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Multi-component reaction (MCR): Synthesis of unsymmetrical dihydro-1H-Indeno [1, 2-b] Pyridines catalyzed by $ZrOCl_2$. $8H_2O$

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ABSTRACT

About 15mol% of $ZrOCl_2.8H_2O$ in ethanol has been found to be an efficient catalyst for the multi-component synthesis of dihydro-1H-Indeno [1,2-b] pyridines by the reaction between 1,3-indandione, ethylacetoacetate, aromatic aldehyde and ammonium acetate at reflux condition. Atom economy, excellent yields, simple workup and mild reaction conditions are some of the important features of this method.

Introduction

Multi-component reactions are important field of organic chemistry to make heterocyclic molecule in single step without the isolation of any intermediate and they are rapid, efficient, time-saving and atom-economical. Dihydropyridines are the important class of heterocyclic compound in biological as well as drug molecule. In particular, indenopyridines are one of the most important medicinal scaffolds for drugs such as nifedipine, nicardipine and amlodipine are effective cardiovascular agents for the treatment of hypertension [1]. The indenopyridine were developed initially as antihistamines [2] are useful inhibitors of spermatogenesis in animals [3] and showed fungicidal activity [4]. Hydrogenated indenopyridines have valuable therapeutic uses [5] and they also have potential anti-depressant activity [6]. Recent studies have been revealed that dihydropyridine exhibit several medicinal activity such as neuroprotectant, platelet anti-aggregatory activity and cerebral anti-schemic activity [7, 8]. There are several methods available to prepare indenopyridines such as two component reaction catalysed by acid and base [9,10], three component reaction under reflux condition [11], four component reaction under microwave irradiation[12], NaOH catalyzed synthesis under solvent free condition[13] and malononitrile catalyzed synthesis in ionic liquids [14]. However, previes method has some disadvantage like requirement of high temperatures, expensive catalysts, long reaction time and poor yield. Hence the development of better method for the synthesis of indenopyridines is challenging for organic chemist, we found an alternative simple method for indenopyridines and was described here.

Experimental

General

All chemicals used were purchased from Sigma-Aldrich and E-Merck chemical company. Melting points of all the compounds has been determined in open glass capillaries and are uncorrected. Infrared spectra (KBr, 4000-400cm-1) have been recorded on AVATAR-300 Fourier transform spectrophotometer. BRUKER AVANCE NMR spectrometer was used to record ^{1}H-NMR and ^{13}C-NMR spectra in $CDCl_3$ solvent using TMS as internal standard.

General synthetic procedure for dihydro-1H-Indeno [1,2-b]Pyridines (5a-5h)

The 1,3-indandione (1.0 mmol), aromatic aldehyde (1.0 mmol), ethylacetoacetate (1.0 mmol) and ammonium acetate (2.5 mmol) were thoroughly mixed in ethanol. To this reaction mixture $ZrOCl_2.8H_2O$ (15mol %) was added and was refluxed for 45-60 mins. The reaction was monitored by TLC using 7:3 hexane and ethylacetate mixture as eluent. After completion of the reaction the solid product formed was filtered, washed twice with water and finally dried in an air oven. The pure product was obtained by recrystalization from 6:4 hexane ethylacetate mixtures and all the products were obtained moderate to good yields.

Spectral data of compound 5a and 5b:

5a: m.p: 270-272^{o}C, yield: 80%, FTIR (KBr pellet) ν=3256, 1652, 1621, 1214, 860 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ=1.12 (t, 3H), 1.51 (s, 3H), 3.86 (q, 2H), 4.8(s , 1H), 6.6 (s, NH), 6.88 (d, 2H), 7.0 (d, 2H), 7.2- 82. (m,5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) 13.9, 19.3, 36.04, 58.0, 106.98, 124.11, 124.90, 127.66, 129.33,

5b: m.p: 212-214^{o}C, yield: 70%, FTIR (KBr pellet) ν=3256, 1658, 1630, 1201, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ=1.05 (t, 3H), 1.53 (s, 3H), 3.02 (s, 3H), 3.80 (q, 2H), 4.88(s , 1H), 6.26 (s, NH), 6.34 (d, 2H), 7.12-7.46 (m,6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) 13.60, 19.72, 36.32, 40.21, 59.00, 106.92, 109.14, 125.01, 125.70, 126.25, 1127.33, 130.11,

Results and discussion

The four component reaction involved in between 1,3-indandione, ethylacetoacetate, aromatic aldehyde and ammonium acetate in ethanol catalyzed by $ZrOCl_2.8H_2O$ afforded dihydro-1H-Indeno [1,2-b] pyridines by one-pot synthetic strategy (scheme-1). The product obtained was moderate to good yield and the detailed physical data was given in table-1. All the synthesized compounds were confirmed by comparing their melting point and spectral data with authentic product reported in literature.

