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Original scientific paper

A novel approach toward the synthesis of some new tridentate Schiff bases from anil-like compounds

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Abstract: A novel method was developed for synthesizing a series of new tridentate Schiff base ligands starting from hydroxynaphthyl pyrimidinyl amines with *o*-phenylenediamines or *o*-aminophenol or 2-amino-3-hydroxy-pyridine in the presence of formic acid catalyst under solvent-free conditions. In these reactions [1+1], the condensation product as half-unit ligand was obtained. Moreover, the reaction of hydroxynaphthylmethylene pyrimidinyl amines with 3,4-diaminopyridine and 1,8-naphthalenediamine leads to the formation of C2-naphthylated imidazopyridine and dihydropyrimidine, respectively. The attractive features of this protocol are use of an inexpensive catalyst, operational simplicity, short reaction times, easy handling, and good yields.

Keywords: Schiff base; anil; *o*-phenylenediamine; *o*-aminophenol; dihydropyrimidine; imidazopyridine.

INTRODUCTION

Condensation of carbonyl compounds with primary amines was discovered in 1864 by Hugo Schiff.[1] This acid-catalyzed reaction is universal and enables a broad variety of azomethines to be obtained. Schiff bases are known to show biological activities, such as antimicrobial,[2–5] antifungal[6] and antitumor,[7] and are used in the production of dyes and pigments.[8] Moreover, Schiff bases are also employed as chelating agents[9] capable of coordinating metal ions to give complexes that serve as models for biological systems.[10,11]

2-Hydroxy Schiff base ligands, derived from the reaction of salicylaldehyde and 2-hydroxy-1-naphthaldehyde with amines, and their complexes have been extensively studied.[12–14] 2-Hydroxy Schiff base ligands are of interest mainly due to the existence of (O–H···N and N–H···O) type hydrogen bonds and tautomerism between the enol–imine and keto–enamine forms. Tautomerism in ortho-hydroxy naphthylmethylene anilines (anils) in solution and in the solid state has been investigated by different spectroscopic techniques.[15–17]

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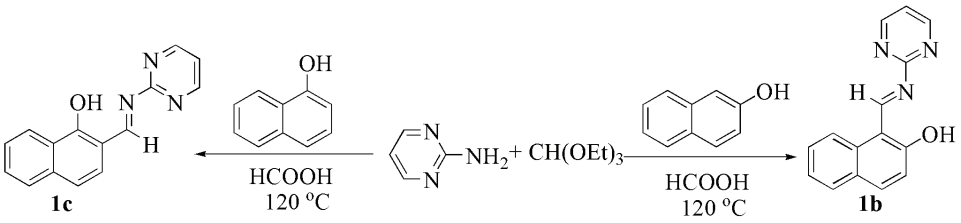
In recent years, environmentally safe synthetic methods have received considerable attention, and some solvent-free protocols have been developed. The catalyzed synthesis of imines under solvent-free conditions may be performed by microwave irradiation, ionic liquids, montmorillonite clays,[18] zeolites, silica, alumina or other matrices.[19,20] However, ortho-hydroxy naphthylmethyleneanilines were synthesized by refluxing in organic solvents such as ethanol and microwave irradiation of naphthaldehyde and amines.

In continuation of ongoing research for the development of simple and efficient methods for the synthesis of various heterocyclic compounds under solvent-free conditions[21–26] and interest in anils derived from naphthols, triethyl orthoformate and heteroaryl amines,[25] it was decided to prepare some new Schiff bases from hydroxynaphthylmethylene pyrimidinyl amines with *o*-phenylenediamines or *o*-aminophenol or 2-amino-3-hydroxypyridine under solvent-free conditions.

RESULTS AND DISCUSSION

Previously, the synthesis of 1-((pyrimidin-2-ylimino)methyl)naphthalene-2,7-diol (**1a**) from 2,7-dihydroxynaphthalene, triethyl orthoformate and 2-aminopyrimidine in the presence of formic acid catalyst under solvent-free conditions was reported.[25] In continuation of this work, the scope of this approach was explored for the synthesis of 1-((pyrimidin-2-ylimino)methyl)naphthalen-2-ol (**1b**) and 2-((pyrimidin-2-ylimino)methyl)naphthalen-1-ol (**1c**), Scheme 1.



Scheme 1. Synthesis of hydroxynaphthylmethylene pyrimidinyl amines **1b** and **1c**.

Initially, to synthesize compound **1b**, the reaction of 2-aminopyrimidine (1.0 mmol), triethyl orthoformate (1.0 mmol) and *β*-naphthol (1.0 mmol), in the presence of formic acid catalyst at 120 °C under solvent-free condition was performed and compound **1b** was afforded in 85 % yield. The same reaction with *α*-naphthol instead of *β*-naphthol afforded compound **1c** in 88 % yield.

