Research Article

Chemical Review and Letters
journal homepage: www.chemrevlett.com
ISSN (online): 2645-4947 (print) 2676-7279

Green and highly efficient synthetic approach for the synthesis of 4-aminoantipyrine Schiff bases

Kovan Dilawer Issa *, Rostam Rasul Braiem

Department of Chemistry, College of Science, Salahaddin University, Erbil, Kurdistan Region-Iraq

ARTICLE INFO

Article history:
Received: 13 June 2022
Received in revised form: 27 June 2022
Accepted: 28 June 2022
Available online:12 September 2022

Keywords:
4-Aminoantipyrine
Schiff Base
Pyrazolone
Organocatalyst
DMEA

ABSTRACT

The analog of 4-aminoantipyrine (4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-*3H*-pyrazole-3-one), is interesting in the field of pharmacology and pharmaceutical chemistry and plays an important role as the ingredients for the production of the drugs and medicines. In the current study, a series of Schiff (including two new compounds) bases have been synthesized from 4-aminoantipyrine and substituted benzaldehydes via a simple and easy procedure in a short time with high yields. The structures of products have been characterized by (FTIR, ^{1}HNMR, ^{13}CNMR, and Elemental Analysis).

1. Introduction

Heterocyclic compounds are major constituents of the drugs and treatments for several diseases, also they are used as antibacterial [1], antifungal [2], anticancer [3], antioxidant [4], anti-inflammatory [5], antipyretic [6], etc. Among the drug formulations, pyrazoles and their derivatives are interesting to be studied because of having a major role in the pharmaceutical and biologically active compounds [7]. Pyrazolones are considered typical derivatives of pyrazoles, in which their application, synthesis, and reactivity are reported. Their important biological activity and medicinal chemistry, such as antimicrobial [8], analgesic, antipyretic [9], antidepressant [10], antitumor [11], etc. as well as their vital characteristic in coordination chemistry [12], have been an important choice for the chemists [13].

The most famous pyrazolone derivative is (4-amino-1,5-dimethyl-2-phenyl-3-pyrazolone) which is known commonly as 4-aminoantipyrine or aminophenazone, a five-membered heterocyclic lactam ring with a lot of biological activities including anti-inflammatory [14], anthelmintic [15], antiviral [16], antibacterial [17], anticancer, and antifungal activity [18]. Among the chemists, new types of chemotherapy drugs that contain Schiff bases are significant consideration and particularly in the case of having aminoantipyrine in their structure to distinguish liver disease and clinical treatments [19].

In 1864, Hugo Schiff has synthesized new compounds containing azomethine group (R_1–N=C–R_2R_3) by the reaction of primary amines (R_1–NH_2) with aldehydes (O=CHR_2) or ketones (O=C–R_2R_3) in which R could be aliphatic or aromatic substituents, the product named after him and called (Schiff base) [20]. Schiff bases are famous to possess biological activities including antimicrobial, antiviral, anticancer, and anti-inflammatory activity [21, 22]. Also, their free radical scavenging effect has been reported by several researchers [23]. On one side, Schiff bases are also utilized as intermediates in organic synthesis [24], catalysts [25], polymer stabilizers, dyes, and pigments [26].

A wide number of Schiff bases can form metal complexes and have a vital role as biologically active compounds, this is a declaration that Schiff bases are not only influenced by organic and coordination chemistry, but they are present in the development of inorganic biochemistry, optical materials, and catalysis [27].

4-Aminoantipyrine can form Schiff bases with aldehydes directly [28] and their importance as free radical scavenger has been recognized against reactive oxygen and nitrogen species, as well as inhibiting oxidative burst of neutrophils [29]. Also, it has been utilized in the protection of prophylactic of many illnesses and oxidative pressure including cancer [20].

* Corresponding author.; Tel.: +9647507809682; e-mail: kovan.dilawer@tiu.edu.iq
https://doi.org/10.22034/crl.2022.347066.1171

Organic catalysts (organocatalysts) are quit important due to several characteristics including availability, easy preparation, selectivity, working under mild conditions, and compatibility with many functional groups [30]. Therefore, an organocatalyst namely N,N-dimethyl ethanolamine (DMEA) (Figure 1) has been selected to produce the desired products, nevertheless there is no experiments for the synthesis of Schiff bases using the mentioned catalyst [31].

