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GLYCEROL IN WATER: A SIMPLE, EFFICIENT AND GREEN PROTOCOL FOR THE SYNTHESIS OF 3-HYDRO- 2 - (2´- SUBSTITUTED INDOL) 9 H- IMIDAZO [1, 2-a] BENZIMIDAZOLES AS INSECTICIDAL AGENTS

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ABSTRACT
An efficient, facile and greener protocol for the synthesis of benzimidazole derivatives viz., 3-hydro-2-(2'-subsituted indol) 9H-imidazo [1, 2-a] benzimidazoles **3**, by the reaction of 2-hydrazino benzimidazoles **1** with 3-acetyl indoles **2** using glycerol-water as solvent and without using any catalyst is described .This methodology has advantage of simple handling, mild reaction conditions and high yields of products in shorter reaction time as well is an environmentally benign synthesis. The synthesized compounds have been characterized by analytical and spectral (IR, ^{1}H and ^{13}C NMR and FAB mass) data and found to display promising activity when screened for insecticidal activity against *Periplenata americana*.
KEYWORDS: 2-Hydrazino benzimidazoles, 3-acetyl indoles, 3-hydro-2-(2´-substituted indol) 9H-imidazo [1, 2-a] benzimidazoles, glycerol-water mediated synthesis, insecticidal activity.

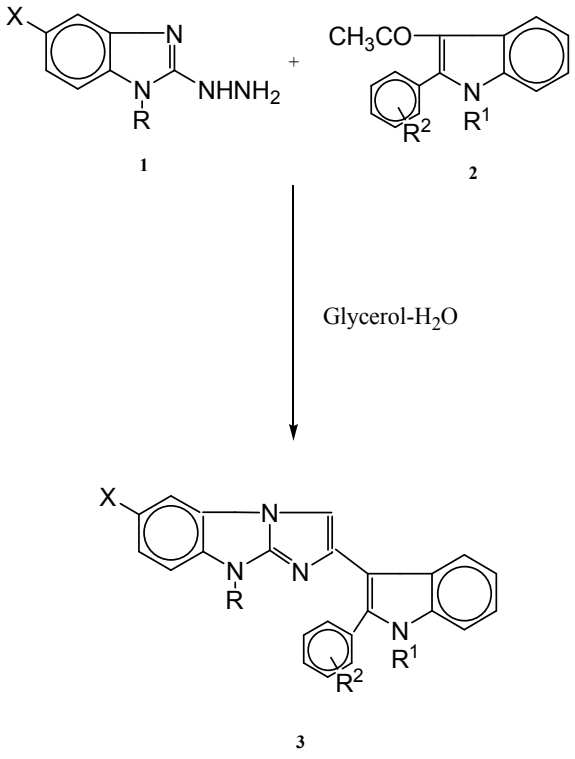
INTRODUCTION

With the increasing awareness in chemical research, the challenge that sustainable environment calls for us is develop clean procedures for synthesis of pharmaceutically important scaffolds. The glycerol which can be obtained as a by-product in biodiesel production can be used as a renewable, non toxic and recyclable solvent in green and sustainable chemistry.

Benzimidazoles possess interesting biological activities such as antibacterial[i], antifungal[ii] , insecticidal [iii] etc. Indole nucleus is present in various biologically active natural products and shows anticancer[iv], CNS depressant[v] , antioxidative[vi], etc activities. In the course of synthesis of bioactive benzimidazoles[vii-x] through greener route, we herein report the synthesis of 3-hydro-2-(2'-substitutedindol) 9H-imidazo [1, 2-a] benzimidazoles **3** by reacting 2-hydrazino benzimidazoles **1** with 3-acetyl indoles **2** using glycerol-water **(Scheme-I)**. Such type of one step cyclization reaction in glycerol-water without using any catalyst has been reported for the first time

We have also investigated the reaction in various solvent systems like ethanol, ethanol-acetic acid, acetic acid, DMF, water, [bmim] PF_6, glycerol and glycerol-water. The best results were

obtained in glycerol-water system with good yield (92-96%). The synthesized compounds **3a-j** showed excellent results for insecticidal activity when screened against *Periplenata americana*.



