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An Efficient Two Step Synthesis of Betti Bases Under Acid Catalyzed Conditions at Ambient Temperature

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***Abstract:** The synthesis of aminobenzylnaphthols is achieved through a multicomponent reaction (MCR) involving 2-naphthol, a variety of amines, and aldehydes as starting materials.*

Aminonaphthols, which possess 1,3-aminooxygenated functional groups, are of considerable interest due to their broad biological activity and synthetic versatility. These compounds frequently serve as key intermediates in the synthesis of pharmaceutical agents and bioactive natural products, and are often recognized as pharmacophores in medicinal chemistry. Their unique structural features make them valuable candidates for further derivatization and development in drug discovery.

***Keywords:** 2-naphthol; Betti bases; azomethines; three-component synthesis.*

I. INTRODUCTION

A wide range of biologically active natural products are known to contain 1,3-amino-oxygenated functional groups [1,2], among which aminonaphthols have garnered particular attention [3]. These compounds not only exhibit potent biological activities [4], but their synthesis continues to be an area of active research in synthetic organic chemistry due to their structural and functional diversity. Historically, an efficient synthesis of aminobenzylnaphthols was reported via a modified Mannich reaction, marking an important milestone in the development of this compound class. Subsequently, various synthetic strategies have been employed using diverse nitrogen sources, further expanding the scope of accessible aminonaphthol derivatives. From a stereochemical perspective, these compounds have shown great potential as chiral auxiliaries and chiral catalysts in stereoselective transformations [6]. Over the past two decades, numerous methodologies have been developed for their synthesis, reflecting both the versatility and significance of these molecules [7–11]. Innovative and environmentally conscious methods have also been explored, including reactions in non-ionic surfactant media in water [12], solvent-free microwave-assisted synthesis [13], and protocols incorporating nano-crystalline MgO in aqueous conditions [14]. Additionally, the use of green nitrogen sources, such as aqueous ammonia, has been investigated as a safer and more sustainable alternative to conventional organic solvents [15].

Some studies have focused on the hydrolysis of aminodialkyl naphthols to obtain target compounds [16], while others have proposed multicomponent reactions and one-pot synthetic strategies for their efficient construction. Given their broad synthetic utility and potential antimicrobial activity, these title compounds are poised to become valuable assets in both medicinal chemistry and organic synthesis.

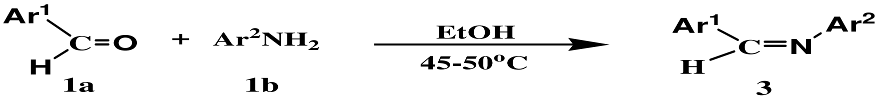
II. MATERIALS AND METHODS

A. General Information

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Spectrospin Avance spectrometer(400 MHz for ^{1}HMR). CD_3OD was used as a solvent; chemical shifts are quoted in δ (ppm) from tetramethylsilane. Infrared spectra were measured on a Nicolet iS50 FTIR Spectrometer.

1) General procedure for the Azomethines

A mixture of amine derivatives (1b, 1.5 mmol) and aldehyde (1a, 1.0 mmol) was dissolved in ethanol (10 mL) and stirred at 45-50℃ under reflux until the reaction reached completion, as monitored by TLC. Upon completion, the solvent was removed under reduced pressure, yielding the corresponding azomethines (Schiff bases) as crude products, which were used in subsequent reactions without further purification.

