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# GREEN SOLVENTS FOR THE SYNTHESIS OF SOME TOLUIDINE-DERIVED SCHIFF BASES

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***Abstract***
*Most of the procedures used in the synthesis of toluidine Schiff bases involve the use of toxic chemicals. The present study reports the use of green solvents (ethanol and water) in the synthesis of some toluidine-based Schiff bases. The results obtained indicate that the use of green solvents, especially an ethanol-water (1:1) mixture, promises a convenient synthetic pathway in terms of work-up procedures, short reaction time and high yields. The spectral data, IR and NMR, of the products are in complete agreement with those of authentic samples.*

**Keywords**: Green chemistry; Schiff bases; solvent-mixture; aqueous medium.

## Introduction

Schiff bases are also called imines, azils or azomethines and are a group of organic compounds with an imino group (-CH=N-) as the functional group. The presence of the imino group may be responsible for the chemical reactivity and biological activities of the Schiff bases [1,2].

Schiff bases have since then been synthesized using a variety of routes and techniques, different or modified from the classical method used by Hugo Schiff [3-6]. The modifications that have been reported in the synthesis of Schiff bases from primary amines and carbonyl compounds include a change in reaction solvent [7] and a change in the technique [8]. The solvents that have been used in the synthesis of Schiff bases include benzene, dimethylformamide [9], dichloromethane [10,11] and methanol [12,13] while the different techniques that have been employed include UV-irradiation [8], microwave irradiation [14-16], direct fusion or solvent-free method [17,18], sonication [19], refluxing [20,21] and stirring at ambient temperature [21,22].

Most organic solvents are known to be toxic to the environment and to human health, thus methods used for the synthesis of compounds should employ and generate substances that have little or no toxicity to the environment and to human health [23]. This benign, eco-friendly process [green chemistry] is highly sought after and sustainable [24-28]. There is need to adopt green routes in the synthesis of Schiff bases and the best route is one which is green, easy, cheap, fast, has an easy work-up procedure with high yields of product [8].

Different toluidine Schiff bases have previously been synthesized using a variety of techniques including direct fusion, sonication and UV-irradiation [8] in high yields and have been tagged as eco-friendly routes because of the limited use of toxic organic solvents.

This work was aimed at expressing the use of green solvents/routes for the synthesis of some toluidine-based Schiff bases and a comparison drawn between each method with respect to its efficiency, cost, work-up procedure and yield. The compounds were then characterized using NMR and IR spectroscopic techniques.

## Materials and methods

The chemicals were from Hopkin and Williams, May and Baker and Sigma Aldrich. The melting points were determined with a melting point apparatus and were uncorrected while thin layer chromatography (TLC) was carried out using a Merck pre-coated silica gel plate (10x10 cm); the Rf values where obtained using ethyl acetate as the mobile phase and the spots located and visualized using an ultraviolet lamp at 256 nm. $^1H$ NMR and $^{13}C$ NMR spectra of the samples were recorded in DMSO-$D_6$ and $CDCl_3$ by employing TMS as an internal standard with a Bruker AVANCE III 500 at 500.13 MHz for $^1H$ and 125.75 MHz for $^{13}C$ while the IR spectra of the samples were recorded on a Perkin-Elmer Spectrum 400 FT-IR/FT-NIR spectrometer in the range of 400-4000 cm$^{-1}$ using KBr pellets.

## Experimental

### Synthesis of 3-{(E)-[(4-Methylphenyl)imino] methyl}phenol (1a) using water

*p*-Toluidine (1.07g, 0.01 mol) was introduced into 20 ml of distilled water in a 150 ml flat bottom flask followed by *m*-hydroxybenzaldehyde (1.22g, 0.01 mol) and the reaction mixture stirred for 20 min at room temperature using a magnetic stirrer. A viscous precipitate was observed and recovered by decanting off the water. The precipitate was subsequently dissolved in hot ethanol, which on cooling, afforded cream coloured flaky precipitates that were filtered and air-dried; yield: 1.597g (75.7%); Rf: 0.69; M.p: 96-98°C; IR-cm$^{-1}$ (KBr): 1619 (C=N), 1575, 3030, 2861, 3500; $^1H$ NMR (DMSO-$d_6$) δ ppm: 2.32 (s, 3H, -$CH_3$); 6.91-7.35 (m, 7H, Ar-H); 8.52 (s, 1H, Ar-H); 9.66 (s, 1H, H-C=N); 11.96 (O-H, exchangeable in $D_2O$); $^{13}C$ NMR (DMSO-$d_6$) δ ppm: 20.58 (s, $CH_3$); 114.13-157.65 (m, aromatic); 159.71 (s, C=N); 118.54

