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A new approach to the synthesis of benzylidene derivatives of 1-(α-aminobenzyl)-2-naphthols (Betti bases), promising chiral inductors

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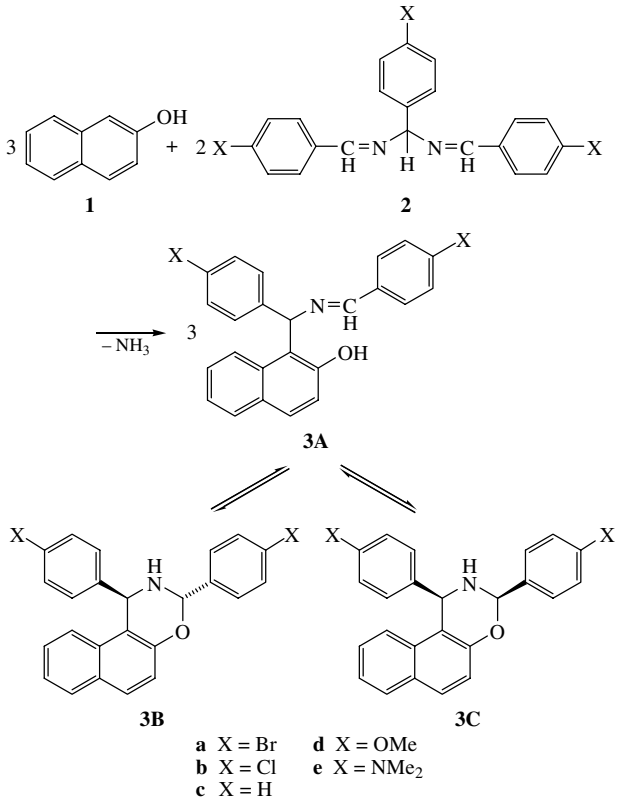
A new approach to the synthesis of precursors of Betti bases is described, in which β-naphthol reacts with 1,3,5-triaryl-2,4-diazapenta-1,4-dienes (3:2) in refluxing benzene.

Interest in identifying new, readily accessible enantiopure chiral compounds for use as inductors (chirality carriers) or starting materials in asymmetric synthesis continues unabated. To a considerable extent, this is due to current requirements for the synthesis of enantiomerically pure pharmaceuticals[1] and resulting recent progress in the chemistry of pure enantiomers. 1-(α-Aminobenzyl)-2-naphthols, eponymously called Betti bases, are quite suitable for these purposes because they are easy to synthesise, the starting reagents are readily available, and separation of the enantiomers is straightforward.[2,3(a)–(r)]

The classical synthesis of the simplest member of the series, 1-(α-aminobenzyl)-2-naphthol, Betti base itself, involves several steps. The three-component condensation of β-naphthol, benzaldehyde and ammonia in ethanol solution at room temperature for several days[4,5] results in imine **A**, which exists in solution in tautomeric equilibrium with two diastereomeric *trans*- and *cis*-1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine structures **B** and **C**.[6(a)–(c)] The imine is then hydrolysed with hydrochloric acid[6] to give an amine hydrochloride, yielding after treatment with alkali the free base, which can be separated.[4,5] Subsequently, a few other methods for the synthesis of similar compounds were suggested.[7(a)–(f)] The product yields reported in the above literature sources range from satisfactory to good.



Scheme 1

The key compounds in all these syntheses are primary condensation products **A**, **B** and **C**. In this study, we suggest a new approach to the synthesis of these Betti bases precursors. The method involves the reaction of β-naphthol **1** with 1,3,5-triaryl-2,4-diazapenta-1,4-dienes **2** in a molar ratio of 3:2 in refluxing benzene for 5–17 h† according to Scheme 1.

The completion of the reaction can be easily determined by cessation of ammonia evolution. All products were obtained as crystalline compounds after the reaction mixture was cooled or the solvent was removed. Reaction products **3a–e** were isolated in yields from 88% to quantitative.

