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SYNERGISTIC EFFECT OF ETHYL LACTATE/GLYCEROL: A NEW ROUTE FOR THE SYNTHESIS OF HEXAHYDRO-4H-INDAZOL-4-ONE AND ITS DERIVATIVES

Jyoti Baranwal,[a] Smriti Kushwaha,[a] Swastika Singh[a] and Archana Jyoti *[a]

[a] Department of Chemistry, S. S. Khanna Girls' Degree College, Prayagraj, Uttar Pradesh, India
***** *archanajyoti952@gmail.com*

Abstract: Here we report a new synthetic strategy based on the synergistic effect of ethyl lactate and glycerol in compliance with the criteria of green chemistry. This solvent system is very efficient and has several advantages such as involving shorter reaction time, formation of no side product, cost-effective, atom economy, operational simplicity, and high yield. The reusability of reaction media attracted much attention and it has the most promising potential as promoting media in many fields. To the best of our knowledge, this is the first catalyst-free synthesis of Hexahydro-4H-indazol-4-one.

Keywords: Synergistic effect, green solvent system, hexahydro-4H-indazol-4-one, N-containing heterocycles.

Introduction

The N-containing heterocyclic framework like pyrazolines[I-V] and indazolones[VI-IX] has a wide range of biological activities like antibacterial, anti-tubercular, anti-inflammatory, anti-oxidant, and anticancer. (Fig.1) Pyrazolines are employed as synthons in organic synthesis, and there are a plethora of pyrazoline synthesis methods in the literature.[X-XII] The research for novel, versatile, and more efficient techniques for the synthesis of pyrazolines and their derivatives is a very active research area. Because of their strong medicinal capabilities, organic chemists are highly interested in synthesizing fragments containing the pyrazolines-indazolone motifs. Due to the presence of the pyrazoline core in various bioactive compounds, the creation of pyrazoline derivatives has also gained increasing attention.[XIII]

Replacement of hazardous chemicals and reduction of unwanted steps by more eco-friendly alternatives is a matter of current interest.[XIV] Because solvents account for 80–90 percent of mass used in a typical fine/pharmaceutical chemical operating process, and therefore for the majority of waste generated in chemical labs and enterprises, the introduction of environmentally friendly solvents is an essential factor.[XV-XVI] Traditionally used solvents are synthesized from fossil fuels and have many harmful impacts on human health and the environment. Water,[XVII] polyethylene glycol,[XVIII] ionic liquids,[XIX] etc. have emerged as the most promising options for current solvent innovation over the last decade. However, their utilization has some drawbacks, pushing scientists to seek out alternative green solvents. In this

backdrop, the synergistic effect of ethyl lactate and glycerol emerged as a wonderful combination where glycerol act as a solvent and ethyl lactate acts as a promoter. Glycerol is produced as a byproduct when vegetable oils are used to make biodiesel fuel. It is a biodegradable, non-hazardous, non-toxic, non-volatile, and recyclable solvent.[XX] Ethyl lactate is a novel kind of green solvent that is an ester of lactic acid. It is a plant-based agrochemical solvent. The solvent is safe for the environment because it degrades gradually into carbon dioxide and water. Ethyl lactate shows remarkable properties such as high boiling point, low surface tension, low vapour pressure and has a high flash point and low volatility.[XXI-XXII] As a proton donor or acceptor, it can establish intramolecular and intermolecular hydrogen bonds.[XXIII] In oils, it can also cause Van der Waals interactions.[XXIV] As a result, ethyl lactate may dissolve in both polar and non-polar media, allowing it to recover compounds with a broad spectrum of polarity without the use of a co-solvent.[XXV] Ethyl lactate is widely utilized in the food, pharmaceutical, and cosmetic sectors because of its favorable hygroscopic and emulsifying qualities.[XXVI-XXVII]

Multicomponent reactions (MCRs) are an useful new approach in synthetic organic chemistry and drug discovery.[XXVIII–XXX] They provide a fast and efficient method for the synthesis of complex organic compounds by combining three or more substrates in a single synthetic operation, resulting in increased atom and time economy, as well as a reduced number of purification steps. [XXXI–XXXII] The current focus on green chemistry has highlighted the value of MCR even more.