Compd.	X	R	R^1	R^2	Compd.	X	R	R^1	R^2
3a	H	H	H	H	3f	H	CH_3	H	H
3b	H	H	H	3-Cl; 4-F	3g	CH_3	H	H	H
3c	H	H	H	4-Cl	3h	CH_3	CH_3	H	H
3d	H	H	H	4-F	3i	CH_3	H	H	4-F
3e	H	H	H	4-CH_3	3j	CH_3	H	H	4-Cl

Scheme-I

EXPERIMENTAL

Melting points are uncorrected and were taken in open glass capillaries using Gallenkamp melting point apparatus. The IR spectra were recorded on a 8400S SHIMADZU IR spectrometer in KBr pellets and band positions are reported in wave numbers (cm^{-1}). The ^1H NMR spectra and ^{13}C NMR spectra have been recorded on JEOL 300 MHz in DMSO-d_6/$CDCl_3$ at 300 and 75 MHz respectively. Chemical shifts (δ) are given in ppm. The mass spectra were recorded on JEOL SX 102 (FAB). Elemental analyses were performed at Central Drug Research Institute, Lucknow, India. Chemicals were purchased from Acros

Organics.2-Hydrazino benzimidazoles [xi] and 3-acetyl indoles [xii] were synthesized according to the literature methods.

General procedure for the synthesis of 3-hydro-2-(2'-subsituted indol) 9H-imidazo [1, 2-a] benzimidazoles 3a-j

To a stirred solution of water (2ml) and glycerol (5ml), 2-hydrazinobenzimidazole **1** (0.01 mole) and 3-acetyl indole (0.01 mole) was added and the reaction mixture was stirred vigorously at 90^0C for further 60-90 min. and progress of reaction was monitored by TLC using Ethyl acetate: Pet. ether(1:9). After completion of the reaction, warm water (5 mL) was added. Glycerol dissolved in water and insoluble crude products were isolated by simple filtration. The solid obtained was crystallized from ethanol to afford the pure compounds **3a-j**. The filtrate containing glycerol was extracted with methyl *tert*-butyl ether (2×5 mL) to remove any organic compounds dissolved in aqueous phase. The aqueous layer was separated and water was evaporated under reduced pressure at 100 ^{o}C to give pure glycerol which was used for next run under similar conditions.

3-Hydro-2-(2´-phenylindol)9H-imidazo [1,2-a] benzimidazole ,3a: Yield 95%, m.p. 201°C. Anal. calcd. for $C_{23}H_{16}N_4$: C, 79.29; H, 4.63; N, 16.08; Found C, 79.26; H, 4.65; N, 16.12%. IR (KBr): 3159 (>NH), 3095 (>NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 6.45-7.63 (m, 13H, Ar-H), 7.82 (s, 1H, =CH), 8.93 (s, 1H, >NH), 9.71 (s, 1H, >NH) ppm. ^{13}C NMR ($CDCl_3$): 159.0 (C-9a), 124 (C-2), 102.1 (C-3), 137.8 -107.5 (20C,Ar-C) ppm. Mass: m/z 348.4 (M^+).

3-Hydro-2-(2´-(3-chloro,4-fluorophenyl)indol)9H-imidazo[1,2a]benzimidazole ,3b: Yield 96%, m.p. 161°C. Anal. calcd. for $C_{23}H_{14}ClFN_4$: C, 68.92; H, 3.52; N, 13.97; Found C, 68.94; H, 3.56; N, 13.93%. IR (KBr) : 3160 (>NH), 3080 (>NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 6.56-7.62(m, 11H, Ar-H), 7.15(s, 1H, =CH), 8.82 (s, 1H, >NH), 9.51 (s, 1H, >NH) ppm. ^{13}C NMR ($CDCl_3$) : 159.2 (C-9a), 123.9(C-2), 102.3(C-3), 137.4 -109.1 (20C,Ar-C) ppm. Mass : m/z 400.8 (M^+).

