A NOVEL SYNTHESIS OF SOME BETTI BASES DERIVATIVES

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Abstract

Synthesis of betti bases by 1- (α-aminobenzyl)-2-naphthol by 2-naphthol, benzaldehyde and ammonia with the help of mannich reactions by conventional methods like green synthesis. Compounds were synthesised properly. NMR and mass spectroscopy gave good results of the compounds All the compounds were synthesized according to the procedure by varying different aldehydes but we obtained good yield in a nitro substituent when compared to other substituents. All compounds gave promising yields according to the literature.
Key words : betti bases, mass spectroscopy, aldehydes and NMR

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Introduction

The study of the chemistry of the Betti bases was started when Betti reported a straight forward synthesis of 1- (α-aminobenzyl)-2-naphthol (the Betti base), starting from 2-naphthol, benzaldehyde and ammonia (Ghandi, et al. 2008; Metlushka, et al. 2008). The Mannich reaction is one of the most frequently applied multicomponent reactions in organic chemistry (Paqett, 1995). One of its special variants is the modified three-component Mannich reaction, in which the electronrich aromatic compounds are 1- or 2-naphthol. In this reaction, the nitrogen sources used (ammonia or amine) largely determines the reaction conditions and the method of isolation of the synthesized Mannich product (Szatmári and Fülöp. 2004). The Betti procedure can be interpreted as an extension of the Mannich condensation, with formaldehyde replaced by aromatic aldehyde, secondary amine by ammonia and the C – H acid by an electron-rich aromatic compound, such as 2- naphthol (Töth, et al. 2006). The preparation of substituted Betti base derivatives by the modified Mannich reaction has subsequently become of considerable importance because a C – C bond is formed under mild experimental conditions (István and Ferenc. 2004). In later years, attention has been paid to the Betti's reaction, and a similar reaction can be performed by either using other naphthols (Pirrone, 1940) or quinolinols (Phillips and Barrall. 1956) or by replacing ammonia with alkylamines (Szatmari, et al. 2003). In addition, a variety of racemic structures related to the Betti's bases have been prepared by addition of naphthols to the preformed imminium salts (Grumbach, et al. 1996). In later years, the effort were done to synthesized the Betti's base derivatives in organic solvents such as

EtOH, MeOH and Et 2 O at room temperature or thermally under solventless condition (Saidi. and Azizi. 2003). In the past decade, interest in the chemistry of the Betti base has intensified. Preparation of the enantiomers of the Betti base and its N-substituted derivatives is of significance since they can serve as chiral catalysts (Lu, et al. 2002). On the other hand, Betti base derivatives provide convenient access to many useful building blocks because the amino and the phenolic hydroxy groups can be converted into a wide variety of compounds (István and Ferenc. 2004). The Betti reaction is a convenient method with which to prepare α - aminobenzylnaphthol derivative (Betti, 1941).