The ^{1}H-NMR spectra of compounds **1b** and **1c** showed two doublet signals for the hydroxyl and CH-imine protons corresponding to strong intramolecular hydrogen bond (O–H···N), as expected. In the ^{13}C-NMR spectra of compounds **1b** and **1c**, the signals at δ 184.19 and 183.55 ppm, corresponding to the carbonyl

group, indicated that these anil-like compounds favor the keto–enamine form over the enol–imine form.

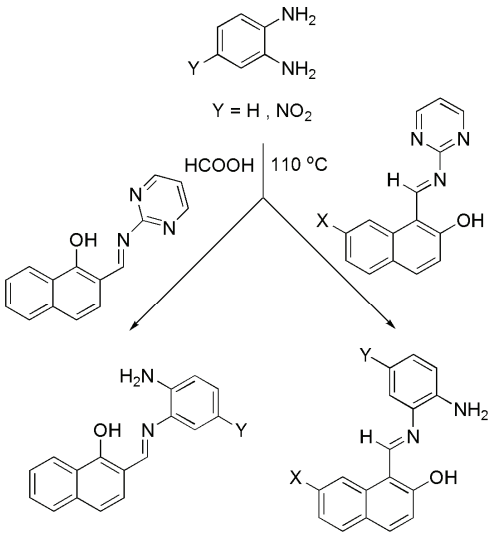
Next, the reactions of hydroxynaphthylmethylene pyrimidinyl amines **1a**–**c** with *o*-phenylenediamines in the presence of formic acid catalyst under solvent-free conditions were studied. For initial feasibility studies, the reaction of *o*-phenylenediamine with compound **1b** was selected as a model reaction. To optimize further the reaction temperature, the two reagents were allowed to react at temperatures ranging from 80 to 150 °C under solvent-free conditions. The results are given in Table I. The yield of product **2b** was increased, and the reaction time was shortened as the temperature increased from 80 to 110 °C (Table I, entries 1–3). However, further increase of the temperature from 110 to 150 °C failed to improve the yield of product **2b** (Table I, entries 4 and 5). Therefore, 110 °C was chosen as the reaction temperature for all further reactions under solvent-free conditions. In this reaction, the [1+1]-condensation product was obtained instead of C2-naphthylated benzimidazole in 80 % yield. In order to gauge the scope of these conditions, *o*-phenylenediamines and hydroxynaphthylmethylene pyrimidinyl amines were examined under the optimized conditions. The results indicate that the reaction proceeded smoothly *via* [1+1]-condensation to give the corresponding half-unit ligands **2** in good yields (Scheme 2).

TABLE I. Temperature optimization for the synthesis of **2b**

Entry	Temperature, °C	Time, min	Yield, %
1	80	60	65
2	100	50	72
3	110	35	80
4	120	35	70
5	150	35	54

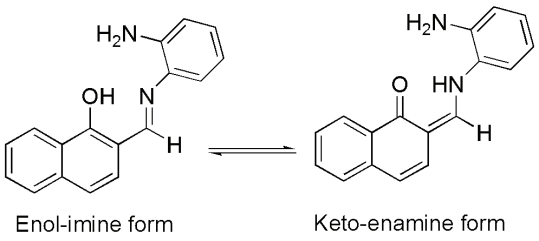
Identification of **2a**–**d** was realized based on the ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectra, and elemental analysis. The corresponding data are given in Supplementary material to this paper. It is very important to mention here that the ^{1}H-NMR spectra of compounds **2a** and **2d** showed two doublet signals for the hydroxyl and CH-imine protons at about δ 15.0 and 9.0 ppm corresponding to a strong intramolecular hydrogen bond (O–H···N), as expected. In the spectrum of compound **2d**, the NH proton was observed at about δ 7.06 ppm. Upon addition of D_2O into the NMR tube containing **2d**, the signals of NH_2, NH and OH disappeared and the signals of the CH-imine moieties collapsed into a single sharp singlet. Therefore, the Schiff base **2a** favors the enol–imine form over the keto––enamine form whereas both forms, the enol–imine and keto–enamine form, were observed in the Schiff base **2d** (Scheme 3).

The ^{1}H-NMR spectra of compounds **2b** and **2c** showed two singlet signals for the hydroxyl and CH-imine protons at about δ 15.0 and 9.6 ppm, respectively.



Scheme 2. Synthesis of tridentate Schiff base ligands **2a**–**d**.

It was suggested that a weak intramolecular hydrogen bond (O–H···N) formed and resonance caused only deshielding of chemical shift of the OH proton. In addition, in the spectrum of compound **2b**, an NH proton at about δ 7.0 ppm was observed, but it is not observed in the spectrum of compound **2c**. Therefore, as in compound **2d**, both the enol–imine and keto–enamine form were observed in the Schiff-base **2b** but in compound **2c** the enol–imine form was favored over the keto–enamine form. The results of the reaction of hydroxynaphthylmethylene pyrimidinyl amines with *o*-phenylenediamines are summarized in Table II.

