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DBUH-I_3 COMPLEX CATALYSED SYNTHESIS OF ARYLIDENE DERIVATIVES OF PYRAZOLE

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Abstract: The new organocatalyst amine-iodine-iodide complex was prepared and used as a catalyst for the synthesis of arylidene derivatives of pyrazole from ethyl acetoacetate, substituted aryl aldehyde and phenylhydrazine. The direct one-step multicomponent efficient synthesis was achieved with remarkable green advantages offered by this protocol such as short reaction time, the broad scope of a substrate, simple experimental procedure and moderate to a good yield of the desired product. The synthesized molecules were confirmed by spectroscopic analysis ^{1}H-NMR and ^{13}C-NMR.

Keywords: DBU-iodine-iodide complex, Pyrazole, Condensation, Arylidene pyrazole, Multicomponent.

Introduction:

Pyrazole derivatives are very useful scaffolds of five-membered heterocyclic compounds, found in numerous natural and medicinal products.[i-ii] They are a precursor for the synthesis of numerous valuable organic molecules, pharmaceutical compounds, biologically active molecules and agrochemicals.[iii] The innumerable advantages of pyrazole in medicinal chemistry as they display a broad spectrum of biological activities such as anticancer,[iv] antibacterial, antifungal,[v] anti-inflammatory,[vi] anti-viral,[vii] antiplatelet,[viii] anti-tubercular[ix] and so on.[x] Pyrazole are privileged five-membered heterocyclic compounds in human and veterinary medicine as well as a versatile building block in organic synthesis, therefore have attracted much attention of synthetic organic chemist.[iv,xi]

The traditional protocol for the synthesis of 4-arylidine-3-methyl-1-phenyl-pyrazol-5(4H)-one derivative consists of two consecutive steps[xii,xiv] viz, a) reaction between phenyl hydrazine and ethyl acetoacetate condensation followed by cyclisation produce 3-methyl-1-phenyl-5-pyrazolone, b) Knoevenagel condensation between 3-methyl-1-phenyl-5-

pyrazolone and aryl aldehyde. Most recently, only a few alternative reports indicate one step multicomponent reaction between phenyl hydrazine, ethyl acetoacetate and aryl aldehyde give corresponding arylidene pyrazole. Few multicomponent one-pot the synthesis of 4-arylidine-3-methyl-1-phenyl-pyrazol-5(4H)-one was reported earlier using silica-supported zinc chloride [xv] and microwave.[xvi]

The synthetic method survey of pyrazole, concludes that each synthetic method has certain merits and demerits. The demerit of a previous protocol is long reaction time, stringent reaction conditions, tedious steps (preparation of nano catalyst) and special conditions (grinding, high temperature, ultrasound, irradiation). Hence there is ample scope to develop a new efficient method for the synthesis of pyrazole. We have prepared a new organocatalyst amine-iodine-iodide complex, fortunately, it catalyses efficiently with process optimization protocol and synthesis of pyrazole. The present protocol offers an eco-friendly and sustainable approach with excellent substrate and functional group compatibility viz, use of organocatalyst, operationally simple, mild condition, inexpensive catalyst, low cost, simple and quick isolation of the product. To the best of my knowledge, no report is available on amine-iodine-iodide complex as a catalyst for the synthesis of pyrazole. The predicted protocol was one pot, one-step, multicomponent reaction for arylidene pyrazole synthesis. Iodine catalysis known for more than a hundred years has potent advantages over transition metal base catalysts but molecular iodine has a drawback such as sublimation and moisture sensitivity.[xvii] To overcome this drawback, convert molecular iodine to amine-iodine-iodide complexes.[xviii] These complexes were shown potent catalysts for the synthesis of arylidene pyrazole.

Experimental Section:

Melting points were determined in open capillary tubes and are uncorrected. All chemicals and solvents were used laboratory grade. The purity and progress of reactions were monitored on TLC. Products were purified by re-crystallization process. NMR data of as-synthesized compounds were recorded on Bruker 500 MHz instrument for their structural identification.

