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Research Article

Isatin Aldazines Synthesis using A Proton Exchanged Algerian Montmorillonite Clay as Acid Eco-friendly Catalyst

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Abstract

An efficient and easy procedure is developed for the synthesis of isatin aldazines or bis-Schiff bases of isatin, catalyzed by a proton exchanged Algerian montmorillonite clay (MMT-H^+) as green catalyst. The products were obtained in two catalyzed steps under conventional heating in ethanol. Isatin-3-hydrazone obtained from the reaction of isatin with hydrazine monohydrate reacts in the second step with the appropriate aromatic aldehydes to give the desired products in good yields. The main advantages of using this protonated solid non-toxic catalyst in this synthesis are its availability and low cost, the simplicity of its use, the recycling possibilities without significant loss of its catalytic activity and its environmentally benign process. Copyright © 2019 BCREC Group. All rights reserved

Keywords: Montmorillonite-H^+; Isatine; Isatin-3-hydrazone; bis-Schiff bases; Isatin Aldazines; Green catalyst

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1. Introduction

Isatin (1H-indole-2,3-dione) and its derivatives possess a broad variety of biological and pharmacological properties [1]. Isatin widely used as starting materials for the synthesis of a broad range of various heterocyclic compounds, including indole, oxoindoles and quinoline [2]. Bis-Schiff bases of isatin also called azines [3] of isatin (Figure 1) are reported to indicate an assortment of biological activities, such as antibacterial [4], antifungal [5], anticancer [6], antiviral [7], antiproliferative [8], anti-inflammatory [9], antiglycation [10], antitubercular [11], antioxidant [12,13], anticonvulsant [14], anti-HIV [15,16], cytotoxicity [17], analgesic [18], CNS, depressant [19] and also considered as corrosion inhibitors [20].

Synthesis of isatin-based azines are generally made by condensation of 3-hydrazinoindolin-2-one with aldehydes or ketones to yield respectively isatin aldazines (R_1 or R_2 = H) or isatin ketazines (R_1 and $R_2 \neq$ H) [21]. Most of these synthesis are based mainly on traditional thermal methods in presence of organic solvents and a range of catalysts, such as: acetic acid [22], HCl [23], triethyl amine [24], $FeCl_3.6H_2O$ [25],

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sulphated titania acid [26], $CH_3CO_2Na/CaCl_2$ [27], nanocrystalline alumina powder [28], or molecular iodine [29]. Therefore, there is a need to use a simple eco-friendly catalyst under moderate conditions to prepare azines.

Green chemistry, in very simple terms, is just a different way of chemistry based mainly on the protection of our environment by preventing pollution and protecting our natural resources. Its basic principles include: avoiding the use of hazardous compounds, using renewable materials and catalysts, improving energy efficiency, etc. [30]. Catalysts used in chemical reactions often have significant environmental problems associated with their chemical nature and reuse as well as the separation and purification of products formed in the reaction mixture. Accordingly, the search for new processes using heterogeneous catalysts more environmentally friendly, represents a major challenge in organic synthesis. Natural and modified mineral clays which are low cost, easily available, as well as environmental friendly, have been used as heterogeneous catalysts for many applications and shown high efficiency in organic synthesis [31].

In this work, we are interested by using this type of catalyst for isatin aldazines synthesis. Therefore, the use of a montmorillonite clay catalyst extracted from North West Algeria, also called Maghnite [35] was proposed, which has already shown interesting catalytic properties [36]. Indeed, montmorillonites which have both Brönsted and Lewis acid sites, produce active acid catalysts when exchanged with high charges density cations, such as: protons. Algerian montmorillonite, compared with other clays, contains a high proportion of SiO_2 and a lower Al_2O_3 concentration. Table 1 shows percentage changes in chemical composition, between raw and proton exchanged algerian MMT. These differences, in particular of SiO_2 and Al_2O_3, must have a significant impact on the physico-chemical properties of this exchanged montmorillonite. In this case, the decrease of Al_2O_3 and the increase of SiO_2 would affect the acid-catalyzed reactions, when using this material [35,36]. In these conditions, isatin aldazine derivatives 5a-e have been synthesized in two catalyzed steps by montmorillonite-H^+ (MMT-H^+) in ethanol under conventional heating.

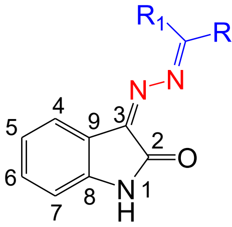


Figure 1. Structure of azines of isatine (or bis-Schiff bases of isatin).

