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An efficient and environmental-friendly synthesis of 4-hydroxy-arylpiperidines using hydrotalcite catalyst

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Abstract

A practical and convenient method for the synthesis of 4-hydroxy-arylpiperidines, starting from bis-ketonic Mannich-bases (bis-[3-aryl-3-oxopropyl]-amines) in the presence of a commercially available non-activated 2:1 Mg:Al hydrotalcite, is described.

Keywords: Hydrotalcite; Arylpiperidinols; Cyclisation; Mannich-bases

1. Introduction

Many natural compounds and drugs contain piperidine derivatives as a structural element, so in the recent years much attention has been paid towards the development of an efficient synthesis of these compounds. 4-Hydroxy-arylpiperidines have been investigated as potential biologically active agents, such as a novel class of dopamine transporter (DAT) inhibitors [1,2], cytotoxic agents [3], or potential anticonvulsant compounds [4]. 4-Piperidinols can be also directly used as intermediates for the synthesis of important compounds e.g. the popular antihistaminic agent phenindamine tartrate (Thephorin) [5,6].

Only few synthetic methods have been described for the preparation of 4-hydroxy-arylpiperidines such as cyclisation of bis-ketonic Mannich-bases (bis-[3-aryl-3-oxopropyl]-amines) with aqueous sodium hydroxide [4,7], or a direct reaction of an amine hydrochloride with an excess of aryl methyl ketone and paraformaldehyde in the presence of a catalytic amount of hydrochloric acid. These reactions require toxic, corrosive basic or acidic catalysts, or long reaction time.

Nowadays the use and design of environmental-friendly solid acid and solid base catalysts has become an important research target. These materials have a lot of useful properties e.g. high versatility, easy treatment and work-up, mild experimental conditions, high yield and selectivity, they are inexpensive and often regenerable. Hydrotalcites (HT), the anionic layered double hydroxides have potential application as adsorbents, anion-exchangers and basic catalysts. Numerous studies on their structure [8], physical properties [9] and their catalytic activity have been reported e.g. in Michael addition [10], Knoevenagel condensation [11], or even in a complex reaction for the preparation of cyclopropane carboxylic acid derivatives [12], too.

During our synthetic activity we investigated the reaction of bis-ketonic Mannich-bases in the presence of different HT types. The applied bases were activated and non-activated Mg:Al 3:1 hydrotalcite and the commercially available Mg:Al 2:1 hydrotalcite.

2. Experimental

^{1}H NMR spectra were recorded on Bruker AW-250 (250 MHz) spectrometer using TMS as internal standard. ^{13}C NMR spectra were recorded on Bruker Avance DRX-500 (125 MHz) spectrometer. Melting points were determined on Gallenkamp apparatus and were uncorrected. TLC

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was performed on Merk Kieselgel plates (60 F_{254}), eluent: acetone. The spectral and physical data of the known compounds were identical with those reported in the literature (see Tables 2 and 3). The new compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and by elemental analysis.

2.1. Synthesis of hydrotalcite

The Mg:Al 2:1 hydrotalcite was the commercially product of Süd-Chemie AG, München (HSA-type).

The Mg:Al 3:1 hydrotalcite was prepared according to the method described by Rao et al. [13]. The activation of the catalyst was modified; the catalyst was first activated by calcining at 723 K, then the solid was cooled under dry nitrogen and rehydrated at room temperature with distilled water, and dried under vacuo at 80 °C for 8 h. The presence of the pure hydrotalcite structure was confirmed by XPS and TG/DTA.

2.2. Synthesis of bis-Mannich-bases

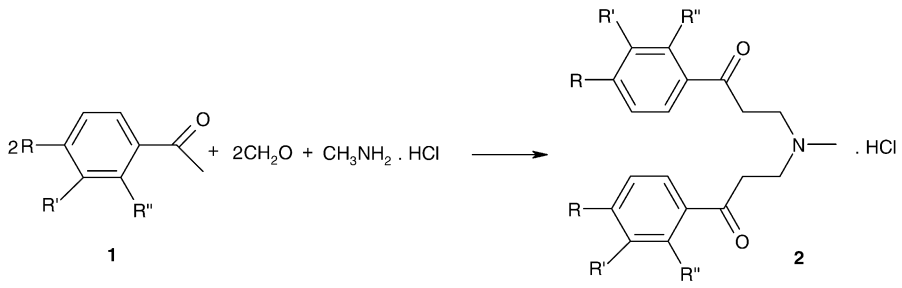
Compounds **1a**, **b**, **c**, **d**, **e**, **f**, **i**, **j**, **k** were prepared according to the method described by Gul et al. [4]. Compounds **1g**, **h** were prepared according to the method described by Plati and Wanner [14]. The known products were characterized by comparing the ^{1}H NMR and melting points data with those reported in the literature.