Synthesis of Pyrazolone derivatives using DBUH-I_3 Catalyst.

The Phenyl hydrazine (1mmol), ethyl acetoacetate(1mmol), aryl aldehyde (1 mmol) and 10 mL ethanol were taken in 25 mL single neck round bottom flask equipped with a condenser. Then, 15 mol % DBUH-I_3 catalyst was added to the reaction mixture. The reaction mass was refluxed for 30 min. The progress and completion of the reaction was confirmed by TLC. After completion of the reaction, solvent was evaporated to get the crude product. The reaction mixture was quenched with an excess 20% sodium thiosulfate solution and extracted with ethyl acetate. The organic layer dried over sodium sulphate and evaporated to obtain a crude solid. The crude solid product was purified by recrystallisation to get a pure product and report the yield. The pure products were characterized by ^{1}H-NMR,^{13}C-NMR and physical constant comparison with reported derivatives.

Result and Discussion:

We have prepared and confirmed the DBU-iodine-iodide complex by the reported procedure, with minor modifications replacing potassium iodide with ammonium iodide[xviii-xix]. This iodine bearing complex is a good alternative for molecular iodine as they overcome sublimation and moisture sensitivity problem[xix]. We have prepared the above complex by dissolving iodine in ammonium iodide aqueous solution and then adding this solution dropwise to the aqueous DBU solution, complex gets precipitated. The amine-iodine-iodide complex has quaternary nitrogen, molecular iodine and iodide ions important constituent responsible for catalytic activity and iodination.

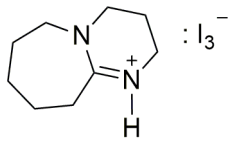
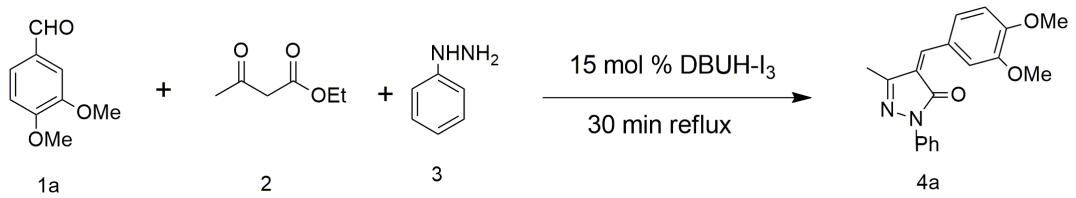


Figure 1 Structure of DBUH + I_3 Complex

The DBUH + I_3 complexes were screen for synthesis of 3-methyl-4-(3,4-dimethoxyaryl) methylene-pyrazole-5-(*4H*)-one in various solvents. The synthesis of pyrazole was achieved by one pot multi-step process, first Knoevenagel condensation of aryl aldehyde with ethyl acetoacetate led to the formation of α, β unsaturated carbonyl compound formation followed by the addition of phenyl hydrazine and cyclisation. All the above processes are efficiently catalysed by DBUH-I_3 complexes with the green chemistry principle.

Firstly, the solvent effect was studied in a multicomponent reaction of 3,4-dimethoxy benzaldehyde, phenyl hydrazine and ethyl acetoacetate as selected as a model reaction to optimize the reaction condition (**Scheme 1**). The screening result of different solvents in DBUH-I_3 complex catalyst indicates ethanol solvent was found better for the synthesis of pyrazole (**Table 1**). We have optimized the process at various temperature and amount of catalyst. In general, polar solvents are better for the synthesis of pyrazole.