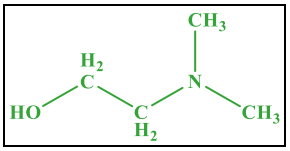


Fig. 1. Structure of N, N-Dimethylethanolamine (DMEA)

The aim of this work is utilization of an organic catalyst (DMEA) for the synthesis of some 4-aminoantipyrine Schiff bases by a simple, efficient, and easy method and in a short duration of time with excellent yield of the products, as well as testing their antioxidant activity.

2. Experimental

2.1. General

All the starting materials have been purchased from Sigma Aldrich, Merk, or Fluka, and used without further purification. Melting points were measured via (Electrothermal 9100) capillary melting point apparatus. Thin layer Chromatography (TLC) plate precoated with silica gel aluminum was used to detect the completion of the reaction with system eluent of (n-Hexane: Ethyl acetate 60:40), as well as utilizing the ultraviolet light at the wavelength of 354 nm for visualization. Infrared spectra have been recorded with KBr disc on FTIR (Schimadzu IR Affinity-1) Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on Varian Inova 500 MHz and 125 MHz, respectively. Elemental analysis was done on LECO model TruSpec CHN analyzer as shown in Electronic Supplementary Information (ESI).

2.2. Synthesis of Schiff Bases

Equimolar of 4-aminoantipyrine (1mmol) and substituted benzaldehydes (1mmol) was mixed in a round bottom flask and (1 mol %) of dimethyl ethanol amine (DMEA) has been added as a homogeneous catalyst. The mixture was stirred at room temperature for appropriate time as mentioned in table 1, the progress of the reaction has been monitored by TLC for disappearance of starting materials. After completion of the reaction the products were separated by addition of water (15 ml) and stirring for 10 minutes. After that the products were filtered out and finally, they are purified by recrystallization with ethanol.

All the products were characterized by melting point, FTIR, ^{1}HNMR, ^{13}CNMR, and elemental analysis (C, H, N).

2.2.1. 4–(benzylideneamino)–1, 5 – dimethyl –2–phenyl–1, 2–dihydro–3H–pyrazol-3-one (C1)

Yield (93 %); White solid; m.p. 169–171 ^{o}C, IRν_{max}cm$^{-1:}$ 3037, 2941, 1654, 1595, 1568. ^{1}HNMR (500 MHz, DMSO, d_6) δ 2.46 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 7.39-7.83 (m, 10 H, Ar), 9.62 (s, H, CH), ^{13}CNMR (DMSO, d_6, 125 MHz): δ 10.15 (CH_3), 35.82 (CH_3), 116.78 (C=C), 124.84, 127.69, 128.69, 129.62, 130.62, 135, 138.15, 152.70 (C=C), 154.80 (C=O), 160.08 (C=N). Anal. Calcd. for $C_{18}H_{17}N_3O$: C: 74.20, H: 5.88, N: 14.42 %. Found: C: 74.18, H: 5.90, N: 14.44 %.

2.2.2. 4–(4-fluorobenzylideneamino)-1,5-dimethyl-2 -phenyl-1, 2-dihydro-3H-pyrazol-3-one (C2)

Yield (95 %); White crystals; m.p. 229-231 ^{o}C, IRν_{max}cm^{-1}: 3070, 2941, 1651, 1598, 1568, 1502. ^{1}H-NMR (500 MHz, DMSO, d_6) δ 2.59 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 7.40-8.02 (m, 9 H, Ar), 9.7 (s, H, CH). ^{13}C NMR (DMSO, d_6, 125 MHz): δ 9.72 (C, CH_3), 35.30 (C, CH_3), 115.64, 115.86, 124.58, 126.90, 129.13, 129.26, 129.34, 134.11, 134.14, 134.49, 152.16, 152.94 (=C-N), 159.51 (C=O), 162.00 (C=N), 164.46 (C–F). Anal. Calcd. for $C_{18}H_{16}FN_3O$: C: 69.89, H: 5.21, N: 13.58 %. Found: C: 69.88, H: 5.24, N: 13.57 %.

