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Natural Acid Catalyzed Synthesis of Schiff Base under Solvent-free Condition: As a Green Approach

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ABSTRACT

The reaction of primary aromatic amines with aryl aldehydes is found to be catalyzed by lemon juice as natural acid under solvent-free conditions to give the corresponding Schiff bases in good yields. This eco-friendly reaction has many advantages like economical, environmental, mild reaction conditions and simple work-up with high product yield.

Keywords: Schiff base, imines, lemon juice, natural acid.

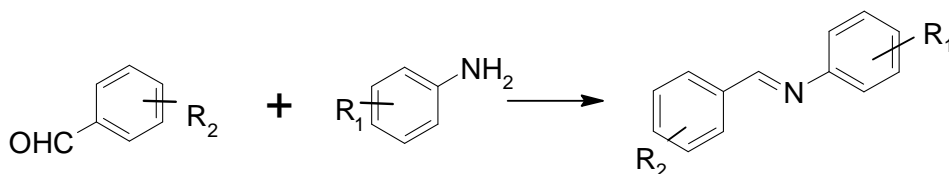
INTRODUCTION

Development of non-hazardous synthetic methodologies for organic synthesis is one of the latest challenges to organic chemists. The growing concern for the environment demands the development of eco-friendly and economic processes wherein even less hazardous byproducts are not desirable. Organic reactions under solvent-free conditions have gained in popularity in recent years[1] since the majority of solvents are either toxic or flammable and add considerably to the cost of an overall synthesis. These solvent-free reactions usually need shorter reaction times, simpler reactors, resulting simpler and more efficient work up procedures, more improved selectivities and easier separations and purifications than conventional solvents[2,3].

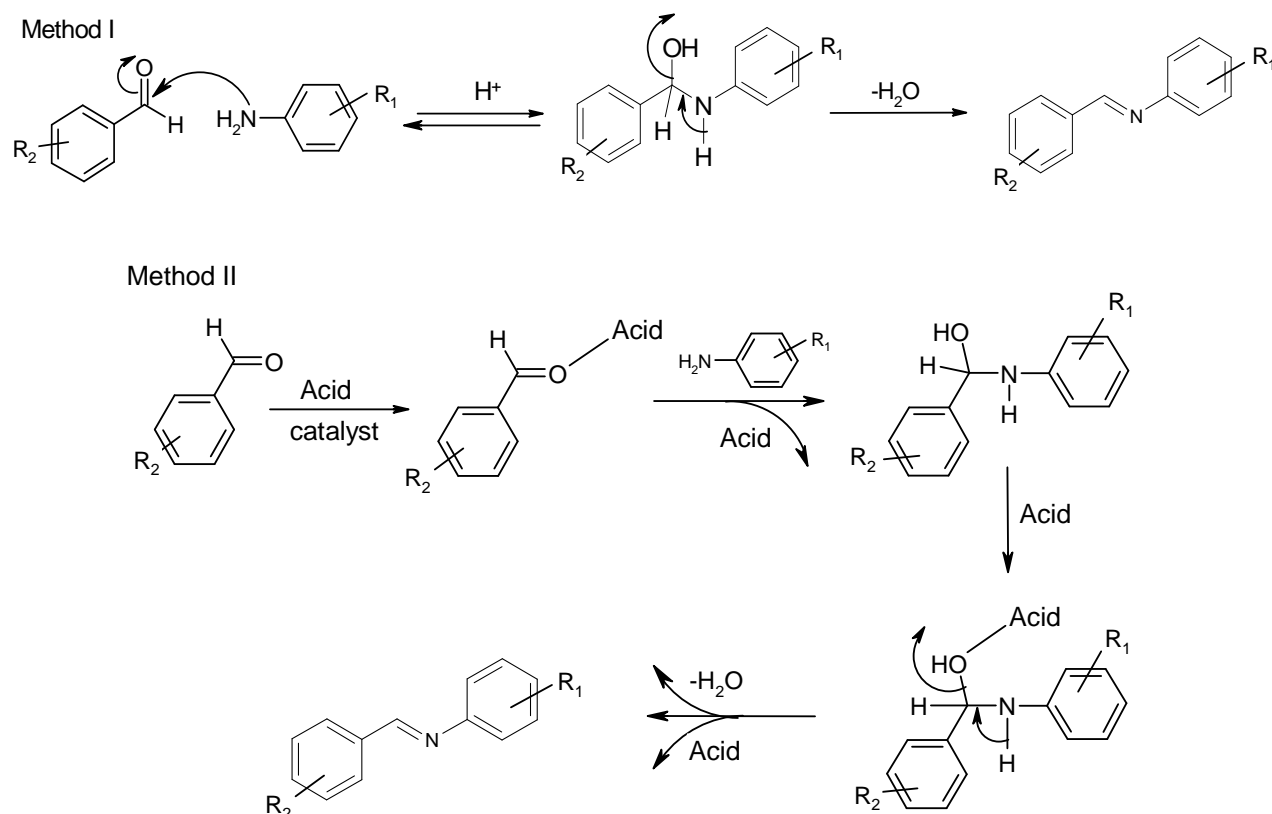
The formation of carbon–nitrogen double bond plays important role in organic synthesis. This can be achieved by the reaction of aldehydes and amines in acidic medium which leads to synthesis of Schiff bases (imines). Schiff bases have attracted considerable attention of organic chemists due to their significant biological activities like anticancer[4], antitumor[5], anti-inflammatory agents[6], insecticidal[7], antibacterial[8], antituberculosis[9], antimicrobial[10], anticonvulsant[11] activity. The Schiff bases are also used as versatile components in nucleophilic addition with organometallic reagents[12] and in cycloaddition reactions[13,14].

