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HIGHLY REGIO- AND DIASTEREOSELECTIVE FRIEDEL-CRAFTS ALKYLATION OF PHENOLS WITH α-AMINO ALDEHYDES. SYNTHESIS OF OPTICALLY ACTIVE EPHEDRINE-LIKE COMPOUNDS

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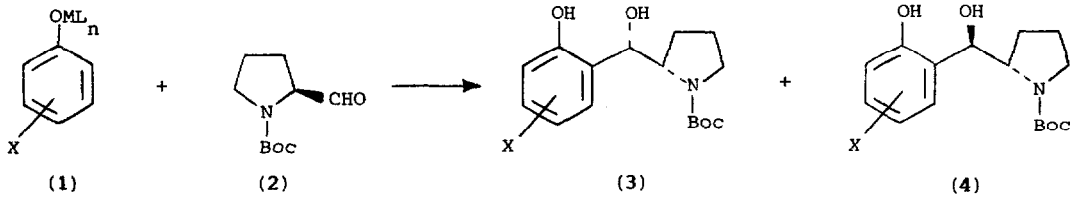
The first direct diastereoselective synthesis of ephedrine-like compounds has been achieved by alkylation of metal phenolates with N-tert-butoxycarbonyl-α-amino aldehydes; β-amino-ortho-hydroxybenzyl alcohols were obtained with good to excellent diastereoselection.

Aryl derivatives of amino alcohols with two stereocenters occur as biologically active natural products, such as ephedrine, and are used as drugs[1] as well as efficient inducers of chirality.[2] They have been prepared so far by multi-steps syntheses[3] and it is still an important goal to achieve an efficient and stereospecific method for the synthesis of these compounds.[4]

In connection with our previous studies on stereoselective Friedel-Crafts alkylation,[5] we report an attractive synthetic strategy consisting of the stereoselective hydroxyalkylation of phenols with N-protected α-amino aldehydes. In such a way we have performed the first direct synthesis of chiral β-amino-ortho-hydroxybenzyl alcohols.

In particular, by reacting metal phenolates (1) with N-tert-butoxycarbonyl(Boc)-L-prolinal (2)[6,7] 2-hydroxy-α-[1-(tert-butoxycarbonylamino)-2-pyrrolidinyl]benzenemethanols (3) and (4) were obtained (Scheme 1).



Scheme 1.

The reaction occurs with a complete regiocontrol giving exclusively ortho- and mono-attack on the phenol ring.

As far as the diastereoselection is concerned, our efforts in searching the conditions to predict the addition mode (syn vs. anti) during carbon-carbon bond formation were successful. Indeed, we obtained syn-amino alcohols (3)[8] with high to excellent level of diastereoselection (94-99.8 % d.e.) by employing magnesium bromide as counterion (ML_n=MgBr) of variously substituted phenolates, possibly via α-chelation-controlled reactions (Table 1, Entries 1-5).[9]

Instead anti-addition products (4) were obtained carrying out the reaction on titanium phenolates with stereochemical reversal (76-84% d.e.), possibly via non-chelate reaction (Table 1, Entries 6,7).[9,10]

However, according to this methodological approach, positive results were obtained only with very reactive phenols.

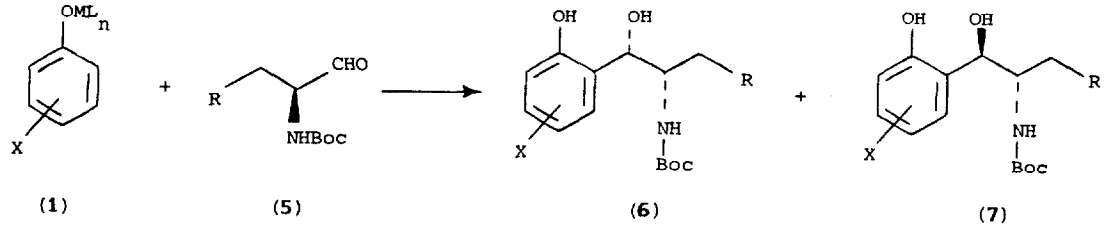
Enantiomeric excess of compounds **3d** and **3e** was determined using MPTA derivatives.[11] HPLC analysis revealed 92% and 93% e.e. respectively.[12]