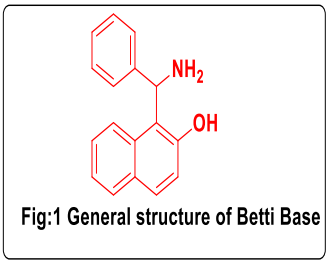


Fig:1 General structure of Betti Base

Many unnatural homochiral amino-phenol compounds have been reported as excellent ligands in metal ion catalyzed asymmetric reactions in current asymmetric synthesis (Yuan, et al. 2002). The ligands, which have the structure of N,N- dialkylBetti base are gaining increasing importance (Liu, et al. 2001). Among them, the derivatives of chiral N-methyl- N-alkyl Betti base have induced satisfactory reactivities and stereoselectivities in their catalyzed asymmetric reactions. The replacement of the N-methyl group in N-methyl-N-alkyl Betti base by a large-sized N-alkyl group did not bring any additional satisfactory results, but made the synthetic procedure more difficult (Yanmei, et al. 2004). Because the aliphatic amino moiety of Betti base has a relatively lower nucleophilic reactivity when compared to its phenoxyl group moiety, the N-alkylation of Betti base seriously lacks for regioselectivity by using routine methods (Vyskocil, et al. 1998). Therefore, no derivatives of chiral N,N-dialkylBetti bases were prepared from nonracemicBetti base . The chiral N-methyl-N-alkyl Betti base was prepared mainly by the Mannich condensation of a chiral amine with benzaldehyde and 2-naphthol to yield a N-alkyl Betti base followed by a N- methylation (Liu, et al. 2001). Since few of the N-alkyl Betti bases prepared by the Mannich condensation had satisfactory diastereopurity (Wang, et al. 2002), the diversity of the N-alkyl group in the N-methyl-N-alkyl Betti base is quite limited. On the other hand, the use of non-racemic amines has opened up a new area of application of these enantiopureaminonaphthols as chiral catalysts in enantioselective transformations (Boga, et al. 2001). Various biologically active natural products possess 1,3-aminooxygenated functional groups [1], [2]. Among these scaffolds the aminonaphthols, so called "Betti bases" [3] represent an important class of such compounds. Owing to several interesting biological activities [4], synthesis of substituted Betti bases has become an important area of synthetic organic chemistry. Mario Betti in 1901 [5] was the first who reported the synthesis of Betti bases by acid hydrolysis of 1,3-diphenylnaphthooxazine formed via modified Mannich reaction of benzaldehyde, ammonia and 2-naphthol. This reaction has been subsequently explored utilizing different *N*-sources. In addition, asymmetric aminonaphthols prepared using chiral amines could be utilized as chiral catalysts in performing enantioselective reactions [6]. In the last decade, Betti bases have received considerable interest and several methodologies for their synthesis have been reported. This involves the use of

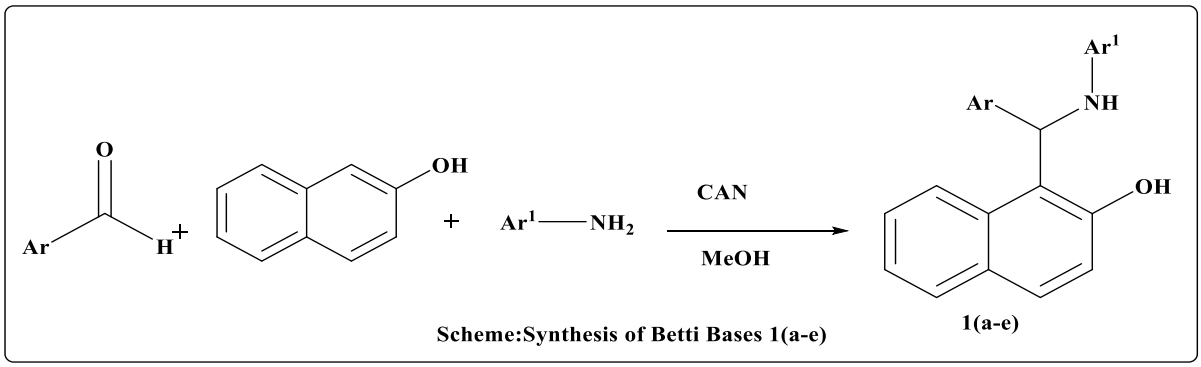
acidic catalysts such as $Fe(HSO_4)_3$ [7], CF_3CO_2H [8], $FeCl_3$-SiO_2 [9], $NaHSO_4$ [10], ionic liquids [11], Triton X-100 non-ionic surfactant in water [12], solvent free conditions utilizing catalytic amounts of *p*-TSA under microwave irradiation [13], and basic nano-crystalline MgO in aqueous medium [14]. A new approach utilizing solid ammonium acetate and formate as a green ammonia source rather than methanolic ammonia solution has been recently reported [15]. Another approach is the hydrolysis of amidoalkylnaphthols [16]. Although these reactions have their advantages, there are demerits such as the use of expensive low selectivity catalysts, environmentally harmful solvents, and requirement of long reaction times and non-applicability to aromatic amines. In order to overcome these problems, a general efficient and green methodology is needed utilizing cerium (IV) ammonium nitrate (CAN) as inexpensive and benign catalyst. CAN has emerged as a potential reagent for the construction of carbon-carbon and carbon-heteroatom bonds via radical intermediates. In addition it possesses many advantages such as excellent solubility in different solvents, low cost, easy handling, high reactivity and ecofriendly nature. In addition, CAN is able to catalyze organic transformations not only as one electron oxidant, but also as a Lewis acid. As a continuation of our and others interest in the synthesis of biologically relevant heterocycles performing multicomponent reactions [17], [18], [19], [20], [21], [22], [23], here in we wish to report an efficient, simple and green modified Mannich type synthesis of Betti bases using CAN as a Lewis acid catalyst at ambient temperature. Only a few reports for the C-N bond formation utilizing CAN as a Lewis acid have been reported [24].

