatives, by the bis substitution of primary achiral and chiral amines. The substitution of secondary amine, methyl piperazine and its enantiomers was also investigated, but due to the high price of the starting methyl-piperazine enantiomers, the optical resolution of the racemic MP was also solved using (*R,R*)-tartaric acid. Despite the effective separation of MP enantiomers, neither the ee nor the yield was suitable for the synthesis of BAMMP enantiomers. Thus, the diastereomers obtained by resolution were directly submitted to Mannich reaction without isolation, yielding the previously unknown BAMMP enantiomers with good enantiomeric purity and acceptable yield.

Acknowledgements

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