If we focus on the mechanism of transformation of aldehydes and amines in to Schiff bases, two synthetic methods are possible which are mechanized in Scheme-II. In method I, there is nucleophilic attack of primary amine on carbonyl carbon affords hydroxyl compound which on dehydration gives Schiff bases. The formation of Schiff bases in the second step largely depends upon the rate of removal of water from reaction mixture. Originally, the classical synthetic route for synthesis of Schiff bases was reported by Schiff[15] which involves condensation of primary amines with carbonyl compounds under azeotropic distillation[16] with the simultaneous removal of water. The removal of water during this condensation also conventionally facilitated by using molecular sieves or a Dean-Stark apparatus[17]. In the literature, for removal of water in situ dehydration method has been employed by using dehydrating solvents such as tetramethyl orthosilicate[18] and trimethyl orthoformate[19].

Scheme I : Schiff bases synthesis



Scheme II: Mechanism for acid catalyzed Schiff base synthesis



To overcome the difficulties in the removal of water, alternative method II has been employed in which Lewis acid is used as catalyst which accelerates nucleophilic attack of amines on carbonyl carbon as well as serving as dehydrating agent for removal of the water in the second step. Several modified methods for synthesis of Schiff bases have been reported in the literature in which Lewis acids were used as catalysts such as ZnCl_2 [20], TiCl_4 [21], alumina[22], P_2O_5 [23] and also by using materials like Hydrotalcite [24].

Environmental-friendly methods for the synthesis of Schiff bases have been reported in the literature. Hossein et al[25] have reported the solvent less synthesis of Schiff base catalysed by $\text{P}_2\text{O}_5/\text{Al}_2\text{O}_3$, resulting in quantitative yields of the product. Varma et al[26] have reported the solvent-free synthesis of Schiff base under microwave conditions using montmorillonite K-10 as a solid support. The synthesis of imines catalyzed by CaO under microwave conditions has been also reported by Gopalakrishnan et al[27]. L. Ravishankara et al have reported Cerium(III) catalyzed synthesis of Schiff bases[28]. Bendale et.al. have reported Schiff base synthesis by using UV chamber, sonicator and also by grinding method[29].

The methodologies reported above have some disadvantages such as prolonged reaction time, the high reaction temperatures, an excess of costly dehydrating reagents/catalysts, moisture sensitive catalysts, and special apparatus, etc. Considering these facts, we have decided to synthesize Schiff bases of various substituted aldehydes and aromatic amines by employing Lemon juice as green catalyst for green approach.