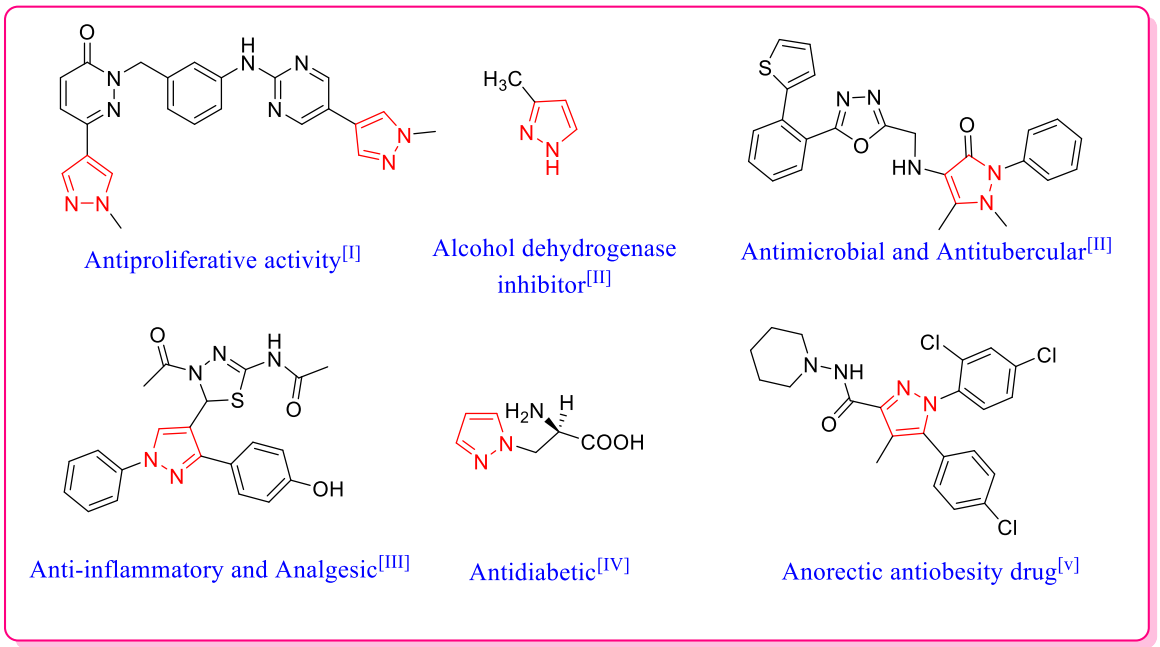
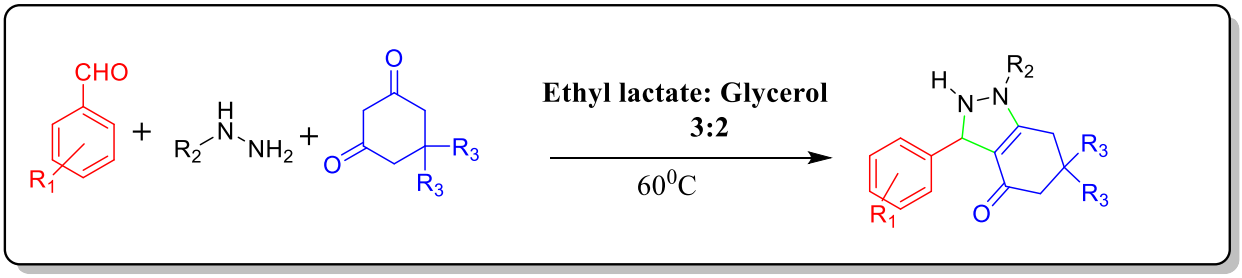


Fig. (1). Examples of some Pyrazoline containing biologically active molecules.