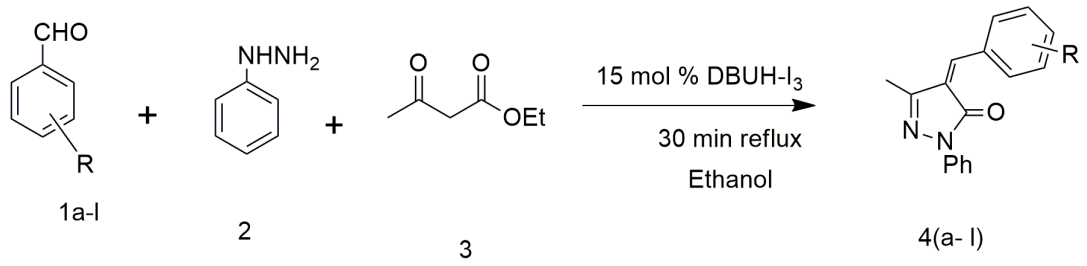


Scheme 1 : Screening of solvent for DBUH-I_3 catalyzed synthesis of 3-methyl-4-(3,4-dimethoxyaryl) methylene-pyrazole-5-(*4H*)-one

Table 1 : Screening of solvent for DBUH-I_3 catalyzed synthesis of 3-methyl-4-(3,4-dimethoxyaryl) methylene-pyrazole-5-(*4H*)-one[a]

Sr. No.	Name of solvent	% Yield[b]
1	Ethanol	86
2	DMF	84
3	DMSO	81
4	Acetonitrile	61
5	Acetic Acid	51
6	Toluene	63
7	$CHCl_3$	54
8	Dioxane	45

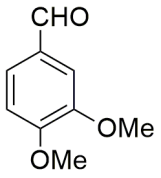
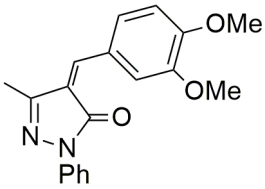
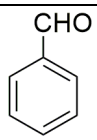
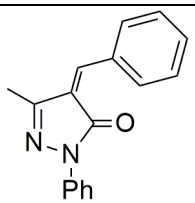
[a]Reaction Condition: 3,4-dimethoxy benzaldehyde (1 mmol), Ethyl acetoacetate (1 mmol), Phenyl hydrazine (1 mmol), Catalyst (15 mol %), ethanol (10 mL) Reflux 30 min. [b] isolated yield after purification.

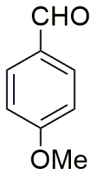
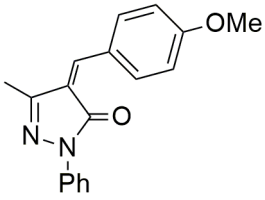
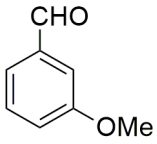
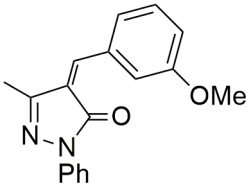
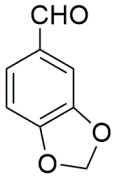
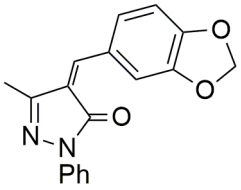
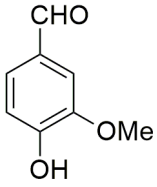
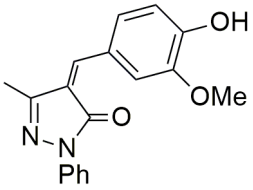
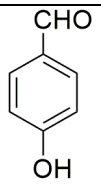
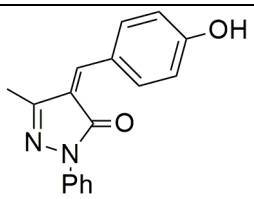
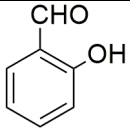
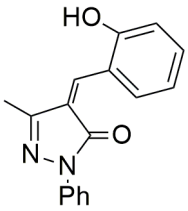
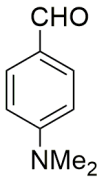
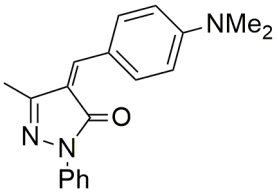