Citrus aurantium, *Citrus indica*, *Citrus limonium* are some important species of citrus family commonly known as lemon. The lemon is indigenous to the north-west regions of India. It is now widely grown in all tropical and

subtropical countries. In India it is also cultivated in home gardens. For the present work, we have used extract of *Citrus limonium* species of lemon as natural catalyst for synthesis of Schiff bases. The main ingredients of lemon juice are moisture (85%), carbohydrates (11.2 %), citric acid (5-7%), protein (1%), vitamin-C (0.5 %), fat (0.9 %), minerals (0.3 %), fibers (1.6 %) and some other organic acids. As lemon juice is acidic in nature ($\text{pH} \approx 2-3$) and percentage of citric acid (5-7%) is more than other acids, it works as acid catalyst for Schiff bases formation.

RESULTS AND DISCUSSION

It is observed that the condensation between a carbonyl compound and an amine leading to the formation of Schiff bases should be a facile reaction due to the good electrophilic and nucleophilic characteristic properties of the carbonyl and amine groups respectively.

Logically, we focused our attention on protonation of heteroatom in organic transformation by natural acids. Recently, we reported that Lemon Juice as Natural Catalyst efficiently catalyzes the Knoevenagel and Biginelli reactions [30,31]. To our satisfaction we found that the use of stoichiometric amount of Lemon Juice resulted in quantitative yield of the corresponding Schiff base at room temperature within 15 min to 2 hrs (Table 1). However, no result was obtained when condensation is carried without employing catalyst, if one of the reactant is deactivated by electronic effect. The role of Lemon juice in catalyzing the reaction was demonstrated by the lack of Schiff base formation when the reaction is carried out in the absence of catalyst.

To establish the scope and limitations of Lemon Juice as a catalyst for Schiff base formation, structurally diverse carbonyl compounds were treated with variously substituted amines such as aniline, 4-methylaniline, 4-methoxyaniline, 4-bromoaniline and 4-nitroaniline under the catalytic influence of lemon juice and the results are summarized in Table 1.

Table 1: Physical characterization of Schiff's bases

Entry	Product		Time min	Yield %	m.p. °C		Ref.
	R ₁	R ₂			Found	Reported	
1	H	H	60	89	65-67	66-68	31
2	H	4-OH	60	89	191-194	--	--
3	H	2-OH	45	90	47-49	--	--
4	H	4-OCH ₃	90	93	84-85	80-82	31
5	H	4-N(CH ₃) ₂	90	97	78-82	--	--
6	H	4-NO ₂	60	85	65-70	--	--
7	4-CH ₃	H	25	90	112-115	--	--
8	4-CH ₃	4-OH	50	94	210-212	--	--
9	4-CH ₃	2-OH	30	94	102-105	--	--
10	4-CH ₃	4-OCH ₃	45	92	93-95	--	--
11	4-CH ₃	4-N(CH ₃) ₂	30	84	92-95	--	--
12	4-CH ₃	4-NO ₂	50	83	121-125	128-130	31
13	4-OCH ₃	H	20	96	154-157	--	--
14	4-OCH ₃	4-OH	42	93	215-220	--	--
15	4-OCH ₃	2-OH	15	91	145-149	--	--
16	4-OCH ₃	4-OCH ₃	30	84	142-145	--	--
17	4-OCH ₃	4-N(CH ₃) ₂	55	93	132-135	--	--
18	4-OCH ₃	4-NO ₂	30	100	68-72	--	--
19	4-Br	H	120	82	61-62	63-65	31
20	4-Br	4-OH	90	87	169-170	--	--
21	4-Br	2-OH	65	88	175-177	--	--
22	4-Br	4-OCH ₃	120	no reaction	--	--	--
23	4-Br	4-N(CH ₃) ₂	145	78	189-192	--	--
24	4-Br	4-NO ₂	110	80	172-175	176-178	31
25	4-NO ₂	H	180	75	138-140	141-143	31
26	4-NO ₂	4-OH	85	42	158-161	--	--
27	4-NO ₂	2-OH	90	85	158-162	--	--
28	4-NO ₂	4-OCH ₃	300	no reaction	--	--	--
29	4-NO ₂	4-N(CH ₃) ₂	180	72	178-182	--	--
30	4-NO ₂	4-NO ₂	150	81	110-117	--	--

The treatment of aniline with 4-dimethylaminobenzaldehyde and 4-nitrobenzaldehyde afforded the corresponding Schiff bases in 97% and 85% yields in 1.5 hr, respectively (entries 5, 6), and a quantitative yield was obtained during the reaction of 4-methoxyaniline with 4-nitrobenzaldehyde in 0.5h (entry 18) at room temperature in the presence of the catalyst.

