

Stereoselective Synthesis of *cis*-Substituted-3'-anilino-2', 3'-dihydro-4-2'-benzo[*b*]furanyl coumarins via Intramolecular Aldol Reactions

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ABSTRACT

The present study reports the reaction of 4-bromomethylcoumarins with salicylidineaniline in acetone with two equivalents of potassium carbonate resulted in the formation of title compounds at room temperature via intramolecular aldolization. The obtained compound is thermodynamically and kinetically stable with highly stereoselective and excellent yield.

Keywords: Aldol Reaction; Stereoselective; Intramolecular; Mild Base; 4-Bromomethylcoumarins; Dihydrobenzofurans

1. Introduction

The 2,3-dihydrobenzofuran skeleton has been associated with diverse biological activities and natural occurrence [1-3]. A variety of coumarin derivatives with substitution at C4 have been found to exhibit anti-coagulant [4], antimicrobial [5] and anti-tumour [6] activity. The dihydrobenzofuranols has recently received considerable attention since they have been shown to possess antimicrobial activity [7]. Some of the structurally similar compounds **1** [8-12] used as drugs for the treatment of vitiligo and are claimed to be potent coronary vasodilators, and plant growth regulating substance.

The new synthetic methods have been extensively investigated [13-18]. Inter and intra-molecular cyclisation reactions play an important role in the construction of dihydrobenzofurans. The intramolecular reaction of carbon nucleophiles with an electrochemically generated intermediate can provide a unique means for generating new carbon-carbon bonds, and this may also be used to generate a reactive intermediate to construct the dihydrobenzofuran skeletons under mild conditions [19]. Similarly proline catalyzed aldol reaction plays an important role as carbon-carbon bond formation **2** [20-23]. Further mechanistic studies, that is Nitrones undergo deoxygenative reductive coupling and subsequent cyclisation to **3** [24]. Hence carbon nucleophiles are generally unstable under electro-oxidative conditions because most

of the nucleophiles possess electron-rich heteroatoms or aromatic rings. Therefore the electrolytic potential is limited to the lower of those of the co-existing nucleophiles and those of the products [25]. On the other hand, it is difficult to construct the corresponding dihydrobenzofuranols directly by the [3 + 2] cycloaddition of unactivated alkenes with hydroxy aldehydes. In fact, the direct intermolecular attack of aliphatic alkenes has not been accomplished even when they were added to the reaction mixture in excessive amounts [26]. Hence only few methods are reported for the synthesis of stereo specifically enriched dihydrobenzofurans [27]. Although there are several photochemical approaches available for the synthesis of the dihydrobenzofuranol skeleton [28-34]. All the methods yield *trans* and *cis* products.

In our earlier efforts the mild base catalyzed formation of benzofuranyl coumarins were obtained as an desired product in the generation of carbanion via intramolecular cyclisation across the carbonyl carbon [35]. In continuation of our recent investigations in asymmetric synthesis towards the bioactive natural products, we have reported a mild base catalyzed asymmetric intramolecular *cis* aldolization affording various 3'-hydroxy-2',3'-dihydro-4-2'-benzo[*b*]furanyl coumarins **4** (Figure 1) [36].

2. Results and Discussions

Here in we wish to report a mild base catalyzed asymmetric intramolecular *cis* aldolization and affording various 3'-Anilino-2',3'-dihydro-4-2'-benzo[*b*]furanyl cou-

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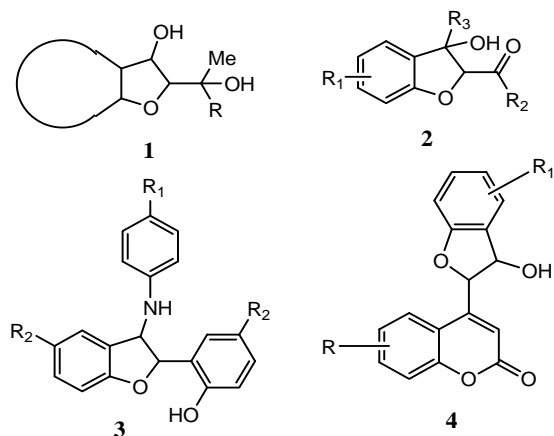