2. Materials and Methods

2.1. Materials

All commercial reagents and solvents were used as supplied without further purification: isatin (98%, Alfa Aesar), 4-hydroxybenzaldehyde (98%, Sigma-Aldrich), furfural (99%, Sigma-Aldrich), 4-bromobenzaldehyde (99%, Sigma-Aldrich), 4-chlorobenzaldehyde (97%, Sigma-Aldrich), 4-Nitrobenzaldehyde (98%, Sigma-Aldrich), hydrazine hydrate (80%, Sigma-Aldrich) and ethanol (96%, Sigma-Aldrich). Thin layer chromatography (TLC) was done on silica gel TLC aluminium plates (E. Merck Kieselgel 60 F-254) and was visualized by exposure to UV-light at 254 nm or to iodine vapor for few seconds. ^1H and ^{13}C NMR spectra were acquired on a Bruker AQS-AVANCE spectrometer (400 MHz) at 25°C using DMSO-d_6 as solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS, $\delta = 0.00$ ppm). FT-IR spectra were recorded on a Bruker ATR spectrophotometer and the values are expressed in cm^{-1}. Melting point in °C was determined in open capillaries using electrothermal melting point apparatus Stuart MPS-10. Algerian montmorillonite clay extracted from North West Algeria was supplied by "E.N.O.F" (National Company

Table 1. Chemical composition of raw and H^+ exchanged Algerian montmorillonite [35].

Sample	SiO_2	Al_2O_3	Fe_2O_3	MgO	CaO	Na_2O	K_2O	TiO_2	SO_3	As	Water loss at 110 °C
Alg-MMT raw (%)	69.39	14.67	1.16	1.07	0.3	0.5	0.79	0.16	0.91	0.05	11
Alg-MMT-H^+ (%)	71.7	14.03	0.71	0.8	0.28	0.21	0.77	0.15	0.34	0.01	11

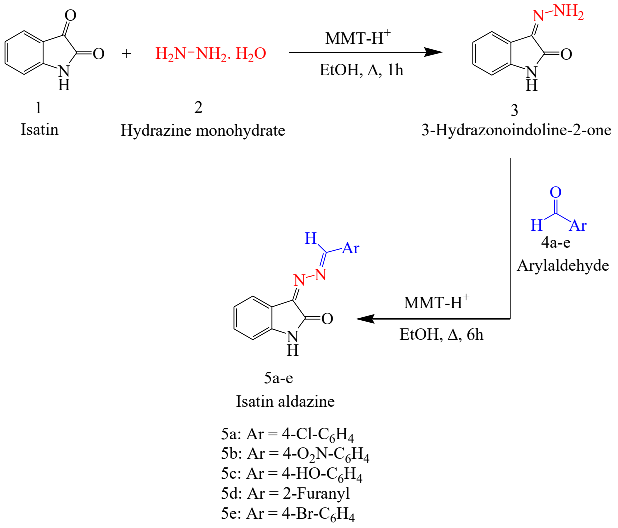
for non-ferrous mining products and useful substances).

2.2 Preparation of Montmorillonite-H$^+$

Exchanged montmorillonite-H$^+$ (MMT-H$^+$) was prepared according to the literature [35]. Raw montmorillonite (20 g) was crushed for 20 min and oven dried at 105 °C for 2 hours. The montmorillonite was then weighted and placed in an erlenmeyer flask together with 500ml of distilled water. The montmorillonite/water mixture was stirred using a magnetic stirrer and combined with 500 mL sulphuric acid solution (0.5 M) until saturation was achieved after two days at room temperature. The mineral was washed with distilled water until became sulphate free and then dried at 105 °C. The montmorillonite-H$^+$ prepared is ready to be used directly to catalyze our reactions.

2.3 General Procedure for the Synthesis of 3-hydrazonoindoline-2-one 3

Isatin 1 (1 mmol) and hydrazine monohydrate 2 (80%, 2 mmol) are added to catalytic amount of montmorillonite-H$^+$ (10%, 0.0147 g) in 10 mL ethanol. The amount of 10% of catalyst was selected after preliminary reaction tests. The reaction mixture was refluxed for 1 h. When the yellowish product was observed and the reaction completed (monitored by TLC), the crude product was dissolved in hot ethanol and then filtered to remove the solid filtered, filtered, washed with cold water, ethanol and dried at 60-70 °C to afford compound 3 catalyst. The filtrate was cooled to give the solid product. The crystalline powder was which was used for next step without any further purification.