To the best of our knowledge, synthetic method of these compounds was previously reported by our research group[XXXIII] and in continuation of our research interest to synthesize heterocyclic molecules by using green methodology [XXXIV-XLIII] we again synthesize this compound by using ethyl lactate and glycerol as a green solvent and this is the only second report for the synthesis of this framework. We have provide a new and efficient, operationally simple, catalyst-free, ethyl lactate/glycerol synergistic effect assisted one-pot synthesis of Hexahydro-4H-indazol-4-one and its derivatives as part of our research work on the development of green synthetic pathways to biologically active heterocyclic compounds (Scheme 1).



(Scheme-1) The synthesis of fragments containing the Pyrazolines-indazolone.

Result and Discussion

The reaction was initiated by reacting the model substrates 4-nitrobenzaldehyde (**1a**, 1 mmol) with phenylhydrazine (**2a**, 1 mmol) and dimedone (**3a**, 1mmol) in water at room temperature (RT). The desired product was formed only in trace amount monitored by TLC even after 12 hr of stirring. (Table 1, entry 1) The experiment was repeated at 60^0C but no improvement was recorded probably due to the unstability of intermediate in water. (Table 1, entry 2) To overcome this problem, we have used different solvents (glycerol, ethyl lactate) for conducting this reaction. (Table 1, entries 3, 4, 5, 6) Further, we carried out a series of experiments using mixture of ethyl lactate and glycerol in different ratios, (Table 1, entries 7, 8, 9, 10,) and at different temperatures. (Table 1, entries 11, 12, 13) From all observations, we have found that the best result was obtained by using a combination of ethyl lactate and glycerol in 3:2 ratio at 60^0C. (Table 1, entry 9)

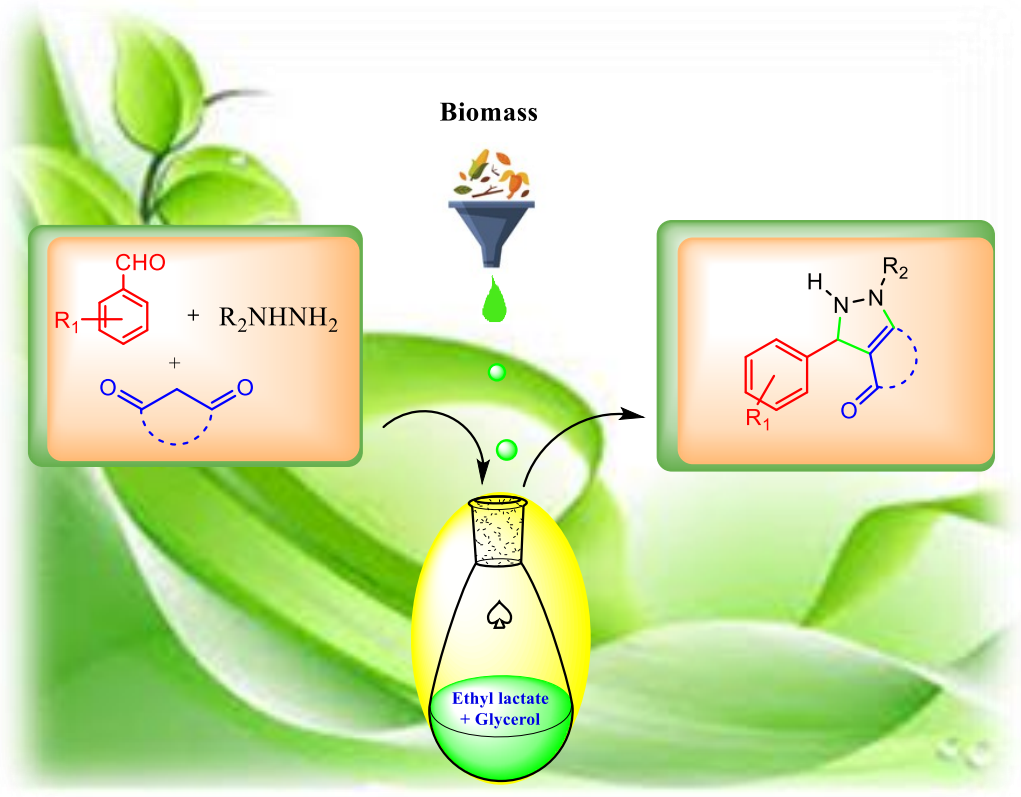
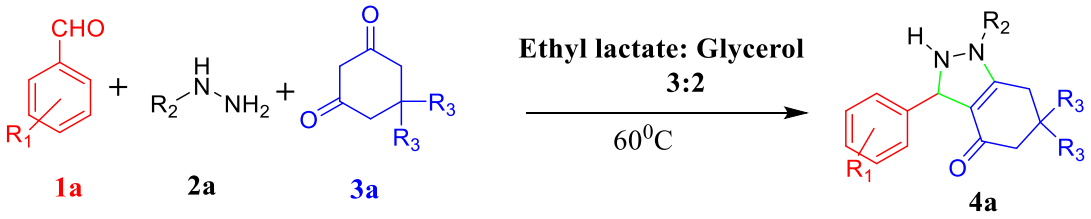