2.2.3. 4-(2-chlorobenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H- pyrazol–3–one (C3)

Yield (94 %); Pale yellow; m.p. 192-193 ^{o}C, IR$_{\nu max}$cm^{-1}: 3049, 2941, 1649, 1581, 1566. ^{1}HNMR (500 MHz, DMSO, d_6) δ 3.17 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 7.39-7.83 (m, 10 H, Ar), 9.62 (s, H, CH), ^{13}CNMR (DMSO, d_6, 125 MHz): δ 11.16 (CH_3), 36.36 (CH_3), 117.38 (=C-N) 126.19 (2C, Ar), 127.92 (1C, Ar), 128.40 (1C, Ar), 128.66 (1C, Ar), 130.42 (2C, Ar) 131.15 (1C, Ar), 132.63 (1C, =C-N), 135.67 (C=C-N), 150.17 (C-Cl), 151.07 (=C-N), 153.9 (C=O), 160.58 (C=N). Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C: 66.36, H: 4.95, N: 12.90 %. Found: C: 66.35, H: 4.97, N: 12.88 %.

2.2.4. 4-(2,6-dichlorobenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H–pyrazol-3-one (C4)

Yield (95 %); Pale yellow solid; m.p. 196-197 ^{o}C, IRν_{max}cm^{-1}: 3061, 2924, 1651, 1581, 1560. ^{1}HNMR (500 MHz, DMSO, d_6): δ 2.42 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 7.39-7.53 (m, 10 H, Ar), 9.77 (s, H, CH), ^{13}CNMR (DMSO, d_6, 125 MHz): δ 10.85 (CH_3), 36.05 (CH_3), 110.2 (C=C), 126.26, 128.7, 130.43, 131.84, 134.69, 151.07 (C=C), 153.91 (C=O), 160.52 (C=N). Anal. Calcd. for $C_{18}H_{15}Cl_2N_3O$: C: 60.02, H: 4.20, N: 11.66 %. Found: C: 59.99, H: 4.22, N: 11.64 %.

2.2.5. 4-(4–hydroxybenzylideneamino)-1,5–dimethyl-2-phenyl-1,2-dihydro-3H–pyrazol-3-one (C5)

Yield (94 %); Brown crystals; m.p. 225-226 ^{o}C, IRν_{max}cm^{-1}: 3057, 2924, 1604, 1577, 1558, 1512. ^{1}HNMR (500 MHz, DMSO, d_6) δ 2.40 (s, 3H, CH_3),

3.10 (s, 3H, CH_3), 6.83–7.64 (m, 9H, Ar), 9.48 (s, H, CH), 9.93 (s, H, OH). ^{13}CNMR (DMSO, d_6, 125 MHz): δ 10.13 (CH_3), 36.05 (CH_3), 116.54 (C=C), 117.51, 124.84, 127.28, 129.72, 135, 152.17, 155.32 (C=O), 160.10 (C–OH), 160.39 (C=N). Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C: 70.34, H: 5.58, N: 13.67 %. Found: C: 70.37, H: 5.56, N: 13.64 %.

2.2.6. 4-(3,4-dimethoxybenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydro- 3H-pyrazol-3-one (C6)

Yield (95 %); Pale yellow; m.p. 185-187 °C, IRν_{max}cm^{-1}: 3076, 2964, 1649, 1595, 1573, 1510. ^{1}HNMR (500 MHz, DMSO, d_6) δ 2.44 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 7.02 (), 7.27-7.53 (m, 10 H, Ar), 9.5 (d, H, CH), ^{13}CNMR (DMSO, d_6, 125 MHz): δ 11.11 (CH_3), 36.8 (CH_3), 56.63, 56.82, 109.79, 112.7, 118.04, 123.23, 125.57, 127.95, 130.36, 131.79, 135.97, 150.29, 150.31, 152.16, 153.13, 155.82 (C=O), 161.11 (C=N). Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C: 68.36, H: 6.02, N: 11.96 %. Found: C: 68.33, H: 6.03, N: 11.97%.

2.2.7. 4-(4-hexyloxybenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H- pyrazol-3-one (C7)

Yield (93 %); Pale yellow; m.p. 189–191 °C, IRν_{max}cm^{-1}: 2953, 2941, 1637, 1608, 1598, 1568. ^{1}HNMR (500 MHz, DMSO, d_6) δ 3.17 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 7.39-7.83 (m, 10 H, Ar), 9.62 (s, H, CH), ^{13}CNMR (DMSO, d_6, 125 MHz): δ 9.76 (CH_3), 13.90 (CH_3), 22.05, 25.15, 28.56, 30.97 (CH_2), 35.51 (CH_3), 67.57 (O–CH_2), 114.60 (=C–N), 116.76, 124.29, 126.68, 128.85, 129.09 (C, Ar), 130.12, 134.65 (=C–N), 151.84 (C=O), 154.30 (=C–O), 160.46 (C=N). Anal. Calcd. for $C_{24}H_{29}N_3O_2$:C: 73.63, H: 7.47, N: 10.73 %. Found: C: 73.60, H: 7.50, N: 10.70 %.