The presence of the methoxy group in 4-methoxybenzaldehyde reduces the electrophilicity of the carbonyl carbon through resonance, and the strong electron withdrawing property of the nitro group in 4-nitroaniline decreases the nucleophilicity of the amine group. The less nucleophilic amines such as 4-nitroaniline and less electrophilic aldehydes such as 4-methoxybenzaldehyde, p-bromobenzaldehyde, 4-hydroxybenzaldehyde, and 2-hydroxybenzaldehyde were employed. Good results are obtained in the later two cases (entry 26, 27) while reactions were not forwarded in case of 4-methoxybenzaldehyde and p-nitroaniline (entry 28) and p-bromoaniline (entry 22) even at improved reaction condition. It was also observed that if one of the reactant is deactivated by its substituent, comparatively more reaction time is required to complete (TLC) the reaction.

MATERIALS AND METHODS

All aldehydes and anilines were obtained from commercial source and used without purification. Melting points were measured on open capillary method and on DBK-programmable melting point apparatus. IR spectra were obtained in potassium bromide wafers on Bruker ALPHA FT-IR Spectrometer. ^1H NMR spectra were measured with a Avance-300 NMR spectrophotometer using CDCl_3 as solvent and TMS as internal standard. Purity of the products was checked by TLC.

General Procedure for Extraction of Lemon Juice:

Fresh lemon was cut by using knife and then pieces were pressed manually using domestic presser to extract juice. Then juice was then filtered through cotton/muslin cloth and then through filter paper to remove solid material and to get clear juice which was used as a catalyst.

Synthesis of 4-methyl-N-[(2-hydroxyphenyl)methylidene]aniline 9 :

The synthesis of **9** is described as a representative example: A mixture of 2-hydroxybenzaldehyde (1.22 g, 10 mmol) and p-toluidine (1.08 g, 10 mmol) and 1/2 ml lemon juice was stirred at room temperature for 30 minutes with monitoring by TLC. Then the reaction mixture was filtered and the pure yellow crystalline product recovered by recrystallization with ethanol. Its identity was confirmed by IR, NMR spectrum and its melting point. Yield 94%; mp 102°C ; IR (KBr): 3320 (-OH), 1642 ($\text{C}=\text{N}$) cm^{-1} ; ^1H NMR (CDCl_3): 2.4 (s, 3H, $-\text{CH}_3$), 6.9 (m, 1H, Ar-H), 7.0 (d, 1H, Ar-H), 7.2 (m, 4H, Ar-H), 7.4 (m, 2H, Ar-H), 8.6 (s, 1H, $=\text{CH}$), 13.4 (s, 1H, -OH).

The experimental procedure is followed for appropriate time to synthesize all the products listed in Table 1. Spectral characterization data for selected Schiff bases were reported in Table 2.

Table 2. Selected characterization data for some Schiff's bases

Compound	^1H NMR chemical shift $=\text{C}-\text{H}$ (ppm)	IR Stretch of $\text{C}=\text{N}$ (cm^{-1})
1	8.4	1625
2	8.6	1640
6	8.4	1650
9	8.6	1642
14	8.5	1634
20	8.6	1645
25	8.5	1640
27	8.5	1645
30	8.4	1640

CONCLUSION

In this article, we are reporting a new eco-friendly route with good yield for the synthesis of Schiff bases by using Lemon Juice, and the products can be purified by recrystallization using appropriate solvents. This solvent-free approach is nonpolluting and does not employ any toxic materials, quantifying it as a green approach for the synthesis of Schiff bases. In addition to this, compared to traditional methods, this new method is cleaner, safer and more eco-friendly, involving mild reaction conditions and simple workup. The reaction conditions such as reaction time, use of hazardous solvents can be reduced by maintaining good yield of product.

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