Table 1: Optimization of reaction conditions [a]



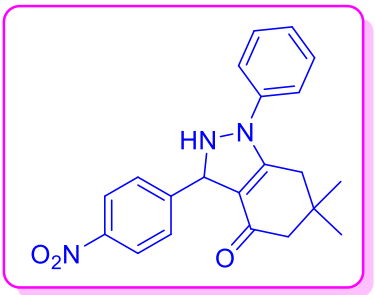
1a **2a** **3a** **4a**

Entry	Solvent	Temp.	Time	Yield (%)
1.	Water	RT	12 hr	Trace
2.	Water	60^{0}C	12 hr	Trace
3.	Glycerol	68^{0}C	6 hr	65
4.	Glycerol : Water	60^{0}C	6 hr	68
5.	Ethyl lactate	60^{0}C	4 hr	78
6.	Ethyl lactate: Water	60^{0}C	4 hr	74
7.	Ethyl lactate: Glycerol / 1:4	60^{0}C	3 hr	80
8.	Ethyl lactate: Glycerol / 2:3	60^{0}C	90 min.	85
9.	**Ethyl lactate: Glycerol / 3:2**	**60^{0}C**	**60 min.**	**92**
10.	Ethyl lactate: Glycerol / 4:1	60^{0}C	60 min	90
11.	Ethyl lactate: Glycerol / 3:2	70^{0}C	60 min	90
12.	Ethyl lactate: Glycerol / 3:2	80^{0}C	60 min	92
13.	Ethyl lactate: Glycerol / 3:2	90^{0}C	60 min	88

[a]All reactions were carried out with aldehyde (1 mmol), phenylhydrazine (1mmol), and dimedone (1mmol) in ethyl lactate/Glycerol (3:2, 5 ml).

Once the appropriate conditions for conducting this reaction were identified, the scope and efficiency of the developed synthetic process were explored using aldehyde, hydrazines, and dimedone with various substituents, to produce the respective indazolones in good-to-excellent yields. It was found that simple hydrazine produced the best results. There was a slight decrease in yield and a modest increase in reaction time in the case of phenylhydrazine. Due to the presence of the strongly electron-withdrawing nitro group on the phenyl ring, there was a substantial drop in yield and increase in reaction time when 2, 4-dinitrophenyl hydrazine was employed. The substituents on 1,3 diketone, on the other hand, had no effect on the yield or reaction time.

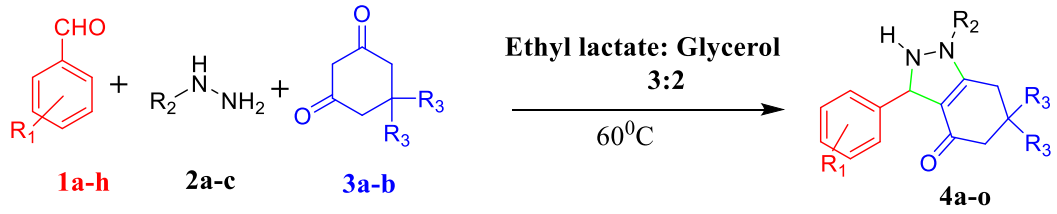
6,6-dimethyl-3-(4-nitrophenyl)-1-phenyl-2, 3, 6, 7-hexahydro-1H-indazol-4(5H)-one (4a): **[XXXIII]**