Spectral and analytical data of the new compounds: bis-[3-[3-methoxyphenyl]-3-oxopropyl]-methylamine hydrochloride (**2g**) – yellow oil, ^{1}H NMR ($CDCl_3$) δ (ppm): 2.91 (s, 3H, N–CH_3), 3.69 (m, 8H, 4 × CH_2), 3.89 (s, 6H, 2 × Ar–OCH_3), 7.14 (d, 2H, Ar–H), 7.34 (m, 2H, Ar–H), 7.48 (s, 2H, Ar–H), 7.52 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ (ppm): 33.73, 40.86, 51.92, 55.62, 111.54, 112.86, 122.22, 129.92, 136.62, 145.80, 160.02, 195.93. $C_{21}H_{26}ClNO_4$ Anal. Calcd. C 64.37, H 6.64, N 3.58, Found C 64.29, H 6.72, N 3.61. Bis-[3-[2-methoxyphenyl]-3-oxopropyl]-methylamine hydrochloride (**2h**) – m.p. 193–195 °C (ethanol, ether), ^{1}H NMR ($CDCl_3$) δ (ppm): 2.86 (s, 3H, N–CH_3), 3.63 (m, 8H, 4 × CH_2), 3.98 (s, 6H, 2 × Ar–OCH_3), 7.04 (m, 2H, Ar–H), 7.11 (m, 2H, Ar–H), 7.54 (d, 2H, Ar–H), 7.77 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ (ppm): 32.87, 41.16, 51.63, 55.58, 111.62, 113.12, 121.18, 128.63, 134.38, 142.69, 159.46, 197.42. $C_{21}H_{26}ClNO_4$ Anal. Calcd. C 64.37, H 6.64, N 3.58, Found C 64.21, H 6.58, N 3.51. Bis-[3-[2-methylphenyl]-3-oxopropyl]-methylamine hydrochloride (**2i**) – m.p. 119 °C (ethanol, ether), ^{1}H NMR ($CDCl_3$) δ (ppm): 2.46 (s, 6H, 2 × Ar–CH_3), 2.87 (s, 3H, N–CH_3), 3.61 (m, 8H, 4 × CH_2), 7.33–7.38 (d + m, 4H, Ar–H), 7.5 (m, 2H, Ar–H), 7.91 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.93, 38.87, 40.13, 50.39, 125.98, 129.10, 131.82, 136.57, 137.58, 200.08. $C_{21}H_{26}ClNO_2$ Anal. Calcd. C 70.10, H 7.23, N 3.89, Found C 70.02, H 7.25, N 3.85. Bis-[3-[2-chlorophenyl]-3-oxopropyl]-methylamine hydrochloride (**2j**) – m.p. 112 °C (ethanol, ether) ^{1}H NMR ($CDCl_3$) δ (ppm): 2.77(s, 3H, N–CH_3), 3.69 (m, 8H, 4 × CH_2), 7.32–7.39 (m, 4H, Ar–H), 7.45 (d, 2H, Ar–H), 7.69 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ (ppm): 34.12, 41.78, 53.06, 128.86, 130.43, 131.06, 135.62, 140.28, 197.62. $C_{19}H_{20}Cl_3NO_2$ Anal. Calcd. C 56.93, H 4.99, N 3.50, Found C 56.89, H 5.05, N 3.54. Bis-[3-[2-bromophenyl]-3-oxopropyl]-methylamine hydrochloride (**2k**) – yellow oil, ^{1}H NMR ($CDCl_3$) δ (ppm): 2.83 (s, 3H, N–CH_3), 3.75 (m, 8H, 4 × CH_2), 7.34–7.42 (m, 4H, Ar–H), 7.52 (m, 2H, Ar–H), 7.8 (m, 2H, Ar–H) ^{13}C NMR ($CDCl_3$) δ (ppm): 33.96, 41.62, 51.83, 120.73, 128.62, 129.96, 131.53, 136.04, 141.31, 199.02. $C_{19}H_{20}Br_2ClNO_2$ Anal. Calcd. C 46.58, H 4.08, N 2.86, Found C 46.53, H 4.05, N 2.91.