Scheme 1. Synthesis of isatin aldazine derivatives 5a-e catalyzed by MMT-H$^+$

Data for 3-hydrazonoindoline-2-one 3: yellow powder (yield 86%), m.p. 225-227 °C (Lit. 226-228 °C) [12,16]; FT-IR (ν_{max} in cm^{-1}): 3354 (N-H), 3151 (N-H Isatin), 1655 (C=O), 1602 (C=N), 1549 (aromatic C=C); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.70 (s, 1H, NH), 10.54 (d, J = 14.2 Hz, 1H, -NH$_2$), 9.56 (d, J = 14.2 Hz, 1H, -NH$_2$), 7.36 (d, J = 7.8 Hz, 1H, H$_7$ of isatin), 7.15 (t, J = 7.5 Hz, 1H, H$_6$ of isatin), 6.97 (t, J = 7.5 Hz, 1H, H$_5$ of isatin), 6.86 (d, J = 7.8 Hz, 1H, H$_4$ of isatin); ^{13}C NMR (100MHz, DMSO-d_6, δ in ppm): 110.43, 117.91, 121.82, 126.65, 127.50, 139.10, 163.24, 206.99 (C=O).

2.4 General Procedure for the Synthesis of Isatin Aldazines 5a-e

The 3-hydrazonoindoline-2-one 3 (1 mmol) is added to arylaldehyde 4a-e (1 mmol) in 10ml ethanol with catalytic amount of montmorillonite-H$^+$ (10%). The reaction mixture is refluxed for 6 h during which the solution color change. The progress of reaction is monitored by TLC. The crude product is dissolved with hot ethanol and then filtered to remove the solid catalyst. The filtrate is cooled to give the solid product. The crystalline powder is filtered, washed with ethanol and dried at 60-70 °C to afford compound 5a-e (Scheme 1).

2.5 Characterization and Spectroscopic Data

Data for 3-((4-Chlorobenzylidene) hydrazono)indolin-2-one 5a: orange powder (yield 84%), m.p. 269-271 °C (lit. 270-272 °C) [21]; FT-IR (ν_{max} in cm^{-1}): 3276 (N-H), 3053 (aromatic C-H), 1718 (C=O), 1611 (C=N), 1590 (aromatic C=C), 749 (C-Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.86 (s, 1H,-NH-), 8.62 (s,1H, -N=CH), 8.00 (d, J = 8.4 Hz, 2H, Ar-H), 7.87 (d, J = 8.4 Hz, 2H, Ar-H), 7.65 (d, J = 7.5 Hz,1H, H$_7$ of isatin), 7.41 (t, J = 7.8 Hz, 1H, H$_6$ of isatin), 7.03 (t, J = 7.8 Hz, 1H, H$_5$ of isatin), 6.91 (d, J = 7.5 Hz, 1H, H$_4$ of isatin); ^{13}C NMR (100MHz, DMSO-d_6, δ in ppm): 111.38, 111.98, 116.79, 122.87, 129.26, 129.84, 130.91, 132.77, 134.33, 137.17, 141.72, 145.60, 150.80, 159.29, 164.88 (C=O).

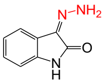
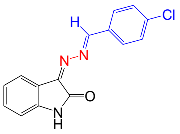
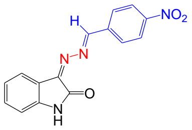
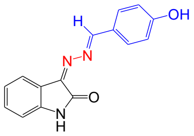
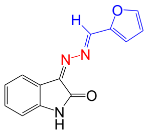
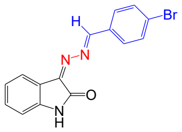
Data for 3-((4-Nitrobenzylidene) hydrazono)indolin-2-one 5b : orange powder (yield 78%), m.p. 252-254 °C (lit. 254-256 °C) [21]; FT-IR (ν_{max} in cm^{-1}): 3277 (N-H), 3052 (aromatic C-H), 1719 (C=O), 1612 (C=N), 1591 (aromatic C=C), 1327 (C-NO$_2$); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.90 (s, 1H,-NH-), 8.67(s, 1H, N=CH), 8.39 (d, J = 8.7 Hz, 2H, Ar-H), 8.21 (d, J = 8.7 Hz, 2H, Ar-H), 7.74 (d, J = 7.8 Hz, 1H, H$_7$ of isatin), 7.42 (t, J = 7.5 Hz, 1H, H$_6$ of isatin), 7.02 (t, J = 7.5 Hz, 1H, H$_5$ of isatin), 6.92 (d, J = 7.8 Hz, 1H, H$_4$ of isatin); ^{13}C NMR (100MHz, DMSO-d_6, δ in ppm): 111.50, 111.85, 116.54, 122.29, 122.94, 124.75, 129.21, 130.16, 134.61, 139.58, 145.78, 149.51, 150.18, 156.77, 164.63 (C=O).