^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 1.76 (s, 6H), 2.53 (s, 2H), 2.58 (s, 2H), 4.26 (s, 1H), 7.54-7.70 (m, 5H), 7.87 (dd, 2H, J= 8.50 & 4.65 Hz), 8.26 (dd, 2H, J= 8.54 & 4.63 Hz), 10.44 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 34.6, 46.1, 63.3, 119.6, 122.7, 124.2, 125.7, 127.4, 128.2, 129.7, 132.6, 134.1, 136.3, 145.5, 168.2, 191.5; MS (ESI): m/z 363; found 364

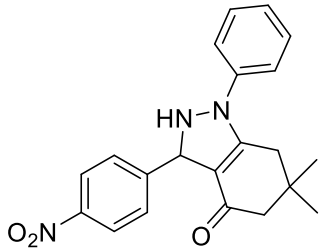
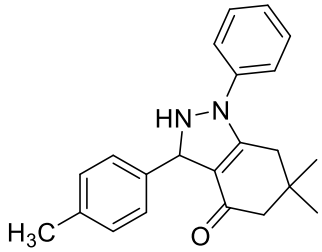
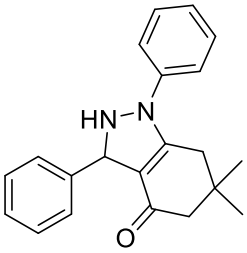
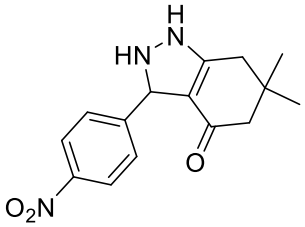
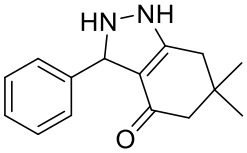
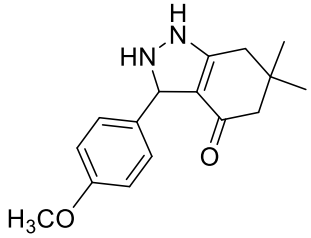
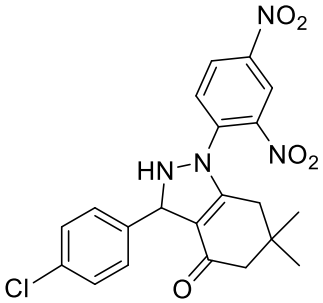
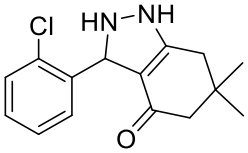
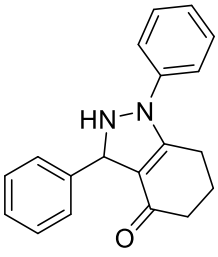
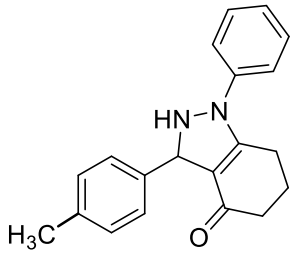
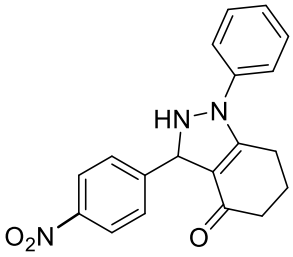
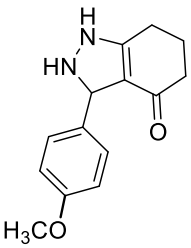
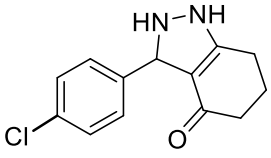
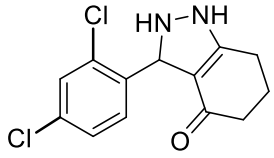
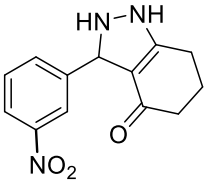
$[M+H]^+$; Anal.Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56; found C, 69.44; H, 5.89; N, 11.51.