Figure 1. 2,3-dihydrofurans.

marins (**Scheme 1**). Initially we studied several solvents with potassium carbonate catalyst (2 eq.) at refluxing temperature to find the necessary reaction condition for the cyclisation of desired product, but we briefly examined the synthetic experimental condition of these reaction of **5** with **6** (**Scheme 1**) afforded pure product **8** which we have earlier reported¹⁵ by dehydration to benzofuran. Then we carried out at room temperature to find appropriate reaction conditions for the cyclisation of the **5** with **6** to favor the desired dihydrobenzofurans **7**. The acetone as solvent gave the best results (approximately more than 80% yields) in an excellent yield with single product, after simple purification by column chromatography by using ethyl hexane: purification by column chromatography by using hexane: ethyl acetate (7:3) (**Table 1**). The

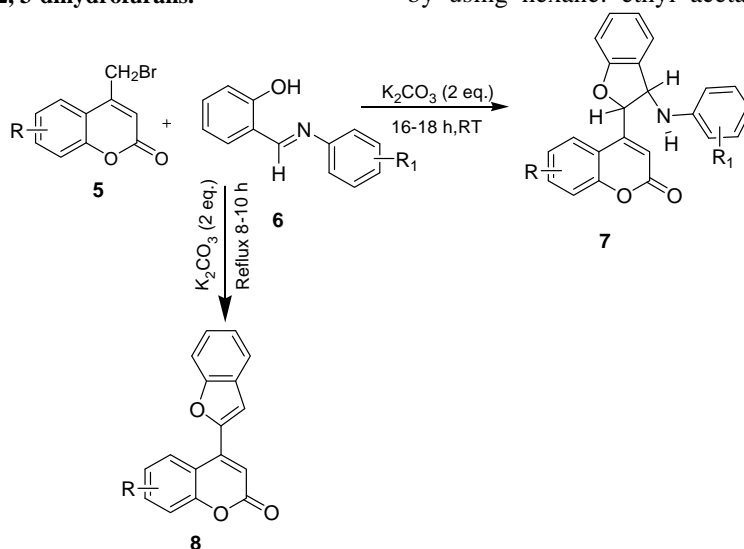
Scheme 1. R = 6-CH₃, 7-CH₃, 6-Cl, 6-OCH₃, R₁ = H, 4-CH₃, 3-Cl.

Table 1. The Physical data of 3'-anilino-2',3'-dihydro-4-2'-benzo[b]furanyl coumarins (7a-l).

Compd.	R	R ₁	Time (in hrs)	M.P. (°C)	Yield (%)
7a	6-CH ₃	H	16	168	85
7b	6-CH ₃	H	16	148	84
7c	6-CH ₃	3-Cl	17	162	80
7d	7-CH ₃	H	16	240	88
7e	7-CH ₃	4-CH ₃	16	158	84
7f	7-CH ₃	3-Cl	17	185	80
7g	6-Cl	H	16	132	81
7h	6-Cl	3-Cl	18	238	79
7i	6-Cl	4-CH ₃	16	158	81
7j	6-OCH ₃	H	16	188	87
7k	6-OCH ₃	4-CH ₃	16	208	89
7l	6-OCH ₃	3-Cl	17	172	82

purified compound showed two characteristic doublets around δ 5.2 and 58 ppm. After the adjustment of the reaction parameters, several salicylidineaniline **6** and 4-bromomethyl coumarin **5** could be transformed *cis*-selectively into the corresponding 3'-Anilino-2',3'-dihydro-4-2'-benzo[*b*] furanyl coumarins **7a-l** (Scheme 1, Table 1). The product **7** could be obtained with decreased yield (55% - 60%) by using solvents such as DMF, 1, 4-dioxane and ethanol.

However, a various 4-bromomethyl coumarins **5** [37] and substituent salicylidineaniline **6** could be cyclized with increased stereoselective products and short reaction time. The reaction to yield the 3'-Anilino-2',3'-dihydro-4-2'-benzo[*b*]furanyl coumarins **7a-l** showed a full conversion after sixteen hours at room temperature, but a much longer reaction time of more than 30 hours, probably the elimination of aromatic amines starts due to the aromatisation of product **7** to **8** was observed (Scheme 1). The absolute configuration of the 3'-Anilino-2',3'-dihydro-4-2'-benzo[*b*]furanyl coumarins **7** was assigned by X-ray structure analysis of **7j** to be *2R,3S* (Figure 2). The *cis* selectivity of the product was further confirmed by comparison of the coupling constants of the methine protons in the ^1H NMR spectra. The coupling constant was found to be 3.3 Hz, which indicates the *cis* configuration of the ring.