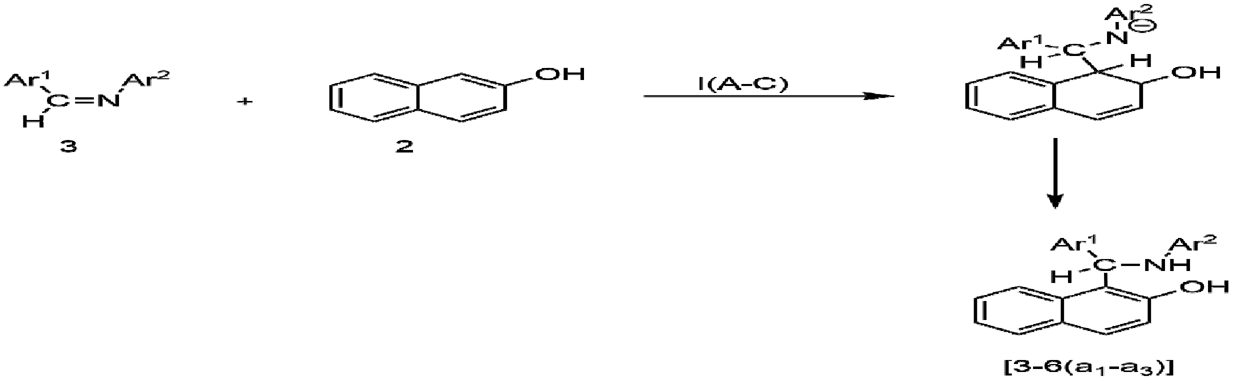


2) General procedure for 1-aminobenzyl-2-naphthol

Azomethines were reacted with 2-naphthol under various reaction conditions to optimize the synthesis of 1-aminobenzyl-2-naphthol. Among the tested procedures, only three reaction schemes proved efficient in yielding the desired product in high yield:

- Scheme IA: Each group of Azomethines were reacted with 2-naphthol in warm THF (45–50 °C) using a catalytic amount of H_2SO_4 and NH_4OAc. The reaction mixture was stirred continuously until completion.
- Scheme IB: Each group of Azomethines were reacted with 2-naphthol in warm THF (45–50 °C) in the presence of a catalytic amount of H_3PO_4 + NaH_2PO_4 in equal mole ratio. The reaction was stirred at 50–55 °C until completion. After two days, the residual solvent was evaporated, leading to the formation of crystalline products.
- Scheme IC: Each group of Azomethines were reacted with 2-naphthol in methanol (MeOH) using a catalytic amount of p-toluenesulfonic acid (TsOH). The mixture was shaken thoroughly and then refluxed at 50–55 °C. Upon completion, the solvent was removed under reduced pressure, and the crude product was isolated by filtration, washed thoroughly with hexane, dried, and crystallized.

In all three schemes, the obtained products were confirmed to be identical to 1-amino-2-naphthols in the later part of our project and as evidenced by matching melting points.



Scheme 1: Synthesis of 1-aminobenzyl-2-naphthols

Table 1: List of Betti bases synthesized

Products	Amines	Aldehydes	Time Taken (in min)	%Yield Reaction Conditions		
				IA	IB	IC
$3a_1$	$4\text{-}NO_2\text{-}C_6H_4NH_2$	C_6H_5CHO	30	30	64	25
$3a_2$	$4\text{-}NO_2\text{-}C_6H_4NH_2$	$4\text{-}Cl\text{-}C_6H_5CHO$	35	33	60	20
$3a_3$	$4\text{-}NO_2\text{-}C_6H_4NH_2$	$4\text{-}OCH_3\text{-}C_6H_5CHO$	40	45	78	35
$4a_1$	$2\text{-}NO_2\text{-}C_6H_4NH_2$	C_6H_5CHO	35	32	62	27
$4a_2$	$2\text{-}NO_2\text{-}C_6H_4NH_2$	$4\text{-}Cl\text{-}C_6H_5CHO$	40	31	67	26
$4a_3$	$2\text{-}NO_2\text{-}C_6H_4NH_2$	$4\text{-}OCH_3\text{-}C_6H_5CHO$	35	47	74	35
$5a_1$	$C_6H_5NH_2$	C_6H_5CHO	30	35	62	24
$5a_2$	$C_6H_5NH_2$	$4\text{-}Cl\text{-}C_6H_5CHO$	45	33	63	29
$5a_3$	$C_6H_5NH_2$	$4\text{-}OCH_3\text{-}C_6H_5CHO$	30	44	73	38
$6a_1$	$4\text{-}CH_3\text{-}C_6H_5NH_2$	C_6H_5CHO	40	30	62	26
$6a_2$	$4\text{-}CH_3\text{-}C_6H_5NH_2$	$4\text{-}Cl\text{-}C_6H_5CHO$	35	34	65	24
$6a_3$	$4\text{-}CH_3\text{-}C_6H_5NH_2$	$4\text{-}OCH_3\text{-}C_6H_5CHO$	40	45	75	35

III. RESULT AND DISCUSSION

An attempted three-component reaction involving an amine, 2-naphthol, and an aldehyde in a 1.15:1:1 molar ratio using H_2SO_4 as a catalyst in THF (20 mL) at 45–50 °C initially yielded unsatisfactory results. Multiple trials were conducted under varying conditions to optimize the reaction, but many resulted in poor yields. However,under three reaction conditions were identified that significantly improved the yield. Among these, Scheme IB proved to be the most efficient, consistently delivering high product yields . In contrast, reactions under Schemes IA and IC did not meet expectations, particularly in terms of yield.