Materials and Methods

Melting points of final products were measured on a Shimadzu-Gallenkamp apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DX instrument (Billerica, USA) (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR); $CDCl_3$ and DMSO-d_6 were used as solvent; chemical shifts are quoted in δ (ppm) from tetramethylsilane. Mass spectra were measured on a GCMS-QP1000EX (EI, 70 eV) mass spectrometer. Starting materials were obtained from Aldrich (Mumbai, India) and used directly.

General procedure

A mixture of aniline (1ml) and substituted aromatic aldehydes (0.2g) was dissolved in (20ml) of ethanol after the appropriate time (2-30min) the precipitate formed then 2-naphthol (1.44g) was added. The mixture was heated under reflux with stirring for an appropriate time(24-120 hrs.), then the solvent was removed at reduced pressure by a rotatory evaporator. The reaction mixture was cooled to ambient temperature and the crude solid residue was recrystallized in ethanol to afford pure crystals.



Scheme:Synthesis of Betti Bases 1(a-e)

Proposed Mechanism

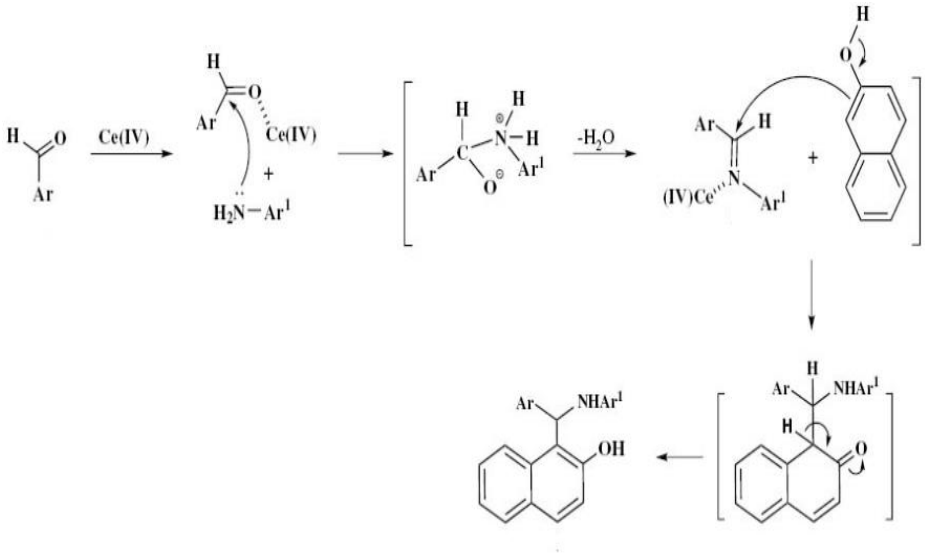
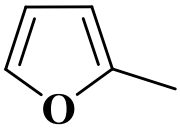
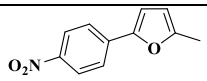
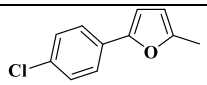
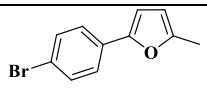
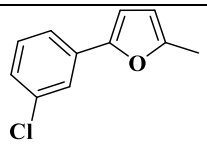


