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Short Note

(*S*,*S*)-1-(Phenyl((1′-4-nitrophenyl-ethyl)amino)methyl)-2-naphthol

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Abstract: The Betti reaction of 2-naphthol, benzaldehyde and (*S*)-1-(4-nitrophenyl)ethylamine without any solvent gave the corresponding aminobenzylnaphthol, that is the (*S*,*S*)-1-(phenyl((1′-4-nitrophenyl-ethyl)amino)methyl)-2-naphthol, in good yield (56%). The absolute configuration of the title compound was attributed by NMR analysis, a procedure that is reliable if compared with the data obtained by X-ray diffraction experiments.

Keywords: Betti reaction; aminobenzylnaphthols; chirality; NMR analysis; solvent free

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1. Introduction

Almost 25 years ago, the research group of Prof. Francesco Naso at the University of Bari initiated the re-discovery [1,2] of the work of Mario Betti, an Italian scientist active at the beginning of the 20th century [3].

Betti was known for the reaction that took his name [3], but his research was almost forgotten during the decades. The Betti reaction is a three-molecule condensation between 2-naphthol, aryl aldehydes and ammonia (or amine) to yield aminobenzylnaphthols [1–3]. The products of this procedure can be resolved into their enantiomers and have found application in asymmetric synthesis [4].

The seminal papers of the Bari group brought the benefits of this old reaction to the attention of the organic chemistry community. Since then, many research groups have used this procedure and have applied the deriving aminobenzylnaphthols. A 2010 article reviewed the progress made on this issue since the re-discovery [4]. A more recent review updated the research to the next decade [5], with particular attention on new synthetic methods and on the application of this valuable procedure to the synthesis of bioactive compounds.

2. Results and Discussion

In 2001, a new synthetic idea was investigated. Instead of resolving the racemic aminobenzylnaphthols deriving from the Betti reaction [1–3], the procedure was performed (Figure 1) with enantiopure amines [6–8].

Forlani et al. reacted 2-naphthol, benzaldehyde and (*S*)-1-phenylethylamine to produce the corresponding aminobenzylnaphthol, studying different reaction conditions, such as solvents, temperatures, catalysts and so on [6]. Eventually, they were able to isolate the (*S*,*S*)-stereoisomer and characterize it by X-ray diffraction [6]. This paper has been overlooked, but today we recognize the relevance of that crystallographic investigation. In fact, as shown later [9,10], the Betti aminobenzylnaphthols are distinguished by the presence of many CH···π interactions [11] that contribute to the stability of the crystals. One of the shortest CH···π interaction ever reported [11] was observed in the crystal analyzed by Forlani et al.

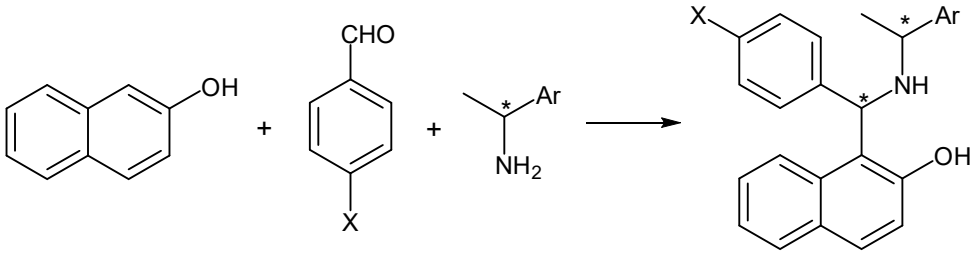

Figure 1. Betti reaction between 2-naphthol, aryl aldehydes and (*S*)- or (*R*)-1-arylethylamines.

A decisive improvement was obtained in the work by Palmieri et al. [7]. They reacted 2-naphthol, aryl aldehydes and (*R*)-1-phenylethylamine at 60 °C without any solvent. In these conditions, they obtained the predominant formation of the (*R*,*R*)-stereoisomer. After a thorough analysis, they explained this favorable stereochemistry with the preferential crystallization of one diastereoisomer ("asymmetric transformation of the second kind") [7].