Data for 3-(2-(4-hydroxybenzylidene) hydrazono)indolin-2-one 5c: orange powder (yield 80%), m.p. 261-263 °C (lit. 261 °C) [10,11,12,33,34]; FT-IR (ν_{max} in cm^{-1}): 3397 (O-H), 3149 (N-H), 3047 (aromatic C-H), 1680 (C=O), 1614 (C=N), 1541 (aromatic C=C), 1092 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.79 (s, 1H,-NH-), 10.36 (s, 1H, -OH), 8.61 (s, 1H, N=CH), 8.10 (d, J = 7.5 Hz, 1H, H$_7$ of isatin), 7.87 (d, J = 8.6 Hz, 2H,Ar-H), 7.39 (t, J = 7.8 Hz, 1H, H$_6$ of isatin), 7.05 (t, J = 7.8 Hz, 1H, H$_5$ of isatin), 6.96 (d, J = 8.6 Hz, 2H, Ar-H), 6.90 (d, J = 7.5 Hz, 1H, H$_4$ of isatin); ^{13}C NMR (100MHz, DMSO-d_6, δ in ppm): 111.15, 116.66, 116.67, 117.23, 122.75, 125.05, 129.38, 131.87, 131.88, 133.78, 145.22, 151.16, 162.10, 163.47, 165.33 (C=O).

Data for 3-((Furan-2-ylmethylene) hydrazono)indolin-2-one 5d: yellow powder (yield 67%), m.p. 209-211 °C (lit. 209 °C) [6]; FT-IR (ν_{max} in cm^{-1}): 3276 (N-H), 3054 (aromatic C-H), 1720 (C=O), 1613 (C=N), 1590 (aromatic C=C); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.82 (s, 1H, -NH-) ,8.50 (s, 1H, N=CH), 8.08 (d, J = 8.1 Hz, 2H, Ar-H), 7.40 (t, J = 7.5 Hz, 1H, H$_6$ of isatin), 7.34 (d, J = 7.8 Hz, 1H, H$_7$ of isatin), 7.04 (t, J = 7.5 Hz, 1H,H$_5$ of isatin), 6.90 (d, J = 7.8 Hz, 1H, H$_4$ of isatin), 6.80 (d, J = 1.7 Hz, 1H, Ar-H); ^{13}C NMR (100MHz, DMSO-d_6, δ in ppm): 111.25, 113.64, 117.18, 120.17, 122.76, 129.51, 134.16, 145.39, 148.52, 149.55, 151.24, 151.80, 165.13 (C=O).

Data for 3-(2-(4-bromobenzylidene) hydrazono)indolin-2-one 5e: Yellow powder (yield 75%), m.p. 200-202 °C; FT-IR (ν_{max} in cm^{-1}): 3274.17 (N-H), 3055 (aromatic C-H), 1719 (C=O), 1612 (C=N), 1590 (aromatic C=C), 750 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 11.00 (s, 1H,-NH-), 8.64 (s,1H, -N=CH), 7.99 (d, J = 8.1 Hz, 2H, Ar-H), 7.62 (d, J = 8.0 Hz, 2H, Ar-H), 8.00 (d, J = 7.8 Hz, 1H, H$_7$ of isatin), 7.60 (t, J = 7.5, 1H, H$_6$ of isatin), 7.57 (t, J = 7.5 Hz, 1H, H$_5$ of isatin), 6.87 (d, J = 7.8 Hz, 1H, H$_4$ of isatin); ^{13}C NMR (100MHz, DMSO-d_6, δ in ppm): 113.59, 114.01, 118.17, 124.88, 130.13, 131.12, 136.80, 139.36, 144.91, 149.34, 149.68, 157.55, 164.17 (C=O).

Table 2. Physical data of the synthesized compounds 5a-e using montmorillonite-H$^+$.

