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Preparation of novel analgesics via diastereoselective nucleophilic addition to 1-dimethylamino-2-methylpentan-3-one

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Abstract—The diastereoselective synthesis of naphthyl amino alcohols via nucleophilic addition to racemic 1-dimethylamino-2-methylpentan-3-one was studied. The use of the appropriate experimental conditions allowed the synthesis of both diastereoisomers. The relative configurations were established via NOESY experiments.

Nucleophilic addition of organolithium derivatives to β-aminoketones is a convenient method for obtaining chiral aryl amino alcohols, owing to the large number of commercially available bromoaryl compounds. To the best of our knowledge, no reports have been published on the diastereoselectivity of this procedure.

We previously reported[1] an easy and efficient synthesis and a preliminary pharmacological profile of naphthyl amino alcohol **1** (Table 1). The synthetic procedure applied starting from (*R*/*S*)-**2**, (*R*)-**2** or (*S*)-**2** led to the isolation of (2*R*,3*R*/2*S*,3*S*)-**1**, (2*R*,3*R*)-**1** or (2*S*,3*S*)-**1**, respectively; only traces of the other isomers were present in the mother liquor. The isomer (2*R*,3*R*)-**1** showed significant binding to μ, κ and δ opioid receptors and demonstrated an interesting in vivo analgesic activity (eudismic ratio = 3.3 in mouse hot plate tests, HPT). Therefore, the availability of (2*R*,3*S*)-**1** and (2*S*,3*R*)-**1** isomers is important for a deeper comprehension of the relevance of the stereochemical features in the antinociceptive activity.

In this paper an efficient diastereoselective synthesis of either the (2*R*,3*R*/2*S*,3*S*) or (2*R*,3*S*/2*S*,3*R*) racemic diastereoisomers of **1**, **3** and **4** (Table 1) via organolithium addition to **2** is reported. We focused our attention on the stereoselective behaviour of this reaction depending on the solvent, temperature, organolithium reagents either with or without chelation control. The diastereoselectivity study started with the preparation of **3**, according to the previously described procedure for **1**[1] with suitable modifications. Quenching of the reaction with water (instead of HCl) followed by an acid–base work-up allowed us to obtain pure **3** as a mixture of two racemic diastereoisomers as clearly indicated by ^{1}H NMR and HPLC analyses [diastereomeric ratio 59/41 (Table 1, entry 1)]. Pure racemic diastereoisomers were obtained by flash chromatography.[2,3] In this way, suitable amounts of the isomers of **3** were obtained for configurational and pharmacological studies.

The configurational assignments for the diastereomeric naphthyl amino alcohols were made using chromatographic and spectral methods, including NOE measurements, in comparison with (2*R*,3*R*/2*S*,3*S*)-**1**·HCl, whose configuration was already established by X-ray analysis.[4] We found that the major diastereoisomers of **3** possessed the (2*R*,3*R*) and (2*S*,3*S*) configuration. All these results will be presented in detail in a full paper.

In order to improve the diastereoselectivity, the nucleophilic addition of the naphthalenic anion, obtained via metal–halogen exchange with R^1–Li, to ketone **2** was investigated under the experimental conditions reported in Table 1 (entries 1–15). The catch-and-release work-up allowed pure compounds to be obtained, directly