The Palmieri hypothesis found a confirmation in a crystallographic investigation [9,10]. We reacted 2-naphthol, aryl aldehydes and (*S*)-1-arylethylamine at 60 °C for two days in solvent-free conditions [9]. The addition of small quantities of ethanol to the crude reaction mixture caused the precipitation of the crystals of the pure (*S*,*S*)-stereoisomers in satisfactory yields (52–68%) [9]. These crystals were subjected to X-ray diffraction analysis.

Since, in our previous work, we reported the synthesis of many aminobenzylnaphthols bearing halogen atoms or the methoxy group on different positions of the two aryl moieties, now, we report the formation of an aminobenzylnaphthol in which one of the aryl groups bears a substituent with different electronic properties. In fact, we reacted 2-naphthol, benzaldehyde and (*S*)-1-(4-nitrophenyl)ethylamine (Figure 2).

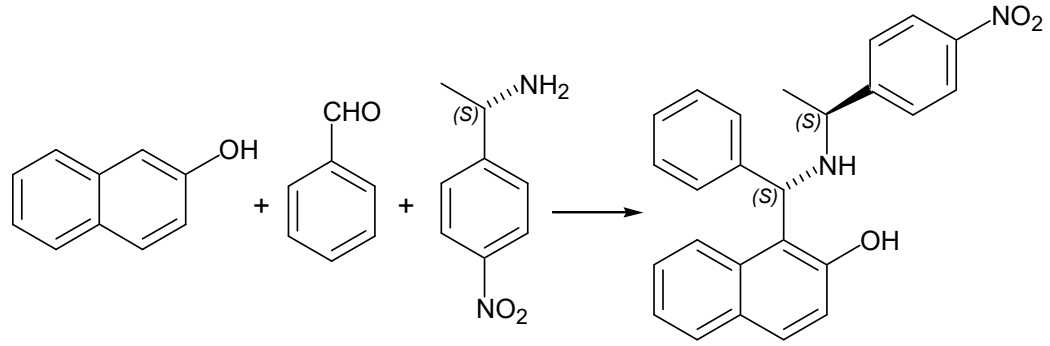

Figure 2. The Betti reaction between 2-naphthol, benzaldehydes and (*S*)-1-(4-nitrophenyl)ethylamine.

As previously reported, the three components were reacted at 60 °C for two days without the addition of any solvent. A first batch of Betti aminobenzylnaphthol can be obtained by adding small amounts of ethanol; a further batch of it can be obtained by a chromatographic separation (see Experimental). The overall yield was 56%, a value that is similar with those previously reported [9].

In the absence of crystals suitable for an X-ray diffraction experiment, the absolute configuration of the stereogenic centers can be attributed with NMR considerations, as previously reported [12,13].

In our experiments, the Palmieri improvement (60 °C reaction temperature, no solvent) [7] provided the formation of the (*S*,*S*)-stereoisomers predominant over the (*R*,*S*)-one (up to 10:1). Larger amounts of the (*R*,*S*)-stereoisomers can be obtained by lowering the reaction temperature, according to the analysis by Forlani et al. [6].

In our work, sometimes we isolated small amounts of the (*R*,*S*)-stereoisomers [9]. It is not an easy task because the (*S*,*S*)-stereoisomers are present in larger quantities and they are the first eluting compounds in chromatographic separations. Therefore, the elution of the (*R*,*S*)-isomers is often accompanied by the residue of the (*S*,*S*)-counterparts. In this

particular case, we did not isolate pure (*R*,*S*)-isomers, but always enriched mixtures that had a residue of the (*S*,*S*)-counterparts. However, since the H(1)-NMR spectra of the (*R*,*S*)- and (*S*,*S*)-stereoisomers have characteristic non-overlapping patterns, they can be used for their discrimination. In the prototypal aminobenzylnaphthol represented in Figure 3, the benzyl hydrogen atom close to the naphthol moiety is very peculiar. According to Table 1, the high field signals in the range of 5.37–5.49 ppm are characteristic of the (*S*,*S*) stereoisomers. The low field signals in the range of 5.61–5.87 ppm are characteristic of the (*R*,*S*) stereoisomers [9].