Table 1. Synthesis of the α-amino-ortho-hydroxybenzyl alcohols (3)and(4)[a]

Entry	Phenol	X	ML_n	Major Product[b]	%Total Yield[c]	M.p. °C	$[\alpha]_D^{20}$(c)[d]	(3):(4)[e]	Configur[f]
1	(1a)	2-$(CH_3)_3C$	MgBr	(3a)	65	82-84[g]	-149.5(0.4)	>100:1	syn (S,S)
2	(1b)	4-CH_3O	MgBr	(3b)	50	foam	- 33.2(1.4)	99:1	syn (S,S)
3	(1c)	H	MgBr	(3c)	65	foam	- 53.8(1.0)	>100:1	syn (S,S)
4	(1d)	3-CH_3O	MgBr	(3d)	70	foam	- 52.5(1.9)	99:1	syn (S,S)
5	(1e)	3,4-OCH_2O	MgBr	(3e)	75	foam	- 44.4(0.6)	97:3	syn (S,S)
6	(1e)	3,4-OCH_2O	$Ti(OCH(CH_3)_2)_3$	(4e)	72	foam	- 2.8(0.8)	8:92	anti (R,S)
7	(1d)	3-CH_3O	$Ti(OCH(CH_3)_2)_3$	(4d)	51	foam	- 8.6(0.9)	12:88	anti (R,S)

[a] Experimental conditions, see the Text. [b]All compounds reported were characterized by complete spectral and analytical data. [c]Isolated yield by silica gel chromatography. [d]Ethanol. Reported values refer to the major product. [e]Molar ratio of diastereisomers, (3) and (4), in Scheme 1, measured on the crude reaction mixture by reversed-phase H.P.L.C. [f] The first configuration refers to benzylic carbon, the second one to pyrrolidine carbon. The configuration of **3a** was stablished by X-ray analysis (see the Text); the configuration of the other products was judged as such on the basis of ^1H NMR spectra[8]. [g]Crystallized from pentane.

We are extending this method to different N-Boc-α-amino aldehydes, in particular to N-Boc-L-phenylalaninal (5i)[6,13] and N-Boc-L-alaninal (5j).[6,13,14] The reactions of 4-methoxy-phenoxymagnesium bromide with amino aldehydes (5i)and(5j) gave rise to the products (6) and (7) with good syn-diastereoselection (88 and 72% d.e. respectively) (Scheme 2).



(1) (5) (6) (7)

Scheme 2. R = H, Ph

In conclusion, we have achieved the first and straightforward synthesis of chiral β-amino-ortho-hydroxybenzyl alcohols via direct ortho-hydroxyalkylation of phenol rings under mild conditions (room temperature) with good yields and good to excellent diastereoselectivity (up to 99.8% d.e.).

Considering the feasibility of employing a variety of N-protected α-amino aldehydes and the importance of ephedrine-like compounds we believe that this method represents a new important approach to a class of potentially sympathomimetic compounds.

2-Hydroxy-3-tert-butyl-α-[1-(tert-butoxycarbonylamino)-2-pyrrolidinyl]benzenemethanol **3a**. (Typical Mg-based Procedure): A solution of 2-tert-butylphenol (1.50 g, 10 mmol) in 10 ml of dry diethyl ether was added to a solution of EtMgBr in diethyl ether (20 ml) (prepared in situ from Mg and EtBr). After stirring for 30 min the solvent was removed under vacuum and replaced by CH_2Cl_2 (30 ml). A solution of N-Boc-L-prolinal(1.99 g, 10 mmol) in CH_2Cl_2 (20 ml) was added at room temperature. After stirring for 3 hr the reaction was quenched with a saturated aqueous solution of NH_4Cl, extracted twice with CH_2Cl_2 and dried (Na_2SO_4). The removal of the solvent gave crude product that was purified by silica gel chromatography; 2.27 g, yield 65%, m.p. 82-84°C (crystallized from pentane) $[\alpha]_D^{20}$ = -149.5 (c, 0.4 in EtOH).