3-Hydro-2-(2´-(4-chlorophenyl)indol)9H-imidazo[1,2a]benzimidazole,3c: Yield 96%, m.p. 166°C. Anal. calcd. for $C_{23}H_{15}ClN_4$: C, 72.15; H, 3.95; N, 14.63; Found C, 72.11; H, 3.91; N, 14.65%. IR (KBr) : 3150 (>NH), 3085 (>NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 6.46-7.80 (m, 12H, Ar-H), 7.91 (s, 1H, =CH), 8.90 (s, 1H, >NH), 9.60 (s, 1H, >NH) ppm. ^{13}C NMR ($CDCl_3$) : 159.2 (C-9a), 123.9(C-2), 102.3 (C-3), 137.8 -109.1 (20C,Ar-C) ppm. Mass : m/z 382.8 (M^+).

3-Hydro-2-(2´-(4-fluorophenyl)indol)9H-imidazo [1,2-a] benzimidazole ,3d: Yield 95%, m.p. 160°C. Anal. calcd. for $C_{23}H_{15}FN_4$: C, 75.39; H, 4.12; N, 15.29; Found C, 75.41; H, 4.14; N, 15.32%. IR (KBr) : 3170 (>NH), 3090(>NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 6.52-7.72 (m, 12H, Ar-H), 7.86(s, 1H, =CH), 8.68 (s, 1H, >NH), 9.56 (s, 1H, >NH) ppm. ^{13}C NMR ($CDCl_3$) : 159.4(C-9a), 123.6(C-2), 102.4 (C-3), 137.5 -109.8 (20C,Ar-C) ppm. Mass : m/z 366.4 (M^+).

3-Hydro-2-(2´-(4-methylphenyl) indol)9H-imidazo [1,2-a] benzimidazole ,3e: Yield 92%, m.p. 221°C. Anal. calcd. for $C_{24}H_{18}N_4$: C, 79.53; H, 5.00; N, 15.46; Found C, 79.56; H, 5.02; N, 15.48%. IR (KBr) : 3180 (>NH),3070(>NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 2.45(s,3H,-$C_6H_4C\mathbf{H_3}$),6.51-7.52 (m, 12H, ArH),7.80 (s, 1H, =CH), 9.02 (s, 1H, >NH), 9.81 (s, 1H,>NH)ppm.^{13}CNMR($CDCl_3$):159.1 (C-9a), 124 (C-2), 102.2 (C-3), 137.8 -109.5 (20C,Ar-C) ppm. Mass : m/z 362.4 (M^+).

3-Hydro-9-methyl-2-(2´-phenylindol)9H-imidazo [1,2-a]benzimidazole,3f: Yield 92%, m.p. 211°C. Anal. calcd. for $C_{24}H_{18}N_4$: C, 79.53; H, 5.00; N, 15.46; Found C, 79.57; H, 5.03; N, 15.43%. IR (KBr) : 3080(>NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 3.98(s,3H,N**C**$\mathbf{H_3}$),6.51-7.62(m, 13H, Ar-H), 7.92 (s, 1H, =CH), 8.91 (s, 1H, >NH) ppm. ^{13}C NMR ($CDCl_3$) : 159.2 (C-9a), 124 (C-2), 102.5 (C-3), 35.5(N**C**H_3),137.5-108.4 (20C,Ar-C) ppm. Mass : m/z 362.4 (M^+).

3-Hydro-6-methyl-2-(2´-phenylindol)9H-imidazo [1,2-a] benzimidazole ,3g: Yield 94%, m.p. 197°C. Anal. calcd. for $C_{24}H_{18}N_4$: C, 79.53; H, 5.00; N, 15.46; Found C, 79.51; H, 5.04; N, 15.49%. IR (KBr) : 3160 (>NH),3082(>NH) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 2.36(s,3H,$C_6H_4C\mathbf{H_3}$),6.51-7.53 (m, 12H, Ar-H), 7.81(s, 1H, =CH), 9.13 (s, 1H, >NH), 9.72(s, 1H, >NH) ppm. ^{13}C NMR ($CDCl_3$) : 159.4 (C-9a), 124 (C-2), 102.8(C-3),29.8($C_6H_4\mathbf{C}H_3$), (137.2-109.0 (20C,Ar-C) ppm. Mass : m/z 362.4 (M^+).