Table 1.Physicochemical data of Betti bases Derivatives

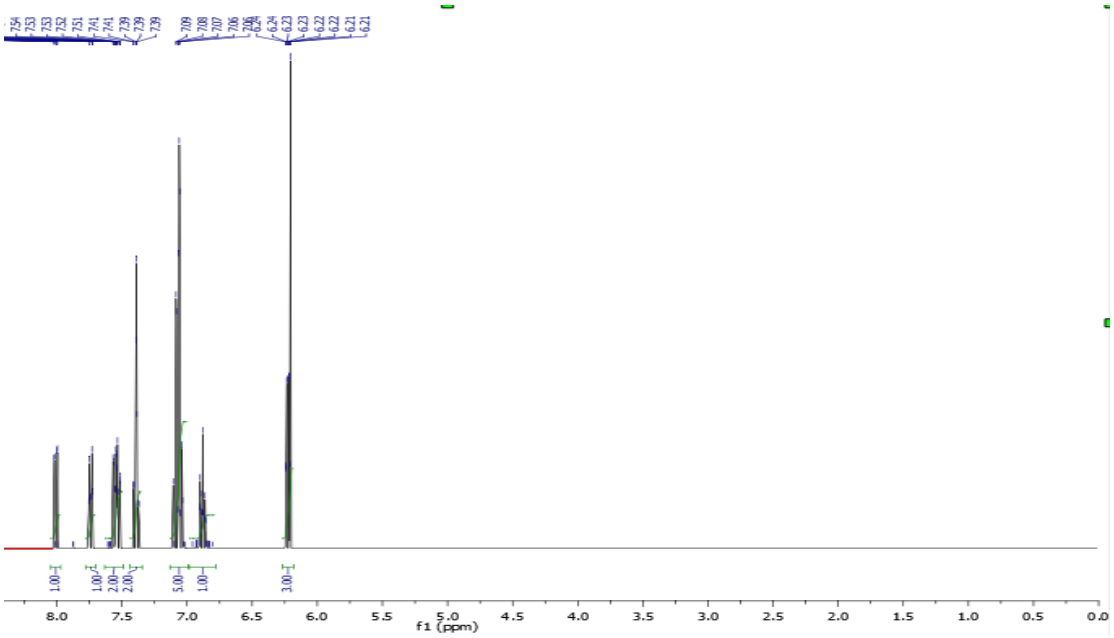
Sl.No	Ar	Ar^1	Colour and Crystal Form	Melting Point (^{0}C)
1a		C_6H_5	Brownish Colour	183
1b		p-ClC_6H_4	Yellow	182
1c		p-BrC_6H_4	White	181
1d		p-No_2 C_6H_4	Brown	180
1e		3-ClC_6H_4	Brown	183

Spectral data of Synthesised Compounds

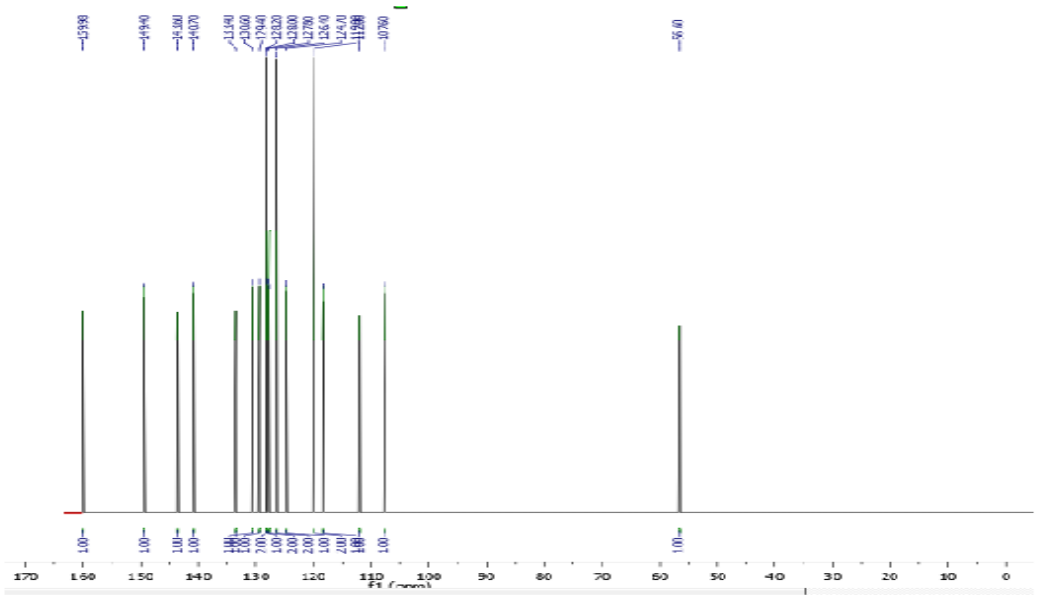
Compound 1a:

^{1}H NMR($CDcl_3$): δ 6.16-6.29 (3H, 6.21 (s), 6.21 (d, *J* = 3.4, 1.2 Hz), 6.24 (d, *J* = 3.4, 1.8 Hz)), 6.88 (1H, t, *J* = 8.1, 1.1 Hz), 6.99-7.16 (5H, 7.05 (d, *J* = 8.3, 1.2, 0.5 Hz), 7.07 (d, *J* = 8.8, 0.5 Hz), 7.08 (d, *J* = 8.3, 8.1, 1.4, 0.5 Hz)), 7.32-7.62 (4H, 7.39 (d, *J* = 7.9, 7.5, 1.9, 0.5 Hz), 7.39 (d, *J* = 1.8, 1.2 Hz), 7.53 (d, *J* = 8.6, 7.5, 1.5 Hz), 7.55 (d, *J* = 8.8, 1.9, 0.5 Hz)), 7.74 (1H, d, *J* = 7.9, 1.9, 1.5, 0.5 Hz), 8.01 (1H, d, *J* = 8.6, 1.9, 0.5 Hz).

^{13}C NMR: δ 56.6 (1C, s), 107.6 (1C, s), 112.0 (1C, s), 118.4 (1C, s), 119.9 (2C, s), 124.7 (1C, s), 126.4-126.5 (2C, 126.4 (s), 126.4 (s)), 127.7-127.8 (2C, 127.7 (s), 127.8 (s)), 128.0 (1C, s), 128.2 (2C, s), 129.4 (1C, s), 130.6 (1C, s), 133.4 (1C, s), 140.7 (1C, s), 143.6 (1C, s), 149.4 (1C, s), 160.0 (1C, s)



