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Solvent-Free Preparation of Novel 2-[Phenyl (Pyridine-2-Ylamino) Methyl] Phenols as Pseudo-Betti Processor for Natural Products

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Background: 2-Aminopyridine and benzaldehydes mixture readily reacted with phenols at 80°C without any solvents to produce novel 2-[phenyl (pyridine-2-yl amino (methyl] phenol derivatives as pseudo-Betti products in good to high yields. These compounds are efficient processor for synthesis of the natural products.
Objectives: We decided to report the synthesis of a series of novel *N*-heteroaryl-arylmethyl phenols via a simple three-component, one-pot method, using aromatic aldehydes, heteroaryl amines, and phenols in the absence of any acid catalysts and under solvent-free conditions.
Materials and Methods: All starting materials were purchased from Merck and Aldrich companies. The IR spectra were recorded on a Perkin-Elmer RXI infrared spectrometer.
Results: The reaction is convenient, operationally simple, proceeds quickly, and does not need solvents or expensive starting materials. The structures of the products were characterized by their spectral (1H NMR and IR) data.
Conclusions: We have developed a new, simple, and efficient method for one-pot aminoalkylation of active phenol compounds with various imines prepared from 2-aminopyrimidine and benzaldehydes in good to high yields (40%-97%).

Keywords: Solvent-Free; Pseudo-Betti; Base; 2-Amino pyridine; Phenols

1. Background

Compounds bearing 1, 3-amino-oxygenated functional motifs are ubiquitous to a variety of biologically important natural products and versatile source for potent drugs, including a number of nucleoside antibiotics and HIV protease inhibitors such as ritonavir and lopinavir (1-3). A series of 2-(amino methyl) phenols was also synthesized and tested in rats and dogs for saluretic and diuretic activity (4). The phenolic hydroxyl and amino groups can be utilized in developing several synthetic building blocks (5). These compounds as optically active Betti bases can be used as ligands to chelate with organometallic reagents in different reactions to provide highly efficient asymmetric induction (6). Reaction of Betti bases with aldehydes also produces 1,3-oxazines as an important biologically active scaffold (7).

The formation of new C-C bonds provides new opportunities in total synthesis, medicinal chemistry, chemical biology, and nanotechnology. In particular, cross-coupling reactions between aromatic and aliphatic compounds have been largely studied. Usually, this type of reactions takes place in the presence of catalysts such as transition metal complexes (8). One-pot, multi-component reactions are effective processes for the discovery of new reactions and the synthesis of complex structures specially using C-C bond formation (9). They enable rapid access to large compound libraries with diverse functionalities, and avoid costly purification processes in addition to protection and deportation steps by systematic variation of the starting material which is either commercially available or easily prepared (10).

One of the classic multi-component reactions is the synthesis of Betti bases (11). The typical Betti reaction is a three-component reaction between an aldehyde, ammonia/urea, and phenol or β-naphthol (12). Several studies have centered on the catalysis of this reaction, using different bases or metal salts (13). The Betti reaction represents a useful method to obtain aminoalkyl phenols or naphthols. The phenolic Mannich reaction is performed using activated phenols or naphthols as nucleophiles and cyclic imines as the electrophilic partner (14). Traditionally, the Betti base derivative synthesis is carried out in organic solvents such as EtOH, MeOH, and Et2O at room temperature for long times or thermally under solventless conditions.

Additionally, the preparation of Betti base derivatives is reported in water as solvent (15). Also, the synthesis of *N*-heteroarylarylmethyl indoles has been reported under solvent-free condition (16). Recently, one-pot synthesis of

new *bis*-Betti bases via condensation of dihydroxynaphthalene, aryl aldehydes, and 3-amino-5-methylisoxazole has also been reported (17). To the best of our knowledge, there is no report of the aromatic aminomethyl phenols synthesis via condensation of heteroaryl amines, aromatic aldehydes, and phenols in solvent-free conditions in literature.

2. Objectives

In continuation of our studies on the solvent-free reaction, we decided to report the synthesis of a series of novel *N*-heteroaryl-arylmethyl phenols via a simple three-component, one-pot method, using aromatic aldehydes, heteroaryl amines, and phenols in the absence of any acid catalysts and under solvent-free conditions as shown in Figure 1. As such, the utilization of environment-friendly conditions (absence of organic solvent) gives the product not only an easy work-up procedure, but also compatibility with green chemistry principles.