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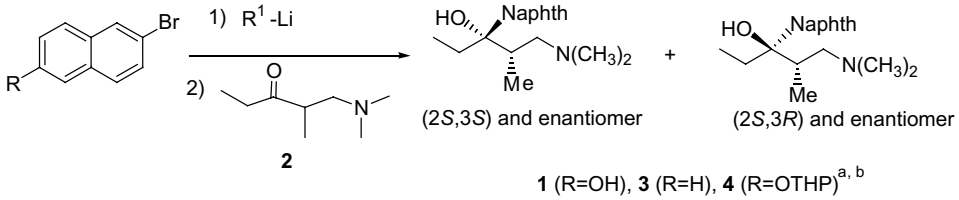
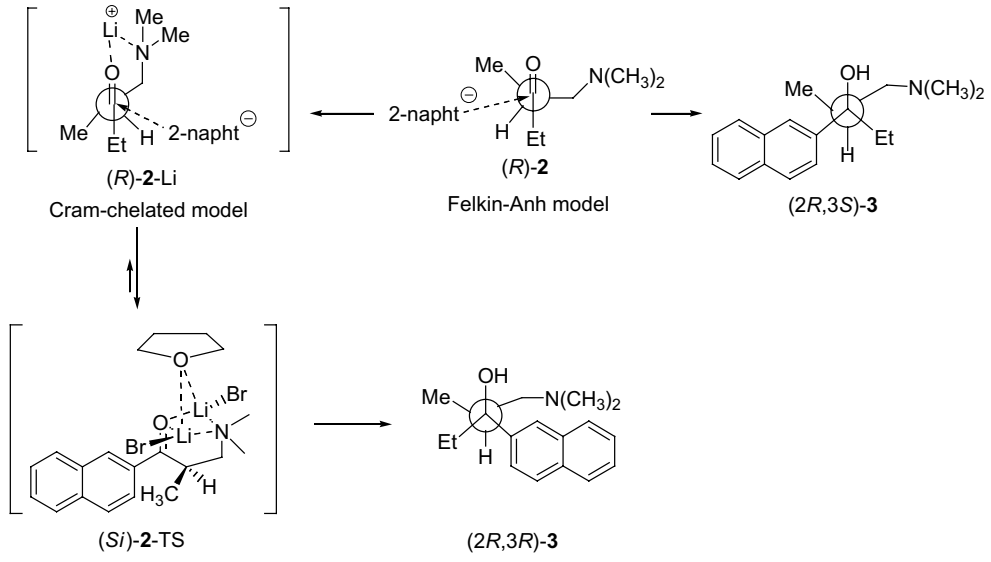
Table 1. Diastereoselective arylation of ketone **2**



1 (R=OH), **3** (R=H), **4** (R=OTHP)[a, b]

Entry	R	R^1	Solvent	*T* (°C)	Diastereomeric ratio[c]
1	H	*n*-Bu	Diethyl ether	−50	59:41
2	H	*n*-Bu	THF	−60	69:31
3	H	*n*-Bu	THF	0	81:19
4	H	*n*-Bu	THF	+10	86:14
5	H	*n*-Bu	THF	rt	83:17
6	H	*n*-Bu	Pentane	−78	—
7	H	*n*-Bu	Pentane	−30	60:40
8	H	*n*-Bu	Pentane	+10	73:27
9	H	*n*-Bu	Toluene	−70	58:42
10	H	*n*-Bu	Toluene	+60	48:52
11	H	*t*-Bu	Pentane	−30	71:29
12	H	*t*-Bu	THF	+10	84:16
13	H	*t*-Bu	Diethyl ether	−70	74:26
14	H	Ph	Pentane	−30	—
15	H	Ph	THF	+10	80:20
16	THP-O[d]	*n*-Bu	THF	+10	72:28
17	THP-O[d]	*n*-Bu	Toluene	+60	71:29
18	THP-O[d]	*n*-Bu	THF	−60	40:60

[a]All compounds were characterized by ^{1}H NMR and elemental analysis.
[b]Procedure: (1) 1.2 equiv of starting material, *n*-BuLi or Ph-Li (1.2 equiv) or *t*-BuLi (2.4 equiv), −78 °C, 1.0 equiv of **2**; (2) quenching (after 4 h) with water; (3) work-up: Amberlyst 15, NH_3 in methanol (3.5 M); (4) purity control of diastereoisomers (HPLC).
[c](2*R*,3*R*/2*S*,3*S*):(2*R*,3*S*/2*S*,3*R*) determined by HPLC.
[d]THP cleavage with DL-tartaric acid (5% solution in water, rt, 30 min).



Scheme 1.

available for HPLC analysis. Concerning the solvents, THF mainly promoted the formation of (2*R*,3*R*/2*S*,3*S*)-**3** (entry 4) whereas toluene led to the formation of (2*R*,3*S*/2*S*,3*R*)-**3** (entry 10). It can be assumed that this difference in the diastereoselection is due to the stability of the Cram-chelate intermediate (*R*)-**2**-Li (Scheme 1) where the bridged lithium atom coordinates both the O and N atoms and activates the CO double bond towards nucleophilic addition. Subsequently, (*R*)-**2**-Li [or (*S*)-**2**-Li] and the O of THF should coordinate a second atom of lithium, giving rise to a more stable polycyclic intermediate (*Si*)-**2**-TS [or (*Re*)-**2**-TS] as reported by

Cimarelli et al.[4] Conversely, the non-coordinating solvent toluene should promote diastereoselective behaviour via the Felkin–Anh model.