Substituent effects on the aromatic aldehyde ring were also evaluated. When electron-donating groups (EDGs) were present on the benzaldehyde derivatives, especially in reactions involving amines from the $3a_3$, $4a_3$, $5a_3$, and $6a_3$ series, the reactions proceeded with high efficiency and yield. The reaction likely proceeds through an acid-catalyzed condensation between the aldehyde and amine, forming a Schiff base (azomethine intermediate). This intermediate subsequently undergoes nucleophilic attack by 2-naphthol, leading to the formation of Betti base derivatives. This mechanism is consistent with classical pathways observed in multicomponent reactions forming aminonaphthol-based compounds.

IV. CONCLUSION

A three-component, one-pot synthesis of aminonaphthols has been successfully developed using a catalytic system comprising phosphoric acid (H_3PO_4) and monosodium phosphate (NaH_2PO4). This method proceeds under mild, ambient temperature conditions, offering a practical and environmentally friendly alternative to conventional multistep processes. The synergistic effect of the dual acid catalyst system promotes high yields and selectivity, making it suitable for sustainable organic synthesis.

The use of equimolar amounts of phosphoric acid (H_3PO_4) and monosodium phosphate (NaH_2PO_4) not only facilitates excellent product yields but also enhances operational simplicity and broadens substrate scope. This efficient, environmentally benign methodology represents a valuable addition to the synthetic toolbox in both organic and medicinal chemistry. Owing to its practical execution and alignment with green chemistry principles, this strategy holds significant promise for the synthesis of structurally diverse and biologically relevant aminonaphthol derivatives.

REFERENCES

[1] Betti M, Gazz. Chem. Ital. 1901, 31, 170-174.
[2] Putino Oj, Cuca LE. Phytochem. Lett. 2011, 4, 22-25.
[3] Armstrong RW, Combs AP, Tempes PA, Brown SD, Keating TA. Acc. Chem. Res. 2013, 29, 123-131.
[4] Domling A, Mgi I, Angew. Chem. Int. ed. 2000, 39, 3168-3210.
[5] Caedellicchio C, Capozzi MAM, Naso F. Tetrahedron Assym. 2010, 21, 507-517.
[6] Cimarelli C, Fratoni D, Mazzanti A, Palmieri G. Eur.J.Org. Chem. 2011, 2011, 2094-2100.
[7] Lu J, Xu X, Wang C, He J, Hu Y. Tetrahedron Lett. 2022, 32, 8376-8369.
[8] Nair V, Panicker SB, Nair Lg, George TG, Augustine A. Synlett. 2003, 2003, 156-166
[9] Hulme C, Bienayme H, Nixey T, Chenera B, Jones W, Tempest P, Smith, A. Methods Enzymol. 2003, 369, 469-496.
[10] Cioc RC, Ruijter E, Orru, RVA. Green Chem. 2014, 16, 2958-2975.
[11] Zarganes-Tzitzikas T, Chandgude AL, Domling, A. Chem. Rec. 2015, 15, 981-996.
[12] Banfi L, Basso A, Giardini L, Riva R, Rocca V, Guanti G, Eur.J.Org. Chem. 2011, 2011, 100-109.
[13] Sadek KU, Al-Qalaf F, Abdelkhalik MM, Elnagdi MH. J. Het. Chem. 2012, 8, 18-24.
[14] Metlushka KE, Kashemirov BA, Zheltulkin VK, Sadkova DN, Buchner B, Hess C, Kataeva CON, Mckenna CE, Alfonsov Va.Chem.A>eur.j.2009,15,6718-6722.
[15] Hamid SR, Yarahamid H, Ghashang M. Bioorg. Med. Chem. Lett. 2008, 18, 788-792.
[16] Das B, Lazminarayana K, Thirupathi B, Ramarao B. Synlett, 2007, 20, 3103-3107.
[17] Hamid SR, Yarahamid H, Arkivoc. 2008, 2, 105-114.
[18] Hamid SR, Yarahamid H, Tetrahedron Lett. 2008, 49, 1297-1300.
[19] Hamid SR, Yarahamid H, Ghashang M, Bioorg. Med. Chem. Lett. 2008, 18, 788-792.
[20] Kumar A, Gopta MK, Kuma M. Tetrahedron Lett. 2010, 51, 1582-1584.
[21] Jha A, Paul MK, Trikha S, Cameron TS. Cand. J.Chem. 2008, 84, 843-85.
[22] Kumar A, Gopta MK, Kuma M. Tetrhedron Lett. 2010, 51, 1582-1584.
[23] Wang C, Wan Y, Wang HY, Zhao LL, Shi JJ, Zhang XX, Wu H. J. Het. Chem. 2013, 50, 496-500.