2.3. General procedure for the cyclisation

A mixture of the bis-Mannich base (5 mmol) and hydrotalcite (0.1 g) in ethanol (10 ml) was stirred at 80 °C for 7 h. Then the catalyst was filtered off and washed with ethanol. The filtrate was evaporated, the residue was dried and crystallised from methanol or ethanol to give the corresponding piperidinol derivative. In some experiments the progress of the reaction was monitored by TLC.

Spectral and analytical data of the new compounds: 3-[4-methoxybenzoyl]-4-[4- methoxyphenyl]- 4- hydroxy- 1-methylpiperidine (**3f**) – m.p. 103–110 °C (ethanol, ether), ^{1}H NMR (DMSO-d_6) δ (ppm): 1.78 (d, 1H, H5a, J = 13.7 Hz), 2.58 (m, 1H, H5e), 2.84 (s, 3H, N–CH_3), 3.55 (m, 4H), 3.86 (s, 6H, 2 × Ar–OCH_3), 5.05 (bs, 1H, OH), 5.34 (dd, 1H, J = 3.5, 11.4 Hz), 7.11 (d, 2H, Ar–H), 7.31 (d, 2H, Ar–H), 7.75 (d, 2H, Ar–H), 7.99 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ (ppm): 38.82, 40.23, 50.45, 55.24, 70.64, 113.64, 113.98, 125.87, 128.80, 129.62, 130.44, 137.38, 158.10, 198.09. $C_{21}H_{25}NO_4$ Anal. Calcd. C 70.98, H 7.04, N 3.94, Found C 70.96, H 7.06, N 3.95. 3-[3-Methoxybenzoyl]-4-[3-methoxyphenyl]-4-hydroxy-1-methyl-piperidine (**3g**) – yellow oil, ^{1}H NMR ($CDCl_3$) δ (ppm): 1.95 (d, 1H, H5a, J = 14 Hz), 2.84 (m, 1H, H5e), 2.87 (s, 3H, N–CH_3), 3.47 (m, 4H), 3.86 (s, 6H, 2 × Ar–OCH_3), 5.1 (bs, 1H, OH), 5.52 (dd, 1H, J = 3.7, 11.2 Hz), 7.08–7.12 (m, 4H, Ar–H), 7.15 (m, 2H, Ar–H), 7.3 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ (ppm): 39.82, 45.76, 50.94, 51.23, 54.44, 55.38, 72.52, 122.63, 125.44, 126.51, 127.09, 128.41, 129.48, 130.13, 134.02, 134.53, 135.42, 137.20, 149.19, 202.21. $C_{21}H_{25}NO_4$ Anal. Calcd. C 70.98, H 7.04, N 3.94, Found C 71.03, H 7.01, N 3.90. 3-[2-Methoxybenzoyl]-4-[2- methoxyphenyl]- 4-hydroxy- 1-methylpiperidine (**3h**) – m.p. 164–165 °C (ethanol, ether), ^{1}H NMR ($CDCl_3$) δ (ppm): 1.73 (d, 1H, H5a, J = 13.5 Hz), 2.76 (m, 1H, H5e), 2.87 (s, 3H, N–CH_3), 3.45 (m, 4H), 4.13 (s, 6H, 2 × Ar–OCH_3), 5.3 (s, 1H, OH), 5.79 (d, 1H, J = 4, 11.5 Hz), 6.83 (d, 1H, Ar–H), 6.99–7.11 (m, 3H, Ar–H), 7.27–7.35 (m, 3H, Ar–H), 7.53 (d, 1H, Ar–H). ^{13}C NMR ($CDCl_3$) δ (ppm): 34.07, 45.21, 51.13, 52.01, 53.78, 55.46, 73.98, 126.18, 127.18, 128.89, 129.02, 129.19, 130.75, 131.43, 131.85, 132.28,



Scheme 1.