The influence of temperature on the diastereomeric ratio was also investigated: by increasing the temperature, increased amounts of (2*R*,3*R*/2*S*,3*S*)-**3** using THF and of (2*R*,3*S*/2*S*,3*R*)-**3** using toluene were observed (Table 1). The organolithium reagents, as well as the chelating agent *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA),[5] did not affect the diastereoselective course of the reaction significantly.

The encouraging results in the synthesis of (2*R*,3*R*/2*S*,3*S*)-**3** prompted us to perform the synthesis of **4** under the same reaction conditions (entry 16); this compound was also obtained as a mixture of two racemic diastereoisomers as was evident from the DOSY (Diffusion Order Spectroscopy) experiment.[6] All these results will be presented in detail in a full paper.

The synthesis of **4** in toluene at +60 °C and in THF at −60 °C (entries 17 and 18) showed an unexpected switchover in the diastereoselectivity with respect to **3**. The tetrahydropyranyl ether in THF at −60 °C could complex the lithium directly, consequently modifying the diastereoselective behaviour according to the Felkin–Anh model; on the other hand the non-coordinating solvent toluene can promote the reaction towards the Cram model (Scheme 1). The major (2*R*,3*R*/2*S*,3*S*)-**4** (entry 16) was identified in the mixture (HPLC) by comparison with (2*R*,3*R*/2*S*,3*S*)-**1**[1] on the basis of the retention times before and after cleavage of the THP group. Subsequently determination of the diastereomeric ratio of **4** was effected directly.

The pharmacological profile of **3** was determined by HPT in mice:[7] the more active diastereoisomer (2*R*,3*S*/2*S*,3*R*)-**3** is 2.5 times more potent than morphine. In conclusion, this method is a simple diastereoselective procedure for preparing a wide variety of aryl amino alcohols, which permits both racemic diastereoisomers to be obtained depending on the experimental conditions employed.

References and notes

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2. Selected spectroscopic data for (2*R*,3*S*/2*S*,3*R*)-**3**: ^{1}H NMR (CD_3OD, 400 MHz) $\delta = 7.80$ (m, 4H, aromatic); 7.48 (m, 3H, aromatic); 3.04 (dd, 1H, N–*H*CH, $J = 13.1$, 6.9 Hz); 2.83 (s, 3H, NCH_3); 2.75 (s, 3H, N–CH_3); 2.68 (dd, 1H, N–HC*H*, $J = 13.1$, 6.9 Hz); 2.42 (qdd, 1H, CH_3–C*H*, $J = 7.1$, 6.9, 6.9 Hz); 2.18 (qd, 1H, CH_3–*H*CH, $J = 7.4$ Hz); 1.94 (qd, 1H, CH_3–HC*H*, $J = 7.4$ Hz); 0.83 (d, 3H, CH_3–CH, $J = 7.1$ Hz); 0.71 (t, 3H, CH_3–CH_2, $J = 7.30$ Hz). Anal. calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.78; H, 9.30; N, 5.15.
3. Selected spectroscopic data for (2*R*,3*R*/2*S*,3*S*)-**3**·HCl: ^{1}H NMR (CD_3OD): 7.92 (m, 4H, aromatic); 7.51 (m, 3H, aromatic); 2.90 (dd, 1H, N–*H*CH, $J = 13.1$, 6.9 Hz); 2.75 (dd, 1H, N–HC*H*, $J = 13.1$, 6.9 Hz); 2.60 (s, 6H, N(CH_3)$_2$); 2.43 (qdd, 1H, C*H*–CH_3, $J = 7.1$, 6.9, 6.9 Hz); 2.02 (m, 2H, CH_3–CH_2); 1.08 (d, 3H, CH_3–CH, $J = 7.1$ Hz); 0.59 (t, 3H, CH_3–CH_2, $J = 7.3$ Hz). Anal. calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.72; H, 9.32; N, 5.32.
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