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Research Article

Synthesis of 4-Aminoantipyrine Derivatives: A Rapid and Eco-Friendly Approach

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ABSTRACT

This study presents an eco-friendly and efficient method for synthesizing 4-aminoantipyrine derivatives through a reaction with aldehydes. Ethanol is employed as a co-solvent, ensuring a sustainable medium, while N,N-dimethylethanolamine acts as a bifunctional organic catalyst, enhancing reaction efficiency. The reaction proceeds efficiently at ambient temperature, thereby minimizing energy usage. This method offers high yields in a short time, making it both cost-effective and practical. The synthesized derivatives were characterized using various spectroscopic techniques to confirm their structural integrity and purity. This green synthetic approach minimizes the use of hazardous reagents and aligns with sustainable chemistry principles, demonstrating its potential for environmentally benign organic transformations.

Key words: 4-aminoantipyrine, Green synthesis, N,N-Dimethylethanolamine, Schiff bases.

1. INTRODUCTION

The Schiff bases, named after Hugo Schiff, who first described them nearly 160 years ago, are formed through the condensation of amines with aliphatic or aromatic aldehydes [1]. These compounds have been extensively studied in inorganic and coordination chemistry due to their ability to form stable complexes with transition metal ions. Their structural versatility, metal ion selectivity, and synthetic adaptability make them fundamental building blocks in the synthesis of amino acids and various bioactive molecules [2]. The presence of the azomethine (-N=CH) group in Schiff bases is particularly significant, as it plays a crucial role in biological transformations and racemization processes [3].

These imines have wide-ranging applications, including their use in molecular electronics, chemosensors, bioimaging, and hole-transporting materials [4]. 4-Aminoantipyrine and its derivatives, in particular, exhibit notable biological activities such as DNA cleavage properties and antioxidant, antibacterial, antifungal, and anticancer effects [5-8]. They also serve as effective ligands in coordination chemistry, forming metal complexes with diverse functionalities depending on the nature of the substituents and metal ions involved. The pharmacological and therapeutic potential of 4-aminoantipyrine derivatives stems from their heterocyclic structure, which incorporates a carbonyl functional group contributing to their medicinal properties. Notably, the antibacterial efficacy of Schiff bases derived from 4-aminoantipyrine is significantly enhanced through complexation with transition metals. For instance, imines are crucial for the metabolic processes that break down α-amino acids in mammals, one of the most important steps in the process that turns light into a nerve signal for the brain's visual cortex is the creation of Schiff base by cells in the retina [9].

We describe the ability of certain Schiff bases based on 4-aminoantipyrines to inhibit corrosion. These compounds have cross-conjugated structures in which the carbon atom (sp2 hybridized) connecting the two consecutive single bonds in the p-conjugated molecules is double-bonded to any group or atom in a third direction. There are various ways to alter the structure of cross-conjugated 4-aminoantipyrine to create new compounds with exceptional electrical characteristics [10]. Imines generated from 4-aminoantipyrine are one of the compounds with intriguing bioactivities that have been identified. Preliminary findings have indicated that these compounds exhibit significant antioxidant qualities in addition to antifungal and antibacterial activity against a variety of microorganisms [6]. 4-aminoantipyrine's coordinating characteristics have been altered to provide a versatile ligand system through condensation with a range of reagents, including carbazide, thiosemicarbazide, aldehydes, and ketones. In some enzymatic processes where an enzyme interacts with an amino or carbonyl group of the substrate, Schiff bases have emerged as crucial intermediates [8]. Schiff bases made from 4-aminoantipyrine have been tested as antibacterial and antiparasitic agents [11].

Organic catalysts are widely used in chemical synthesis due to their high selectivity and efficiency under mild reaction conditions [12]. One such catalyst, N,N-dimethylethanolamine (DMEA), has been employed in the synthesis of Schiff bases and metallophthalocyanines [13]. In this study, we report an environmentally friendly synthesis of

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4-aminoantipyrine derivatives using DMEA as an organic catalyst, with ethanol as a co-solvent. This green approach enhances reaction efficiency, achieving high yields under mild conditions, and contributes to the advancement of sustainable synthetic methodologies.