138.31, 142.11, 201.90. $C_{21}H_{25}NO_4$ Anal. Calcd. C 70.98, H 7.04, N 3.94, Found C 71.02, H 7.08, N 3.96. 3-[2-Bromobenzoyl]-4-[2-bromophenyl]- 4- hydroxy- 1-methylpiperidine (**3k**) – m.p. 180 °C (ethanol, ether), ^{1}H NMR (methanol-d_4) (ppm): 1.71 (d, 1H, H5a, $J = 12.6$), 2.79 (m, 1H, H5e), 2.93 (s, 3H, N-CH_3), 3.53 (m, 4H), 5.03 (bs, 1H, OH), 5.36 (dd, 1H, $J = 4$, 11.5 Hz), 6.98–7.02 (m, 2H, Ar–H), 7.12–7.28 (m, 4H, Ar–H), 7.86 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ (ppm): 34.02, 46.18, 50.78, 51.52, 53.26, 73.22, 126.63, 127.11, 128.57, 128.74, 128.96, 130.55, 131.46, 131.92, 132.37, 138.43, 142.17, 204.87.

3. Results and discussion

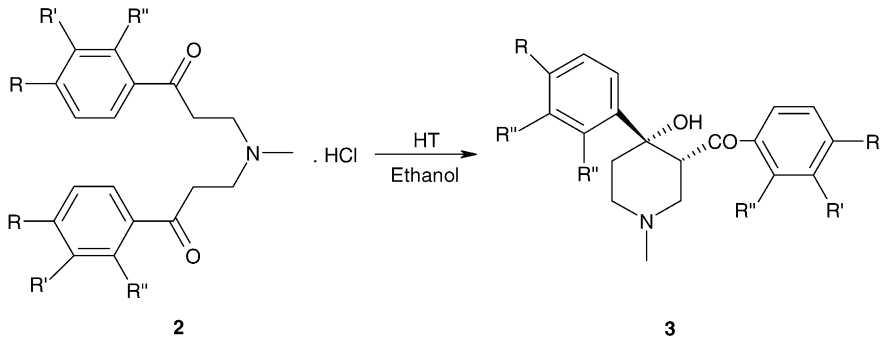
Bis-Mannich-bases were synthesized using known methods published either by heating paraformaldehyde with methylamine hydrochloride and acetophenone or substituted acetophenones without solvent (A) [4], or by refluxing the ethanolic solution of these compounds for 5h (B) (Scheme 1) [14].The results are summarized in Table 1. In some cases (**2a**, **e**, **f**) we obtained higher yield than the described ones. Compounds **2h**, **i**, **j**, **k** have not been described in the literature yet and the *meta*-methoxy derivative **2g** was described only as oxalate salt. The structure of these new compounds were confirmed by their spectroscopical and analytical data (see Section 2).

When **2a** was treated with catalytic amount of rehydrated Mg:Al 3:1 hydrotalcite under reflux in ethanol (Scheme 2), the corresponding 4-hydroxypiperidine **3a** was obtained in good yield (Table 2). As it was shown earlier [6], during the cyclisation only the diastereoisomer **3** depicted in Scheme 2 was formed, because of steric hindrance and the possibility of an hydrogen-bond formation between the carbonyl oxy-

Table 1
Synthesis of bis-Mannich-bases

2	*R*	*R′*	*R″*	Method	Melting point (°C) (lit.)	Yield (%)[a]
a	H	H	H	A	163.5 (166–169[14])	89
b	Cl	H	H	A	161.5 (165[4])	42
c	Br	H	H	A	187 (189–191[6])	40
d	F	H	H	A	348 (350[17])	44
e	CH_3	H	H	A	161 (161.5[4])	57
f	CH_3O	H	H	A	150 (151[4])	64
g	H	CH_3O	H	B	Yellow oil	38
h	H	H	CH_3O	B	193–195	28
I	H	H	CH_3	A	119	80
j	H	H	Cl	A	112	21
k	H	H	Br	A	Yellow oil	25

[a] Isolated yield.



Scheme 2.

