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Synthesis and stereochemical stability of new atropisomeric 1-(substituted phenyl)pyrrole derivatives

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Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract

Addition of organometallic reagents to optically active methyl 1-(2-methoxycarbonyl-6-trifluoromethylphenyl)pyrrole-2-carboxylate provided the corresponding tetrasubstituted diols and/or pyrrolo[1,2-*a*]benzoxazepines as pure enantiomers or racemates depending on the organometallic reagents used. Rotational energy barriers around the interconnecting C–N bonds were estimated by molecular modeling calculations and NMR measurements with the aim of clarifying the stereochemical stability order of the new atropisomeric compounds. NMR methods for the determination of the enantiomeric purity of the new compounds are proposed.

Keywords: Atropisomers; 1-Arylpyrroles; Rotational energy; Stereochemical stability; Organometallics

1. Introduction

Optically pure atropisomers of axially chiral biaryls have been widely studied for their applications as chiral ligands or auxiliaries.[1,2] In the last decades numerous C_2 symmetrical compounds were synthesized and investigated, such as the BINOL[3] and biphenyl[4] derivatives, but significant results have been published on the successful applications of several C_1 symmetrical compounds, too.[5]

Recently, efficient synthesis and optical resolution of the very first representative of atropisomeric 1-arylpyrrole derivatives have been published by our laboratory.[6] The optically active 1-(2-carboxy-6-trifluoromethylphenyl)pyrrole-2-carboxylic acid (**1**) was successfully applied as chiral discriminating agent in the ee determination of different chiral amines by NMR spectroscopy.[7] These preliminary works showed that the atropisomers of **1** are stable at ambient temperature. Thus we focused our interest on the simultaneous transformation of the two carboxylic groups into ester and carbinol functions with the aim of producing new members of that atropisomeric 1-arylpyrrole family (potential chiral ligands or organocatalysts) and investigating their conformational stability.

2. Results and discussions

2.1. Preparation of compounds 2–6

Synthesis of the desired atropisomeric diols **3** and **4** was accomplished starting from *R*-(−)-**1** via its dimethyl ester (*R*-(−)-**2**, Scheme 1). The phenyl groups (in **3**) were introduced by addition of an excess of phenyllithium. Usual workup procedure provided the optically active 1-(2-diphenylhydroxymethyl-6-trifluoromethylphenyl)-2-diphenylhydroxymethylpyrrole (*R*-(−)-**3**) in good yield. However, the same procedure resulted in the formation of practically racemic 4,4,6,6-tetramethyl-10-trifluoromethyl-4*H*,6*H*-pyrrolo[1,2-*a*]

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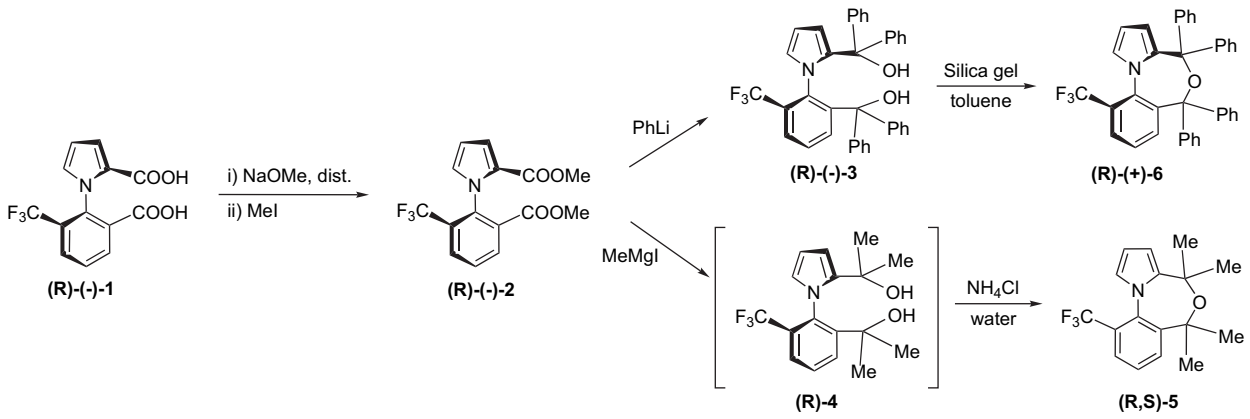

Scheme 1. Synthesis of compounds (*R*)-**3**, (*R*,*S*)-**5**, and (*R*)-**6**.

[4,1]benzoxazepine (**5**) as the main product and the diol **4** could not be separated in pure form when methylmagnesium iodide was used for the preparation of the tetramethyl derivative (**4**). Attempts to avoid spontaneous ring closing reaction and racemization during the aqueous workup procedure and chromatographic purifications have failed even neutral or basic conditions were applied.