2. EXPERIMENTAL

2.1. Materials and Methods

All the required chemicals were purchased from Loba Chemie Pvt. Ltd. The Fourier transform infrared spectroscopy (FTIR) spectra of the synthesized derivatives were recorded on Bruker ATR spectrometer, while their 13C nuclear magnetic resonance (NMR) and 1H NMR spectra were obtained in DMSO-d6 as a solvent on a Bruker 600 MHz spectrometer. Mass spectra of synthesized derivatives were obtained using a Waters 3,100 mass detector, and ultraviolet (UV)-visible spectra were recorded on a PerkinElmer Lambda 365 instrument.

2.2. Synthesis of Schiff Bases

In this study, derivatives 3a–3h of 4-aminoantipyrine were synthesized using an efficient and environmentally friendly approach. Equimolar quantities of 4-aminoantipyrine (1 mmol) and substituted aromatic aldehydes (1 mmol) were dissolved in a minimal amount of ethanol, used as a green co-solvent. A catalytic amount of DMEA was then added as an organic catalyst to the reaction mixture. The reaction mixture was stirred at room temperature to ensure optimal interaction between the reactants. The progress of the reaction was monitored through thin-layer chromatography using a mobile phase of n-hexane and ethyl acetate (9:1). Upon completion, the crude product was purified through recrystallization to obtain the desired derivatives in high purity. The reaction for all derivatives (3a–3h) was completed within 9–11 min, demonstrating the efficiency of this methodology.

3. RESULTS AND DISCUSSION

In this present study, a model reaction [Scheme 1] was carried out using 4-aminoantipyrine (1 mmol) and benzaldehyde (1 mmol) to optimize reaction conditions. When the model reaction was carried out without any catalyst or solvent, only a trace amount of the product was obtained.

Raafat M. Issa and co-workers reported the synthesis of Schiff bases by refluxing a mixture of 4-aminoantipyrine and aldehydes in ethanol within 2–5 h [14]. Kovan Dilawer Issa and Rostam Rasul Braiem employed homogeneous organic catalyst DMEA for the synthesis of these Schiff bases, and the desired products were obtained within 40 min [12].

In the present methodology, Schiff bases were synthesized at room temperature by employing alcohol as a co-solvent and DMEA as an organic catalyst. Remarkably, the desired products were obtained within just 10 min, significantly reducing the reaction time. The reaction proceeded efficiently, affording high yields of the products [Table 1].

DMEA plays a dual functional role in organic transformations due to its distinctive structure containing both a hydroxyl group and tertiary amine, and the structure is represented in Figure 1. The catalyst N,N-dimethylethanolamine (DMEA) functions as a mild base by facilitating proton abstraction, while its hydroxyl group engages in hydrogen bonding with reaction intermediates, thereby stabilizing them. It activates the carbonyl group and facilitates the attack of nucleophile. It supports green chemistry principles by facilitating reactions without toxic or heavy-metal catalysts.

DMEA is miscible with ecofriendly solvent ethanol enhancing its utility in green synthesis and reduces the reaction time significantly.

Catalyst optimization for the model reaction was investigated using varying concentrations of DMEA (5, 10, 15, 20, 25, and 30 mol%) in the presence of ethanol as a co-solvent at room temperature. The corresponding product yields were found to be 78%, 83%, 85%, 92%, 92%, and 92%, respectively. These results indicate that 20 mol% of DMEA is sufficient to efficiently drive the reaction forward. In the presence of the organic catalyst DMEA, 4 cm^3 of ethanol as a co-solvent was found to be sufficient to efficiently carry out the reaction.

To validate the efficiency of this methodology under optimized reaction conditions, a variety of structurally diverse aldehydes were employed for the synthesis of Schiff bases (3a-h). The results are summarized in Table 1.

Spectroscopic analysis was conducted, and the results were found to be consistent with those reported in the literature. The FTIR spectra of the synthesized derivatives show a characteristic peak in the range of 1560–1590 cm^{-1}, corresponding to the azomethine group which is formed via the condensation of the amino group of 4-aminoantipyrine with the carbonyl group of aldehydes. In addition, a peak in the range of 9.50–9.61 ppm in the 1H NMR spectrum confirms the presence of azomethine hydrogen.

3.1. Representative Spectroscopic Analysis

3.1.1. (E)-4-(benzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one

Color: Pale yellow, melting point: 195°C [16]. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): 2.48 (3H, s); 3.20 (3H, s); 7.39–7.84 (10 H, s); 9.61 (1H, s); ^{13}C NMR (300 MHz, DMSO-d_6): 10.22, 35.79, 116.74.