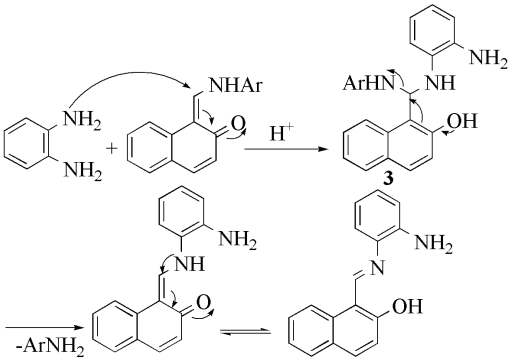


Scheme 3. Tautomeric equilibrium in compound **2d**.

TABLE II. Synthesis of compounds **2**

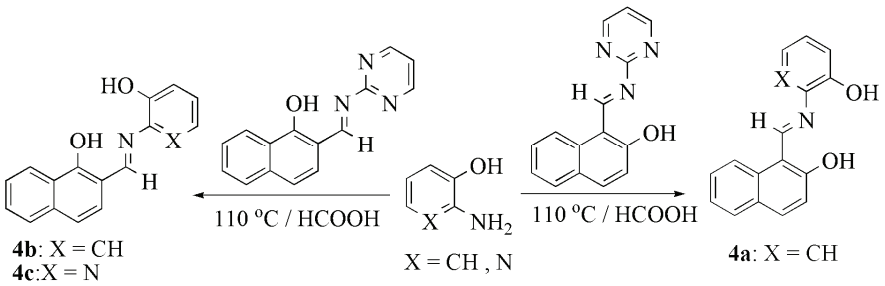
Entry	Product	Time, min	Yield, %
1	**2a**	25	84
2	**2b**	35	80
3	**2c**	30	78
4	**2d**	20	88

Based on the experimental results, a possible mechanism for the formation of compound **2b** is presented in Scheme 4. Initially, the reaction proceeds *via* the formation of intermediate **3**, which is formed *in situ* by Michael addition of *o*-phenylenediamine to the activated keto–enamine form of the compound **1b**. This intermediate undergoes de-amination to afford the corresponding product **2b**.



Scheme 4. Proposed mechanism for the synthesis of compound **2b**.

During the course of this work, the reaction of hydroxylnaphthylmethylene pyrimidinyl amines **1b** and **1c** with *o*-aminophenol and 2-amino-3-hydroxypyridine in the presence of formic acid catalyst under solvent-free conditions was studied. By evaluation of the temperature, it was observed that 110 °C is an effective temperature in terms of reaction time and obtained yield (Scheme 5). The results are summarized in Table III.



Scheme 5. Synthesis of Schiff base ligands **4a**–**c**.

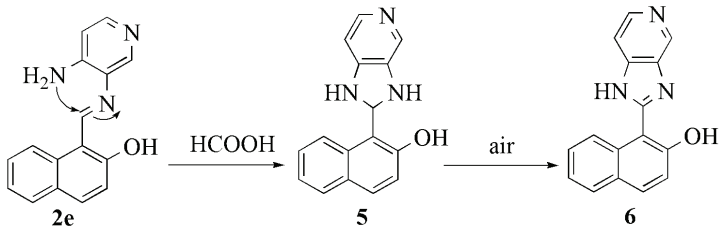
TABLE III. Synthesis of Schiff base derivatives **4**

Entry	Product	Time, min	Yield, %
1	**4a**	25	88
2	**4b**	20	85
3	**4c**	25	81

In these reactions, the [1+1]-condensation product was obtained instead of C2-naphthylated benzoxazoles/oxazolopyridine in 81–88 % yield. Identification

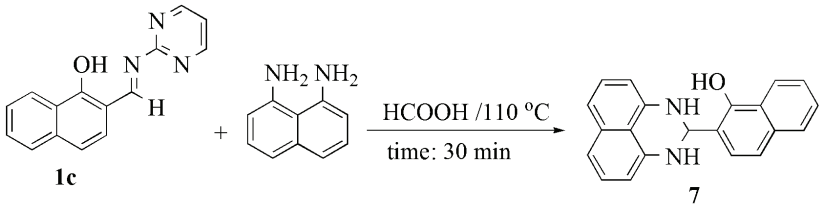
of **4a**–**c** was realized based on ^{1}H-NMR, ^{13}C-NMR, IR and mass spectra and elemental analysis (Supplementary material). The ^{1}H-NMR spectra of compounds **4a**–**c** showed two doublet signals for the hydroxyl and CH-imine protons at about δ 14.5 and 9.0 ppm, respectively. Moreover, in compound **4b**, an NH signal was observed at about δ 7.0 ppm. It is suggested that both the enol–imine and keto––enamine form are observed in the Schiff base **4b**. On the other hand, the enol––imine form is favored over the keto–enamine form in compounds **4a** and **4c**. In addition, a strong intramolecular hydrogen bond (O–H···N) was observed in these compounds.