Table 2
Results of the cyclisation of **2a** (5 mmol) with various hydrotalcites

Entry	Catalyst type	Catalyst amount (g)	Yield (%)[a]
1	Rehydrated MgAl 3:1 HT	0.3	68
2	Rehydrated MgAl 3:1 HT	0.1	70
3	Non-activated MgAl 3:1 HT	0.1	71
4	Non-activated MgAl 2:1 HT	0.1	70

[a] Isolated yield after crystallisation.

gen and the hydrogen of the the hydroxyl group. This was verified by the coupling constants of the product (see Section 2), which were in agreement with those described in [6].

In order to find the most suitable base catalyst for this reaction, we examined the effect of different hydrotalcites used in different amount. The results (see Table 2) showed that the Mg:Al ratio, the amount of the catalyst and the pretreatment of the catalyst did not effect the yield. Although the Mg:Al 2:1 HT is considered as the less basic species of the samples used, it showed the same activity after a simple drying at 120 °C for 1h as the other samples even in a 0.1 g/5 mmol **2a** scale. This sample was the HSA-type commercial product of Süd-Chemie AG. Based on the data of the manufacturer its molecular formula is $[Mg_4Al_2(OH)_{12}]CO_3$, specific surface (BET) is 80 m^2/g, and the pH of its 5% suspension (filtered) is 8.6. The elemental analysis of the product dried at 110 °C for 2 h gave Al_2O_3 20.5%, MgO 33.8%, CO_2 11.0%, Cl^- <0.1%, $SO_4{}^{2-}$ <0.1%, Na^+ <0.5%. To our best knowledge till now there was only patents published the use of these material as catalyst for some polymerisation reaction in the literature [15,16]. We continued the experiments with this type of hydrotalcite. Thus, a wild range of bis-Mannich-bases were reacted with the same manner as **2a** and the appropriate piperidinols **3** were generally obtained with satisfactory to good yield (Table 3).

Among the *para*-halogene-substituted compounds the fluoro-derivative **2d** gave the best result. The *ortho*-, *meta*- and *para*-methoxy derivatives **2f**,**g**,**h** gave the same result. In the case of the *ortho*-halogene derivatives **2j**,**k** we obtained poorer results, probably due to steric hindrance, while the methyl derivative **2i** failed to react. The ^{1}H NMR spectra and the melting points of the products and their elemental analyses undoubtfully verified that the free bases were obtained during the cyclisation. This was verified also by converting **3a** with alcoholic hydrochloric acid into its HCl-salt. The melting point, the ^{1}H NMR spectrum and the elemental analysis of this known product was in good agreement with the described data [4]. In the absence of hydrotalcite using the free base deliberated from **2a** only 20% of **3a** was obtained. This result showed the catalytic effect of the hydrotalcite in this reaction. The derivatives **3f**, **g**, **h**, **k** have not been described in the literature yet. The bromo derivative **3k** contained small amount of an unseparable impurity.

Table 3
Synthesis of 4-hydroxypiperidines catalysed by non-activated Mg:Al HT (2:1)

3	*R*	*R′*	*R″*	Melting point (°C) (lit.)	Yield (%)[a]
a	H	H	H	140 (142[18])	70
b	Cl	H	H	193.5[b] (168–170[1])	52
c	Br	H	H	165 (170–173[19]) (181[1])	55
d	F	H	H	145 (148–156[19])	75
e	CH_3	H	H	142 (143–145[1])	76
f	CH_3O	H	H	103–110	55
g	H	CH_3O	H	Yellow oil	54
h	H	H	CH_3O	164–165	50
I	H	H	CH_3	–	–
j	H	H	Cl	184–186 (83–85[1])	47
k	H	H	Br	180	30

[a] Isolated yield.
[b] Crystals with 0.25 mol ethanol.

4. Conclusion

In summary, the present report describes a simple and efficient method for the cyclisation of bis-Mannich-bases to 4-hydroxy-arylpiperidines. We have shown that the commercially available non-activated Mg:Al 2:1 hydrotalcite is a convenient and efficient basic catalyst for this reaction. The advantages of our method developed are the following: the reaction is eco-friendly since it does not involve harmful reagents; the experimental and work-up procedure is very simple; the catalyst does not require any complicated pretreatment.

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