3-Hydro6,9-dimethyl-2-(2´-phenylindol)9H-imidazo [1,2-a] benzimidazole ,3h: Yield 92%, m.p. 206°C. Anal. calcd. for $C_{25}H_{20}N_4$: C, 79.76; H, 5.35; N, 14.88; Found C, 79.79; H, 5.38; N, 14.86%. IR (KBr) : 3080(>NH) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 2.41(s,3H,$C_6H_4C\mathbf{H_3}$),4.05(s,3H,$NC\mathbf{H_3}$),6.53-7.68 (m, 13H, Ar-H), 7.94 (s, 1H, =CH), 8.92(s, 1H, >NH) ppm. ^{13}C NMR ($CDCl_3$) : 159.4 (C-9a), 124.1(C-2), 102.7(C-3), 37.8($N\mathbf{C}H_3$), 29.5($C_6H_4\mathbf{C}H_3$), 137.6 -108.4 (20C,Ar-C) ppm. Mass : m/z 376.4 (M^+).

3-Hydro-6-methyl-2-(2´-(4-fluorophenyl)indol)9H-imidazo [1,2-a] benzimidazole ,3i: Yield 95%, m.p. 193°C. Anal. calcd. for $C_{24}H_{17}FN_4$: C, 75.77; H, 4.50; N, 14.72; Found C, 75.79; H, 4.52; N, 14.75%. IR (KBr) : 3160 (>NH), 3045 (>NH) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 2.38(s,3H,$C_6H_4C\mathbf{H_3}$),6.45-7.68 (m, 11H, Ar-H), 7.76 (s, 1H, =CH), 9.03 (s, 1H, >NH), 9.80 (s, 1H, >NH) ppm. ^{13}C NMR ($CDCl_3$) : 159.6 (C-9a), 124.5 (C-2), 102.5 (C-3), 29.2($C_6H_4\mathbf{C}H_3$), 137.8 -109.7 (20C,Ar-C) ppm. Mass : m/z 380.4 (M^+).

3-Hydro-6-methyl-2-(2´-(4-chlorophenyl)indol)9H-imidazo [1,2-a] benzimidazole ,3j: Yield 94%, m.p. 198°C. Anal. calcd. for $C_{24}H_{17}ClN_4$: C, 72.63; H, 4.32; N, 14.12; Found C, 72.65; H, 4.35; N, 14.16%. IR (KBr) : 3170 (>NH), 3040(>NH) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.42(s, 3H, $C_6H_4C\mathbf{H_3}$), 6.58-7.73 (m, 11H, Ar-H), 7.79 (s, 1H, =CH), 8.99 (s, 1H, >NH), 9.78 (s, 1H, >NH) ppm. ^{13}C NMR ($CDCl_3$) : 159.4 (C-9a), 124 (C-2), 102.8 (C-3), 29.8($C_6H_4\mathbf{C}H_3$), 137.4 -108.9 (20C,Ar-C) ppm. Mass: m/z 396.8 (M^+).

EVALUATION OF INSECTICIDAL ACTIVITY

Insecticidal activity[xiii, xiv] was evaluated by taking insect *Periplaneta americana* where 1 and 2 % solutions of prepared compounds were injected in the abdominal region of the cockroach with the help of microsyringes. At the time of death the antennae become motionless, the appendages shrunk and folded towards central side and the cockroach lay dorsally which was noted as KD (Knock down) value. The KD values of synthesized heterocyclic derivatives were compared with control drug (Cypermethrin).The results are recorded in **Table 1**.

For insecticidal activity, result shows that compounds **3b**, **3d**, **3c** and **3j** showed better activity than standard drug, having less KD value. The activity of these compounds is due to presence of fluoro and chloro substitution in the compounds. Compounds **3b**, **3d** and **3i** have less KD value than **3i** and **3j**.This shows that fluoro substituted derivatives are most active. Other compounds **3a**, **3e**, **3f**, **3g** and **3h** show moderate activity.