(s, C-$CH_3$, aromatic); 148.76 (s, C-N, Aromatic); 157.65 (s, C-OH, phenolic).

**Synthesis of 2-Methoxy-4-{(E)-((2-methylphenyl) imino)methyl}phenol (1b) using water**

The procedure as in compound (1a) was employed with *o*-toluidine (1.07g, 0.01 mol) and *p*-vanillin (1.52g, 0.01 mol) to give cream flaky precipitates; yield: 1.709g ( 70.9%); Rf: 0.79; m.p: 110-112°C;IR-$cm^{-1}$ (KBr): 1622 (C=N), 1586, 3001, 2962, 1153, 3552; $^1H$ NMR (DMSO-$d_6$) δ ppm: 2.28 (s, 3H, -$CH_3$); 3.85 (s, 3H, -$OCH_3$); 6.89-7.55 (m, 6H, Ar-H); 8.32 (s, 1H, Ar-H); 9.71 (s, 1H, H-C=N); 11.98 (O-H, exchangeable in $D_2O$); $^{13}C$ NMR (DMSO-$d_6$) δ ppm: 17.59 (s, $CH_3$); 55.55 (s, $OCH_3$); 110.70-150.89 (m, aromatic); 159.35 (s, C=N, azomethine); 115.37 (s, C-$CH_3$, aromatic); 147.95 (s, C-N, Aromatic); 150.11 (s, C-$OCH_3$, aromatic); 150.89 (s, C-OH, phenolic).

**Synthesis of 2-Methoxy-4-{(E)-[(4-methylphenyl) imino]methyl}phenol (1c) using water**

The procedure as in compound (1a) was employed with *p*-toluidine (1.07g, 0.01 mol) and *p*-vanillin (1.52g, 0.01 mol) to afford pale yellow flakes; yield: 1.999g (83.0%); Rf: 0.82, m.p: 114-116°C; IR-$cm^{-1}$ (KBr): 1621 (C=N), 1583, 3034, 2962, 1154, 3558; $^1H$ NMR (DMSO-$d_6$) δ ppm: 2.31 (s, 3H, -$CH_3$); 3.84 (s, 3H, -$OCH_3$); 6.88-7.51 (m, 6H, Ar-H); 8.44 (s, 1H, Ar-H); 9.70 (s, 1H, H-C=N); 12.10 (O-H, exchangeable in $D_2O$); $^{13}C$ NMR (DMSO-$d_6$) δ ppm: 20.54 (s, $CH_3$); 55.53 (s, $OCH_3$); 110.26-150.03 (m, aromatic); 159.31 (s, C=N, azomethine); 115.30 (s, C-$CH_3$, aromatic); 147.95 (s, C-N, Aromatic); 149.28 (s, C-$OCH_3$, aromatic); 150.03 (s, C-OH, phenolic).

**Synthesis of 3-{(E)-[(4-Methylphenyl) imino] methyl}phenol (1a) using ethanol-water**

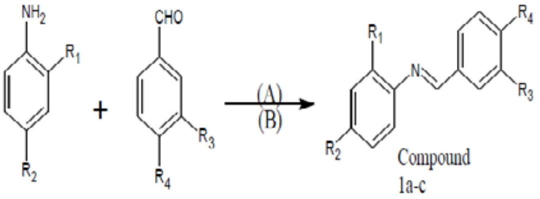
*p*Toluidine (1.07g, 0.01 mol) was introduced into ethanol-water (1:1) mixture (20 ml) in a 150 ml flat bottom flask followed by *m*-hydroxybenzaldehyde (1.22g, 0.01 mol) and a few drops of 10% KOH. The reaction mixture was stirred with a magnetic stirrer for 20 min at about 40°C. At the end of the reaction, the hot mixture was poured into a 50 ml beaker and allowed to cool and gave a solid precipitate. The product was collected using vacuum filtration, recrystallized from ethanol, filtered and air-dried. The reaction was monitored to completion using thin layer chromatography (ethyl acetate) and afforded cream flaky crystals; yield: 2.038g (96.6%); Rf: 0.69; m.p: 96-98°C; spectral data same as above.

