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One Pot and Three Component Synthesis of 4-aryl-3-Methylisoxazole-5(4H)-One Derivative in the Presence of Sodium Hypophosphite

Amit P.Tayade[*1], Ramkrushna P. Pawar[2], Rajiv V. Khobare [3], Chandakant B.Mane [4] and Nitin P. Tayde [5]
[1,3] Department of chemistry , Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (MS) 431004
[2] Department of chemistry, Govt. Vidarbha Institute of Science and Humanities, Amravati (MS) 444604
[4] Department of chemistry, shri Vijaysinha Yadav Arts & Science college, pethvadgaon Dist Kolhapur(MS)
[5] Department of chemistry, Anuradha Engineering College, ChikhliI Dist Buldhana (MS)43201

Abstract:- sodium hypophosphite is also an effective catalyst use for one pot three component reaction contain ethyl acetoacetate react with hydroxylamine hydrochloride and various aromatic aldehyde, gives iso-oxazole. This reaction carried out in water at 800 C temperature . The product obtained with high yield in convenient time up to 1-2 hours.

Keywords:- *MCR, Aldehyde , Ethyl Acetoacetate , Hydroxylamine Hydrochloride , Sodium Hypophosphite, Green.*

I. INTRODUCTION

In 1850 strecker was introduce first multicompontents reaction (MCR). Multicomponent reaction gives high yield, mild reaction conditions, ecofriendly and reduces the time period. Other than this MCR gives three components reacton gives best result in short time with good yield . In one pot three components system easy constructional with organic substance hence it avoid the complicated process. The green media i.e. water is most suitable system. The synthesis of 4-aryl-3-methylisoxazol-5-(4H)-one derivatives can be prepared by using various reagents and catalyst in basic medium such as sodium sililcate (30), sodium benzoate(29), sodium azide(25), sodium saccharin(26), sodium citrate(27), sodium sulfide(29), Dowex 1-x8OH(28), boric acid(24).

Isoxazole scaffold structure is ad imp for heterocyclic which having favorable properties for pharmacy industry. It also show inhibitor (10) anticonvulsant (3) antifungal (12) antitumor (13) antioxidant (14) antimicrobial (16) anti-inflammatory (17) antiviral (18) antituberculsis etc. due to this imp of isoxazole derivaties , we are synthesis arylmethylene – isoxazole 5-4H-one in water ate high with catalyst.

The green media like water is most common and best solvent. it is safe ,non –toxic , clean , in -expensive and soluble in water. Sodium salt of hypophosphaous acid is odorless white crystal soluble in water clean in use and commercially easily available.

II. EXPERIMENTAL

➢ *Experimental Section*

All chemical were purchased from Merck, sdfcl were commercially available and were used as received without further purification. The melting points were measured by open capillary method incorrectly. IR data collected on (range 4000-400)). NMR Data recorded in DMSO –d6 as solvent by Bruker Avance Neo 500 MHz spectrometer.

➢ *General Procedure Foe the Synthesis of Azolactone*

The appropriate reaction mixture ethyl acetoacetate (2mmol), hydroxylamine hydrochloride (2mmol), aromatic aldehyde (2mmol) and NaH_2PO_2 in 15 ml water was stirred at 80 ^{0}C up to 1-3 hours as per required. After 1-3 hours stirring precipitate gradually is formed during reaction (monitored by TLC analysis). The precipitated was wash with 5% water and recrystallized using 95 % ethanol to afford the product.

All products are known compound and identified by physical data with reported in this literature.

➢ *Reaction*

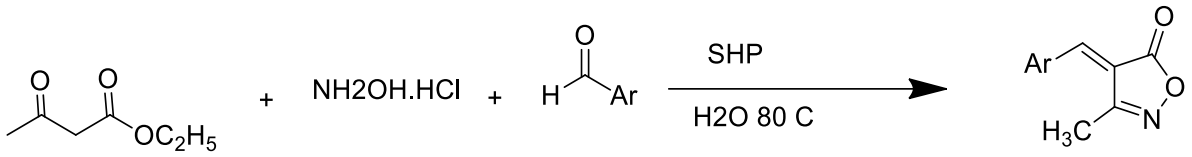

Fig 1:- one pot three component condensations of ethyl acetoacetate, hydroxylamine hydrochloride and aldehyde with sodium hypophosphite gives isoxazole.