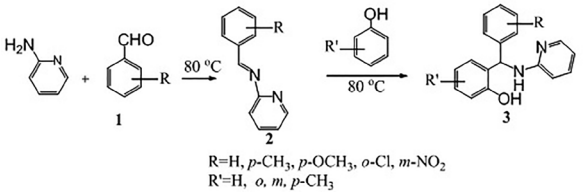

Figure 1. One-Pot Synthesis of Hetero-aminoalkyl Phenols

Table 1. One-Pot Synthesis of Aminoalkyl Phenols Using Aldehydes, 2-Aminopyridine and Phenols at 80°C [a]

Entry	R-R′	Product	Time, min	Yield, %
01	H-H	3a	120	52
02	H-*o*-CH_3	3b	30	72
03	H-*m*-CH_3	3c	30	74
04	H-*p*-CH_3	3d	30	78
05	*p*-CH_3-H	3e	120	50
06	*p*-CH_3-*o*-CH_3	3f	80	75
07	*p*-CH_3-*m*-CH_3	3g	80	78
08	*p*-CH_3-*p*-CH_3	3h	80	80
09	*p*-OCH_3-H	3i	120	---
10	*p*-OCH_3-o-CH_3	3j	120	40
11	*p*-OCH_3-*m*-CH_3	3k	120	43
12	*p*-OCH_3-*p*-CH_3	3l	120	48
13	*o*-Cl-H	3m	50	60
14	*o*-Cl-*o*-CH_3	3n	30	80
15	*o*-Cl-*m*-CH_3	3o	30	90
16	*o*-Cl-*p*-CH_3	3p	30	95
17	*m*-NO_2-H	3q	41	78
18	*m*-NO_2-*o*-CH_3	3r	30	90
19	*m*-NO_2-*m*-CH_3	3s	30	92
20	*m*-NO_2-*p*-CH_3	3t	30	97

[a] All products were confirmed by comparison with authentic samples (IR, ^{1}HNMR and TLC).

3. Materials and Methods

3.1. Reagents and Materials

All starting materials were purchased from Merck and Aldrich companies. The IR spectra were recorded on a Perkin-Elmer RXI infrared spectrometer. ^{1}H NMR spectra were recorded with a 500 MHz Bruker FT-NMR spectrometer. TLC accomplished the purity of substrates, and reactions were monitored on silica gel polygram SIGL/UV254 plates. Melting points were determined by open capillary method using a Mettler melting point apparatus and are uncorrected.

3.2. General Procedure for the Synthesis of Pyridyl-aminoalkyl Phenols 3a-3t

A mixture of amine (1.0 mmol), and aldehyde (1.2 mmol) was stirred in oil bath at 80°C. Phenol (1 mmol) was added after 10 min, and the mixture was heated until TLC (*n*-hexane: ethyl acetate; 4:1) monitoring showed the completion of the reaction (30-120 min). Then, the reaction mixture was extracted with diethyl ether (2 × 20 mL). The combined solutions were dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded the product. The crude product was stirred for 5 min in boiling *n*-hexane (20 mL) and the resulting white precipitate was filtered.

4. Results

Activated phenols, *o*, *m*, *p*-cresol, react with imines, which can be prepared from aldehydes and 2-aminopyridine, affording products 3a-t in 30 minutes as shown in Figure 1, and the aminoalkyl phenol products were obtained in good to high yields as shown in Table 1. The reaction is convenient, operationally simple, proceeds quickly, and does not need solvents or expensive starting materials. The structures of the products were characterized by their spectral (^{1}H NMR and IR) data (18).

5. Discussion

As the results indicate on Table 1, phenol was reacted with imine, which is prepared from condensation of 2-aminopyridine and benzaldehyde, in oil bath at 80°C without any solvent affording amino products 3a-d. It was found that at least 2 hours were needed for the reaction to be completed. In the next step, the reaction was performed by activated phenols such as *o*-, *m*-, and *p*-cresol and completed in 30 min. In order to study the electron-donating and electron-withdrawing groups effects, we decided to perform this reaction with substituted benzaldehydes such as *p*-CH_3, *p*-OCH_3, *o*-Cl and *m*-NO_2. It was found that electron-withdrawing group on benzaldehyde efficiently afforded products in 30 minutes with high yields, at 80°C. This method offers marked improvement compared with previously reported ones. Its advantages included operational simplicity, low reaction time, and high yields of products.