1HNMR spectra of Compound 1a

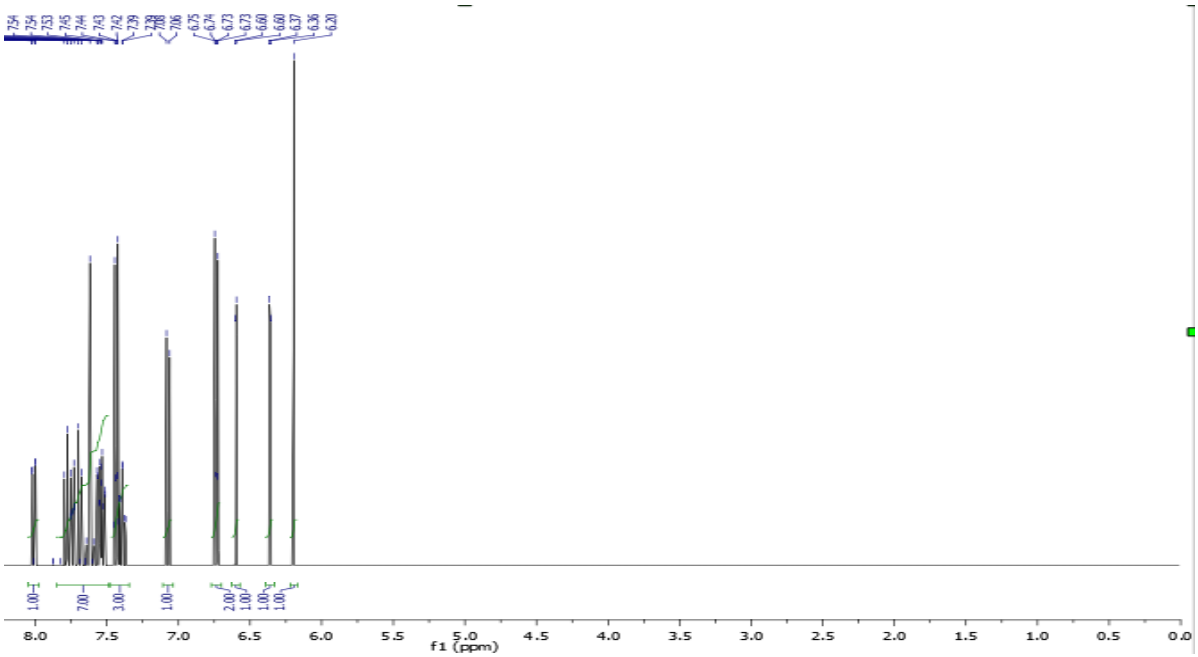


C13NMR Spectra of Compound 1a

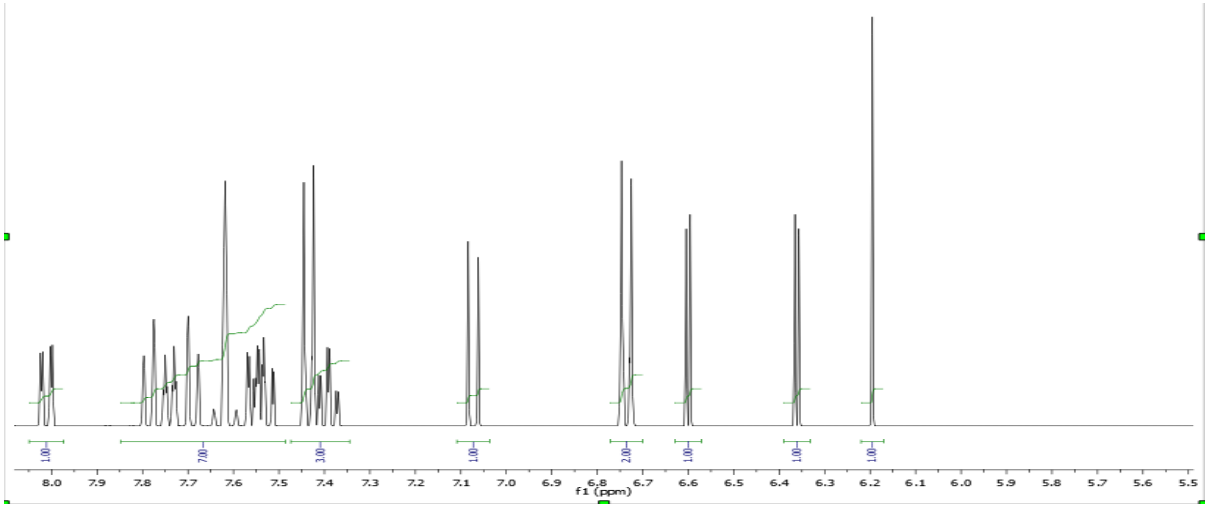
Compound 1b

^{1}H NMR($CDCl_3$): δ 6.20 (1H, s), 6.36 (1H, d, *J* = 3.4 Hz), 6.60 (1H, d, *J* = 3.4 Hz), 6.74 (2H, d, *J* = 8.3, 1.5, 0.5 Hz), 7.07 (1H, d, *J* = 8.8, 0.5 Hz), 7.32-7.80 (10H, 7.39 (d, *J* = 7.9, 7.5, 1.9, 0.5 Hz), 7.43 (d, *J* = 8.3, 1.7, 0.5 Hz), 7.53 (d, *J* = 8.6, 7.5, 1.5 Hz), 7.56 (d, *J* = 8.8, 1.9, 0.5 Hz), 7.65 (d, *J* = 8.8, 1.5, 0.5 Hz), 7.71 (d, *J* = 8.8, 1.5, 0.5 Hz), 7.74 (d, *J* = 7.9, 1.9, 1.5, 0.5 Hz)), 8.01 (1H, d, *J* = 8.6, 1.9, 0.5 Hz).