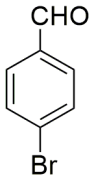
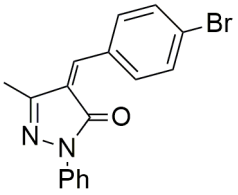
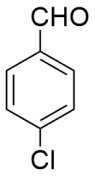
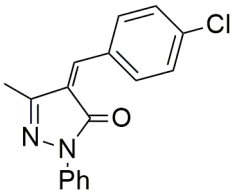
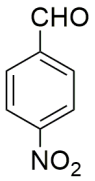
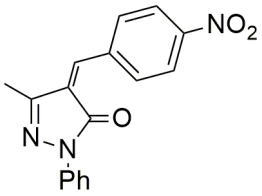
Scheme 2 : Synthesis of substituted arylidene pyrazole

In this work, DBUH-I_3 complex is explored as a catalyst for a three-component reaction to achieve the synthesis of 3-methyl-4-(aryl substituted) methylene-pyrazole-5-(*4H*)-one derivatives (**4a-l**) **(Scheme 2**). The multicomponent reaction of ethyl acetoacetate, phenyl hydrazine and substituted aryl aldehyde catalysed efficient synthesis of pyrazole. The aryl aldehyde bearing electron donating groups such as methoxy and amino more efficiently catalysed by DBUH-I_3 lead to the formation of product (**4a, 4c, 4e, 4f, 4g, 4i**) and aryl aldehyde bearing electron withdrawing group such as 3-methoxy and the nitro group also formed the product comparatively in lower yield form (**4d & 4l**). The halogen group bearing aryl aldehyde gets converted to pyrazole with moderate yield (**4j, 4k**) and ortho-substituted aryl aldehyde gave comparatively poor yield (**4h**). The substituted electron rich aryl aldehyde gives high yield than electron deficient aryl aldehyde. The product was purified by recrystallisation in ethanol and the yield reported. The product formation was confirmed by ^{1}HNMR, methyl signal (~2.25 δ) olefinic hydrogen singlet in aromatic region and corresponding ^{13}CNMR signal. The yield was reported after purification and physical constant compared with reported derivatives. The proposed multicomponent reaction catalysed by DBUH-I_3 for the synthesis of arylidene pyrazole was efficiently applicable to electron rich aryl aldehyde (**Table 2**).

Table 2 : Synthesis of 4-arylidine-3-methyl-1-phenyl-pyrazol-5(4H)-one[a]

Entry	**Arylaldehyde**	**Product (4)**	**% Yield[b]**	**Observed M. P.**	**Reported M. P.**
1		 4a	86	156-158℃	---
2		 4b	81	197-199℃	195-197℃[XX]

3		 4c	85	105-107℃	100-106℃[xiv]
4		 4d	75	228-230℃	227-228℃[xx]
5		 4e	88	158-160℃	---
6		 4f	78	165-167℃	160-164℃[xiv]
7		 4g	71	238-240℃	208-212℃ [xiv]
8		 4h	65	170-172℃	173-175℃[xx]
9		 4i	82	200-202℃	204-205℃[xx]

10		 4j	73	119-121℃	117-120℃[xvi]
11		 4k	71	198-200℃	201-203℃[xx]
12		 4l	62	195-197℃	192-195℃[xx]

[a] Reaction Condition: Arylaldehyde (1 mmol), Ethyl acetoacetate (1m mol), Phenyl hydrazine (1 mmol), Catalyst (15 mol %), ethanol (10 mL) reflux 30 min.
[b] Isolated yield after purification by recrystallisation in ethanol.

Conclusion: We have developed an efficient homogeneous catalysis system for the synthesis of arylidene pyrazole. The proposed protocol offers several advantages over traditional methods.

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