Table 1: Synthesis of 4-aminoantipyrine derivatives.[(a)]

Entry	4-aminoantipyrine	Aldehydes	Schiff bases	Time (min)	Yield (%)[(b)]	Melting point (°C)
1	$C_{11}H_{13}N_3O$	C_6H_5CHO	3a	10	92	195 [15]
2	$C_{11}H_{13}N_3O$	4-Br C_6H_4CHO	3b	10	92	223 [16]
3	$C_{11}H_{13}N_3O$	4-Cl C_6H_4CHO	3c	12	90	250 [16]
4	$C_{11}H_{13}N_3O$	2-Cl C_6H_4CHO	3d	11	92	192 [12]
5	$C_{11}H_{13}N_3O$	4-F C_6H_4CHO	3e	11	90	231 [12]
6	$C_{11}H_{13}N_3O$	4-OH C_6H_4CHO	3f	14	89	225 [12]
7	$C_{11}H_{13}N_3O$	3,4-$(OCH3)_2C_6H_3CHO$	3g	15	90	187 [12]
8	$C_{11}H_{13}N_3O$	4-$OCH_3C_6H_4CHO$	3h	14	92	182 [12]

[(a)]Reaction conditions: 4-aminoantipyrine (1 mmol) and benzaldehyde (1 mmol) and 20 mol% dimethyl ethanolamine (DMEA) in 4 cm^3 of ethanol at room temperature. [(b)]Isolated yields

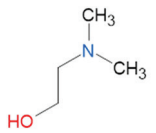
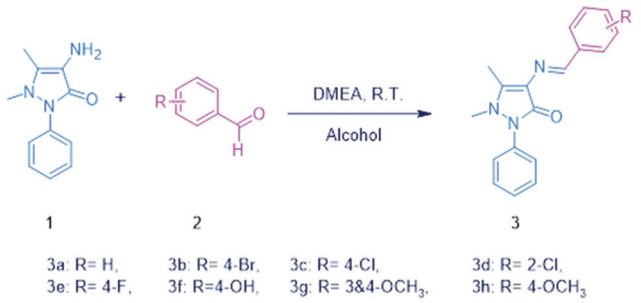


Figure 1: Structure of N,N-dimethylethanolamine.



Scheme 1: Synthesis of Schiff bases.

125.11, 127.40, 127.69, 129.21, 129.63, 130.63, 135.02, 137.99, 152.66, 154.81, 160.07; IR (stretching frequency v cm^{-1}): 1647 (C=O), 1590 (C=N), 1378 (C-N); mass (m/z): 292 (M+1)+; UV-visible spectrum; (DMSO) 323 nm.

3.1.2. (E)-4-((4-bromobenzylidene)amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one

Color: Pale yellow, melting point: 223°C [16]. ^{1}H NMR (300 MHz, DMSO d_6, δ): 2.48 (3H, s), 3.21 (3H, s), 7.39–7.79 (9 H, m), 9.57 (1H, s); 13C NMR (300 MHz, DMSO-d6): 10.17, 35.64, 110.58, 123.84, 125.31, 127.57, 129.48, 129.66, 132.22, 134.89, 137.21, 152.63, 153.22, 159.90; IR (stretching frequency v cm^{-1}): 1644 (C=O), 1590 (C=N), 1376 (C-N); mass (m/z): 371.4 (M+1)+; UV-visible spectrum, (DMSO) 304 nm.

4. CONCLUSION

The derivatives of 4-aminoantipyrine have significant applications in pharmaceuticals, biological research, and coordination chemistry. In this study, a modified approach was explored to synthesize these derivatives efficiently. By refining the existing method, the reaction was carried out under mild conditions at room temperature, leading to reduced reaction time and improved yields. This optimized procedure provides a simple, eco-friendly, and effective alternative for the synthesis of 4-aminoantipyrine derivatives, making it a valuable contribution to green chemistry practices.

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***Bibliographical Sketch**

Dr. Dattatray V. Patil has been serving as an Associate Professor at Kirti M. Doongursee College, Mumbai, since 16th August 2003. With over 21 years of teaching experience at both undergraduate and postgraduate levels, he is recognized as a dedicated and passionate educator. Known for his excellent teaching skills, he remains a committed academician.

Dr. Patil has authored 14 research articles published in reputed national and international journals. His research interests span a diverse range of areas, including Coordination Chemistry, Green Chemistry, and Heterocyclic Chemistry. His commitment to academic excellence and sustainable chemical practices continues to inspire students and peers alike.