**Synthesis of 2-Methoxy-4-{(E)-((2-methylphenyl) imino)methyl}phenol (1b) using ethanol-water**

The procedure was same as explained for compound 1a but with *o*-toluidine (1.07g, 0.01 mol) and *p*-vanillin (1.52g, 0.01 mol) to give cream flakes; yield: 2.262g (93.9%); Rf: 0.79; m.p: 110-112°C; spectral data same as above.

**Synthesis of 2-Methoxy-4-{(E)-[(4-methylphenyl) imino]methyl}phenol (1c) using ethanol-water**

The procedure was same as explained for compound 1a but with *p*-toluidine (1.07g, 0.01 mol) and *p*-vanillin (1.52g, 0.01 mol) to afford pale yellow flaky crystals; yield 2.208g (91.7%); Rf: 0.82; m.p: 114-116°C; spectral data same as above.



| Compounds | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| 1a | H | $CH_3$ | OH | H |
| 1b | $CH_3$ | H | $OCH_3$ | OH |
| 1c | H | $CH_3$ | $OCH_3$ | OH |

(A): water at room temperature, 15-20 mins
(B): ethanol-water (1:1), 40°C, 15-20 mins

**Scheme 1: Synthesis of Schiff bases 1a-c using water (A) and ethanol-water (B).**

**Results and discussion**

As aforementioned, Schiff bases have been synthesized using a variety of routes and solvents. Most of these solvents have been found to be toxic [29] and there is need to employ green solvents in the synthesis of these compounds. The solvents (ethanol and water) employed in this work are harmless to the environment when compared to other popular toxic organic solvents and the synthetic routes explained here require minimal energy and time. The two synthetic routes involved stirring the reactants in water for 15-20 mins at room temperature and stirring them in an ethanol-water (1:1) mixture for 15-20 mins at about 40°C in the presence of a catalyst.

The present report illustrates the use of an ethanol-water (1:1) mixture at a shorter reaction time and temperature. The two routes used in this work are both classified as eco-friendly but the first method involving water is cheaper though the work-up procedure which accounts for speed and efficiency is very rigorous. This is attributed to the insoluble nature of the reactants in water which led to the formation of a very viscous precipitate in the reaction flask during stirring. On the other hand, the second route was easier because the reactants were soluble in ethanol, however, the presence of 50% water made them less soluble, thus, an attempt to stir the reactants in this mixture at room temperature still gave a daunting work-up process, but not as tasking as the first, therefore some heat (about 40°C) was required to assist their dissolution in the second solvent, thus preventing the difficulty in stirring caused by insolubility. Furthermore, on cooling, the title compound was observed without much hassle and its extraction from the solvent was straightforward. It is worth mentioning that these routes are simple and do not require sophisticated and expensive equipments like an ultrasonic bath, a UV-chamber or even a microwave, therefore in the absence of these; a magnetic stirrer will suffice.

In terms of yield, the ethanol-water mixture gave higher yields for the three compounds when compared to that observed with water. The synthesis of compound (1a), (1b) and (1c) using water alone gave yields of 75.7%, 70.9% and 83.0% respectively while the synthesis in ethanol-water gave yields of 96.6%, 93.9% and 91.7% respectively. The slightly lower yield observed in the reaction in water may be due to the possible loss of product during the tedious work-up procedure. Abood in 2014 [17], reported the green synthesis of a *p*-toluidine Schiff base using the direct fusion method while heating in an oil bath for about 30 mins but this gave a very low yield of 25% whereas, Bendale *et al*., 2011 [8] also reported the synthesis of a similar Schiff base with a yield of 95.8% using the direct fusion method (mortar and pestle) under sonication using methanol as solvent at 45°C for 13-15 mins gave 97% yield and UV-irradiation for 15 mins gave 96.9% yield of the same product. Although these methods are all green methods, the yield varies probably because of the difference in reaction method. The solvents used in this work are readily available and harmless and the reaction techniques used are easy and fast with the second method involving ethanol-water being the most preferred.