Table 2: Substrate scope [a, b]



1a-h **2a-c** **3a-b**

1a R_1= 4-NO_2 **2a** R_2= Ph **3a** R_3= CH_3
1b R_1= 4-CH_3 **2b** R_2= H **3b** R_3= H
1c R_1= H **2c** R_1= 2,4-NO_2 Ph
1d R_1= 4-Cl
1e R_1= 2-Cl
1f R_1= 4-OCH_3
1g R_1= 3-NO_2
1h R_1=2,4-Cl

 **4a**: 92 %, 60 min.	 **4b**: 80 %, 80 min.	 **4c**: 84 %, 95 min.	 **4d**: 92 %, 60 min.
 **4e**: 88 %, 70 min.	 **4f**: 85 %, 70 min.	 **4g**: 75 %, 2 hr	 **4h**: 90 %, 75 min.
 **4i**: 90 %, 80 min.	 **4j**: 86 %, 90 min.	 **4k**: 88 %, 60 min.	 **4l**: 86 %, 85 min.
 **4m**: 86 %, 65 min.	 **4n:** 88 %, 65 min.	 **4o:** 90 %, 60 min.	

[a]All reactions were carried out with aldehyde 1a-h (1 mmol), hydrazine 2a-c (1 mmol), and 1,3-diketone 3a-b (1 mmol), in Ethyl lactate/Glycerol mixture (3:2).[b]Yields reported were isolated.

Mechanism

The plausible mechanism for the synthesis of hexahydro-4H-indazol-4-one derivatives is shown below in fig. 2. The reaction proceeds through the activation of C=O bond of benzaldehyde (1) via Glycerol, Ethyl lactate assisted formation of the anion I. Hydrazine (2) attack on the anion I through the Knoevenagel condensation to form intermediate II which undergoes Michael addition with dimedone resulting in cyclization, leading to the formation of the final product.