Compound	Aldehydes	Time	Yield	Found mp
A1	4-$MeOC_6H_5CHO$	2	80	170-175
A2	2-OH C_6H_5CHO	2	80	190-195
A3	4-OH -$3CH_3C_6H_5CHO$	2	75	142-144
A4	4-Cl-C_6H_5CHO	3	trace	-------
A5	C_6H_5CHO	2	80	142-143
A6	3 $NO_3C_6H_5CHO$	3	-----	-------
A7	Furfural	2	70	230-235

Experimental Table 1:- synthesis of 3- methyl 4-arylmethylidene isoxazole from various aldehyde

Spectral data for selected product:
Characterization of compounds:

1) ENTRY A1-4-(4-methoxylbenzylidene)-3-methylisoxazole -5(4H)-one

Yellow crystal: mp-170-175 ^{0}C
1H-NMR (500 MHz-DMSO d)- δ 8.51 , δ 7.86 , δ 7.14, δ 3.90, δ 2.26
13 C –NMR – δ 168.46 , δ 164.11, δ 162.11, δ 151.07 , δ 136.75 , δ 125.66 , δ 114.53 , δ 55.70, δ 11.12

2) ENTRY A5- 4-(benzylidene-3- methylisoxazole -5(4H)-one

Yellow crystal: mp 142-144
1H-NMR (500MHz-DMSO d)- δ 8.42 , δ 7.94, δ 7.56-7.61 , δ 7.56 , δ 2.29
13 C –NMR – δ 167.64 , δ 162.00 , δ 151.41 , δ 132.28 , δ 130.99 , δ 128.51 , δ 118.69 , δ 11.11

III. RESULTS AND DISCUSSION

Water is one of the best solvents due to its properties like safe, eco-friendly, nontoxic, non flammable, clean, green, inexpensive etc. sodium hypophosphite is water soluble catalyst when react with ethyl acetoacetate, aldehyde with hydroxylamine hydrochloride gives arylmethylene isoxazol-5-(4H)-one derivatives via the one pot three component process. There was no product formation observed in the absence of solvent. The use of ethanol, acetone, dichloromethane and acetonitrile, water green media i.e. water gives best result, when sodium hypophosphite gives more yield. Reaction carried out in two parts, in first stage, ethyl acetoacetate reacts with hydroxylamine hydrochloride to gives ethyl 3-(hydroxyimino) butanoate. In second stage aldehyde react with above product gives Knoevenagel reactions gives 3 –methyl -4- arylmethylene isoxazole-5(4H) one as final product.

Entry	Solvent	Catalyst	Time	T ^{o}c	Yield %
1	Ethanol	10	3hr	Reflux/ 80	70
2	CH_2Cl_2	10	3hr	reflux	No reaction
3	CH_3CN	10	3hr	Reflux/80	52
4	WATER	10	2hr	80	80
5	Acetone	10	3hr	Reflux/80	Trace

Table 2:- effect of solvent and temp

Enter	Catalyst %	time	Temp	Yield
1	5	2.5	80	70
2	10	2	80	84
3	15	3	80	82
4	20	3	80	60

Table 3:- percentage of catalyst

IV. CONCLUSION

In conclusion, aromatic aldehyde were react with eaa and hydroxylamine hydrochloride in presence of sodium hypophosphite 10% catalyst in water all result are show in table. The aromatic aldehyde are with electron donating group gives the product with good in short time . ortho substitute group required more time and low yield for 2- hydroxyl benzaldehyde , while electron withdrawing group are not gives product. The one pot three compound systems gives 3 methyl 4arylmethalen isoxazole in water at 80 ^{0}C temperature in short time.

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CONFLICT OF INTEREST

The author have declared that no conflict of interest exists

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