The mechanism of this transformation involves the intermediacy of an imine, followed by the addition of phenol as shown in Figure 2. The OH group of phenol protonates the C = N nitrogen through a 'double' activation pathway. This activation consists of increasing the elecrtophilicity of the imine and the enhancement of the electron density at the ortho position of the phenol. Thus, the new carbon–carbon bond is formed ortho to the hydroxyl group. Regioselectivity is probably due to hydrogen bond formation in the transition state, as depicted in Figure 2 for the reaction of imine with phenols to form products (12).

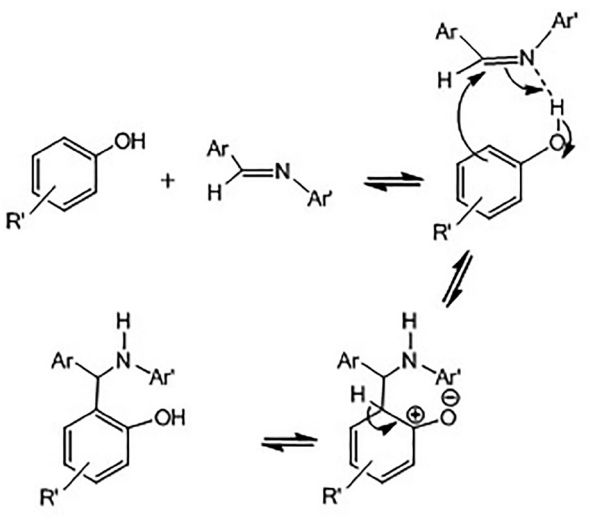

Figure 2. Mechanism of amino alkyl Phenols Synthesis

5.1. Characterization of Products

The selected spectral data for the synthesis of pyridylaminoalkyl phenols 3a-3t are as follows:

2-(phenyl (pyridin-2-ylamino) methyl) phenol-(3a): IR ($\bar{\upsilon}$/cm^{-1}): 3360 (OH), 3291 (NH), 1620 (C = N), 1554, 1470 (C = C Ar). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 4.1 (1H, bs, NH), 5.2 (1H, s, CH), 6.5-8.2 (13H, m, aromatic and heteroaryl), OH not assigned; ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δC 59.6, 106.9, 116.1, 117.3, 119.5, 121.7, 126.1, 127.9, 128.1, 129.3, 130.3, 138, 140.1, 147.5, 156.8, 159.2-methyl-6-(phenyl (pyridin-2-ylamino) methyl) phenol-(3b): IR ($\bar{\upsilon}$/cm^{-1}): 3352 (OH), 3291 (NH), 1620 (C = N), 1553, 1470 (C = C Ar). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 2.2 (3H, s, CH3), 4 (1H, bs, NH), 5.2 (1H, s, CH), 6.5-8.2 (12H, m, aromatic and heteroaryl), OH not assigned; ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δC 16.2, 59.5, 106.9, 116.1, 117.3, 119.5, 121.7, 123.1, 126.9, 128, 129.3, 130.3, 138, 140.1, 147.5, 156.8, 159.5-methyl-2-(phenyl (pyridin-2-ylamino) methyl) phenol-(3c): IR ($\bar{\upsilon}$/cm^{-1}): 3351 (OH), 3291 (NH), 1620 (C = N), 1552, 1470 (C = C Ar). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 2 (3H, s, CH_3), 4 (1H, bs, NH), 5.2 (1H, s, CH), 6.5-8.2 (12H, m, aromatic and heteroaryl), OH not assigned; ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δC 20.2, 59.5, 106.9, 116.1, 117.3, 119.5, 122.7, 123.9, 126.1, 128, 129.3, 130.3, 138, 140.1, 147.5, 156.8, 159.4-methyl-2-(phenyl (pyridin-2-ylamino) methyl) phenol-(3d): IR ($\bar{\upsilon}$/cm^{-1}): 3370 (OH), 3291 (NH), 1610 C = N), 1553, 1470 (C = C Ar). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 2.1 (3H, s, CH_3), 4 (1H, bs, NH), 5.2 (1H, s, CH), 6.5-8.2 (12H, m, aromatic and heteroaryl), OH not assigned; ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δC 21.4, 59.8, 106.9, 116, 117.3, 119.5, 122.7, 123.9, 126.1, 128, 129.3, 130.1, 135, 140.1, 147.5, 156.8, 159.(2-((pyridin-2-ylamino) (*p*-tolyl) methyl) phenol-(3e): IR ($\bar{\upsilon}$/cm^{-1}): 3510 (OH), 3305 (NH), 1618 (C = N), 1551, 1470 (C = C Ar). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 2.35 (3H, s, CH_3), 4.2 (1N, bs, NH), 5.1 (1H, s, CH), 6.6-8.2 (12H, m, aromatic and heteroaryl), OH not assigned; ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δC 20.2, 59.5, 106.5, 116, 117.3, 119.5, 122.7, 123.9, 126.1, 128, 129.3, 130, 133, 140.4, 147.5, 157.5, 159.2-methyl-6-((pyridin-2-ylamino) (*p*-tolyl) methyl) phenol-(3f): IR ($\bar{\upsilon}$/cm^{-1}): 3502 (OH), 3306 (NH), 1620 (C = N), 1550, 1470 (C = C Ar). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 2.12 (3H, s, CH_3), 2.33 (3H, s, CH_3), 4.2 (1H, bs, NH), 5.1 (1H, s, CH), 6.6-8.2 (11H, m, aromatic and, heteroaryl), OH not assigned; ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δC 15.2, 20.2, 59.5, 106.5, 116, 117.3, 119.5, 122.7, 123.9, 126.1, 128, 129.3, 130, 133, 140.4, 147.5, 157.5, 159.2-((2-chlorophenyl) (pyridin-2-ylamino) methyl) phenol-(3m): IR ($\bar{\upsilon}$/cm^{-1}): 3515 OH), 3335 (NH), 1635 (C = N), 1552, 1470 (C = C Ar). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 4.2 (1H, bs, NH), 5.2 (1H, s, CH), 6.6-8.2 (12H, m, aromatic and heteroaryl), OH not assigned; 13C NMR (400 MHz, $CDCl_3$, TMS) δC 54.7, 106, 115, 117, 119.5, 122.7, 123.9, 126.1, 128, 129.3, 130, 133, 140.4, 147.5, 157.5, 159.2-((2-chlorophenyl) (pyridin-2-ylamino) methyl) -4-methylphenol-(3p): IR ($\bar{\upsilon}$/cm^{-1}): 3500 (OH), 3325 (NH), 1632 (C = N), 1550, 1470 (C = C Ar). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 2.15 (3H, s, CH_3), 4.2 (1H, bs, NH), 5.2 (1H, s, CH), 6.6-8.2 (11H, m, aromatic and heteroaryl), OH not assigned; ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δC 21.2, 58.2, 106, 115, 117.5, 119, 122, 123, 126.4, 128, 129.2, 130, 133, 140, 147, 156, 159.2-((3-nitrophenyl) (pyridin-2-ylamino) methyl) phenol-(3q): IR ($\bar{\upsilon}$/cm^{-1}): 3526 (OH), 3318 (NH), 1640 (C = N), 1557, 1474 (C = C Ar), ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 4.8 (1H, bs, NH), 5.19 (1H, s, CH), 6.6-8.2 (12H, m, aromatic and heteroaryl), OH not assigned; ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δC 59.3, 106.4, 115, 117, 119.5, 122, 123, 126.4, 128, 129.2, 130.9, 133.1, 140, 147, 148.6, 156, 159.4-methyl-2-((3-nitrophenyl) (pyridin-2-ylamino) methyl) phenol-(3t): IR ($\bar{\upsilon}$/cm^{-1}): 3520 (OH), 3320 (NH), 1638 (C = N), 1555, 1471 (C = C Ar). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δH 2.32 (3H, s, CH_3), 4.2 (1H, bs, NH), 5.28 (1H, s, CH), 6.6-8.2 (11H, m, aromatic and heteroaryl), OH not assigned; ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δC 21.5, 58.4, 106, 115.4, 117, 119.5, 122.1, 123, 125.4, 128, 129.2, 130, 133, 140, 147.1, 148, 156, 159.In conclusion, we have developed a new, simple, and efficient method for one-pot aminoalkylation of active phenol compounds with various imines prepared from 2-aminopyrimidine and benzaldehydes in good to high yields (40%-97%).

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