2.2.8. 4–(2–fluorobenzylideneamino)–1,5–dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (C8)

Yield (95 %); Pale yellow; m.p. 176-177 °C, IRν_{max}cm^{-1}: 3059, 2941, 1651, 1595, 1573, 1517. ^{1}HNMR (500 MHz, DMSO, d_6) δ 3.19 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 7.39-7.83 (m, 10 H, Ar), 9.62 (s, H, CH), ^{13}CNMR (DMSO, d_6, 125 MHz): δ 10.14 (CH_3), 35.59 (CH_3), 117.19 (C=C), 125.15, 125.3, 126.45, 127.52, 129.59, 132.36, 134.85, 146.84 (C=C–N), 152.78 (C=O), 159.83 (C=N). Anal. Calcd. for $C_{18}H_{16}FN_3O$: C: 69.89, H: 5.21, N: 13.58 %. Found: C: 69.91, H: 5.20, N: 13.56 %.

2.2.9. 4-(4-nitrobenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (C9)

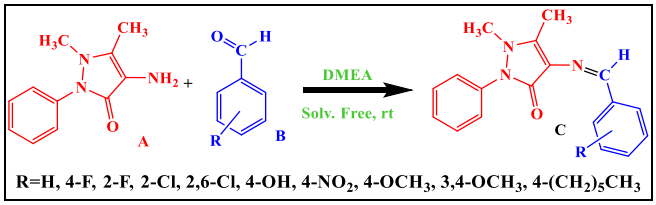
Yield (92 %); Yellow solid; m.p. 253-255 °C, IRν_{max}cm^{-1}: 3051, 2932, 1647, 1575, 1554, 1519. ^{1}HNMR (500 MHz, DMSO, d_6) δ 3.23 (s, 3H, CH_3), 3.27 (s, 3H, CH_3), 7.36-7.55 (m, 10 H, Ar), 9.66 (s, H, CH), ^{13}CNMR (DMSO, d_6, 125 MHz): δ 10.96 (CH_3), 35.82 (CH_3), 109.99 (C=C), 125.26, 126.5, 129.14, 130.48, 152.17, 153.91 (C=O). Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C: 64.28, H: 4.79, N: 16.66 %. Found: C: 64.29, H: 4.76, N: 16.65%.

2.2.10. 4-(4-methoxybenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (C10)

Yield (94 %); White solid; m.p. 181-182 °C, IRν_{max}cm^{-1}: 3051, 2966, 1645, 1608, 1593, 1508. ^{1}HNMR (500 MHz, DMSO, d_6) δ 3.13 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 7.39-7.83 (m, 10 H, Ar), 9.62 (s, H, CH), ^{13}CNMR (DMSO, d_6, 125 MHz): δ 10.23 (CH_3), 35.99 (CH_3), 55.75, 114.66, 117.28 (C=C), 124.80, 127.15, 129.31, 129.54, 130.81, 135.18, 152.29, 154.8, 160.30 (C=O), 161.49 (C=N). Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C: 71.01, H: 5.96, N: 13.08 %. Found: C: 70.09, H: 5.98, N: 13.07%.

3. Result and Discussion

The antipyrine based Schiff bases have been synthesized from the condensation reaction of different substituted benzaldehyde with 4-aminoantipyrine under solvent free condition at room temperature with producing excellent yield of products at a short time of duration (Scheme 1) (Table 1).