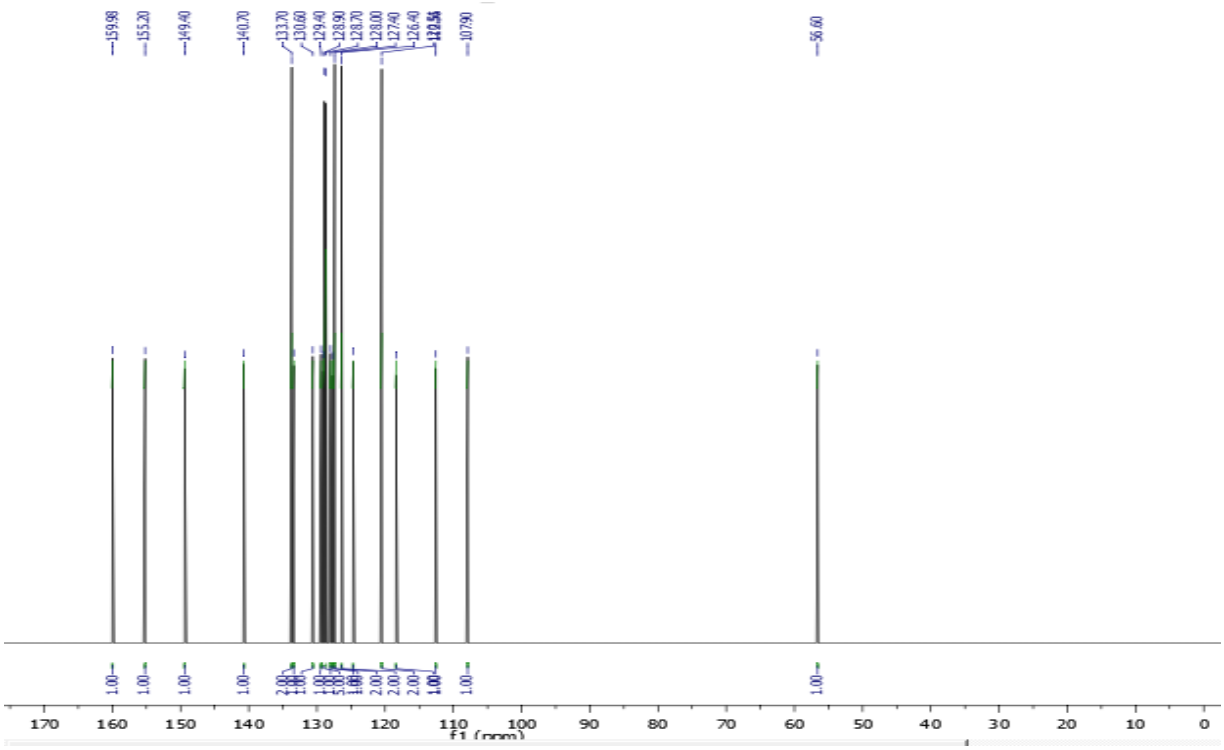
^{13}C NMR: δ 56.6 (1C, s), 107.9 (1C, s), 112.6 (1C, s), 118.4 (1C, s), 120.5 (2C, s), 124.7 (1C, s), 126.4-126.5 (2C, 126.4 (s), 126.4 (s)), 127.4 (2C, s), 127.7 (1C, s), 128.0 (1C, s), 128.7 (2C, s), 128.9 (2C, s), 129.1 (1C, s), 129.4 (1C, s), 130.6 (1C, s), 133.4 (1C, s), 133.6-133.8 (2C, 133.7 (s), 133.7 (s)), 140.7 (1C, s), 149.4 (1C, s), 155.2 (1C, s), 160.0 (1C, s).



1HNMR spectra of Compound 1b



Expanded 1HNMR spectra of Compound 1b



C13 NMR Spectra of Compound 1b

Compound 1C

^{1}H NMR: δ 6.08 (1H, s), 6.26-6.45 (4H, 6.32 (d, *J* = 3.4 Hz), 6.39 (d, *J* = 8.3, 1.5, 0.5 Hz), 6.38 (d, *J* = 3.4 Hz)), 6.93 (2H, d, *J* = 9.0, 1.1, 0.5 Hz), 7.07 (1H, d, *J* = 8.8, 0.5 Hz), 7.22 (2H, d, *J* = 8.3, 1.6, 0.5 Hz), 7.32-7.62 (5H, 7.39 (d, *J* = 7.9, 7.5, 1.9, 0.5 Hz), 7.39 (d, *J* = 9.0, 1.5, 0.5 Hz), 7.53 (d, *J* = 8.6, 7.5, 1.5 Hz), 7.56 (d, *J* = 8.8, 1.9, 0.5 Hz)), 7.74 (1H, d, *J* = 7.9, 1.9, 1.5, 0.5 Hz), 8.01 (1H, d, *J* = 8.6, 1.9, 0.5 Hz).