The yields of **2** are high (72–97%)[8(a)–(c)] for the majority of substituted benzaldehydes used. Thus, the overall yields of compounds **3a–e** obtained using our method exceed those reported in literature (Table 1). All the reactions occur without formation of by-products. The structures of the end products were established by ^{1}H NMR, IR spectroscopy, elemental analyses

† *General method for the synthesis of compounds* **3a–e**. β-Naphthol (0.03–0.055 mol) was dissolved with heating in anhydrous benzene (30–35 ml) and compound **2** (0.02–0.036 mol) was added (molar ratio **2**:β-naphthol = 2:3). The reaction mixture was refluxed until ammonia evolution ceased, which required 5 to 17 h depending on the substituent at the aryl fragment in compound **2**.

If the product was formed as a crystalline precipitate, it was filtered off, the filtrate was concentrated to half volume, and the precipitate that formed was separated again. If the product did not precipitate at once, the solvent was removed *in vacuo* from the reaction mixture, and the viscous residue was triturated with a small amount of diethyl ether. The resulting crystalline compound was dried in a vacuum of a water-jet pump and recrystallised from a suitable solvent.[3(m),6(c)]

The yields, melting points, and fractions of tautomers **A**, **B** and **C** calculated from the integral intensities of characteristic proton signals in the ^{1}H NMR spectra of the products obtained are listed in Table 1.

Table 1 Yields, melting points, and fractions of tautomers **A**, **B** and **C** in $CDCl_3$ solutions for compounds **3a–e**.

Product	X	Yield / overall yield[a] (%)	Mp/°C	Tautomer fractions (%) (^{1}H NMR)			Published data		
				A	**B**	**C**	Yield (%)	Mp/°C	Reference
3a	Br	94 / 70	184–185[b]	13.8	78.3	7.9	48	125–126	3(*m*)
3b	Cl	88 / 78	153–154	15.5	77.0	7.5	78	155–156	6(*c*)
3c	H	94 / 92	145–147	26.9	63.8	9.3	90	145–147	6(*c*)
3d	OMe	99 / 96	182–184	56.9	37.8	5.3	76	182–184	6(*c*)
3e	NMe_2	96 / 86	224–226	92.2	7.0	0.8	—	—	—

[a]Yields of **3a–e** with the count of yields of **2a–e**. [b]The melting point of **3a** from different experiments was checked repeatedly. Spectral and elemental analysis data for the synthesised compound correspond to the structure of **3a** and are consistent with published data.[3(*m*)]

and, for known compounds, by comparison of their spectroscopic constants with literature values.

As expected, in agreement with published data,[6(*c*)] compounds **3a–e** in $CDCl_3$ solution exist as mixtures of tautomers **A**, **B** and **C** due to ring–chain tautomerism. Their % fractions in the mixture as determined by integration of the H_{C1} and H_{C3} signals are shown in Table 1. One can see from Table 1 that the presence of donor substituents in starting compound **2** results in the formation of products in which imine form **A** predominates, whereas acceptor substituents stabilise oxazine forms **B** and **C**. Indeed, the hitherto unknown bis(dimethylamino) derivative **3e**‡ containing the strongest *n* electron pair-donor (dimethylamino) groups at the *para* positions of both phenyl rings is characterised by the highest fraction of imine form **A**, namely, 92.2%.

In summary, we have presented a new method for the synthesis of Betti base precursors by reaction of β-naphthol with 1,3,5-triaryl-2,4-diazapenta-1,4-dienes. The new method provides Betti bases in high yield and purity, facilitating subsequent separation into the individual enantiomers.

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‡ *1-[α-(4''-Dimethylaminobenzylidene)amino-4'-dimethylaminobenzyl]-naphth-2-ol* **3e**: yield 96%; mp 224–226 °C (benzene). ^{1}H NMR ($CDCl_3$) δ: (tautomer **A**) 2.90 (s, MeN), 3.03 (s, Me′N), 6.34 (s, CHN), 8.43 (s, CH=N); (tautomer **B**) 2.90 (s, MeN), 2.98 (s, Me′N), 5.64 (s, CHN), 5.74 (s, CHO); (tautomer **C**) 2.96 (s, MeN), 3.00 (s, Me′N), 5.80 (s, CHN), 5.93 (s, CHO); (tautomers **A** + **B** + **C**) 6.65–7.92 (m, CH_{arom}). Found (%): C, 80.09; H, 7.24; N, 9.95. Calc. for $C_{28}H_{29}N_3O$ (%): C, 79.40; H, 6.90; N, 9.91. For the tautomer ratios, see Table 1.

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