Entry	Product	Yield* (%)	M.P. (°C)
		Exp. ** (Lit.)	Exp. ** (Lit.)
1	 3	86 (77.9)	225-227 (226-228) [12,16]
2	 5a	84 (78)	269-271 (270-272) [21]
3	 5b	78 (66)	252-254 (254-256) [21]
4	 5c	80 (60)	261-263 (261) [10,12,33 ,34]
5	 5d	67 (55)	209-211 (209) [6]
6	 5e	75	200-202

(*) Isolated yield of product using montmorillonite-H$^+$. The structure of products are determined by NMR and all spectral data are in good agreement with those of literature.
(**) Exp.: Experimental value (Lit.: literature value).

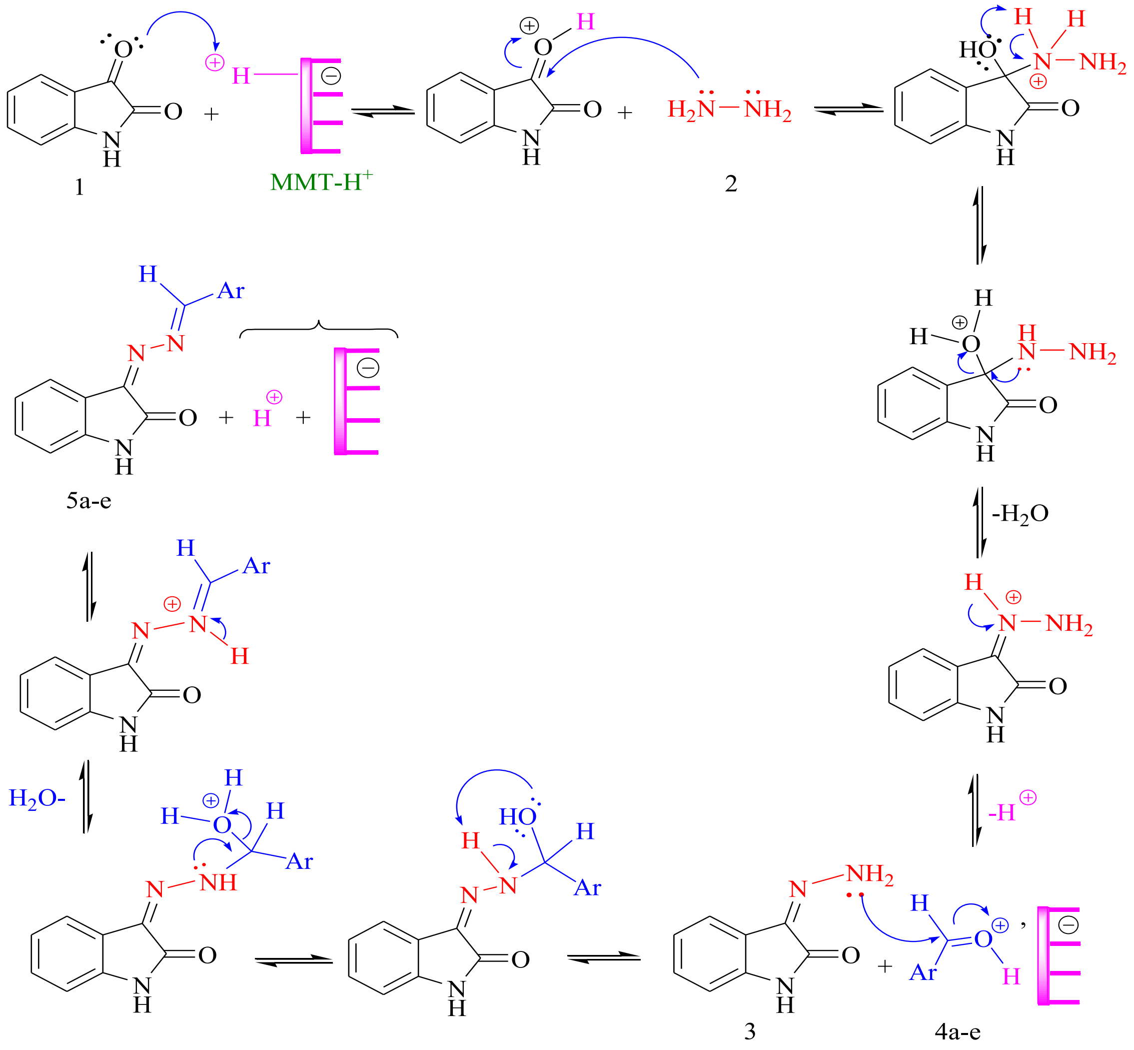
3. Results and Discussion

The reaction of isatin 1 with hydrazine hydrate 2 provides 3-hydrazonoindoline-2-one 3 which is condensed with aromatic aldehydes 4a-e to yield the desired products 5a-e (Scheme 1). This two steps reactional sequence is catalyzed by proton exchanged Algerian montmorillonite (MMT-H$^+$). The experimental results (Table 2) obtained by these reactions show good yields compared to those of the literature. Furthermore, the catalyst can be removed from the reactional mixture and recycled up to three times without loss of catalytic activity.

A mechanism, presented in Scheme 2, is proposed to explain the role of the proton exchanged montmorillonite catalyst (MMT-H$^+$) in the two steps isatin aldazines synthesis 5a-e. The structures of compounds 5a-e were confirmed by their melting points and the analysis of their spectral data (FT-IR spectroscopy, ^{1}H and ^{13}C), compared to the values of the literature.

3.1. Infrared Spectroscopy (FT-IR)

The FT-IR spectrum of all synthesized compounds show characteristic bands at 3354-3400, 3149-3277, 1680-1720 cm^{-1} and a weak broad band in 1611-1673 cm^{-1} region, which can be assigned respectively to -NH_2, N–H (isatin), C=O and C=N (azomethine linkage) vibrations of 3-hydrazinoindolin-2-one 3 [6,15,16]. This is a direct evidence of the condensation of hydrazine hydrate 2 on the carbonyl in position 3 of isatin 1 and confirms the formation of the desired Schiff bases. The IR spectra of isatin aldazine derivatives 5a-e showed new strong bands at 1536-1591 and 1006-1027 cm^{-1} regions, which assignable to aromatic (C=C) and hydrazinic (N-N) vibrations respectively. IR spectrum of 