Scheme 1. Synthesis of 4-Aminoantipyrine Schiff base

Table 1. Characteristic of Synthesized Aminoantipyrine Schiff bases

Compound	Formula	Time/min.	Yield %
C1	$C_{18}H_{17}N_3O$	40	94
C2	$C_{18}H_{16}FN_3O$	38	94
C3	$C_{18}H_{16}ClN_3O$	38	94
C4	$C_{18}H_{15}Cl_2N_3O$	40	95
C5	$C_{18}H_{17}N_3O_2$	38	94
C6	$C_{20}H_{21}N_3O_3$	39	95
C7	$C_{24}H_{29}N_3O_2$	40	93
C8	$C_{18}H_{16}FN_3O$	39	95
C9	$C_{18}H_{16}N_4O_3$	40	92
C10	$C_{19}H_{19}N_3O_2$	39	94

Choosing an organic catalyst for producing the desired compounds required several entries of the reaction conditions as well as implementing different type of solvents, then using the DMEA as a catalyst with different concentrations in order to produce and isolate highest amount of the products. The advantageous role of DMEA comes from its bifunctional group (H donor and H acceptor) for the activation of the reaction, the possible interaction of the catalyst is shown in Figure 2.

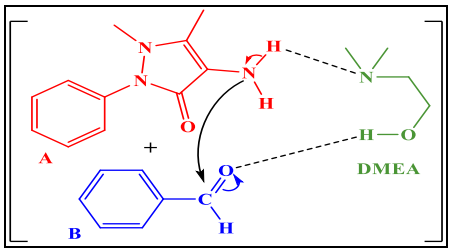


Fig. 2. Plausible DMEA bifunctional interaction

The yield percent of the model product C1 (benzaldehyde with 4-aminoantipyrine) have been illustrated in Table 2, as well as optimizing the reaction to obtain best amount of the products.

Table 2. Optimization of Reaction Conditions

Entry	Solvent	Catalyst (mol %)	Method	Time/ min.	Yield %
1	H_2O	–	Reflux	240	83 %
2	EtOH	–	Reflux	130	88 %
3	DMF	–	Reflux	150	89 %
4	–	DMEA (5 mol%)	Stirring	40	93 %
5	–	DMEA (10 mol%)	Stirring	40	93 %
6	–	DMEA (15 mol%)	Stirring	40	93 %
7	H_2O	–	U.S.	90	93 %

DMEA= N, N–Dimethylethanolamine, EtOH= Ethanol
U.S.= Ultrasonic bath, DMF= Dimethylformamide

In the presence of water as a solvent (entry 1) the reactants were reacted at reflux temperature for about 4 hours and yielded 83%, but when the solvent has changed to ethanol (entry 2) the yield percent increased to 88% in shorter time nearly 2 hours. In other hand, more time required (3 hours) when dimethyl formamide is used as a solvent but higher amount of the product is obtained (89% yield).

In contrast, in the case of solvent free and room temperature condition, the DMEA has used as a catalyst (entry 3,4, and 5), the reactants were condensed in an excellent amount (93 %). The yields were the same by changing the amount of the catalyst from 5 to 15 mol%, it reveals that, the amount of the catalyst has the same effect on the production of the Schiff bases. On the other hand, the amount of the products synthesized via ultrasonic irradiation (entry 7) has the identical yield with 5 mol % DMEA, but the predominance of the latter comes from its ability to perform the reaction in a shorter time without any solvents at room temperature. The structure of all the synthesized compounds were clarified by FTIR, ^{1}HNMR, ^{13}CNMR, and elemental analysis, and their data are given in the experimental section.

4. Conclusion

In spite of the developments in the production of new and modern chemical compounds for several and variety of applications, still the interest toward the production of Schiff bases is highly considerable due to their importance in several fields and applications, such as biological and pharmaceutical activity, inorganic and coordination chemistry, biochemistry, etc.

Therefore, we have implemented an ecofriendly procedure to synthesize a series of Schiff bases derived from 4-aminoantipyrine and substituted benzaldehydes by the direct condensation reaction at room temperature under solvent free condition, in which the products were synthesized with excellent yield and simple workout. Choosing the DMEA as an organic catalyst (it is available and inexpensive) in which leads to synthesize the products including two new products ((4-(3,4-dimethoxybenzylideneamino)-1,5-dimethyl-2 -phenyl-1,2-dihydro- 3H-pyrazol-3-one) and (4-(4-hexyloxybenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydro- 3H-pyrazol-3-one)) in a very fast reaction method that there is no reports have been documented in this manner, as well as the safety of the catalyst and its easy removal from the product by addition of water only.

Acknowledgements

Financial support by Salahaddin University is gratefully acknowledged.
Dr. Soma Majedi your effort and support are highly appreciated.

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