3. Conclusion

In conclusion, we accomplished the synthesis of title compound 3'-Anilino-2',3'-dihydro-4-2'-benzo[*b*]furanyl coumarins derivatives through a combination of **5** and **6** strategy reaction by intramolecular aldol reaction affording *cis*-selectively using mild base potassium carbonate and this can be used for new method for stereoselective synthesis of substituted amino dihydrobenzofurans.

4. Experimental

Melting points were determined by using open capillary method and are uncorrected. IR spectra were recorded on a Nicolet-impact—410 FT infrared spectrometer. The NMR was recorded on a Bruker 300 MHz FT NMR spectrometer. ^1H and ^{13}C Chemical shift were represented as δ -values relative to the internal standard, tri-methylsilane. LC-MS spectra were recorded on MPS-SCIEX-API-2000. The 4-bromomethylcoumarin **5** was prepared according to our earlier report. Salicylaldehyde and substituted aromatic amines were commercially available and used after purification. All reaction were carried out under nitrogen atmosphere.

Typical experimental Procedure for the Preparation of 3'-Anilino-2',3'-dihydro-4-2'-benzo[*b*] furanyl coumarins (7a-l). A mixture of anhydrous potassium carbonate (700 mg, 0.005 mol) and salicylidineaniline (**6**) (500 mg,

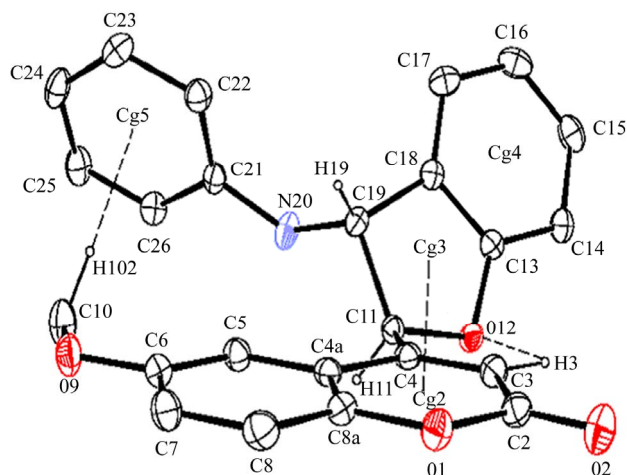


Figure 2. X-ray structure of **7j**: CCDC contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK].

0.002 mol) was stirred for about half an hour in dry acetone (20 mL). To this 4-bromomethyl coumarins (**5**) (600 mg, 0.002 mol) were added and the stirring was continued for 16 - 18 h at room temperature. The mixture was diluted with crushed ice. Separated solid was filtered and washed with water, then washed with dilute HCl (1:1) and then with water. The residual solid was purified by silica gel column chromatography using hexane-ethyl acetate (7:3) afforded 720 mg (82%) or purified by crystallization using ethanol afforded less than 60%. (**7a**). IR (KBr) 1720, 3358 cm^{-1} ; ^1H NMR (DMSO-*d*₆) δ 2.46(s, 3H, 6-CH₃ of coum), 4.24(s, 1H, NH), 5.24(d, 1H, C₃-H, $J = 3.3$ Hz), 5.82(d, 1H, C₂-H, $J = 3.3$ Hz), 6.45(s, C₃-H of coum), 6.69 - 7.67(m, 12H, Ar-H); ^{13}C -NMR (300 MHz) δ 21.87, 61.24, 84.97, 108.63, 110.77, 112.02, 114.52, 117.61, 118.70, 121.14, 122.42, 125.54, 126.78, 128.52, 130.12, 130.57, 146.00, 148.58, 154.25, 156.56, 159.64, 161.89, MS (LCMS), m/z 369, 276 (base peak).

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