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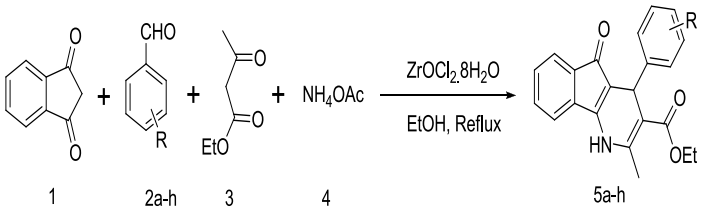
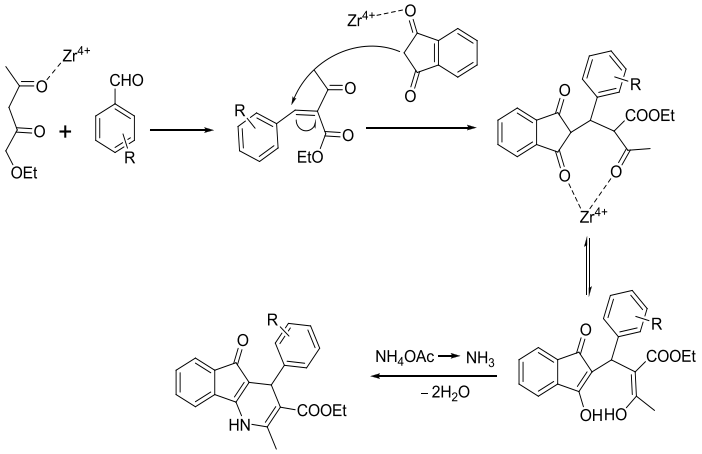


Scheme-1: Synthesis of dihydro-1H-Indeno [1,2-b]Pyridines (5a-5h)

We also examined the effect of various substituent and amount of catalyst on the model reaction (5a) and it was observed that aldehyde having electron donating group afforded good yield with shorter time than the aldehyde having electron withdrawing group. We changed the amount of catalyst on model reaction in order to determine the suitable mol% of catalyst and found that maximum yield was obtained when used 15mole% of the catalyst. Furthermore, we performed the above model reaction in different solvent medium and found that ethanol is best solvent to obtain good yield than the other solvents. We also found that there is no product formation when same reaction performed in room temperature and so decided that reflux condition is necessary for product formation.



Scheme 2: Proposed mechanism for the synthesis of dihydro-1H-Indeno [1,2-b]Pyridines (5a-5h)

Table-1: Physical data of dihydro-1H-Indeno [1,2-b]Pyridines (5a-5h)

Code	R (substituent)	Time (Min)	Yield (%)	M.p°C (Obs/report[15&16])
5a	H	40	80	270 (272)
5b	4-OMe	40	70	210 (214)
5c	2-OH	40	75	235 (238)
5d	4-Me	40	60	166 (163)
5e	4-Cl	60	75	210 (213)
5f	4-NO_2	60	70	214(216)
5g	3-OMe, 4-OMe	45	75	122 (123)
5h	3-OH	50	70	230 (236)

Table-2: **Synthesis of 5a in the presence of various mol% of $ZrOCl_2.8H_2O$**

Entry	Catalyst (mol %)	Time (min)	Yield (%)
1	5	20	70
2	10	15	72
3	15	10	87
4	20	20	80

Table-3: **Synthesis of 5a in different solvent medium with 15% of the $ZrOCl_2.8H_2O$**

Entry	Solvent	Time (min)	Yield (%)
1	Water	120	50
2	Acetonitrile	60	35
3	Ethanol	40	80

Conclusion

We described a simple, efficient, and eco-friendly synthetic protocol for the synthesis of dihydro-1H-Indeno [1,2-b]Pyridines catalyzed by $ZrOCl_2.8H_2O$. The advantages of our methods are short reaction time, cheapest, readily available catalyst and simple purification method.

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