In the case of the tetraphenyl diol **3** the ring closing reaction had to be accelerated with addition of silica gel and warming of the toluene solution of **3** for several hours. Under these conditions optically active 4,4,6,6-tetraphenyl-10-trifluoromethyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (*R*-(+)-**6**) could be obtained in good yield. It should be mentioned that the synthesis of compounds **2**, **3**, and **6** was also accomplished starting from *S*-(+)-**1** enantiomer resulting in the corresponding optically active products in the *S* atropisomeric series.

2.2. Determination of the enantiomeric excess values

Solution NMR spectroscopic methods have been developed to assess the enantiomeric compositions of the starting material (**1**), the intermediates (**2** and **3**), and the products (**5** and **6**). The enantiomeric purities of **1** and **2** were determined by ^{19}F NMR spectroscopy in aqueous solution using 2-hydroxypropyl-β-cyclodextrin (2HP-β-CD) as chiral complexing agent. Fluorine based detection has been previously developed for the ee determination of **1** with β-cyclodextrin[6] (β-CD) to overcome selectivity and sensitivity problems due to the excess of the auxiliary agent. Improving the method with the application of the better soluble 2HP-β-CD allowed us to achieve good selectivity with **2**, which had lower solubility than **1**. Esterification of both *R*-(−)-**1** and *S*-(+)-**1** was verified for enantioselectivity in parallel. Figure 1a shows that the CF_3 signals of the (+) and (−) enantiomers of **2** are baseline separated at −61.97 and −62.01 ppm. Standard addition of (−)-**2** was introduced to verify validity of the method (Fig. 1b). One advantage of the proposed method is that optical impurities smaller than 1% can be quantitatively determined by exploiting the 0.55% integrals of the natural abundance of ^{13}C satellites. The corresponding signals of **1** were found to be at −60.46 and −60.48 ppm. On the basis of these measurements the ee values of the samples **1** and **2** were calculated and we concluded that the esterification of **1** occurred without any racemization.

Signals of compounds **3**, **5**, and **6** were not separable by cyclodextrines to the level suitable for ee determination. We therefore applied Yb(TFC)$_3$ lanthanide shift reagent in apolar aprotic solvent, another well established methodology[8–10] available for the ee measurements of these compounds. Gratifyingly, the exchange between the complexed and uncomplexed forms of the investigated compounds was found to be very fast on the chemical shift timescales (^{1}H and/or ^{19}F) owing to the weak interaction with Yb(TFC)$_3$. Because of this, no signal broadening has interfered the baseline separation of the enantiomeric resonance pairs. Figure 2 shows the ^{19}F NMR spectra used for the analysis of the enantiomeric purity of **3**. The singlets of the CF_3 groups representing the enantiomers of **3** were found at −57.78 and −57.84 ppm. The same methodology was extended to the NMR analysis of **5** as well. The methyl resonances of compound **5** showed enantiodiscrimination in the presence of Yb(TFC)$_3$ therefore the basic ^{1}H NMR

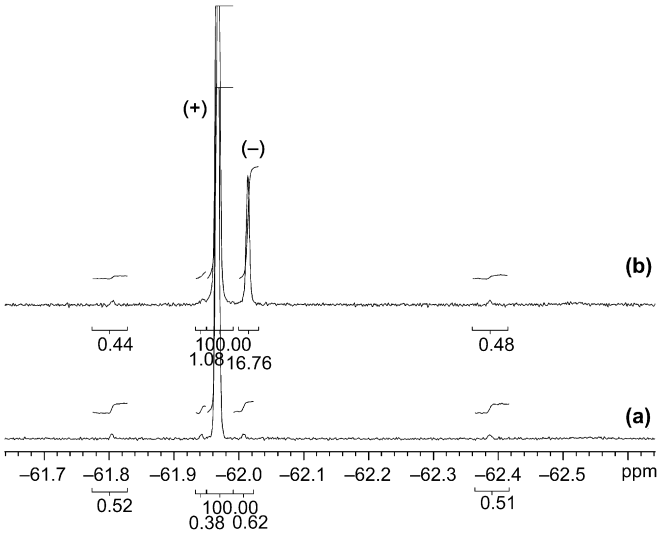

Figure 1. (a) ^{19}F NMR (470 MHz) spectrum of optically pure (+)-**2** (2 mM) in the presence of 8 mM 2HP-β-CD (D_2O, 25 °C). (b) Spectrum spiked with (−)-**2** to confirm enantioselectivity of the proposed NMR method. We note that fluorine coupled ^{13}C satellites are visible in both spectra.