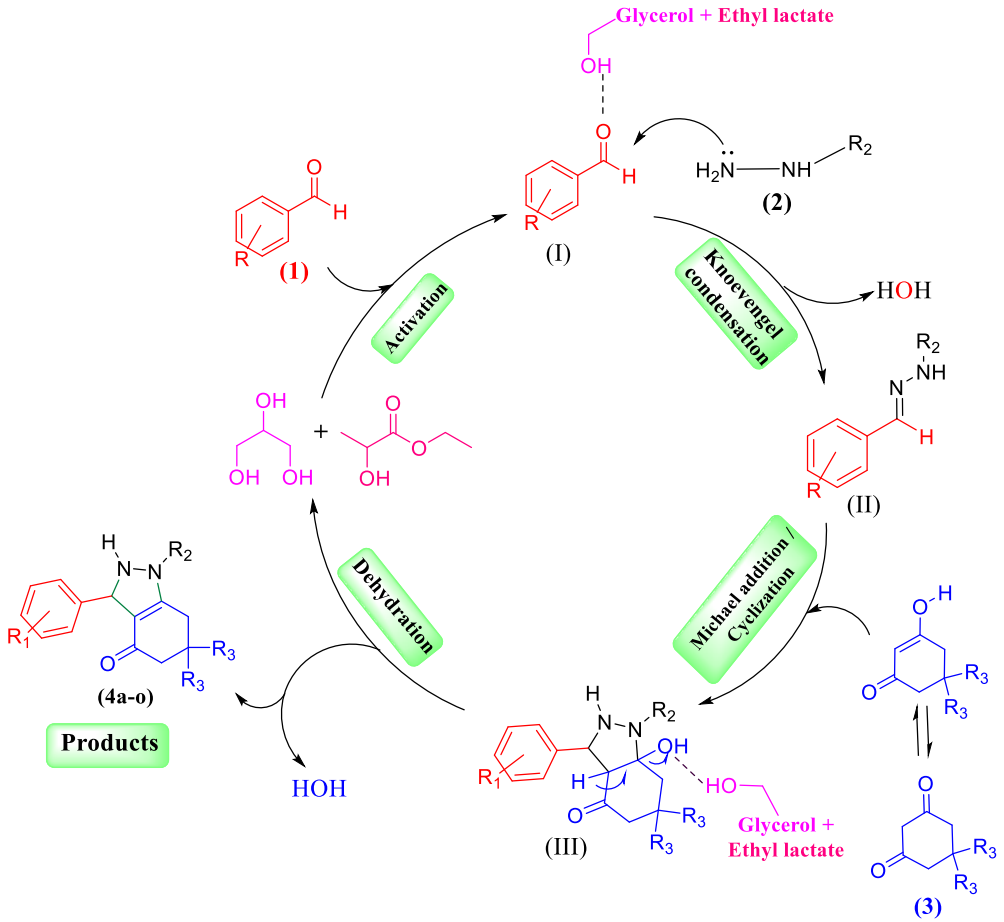


Fig. (2). Plausible mechanism for the formation of indazolones.

Recycling of the solvent

The recyclability of solvent was studied using the model reaction under the optimized conditions. Glycerol is separated from the reaction mixture by adding hot water because of its strong hydrophilicity. The glycerol dissolved in hot water, but the product remained water-insoluble. Using simple filtration process, the crude product was obtained. The same reactants were utilized in the reaction with the glycerol-containing filtrate. Furthermore, we observed that the product yield remained almost unaffected. As a result, glycerol's recyclability makes it an excellent solvent for MCRs in chemical synthesis.

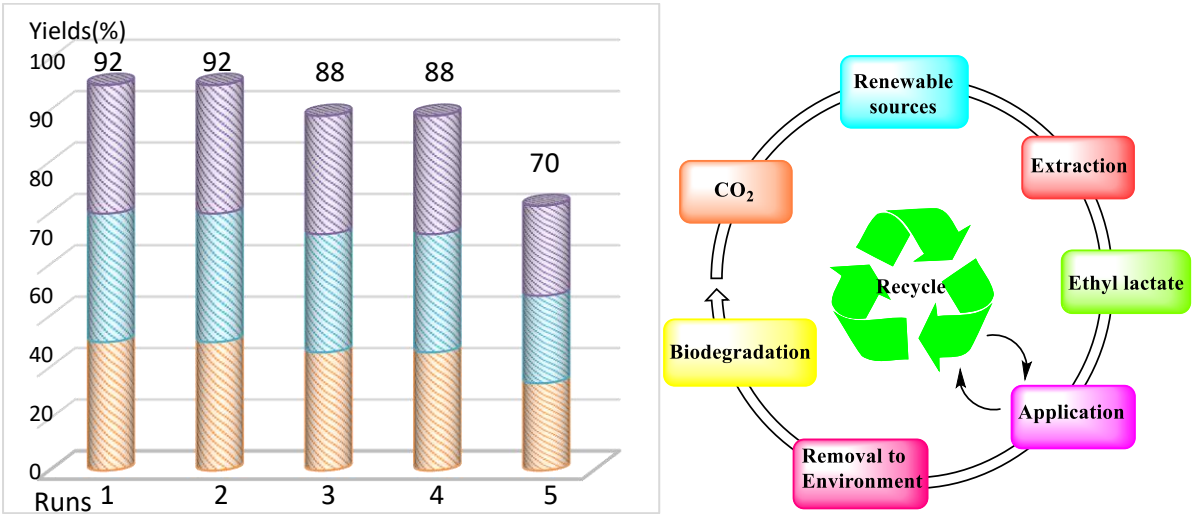


Fig. 3. Recyclability of solvent

Conclusion

In summary, we have developed a simple and efficient, Ethyl lactate/glycerol promoted green protocol for the synthesis of Hexahydro-4H-indazol-4-one motif, which are potentially privileged scaffolds. To the best of our knowledge this is the first catalyst free synthesis of Hexahydro-4H-indazol-4-one. Operational simplicity, use of mild reaction conditions, short reaction times, enabling use of a wide range of substrates, easy workup procedure, high atom economy and high yields make this method a preferred method for the synthesis of diverse Hexahydro-4H-indazol-4-one derivatives.

Acknowledgements

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