2-hydroxy-4-methoxy-[1-(tert-butoxycarbonylamino)-2-pyrrolidinyl] benzenemethanol **4d**. (Typical Ti-based Procedure): A solution of 4-methoxyphenol (1.24 g, 10 mmol) in toluene (20 ml) was added to a solution of Ti $(OPr^i)_4$ (10 mmol) in toluene (30 ml). The mixture was distilled in order to remove the propan-2-ol formed; the toluene was removed and replaced with CH_2Cl_2 (30 ml). A solution of N-Boc-L-prolinal (1.99 g, 10 mmol) in CH_2Cl_2 (20 ml) was added at room temperature. After stirring for 48 hr the reactions was quenched with a saturated aqueous solution of NH_4Cl. Work-up as above gave 1.45 g of **4d** (yield 45%) as a foam, $[\alpha]_D^{20}$ = -8.6(c,0.9 in EtOH).

X-ray Analysis: X-ray quality crystals of (-)-(S,S)-**3a** were obtained from pentane Crystal data: $C_{20}H_{31}NO_4$, M = 349.5, orthorhombic, space group $P2_12_12_1$, a = 17.610(2), b = 18.256(2), c = 6.522(3) Å, U = 2096.8 Å^3, Z = 4, D_c = 1.11 gcm^{-3}, λ = 1.5418 Å, μ (Cu-Kα) = 5.8 cm^{-1}, F(000) = 380. Intensities were collected on a Siemens AED single crystal diffractometer equipped with a General Automation Jumbo 220 Computer, at room temperature using a specimen of 0.3x0.5x0.6 mm. Of the 4467 collected reflections (±h, k, l) the merging procedure give a total of 2101 unique observed reflections ($I \geq 2\sigma(I)$; R_{int} = 0.012). The data were corrected for Lorentz and polarization effects, the absorption was ignored. The structure was solved by direct methods with MULTAN80[15] and refined anisotropically by bloc matrix least-squares with SHELX86[16] system of programs. All the hydrogens were found in a F map and refined isotropically. The final conventional R factor was 0.053 and R_w was 0.074. The enantiomeric structure, refined separately, converged to R = 0.059. Moreover the absolute configuration is consistent with that defined by chemical methods. All the calculations were performed on an AT IBM computer with the CRYSRULER package.[17]
A view of the molecule is shown in the Figure 1.

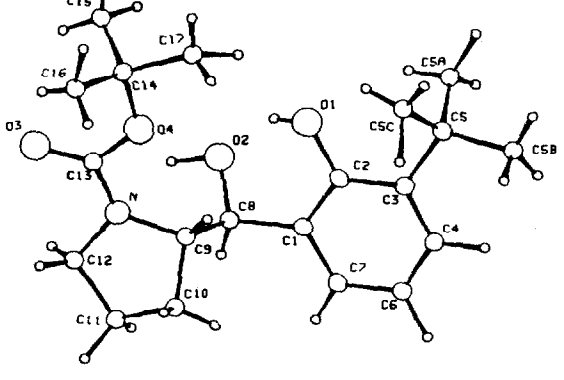


Figure 1. Molecular structure of **3a**.

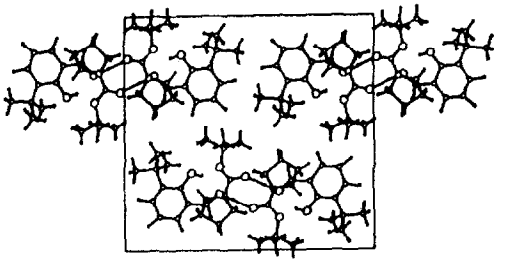


Figure 2. Crystal packing along [001].

Since the configuration of C9, that corresponds to the unaltered chiral center of the starting amino aldehyde (2), is (S), we can deduce that the new chiral carbon atom C8 has (S) absolute configuration, corresponding to a syn relative stereodisposition of the two chiral centres. The angle H-C8-C9-H is 107(2)°. An intramolecular hydrogen bond H-O1...O2 1.87(4) Å is observed. The molecules in the crystal are joined in dimers by very strong intermolecular hydrogen bonds: O2-H...O3^{1} (i = -x + 1/2, -y, 1/2 + z) = 1.57(6) Å, O2-H...O3^{1} = 172(5)°.

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