^{13}C NMR: δ 56.6 (1C, s), 107.9 (1C, s), 112.6 (1C, s), 114.3 (2C, s), 118.4 (1C, s), 121.9 (2C, s), 122.3 (1C, s), 124.7 (1C, s), 126.0 (2C, s), 126.4-126.5 (2C, 126.4 (s), 126.4 (s)), 127.7 (1C, s), 128.0 (1C, s), 129.1 (1C, s), 129.4 (1C, s), 130.6 (1C, s), 131.7 (2C, s), 133.4 (1C, s), 140.7 (1C, s), 148.4 (1C, s), 149.4 (1C, s), 155.2 (1C, s), 160.0 (1C, s)

Compound 1d

^{1}H NMR($CDCl_3$): δ 6.20 (1H, s), 6.36 (1H, d, *J* = 3.4 Hz), 6.60 (1H, d, *J* = 3.4 Hz), 6.74 (2H, d, *J* = 8.3, 1.5, 0.5 Hz), 7.07 (1H, d, *J* = 8.8, 0.5 Hz), 7.32-7.80 (10H, 7.39 (d, *J* = 7.9, 7.5, 1.9, 0.5 Hz), 7.43 (d, *J* = 8.3, 1.7, 0.5 Hz), 7.53 (d, *J* = 8.6, 7.5, 1.5 Hz), 7.56 (d, *J* = 8.8, 1.9, 0.5 Hz), 7.65 (d, *J* = 8.8, 1.5, 0.5 Hz), 7.71 (d, *J* = 8.8, 1.5, 0.5 Hz), 7.74 (d, *J* = 7.9, 1.9, 1.5, 0.5 Hz)), 8.01 (1H, d, *J* = 8.6, 1.9, 0.5 Hz).

^{13}C NMR: δ 56.6 (1C, s), 107.9 (1C, s), 112.6 (1C, s), 118.4 (1C, s), 120.5 (2C, s), 124.7 (1C, s), 126.4-126.5 (2C, 126.4 (s), 126.4 (s)), 127.4 (2C, s), 127.7 (1C, s), 128.0 (1C, s), 128.7 (2C, s), 128.9 (2C, s), 129.1 (1C, s), 129.4 (1C, s), 130.6 (1C, s), 133.4 (1C, s), 133.6-133.8 (2C, 133.7 (s), 133.7 (s)), 140.7 (1C, s), 149.4 (1C, s), 155.2 (1C, s), 160.0 (1C, s).

Compound 1e

^{1}H NMR($CDCl_3$): δ 6.16-6.29 (3H, 6.21 (s), 6.21 (d, *J* = 3.4, 1.2 Hz), 6.24 (d, *J* = 3.4, 1.8 Hz)), 6.88 (1H, t, *J* = 8.1, 1.1 Hz), 6.99-7.16 (5H, 7.05 (d, *J* = 8.3, 1.2, 0.5 Hz), 7.07 (d, *J* = 8.8, 0.5 Hz), 7.08 (d, *J* = 8.3, 8.1, 1.4, 0.5 Hz)), 7.32-7.62 (4H, 7.39 (d, *J* = 7.9, 7.5, 1.9, 0.5 Hz), 7.39

(d, *J* = 1.8, 1.2 Hz), 7.53 (d, *J* = 8.6, 7.5, 1.5 Hz), 7.55 (d, *J* = 8.8, 1.9, 0.5 Hz)), 7.74 (1H, d, *J* = 7.9, 1.9, 1.5, 0.5 Hz), 8.01 (1H, d, *J* = 8.6, 1.9, 0.5 Hz).
^{13}C NMR: δ 56.6 (1C, s), 107.6 (1C, s), 112.0 (1C, s), 118.4 (1C, s), 119.9 (2C, s), 124.7 (1C, s), 126.4-126.5 (2C, 126.4 (s), 126.4 (s)), 127.7-127.8 (2C, 127.7 (s), 127.8 (s)), 128.0 (1C, s), 128.2 (2C, s), 129.4 (1C, s), 130.6 (1C, s), 133.4 (1C, s), 140.7 (1C, s), 143.6 (1C, s), 149.4 (1C, s), 160.0 (1C, s)

Result and discussion

All final compounds reported in this paper are new and not found in the chemical literature and were completely characterized by spectroscopic means. All the compounds were synthesized according to the procedure by varying different aldehydes but we obtained good yield in a nitro substituent when compared to other substituents. All compounds gave promising yields and melting point according to the literature.

Conclusion

In conclusion, we have documented a three-component, one-pot synthesis of Betti bases using can as a Lewis acid catalyst at room temperature. Considering the advantages such as readily available starting materials, simple operations as well as the high yields, our methodology will potentially find its application to the well-known Betti bases synthesis.

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