3-(2-(4-hydroxybenzylidene) hydrazono)indolin- 2-one 5c show a large absorption band in the region of 3400-3393 cm^{-1} assignable to O–H (intermolecular hydrogen bonded) stretching [10-12,33,34]. The IR spectra of compound 3-((4-nitrobenzylidene)hydrazono)indolin-2-one 5b show strong band at 1290-1330 cm^{-1} assigned to (N–O) stretching vibrations in nitro group. For compounds 3-((4-chlorobenzylidene)hydrazono)indolin-2-one 5a and 3-(2-(4-bromobenzylidene)hydrazono) indolin-2-one 5e, C-halogen bonds displayed absorption around 610-750 cm^{-1} which can be assigned to (C–Cl) and (C–Br) stretching vibrations respectively. The furanyl derivative 3-((furan-2-ylmethyl ene)hydrazono)indolin-2-one



Scheme 2. Proposed mechanism for the synthesis of isatin aldazine 5a-e in two steps using MMT-H$^+$

5d shows absorption bands at 1283-1328 cm^{-1}, attributed to (C-O) covalent bond.

3.2. Nuclear Magnetic Resonance (NMR)

In ^1H-NMR, spectra of all synthesized compounds show singlet at 10.79-11.11 ppm indicating the presence of secondary amino group (NH) of isatin skeleton. The aromatic protons resonate as multiplet in the region of δ 6.80-8.39 ppm. The spectrum of 3-hydrazinoindolin-2-one 3 shows the $-NH_2$ signal around 10.54-9.56 ppm. The signal of azomethine (-CH=N) appear at δ 8.50-9.00 ppm in all the 5a-e compounds [10,21,33,34]. The absence of $-NH_2$ signal clearly indicates the formation of isatin aldazines 5a-e. Moreover, the ^1H-NMR spectrum of 5c reveal the presence of a singlet at 8-10.36 ppm corresponding to hydroxyl group O-H. All ^1H- and ^{13}C- NMR spectral data are in good agreement with those of literature.

4. Conclusions

The montmorillonite-H^+ (MMT-H^+) was found to be an efficient green heterogeneous acidic catalyst for the synthesis of isatin aldazine derivatives. This catalyst was easy to prepare, environmentally friendly, highly stable and can be recycled without significant loss of activity. The distinguished advantageous of present synthetic method are use of inexpensive catalyst, simple reaction workup, good yields and reusability of catalyst. Other applications of this catalyst in synthetic processes are under study.

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