Table 1: Results of Insecticidal activity against *Periplaneta americana* (KD values in min) of compounds **4-7**

Compound	Time (min)	
	1% (Conc.)	2% (Conc.)
3a	8	7
3b	5	3
3c	6	4
3d	5	3
3e	9	7
3f	10	8
3g	8	7
3h	10	8
3i	5	3
3j	6	4
Cypermethrin	7	5

RESULTS AND DISCUSSION

We have investigated the one pot reaction of **1** and **2** to obtain compound **3a** in different solvent systems such as ethanol, ethanol-acetic acid, acetic acid, DMF, water, [bmim] PF_6, glycerol, glycerol-water and best results were obtained in glycerol-water as a green solvent system. The purpose of this study was to explore the scope and limitations of glycerol as alternative green reaction medium. For our initial condensation reaction in aqueous glycerol with stirring at room temperature, it was observed that the starting materials were consumed after long time as indicated by TLC analysis. To optimize the reaction conditions and to afford the desired compound in good yields, some reactions were conducted at different reaction temperature and it was observed that as temperature increases, rate of reaction increases and a good amount of yield (92-96%) was obtained at 90 ^{0}C within 1 hr (**Table-2).** Once more, the advantage to this protocol is that after the workup procedure glycerol is successfully recovered and can be reused for another reaction without affecting the yields. In order to study the effect of solvent on the rate of reaction, the same reaction was executed in absence of water but the yield of the product decreased drastically. It was observed that in ethanol, ethanol-acetic acid and DMF solvent systems, the reaction was not completed even after heating for a long time (5 hr) as indicated by TLC analysis and in water reactants are not soluble. The reaction was completed in [bmim] PF_6, glycerol and glycerol-water. The yield was found to be low in ionic liquid and glycerol only. The ionic liquid is costly; therefore, one pot reaction was done in glycerol-water due to economic and environmental point of view.

Subsequently, the possibility of recycling glycerol was investigated. After first cycle for the model reaction, the product was poured into water and extracted with methyl *tert*-butyl ether to remove any organic compounds dissolved in aqueous phase. The aqueous layer was separated and water was evaporated under reduced pressure at 100 ^{o}C to give pure glycerol which was used for next run under similar conditions[xv].

The explanation for formation of compounds **3** were assumed to proceed through two step domino sequence. The first step is believed to be formation of hydrazone after reaction of **1** and **2.** The next step is the cyclization and ring closure to give 9H-imidazo [1, 2-a] benzimidazoles **3**. The one step formation of 9H-imidazo [1, 2-a] benzimidazoles **3** were

confirmed by IR spectra in which it shows no peaks due to >NHN= at 3400-3300 cm^{-1} and due to–NHN=C bond at 1605-1620 cm^{-1}. ^1H NMR shows no peak at δ 10-11 ppm for >N**H**N=C and 1.75-2.00 ppm for $=\overset{|}{C}-CH_3$ instead it shows a singlet at δ 7.7-7.8 ppm due to =C**H**. ^{13}C NMR shows no peak at δ 164.4 and 28.5 ppm for **C**=N and $=\overset{|}{C}-CH_3$ respectively instead it shows peaks at δ 124 and 102 ppm due to =**C**H and $=\overset{|}{C}-$. Further, mass spectrum shows M^+ at m/z 348.4 (**3a)**.

Table 2: Optimization of reaction condition for model reaction generating **3a**

Compound	Solvent	Time (h)	Temp. (°C)	Yield (%)
3a	Ethanol	5	reflux	Nil
3a	Ethanol-AcOH	5	reflux	Nil
3a	AcOH	5	reflux	Nil
3a	DMF	5	180	Nil
3a	H_2O	5	100	Nil
3a	[bmim]PF_6	5	85 ± 2	25
3a	Glycerol	5	50 ± 2	57
3a	Glycerol	3	90 ± 2	63
3a	Glycerol-H_2O (2.5:1)	10	Room temp.	12
3a	Glycerol-H_2O (2.5:1)	2	50 ± 2	75
3a	Glycerol-H_2O (2.5:1)	1	90 ± 2	96

CONCLUSION

In conclusion the present study reports the synthesis of novel 3-hydro-2-(2′-substituted indol) 9H-imidazo [1, 2-a] benzimidazoles **(3a-j)** using glycerol-water as a solvent. The importance of this method is that, this is an environmentally benign synthesis in good yields and solvent is reused for further reactions thus making synthesis cheaper. Data of insecticidal activity evaluation shows that some of the compounds are good insecticidals.

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