The use of physicochemical analytical methods (melting point, colour, retention factor) assisted in ascertaining the similarity of the compounds given by both methods. In the IR data of compound (1a), the absence of the NH and C=O bands at 3400-3250cm$^{-1}$ and 1740-1720cm$^{-1}$ respectively and the presence of the C=N band at 1619cm$^{-1}$ suggested the complete formation of the Schiff base. For the $^1$H NMR spectrum, the protons in the amine portion of the Schiff base appeared more up field (δ6.91-7.22) while those in the aldehyde portion appeared downfield (δ7.29-8.52) with the azomethine proton (H-C=N) at δ9.66 and the aromatic protons observed at δ6.91-7.35. This may be attributed to the electron withdrawal ability of the azomethine group (C=N). It is expected that all the electrons are pulled out of the aldehyde ring and into the amine ring, causing an increased shielding of the protons in this region. In the $^{13}$C NMR spectrum of compound (1a), it was observed that the presence of heteroatoms, N and O, bonded to the aromatic carbon atoms led to the appearance of peaks at more downfield positions when compared to those free of heteroatoms. This is due to high deshielding of electrons in those carbon atoms as a result of the high electronegativity of the heteroatoms. Furthermore, since nitrogen is less electronegative than oxygen, it would explain why $^{13}$C-N (148.76) appears more upfield than $^{13}$C-O (157.65).

In the IR spectrum of compound (1b) , the absence of the NH and C=O bands at 3400-3250cm$^{-1}$ and 1740-1720cm$^{-1}$ respectively and the presence of the C=N band at 1622cm$^{-1}$ suggested the complete formation of the Schiff base. For the $^1$H NMR spectrum in DMSO-$d_6$, the protons in the amine portion of the Schiff base appeared more upfield (δ6.89-7.22) while those in the aldehyde portion are downfield (δ7.34-8.32) (as observed for compound (1a)) with the azomethine proton (H-C=N) at 9.71 ppm and the aromatic protons observed at δ6.89-7.55. The effect of the heteroatoms was also observed in the $^{13}$C NMR spectrum of compound (1b), thus, $\underline{C}$-N, $\underline{C}$-$OCH_3$ and $\underline{C}$-OH were more deshielded and appeared at positions 147.95, 150.11, 150.89 respectively.

For compound (1c), the IR spectrum also suggested the formation of the Schiff base with the absence of the NH and C=O bands at 3400-3250cm$^{-1}$ and 1740-1720cm$^{-1}$ respectively and the presence of the C=N band at 1621cm$^{-1}$. For the $^1$H NMR spectrum, the electron withdrawal capability of the azomethine group caused the protons in the amine portion of the Schiff base to appear more upfield (δ6.88-7.20) while those in the aldehyde portion appeared downfield (δ7.30-8.44) with the azomethine proton (H-C=N) at δ9.70 and the aromatic protons observed at δ6.88-7.51. The $^{13}$C NMR also showed heteroatom effect with $\underline{C}$-N, $\underline{C}$-$OCH_3$ and $\underline{C}$-OH more deshielded and thus appeared at positions 147.95, 149.28, 150.03 respectively.

## Conclusion

The results obtained from this research proved that toluidine-based Schiff bases can be synthesized using eco-friendly solvents and routes. It is apparent that modifications can be made in order to achieve good yields in short reaction times without resorting to the use of toxic chemicals and sophisticated equipments. This work has shown that the use of the green solvent-pair was more convenient, easy, fast, slightly cheaper, had a straightforward and hassle-free work-up procedure and gave a high yield of the product when compared to the synthesis with water. Not much has been reported about green solvent-pairs in the synthesis of Schiff bases in general, thus the results obtained in this research add to the viability of this synthetic route. Furthermore, the spectral studies using NMR and IR spectroscopy assisted in the structural elucidation of the toluidine Schiff bases.

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