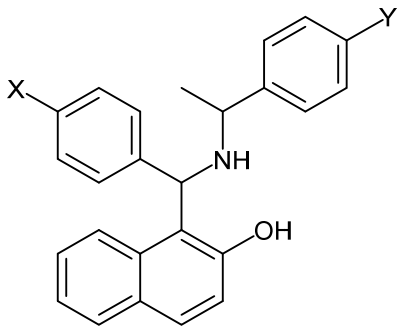

Figure 3. A prototypal X- and Y-substituted aminobenzylnaphthol.

Table 1. H(1)-NMR chemical shift in ppm of the Ar_1Ar_2C-H benzyl hydrogen atom in the aminobenzylnaphthol of Figure 3, in which X and Y are the substituents on the respective aryl groups.

X	Y	(*S*,*S*) [1]	(*R*,*S*) [2]
H	H	5.46	5.87
F	H	5.49	5.61
Cl	H	5.41	5.81
Br	H	5.40	5.81
Me	H	5.43	5.84
MeO	H	5.41	5.82
H	MeO	5.46	5.85
H	NO_2	5.37	5.86

[1] Referring to the (*S*,*S*)-stereoisomers. [2] Referring to the (*R*,*S*)-stereoisomers.

The basis of this high-field/low-field pattern was explained in our previous work [12,13] and was confirmed many times by the comparison with the absolute configurations of the Betti aminobenzylnaphthols that we succeeded to attribute with X-ray diffraction experiments [9,10,14]. Since the molecule synthesized in the present work shows the benzyl hydrogen atom having a 5.37 ppm signal, the (*S*,*S*) configuration can be safely attributed to this compound. The usual trend whereby an (*S*,*S*)-compound was obtained prevalently in the Betti reaction when an (*S*)-1-arylethylamine was employed as a reactant was confirmed.

3. Materials and Methods

Chemicals were used as received. NMR spectra were recorded on a Bruker AM500 spectrometer. MS spectra were performed with an Agilent HPLC QTOF spectrometer via direct infusion of the samples.

(*S*)-1-4-nitrophenylethylamine (0.81 g, 4.88 mmol) was added to benzaldehyde (0.58 g, 5.46 mmol) and stirred for 10 min at room temperature. 2-Naphthol (0.68 g, 4.72 mmol) was added and the mixture was heated to 60 °C for two days. The crude reaction mixture was cooled and treated with 2 mL of ethanol. In these conditions, 0.48 g of the title compound precipitated. The mother liquor can be subjected to chromatographic separation (silica gel, eluent *n*-hexane/ethyl acetate 7:3) to yield a further batch of product (0.58 g). The overall yield was 1.06 g (2.66 mmol, 56% yield). Pale yellow crystals; mp 148 °C–150 °C (ethanol). $[\alpha]_D^{20}$ = + 157.3 (*c* = 2, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 13.14–13.00 (broad s, 1 H, OH), 8.31–8.24 (m, 2 H, H_{ar}), 7.82–7.72 (m, 2 H, H_{ar}), 7.38–7.32 (m, 3 H, H_{ar}), 7.25–7.19 (m, 8 H, H_{ar}), 5.37 (s, 1 H, $HCAr_2$), 4.08–4.00 (broad, 1 H, HC-Me), 2.40–2.29 (m, 1 H, NH), 1.53 (d, J = 6.9 Hz, 3 H, CH_3).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ 156.8 (C-OH), 150.7 (C_{Ar}), 147.6 (C_{Ar}), 140.8 (C_{Ar}), 132.3 (C_{Ar}), 130.0 (C_{Ar}), 129.2 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.3 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 126.7 (C_{Ar}), 124.3 (C_{Ar}), 122.6 (C_{Ar}), 120.7 (C_{Ar}), 119.9 (C_{Ar}), 112.5 (C_{Ar}), 60.4 ($HCAr_2$), 55.9 (HCArMe), 22.9 (CH_3).

HRMS (ESI-TOF), *m*/*z*: calcd for $C_{25}H_{21}N_2O_3$ $[M\text{-}H]^-$, 397.1552, found 397.1541.

Graphical representations of the NMR and HRMS spectra are available in the Supplementary Materials.

Supplementary Materials: The following are available online. Spectral properties of the title compound.

Author Contributions: M.A.M.C. and C.C. contributed in the same way to all the steps of the work. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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