When the reaction of 3,4-diaminopyridine with anil-like **1b** was conducted under the same reaction conditions, the C2-naphthylated imidazopyridine **6** was obtained in good yield (80 %) after 35 min. A mechanistic rationalization for this reaction is provided in Scheme 6. Similar to condensation of *o*-phenylenediamines with compound **1b**, the [1+1]-condensation product **2e** is formed in the initial step. In the second step, the reaction proceeds *via* dihydroimidazopyridine **5**, which was formed by the intramolecular nucleophilic addition of the amino group to the activated imine group. Finally, the intermediate **5** was oxidized to the corresponding imidazopyridine **6** by air oxygen (Scheme 6). In addition, the ^{1}H-NMR spectrum of compound **6** exhibited both the enol–imine form and the keto–enamine form.



Scheme 6. Proposed mechanism for the synthesis of compound **6**.

Next, the scope of this domino reaction of compound **1c** with 1,8-naphthalenediamine was explored under the optimized conditions. The results indicated that compound 2-(2,3-dihydro-1*H*-perimidin-2yl)naphthalen-1-ol (**7**) was synthesized in 81 % yield (Scheme 7).



Scheme 7. Synthesis of compound **7**.

EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. The melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Bruker DRX-300 Avance spectrometer. The chemical shifts (δ) are reported in parts per million and are referenced to the NMR solvent. The mass spectra of the products were obtained with a HP 5973 (Agilent technologies) mass selective detector. Elemental analyses were realized using a CHN–O–Rapid Heraeus elemental analyzer (Wellesley, MA).

*General procedure for the synthesis of compounds **1b** and **1c***. Formic acid (98 % aqueous solution, 0.1 mmol) was added to a mixture of 2-aminopyrimidine (1 mmol), triethyl orthoformate (1 mmol), and 1-naphthol or 2-naphthol (1 mmol). The reaction mixture was magnetically stirred on a preheated oil bath at 120 °C for 15 min. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was cooled to room temperature, and CH_3CN (5 mL) added. The precipitate was filtered, washed with cold CH_3CN, dried, and purified by recrystallization from CH_3CN to give the hydroxynaphthylmethylene pyrimidinyl amines **1b** and **1c** as colored crystals.

The characterization data for **1b** and **1c** are given in the Supplementary material to this paper.

*General procedure for the synthesis of compounds **2a–d, 4a–c, 6** and **7***. Formic acid (98 % aqueous solution, 0.1 mmol) was added to a mixture of compounds **1a** or **1b** or **1c** and *o*-phenylenediamines (1 mmol) or *o*-aminophenol (1 mmol) or 2-amino-3-hydroxypyridine (1 mmol). The reaction mixture was magnetically stirred on a preheated oil bath at 110 °C for the appropriate time. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the crude product was purified by column chromatography using ethyl acetate/hexane to give the corresponding Schiff bases **2a–d**, **4a–c** and products **6** and **7**.

The characterization data for **2a–d**, **4a–c**, **6** and **7** are given in the Supplementary material to this paper.

CONCLUSIONS

In conclusion, a simple and efficient procedure for the synthesis of new anils using hydroxynaphthylmethylene pyrimidinyl amines with *o*-phenylenediamine or *o*-aminophenol or 2-amino-3-hydroxypyridine under solvent-free conditions was demonstrated. The reaction proceeds by [1+1]-condensation and the products were obtained in good yields, showing that the synthetic route allows blocks of half-unit ligand of the new Schiff-base derivatives to be built. Moreover, the simple experimental procedure combined with the easy workup and shorter reaction time, are salient features of the presented method.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

И З В О Д

НОВ ПРИСТУП СИНТЕЗИ НОВИХ ТРИДЕНТАТНИХ ШИФОВИХ БАЗА ИЗ ЈЕДИЊЕЊА ТИПА АНИЛА

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Развијен је нов поступак за синтезу тридентатних Шифових база као лиганада, полазећи од хидроксинафтилметиленпиримидинилимина и *о*-фенилендиамина или *о*-аминофенола или 2-амино-3-хидроксипиридина у присуству мрављe киселине као катализатора, у одсуству растварача. Овим реакцијама добијен је производ [1+1] кондензације. Осим тога, реакцијом хидроксинафтилметиленпиримидинилимина са 3,4-диаминопиридином и 1,8-нафталендиамином настају С2-нафтил-имидазопиридини и дихидропиримидини, редом. Предности оваквог приступа синтези су: приступачан и јефтин катализатор, једноставност поступка, кратко реакционо време и добар принос.

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