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Synthesis of 2, 4, 6-Triaryl Pyridines under Solvent Free Condition

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Abstract

Synthesis of 2, 4, 6 triaryl pyridine under solvent free condition is described. Ammonium carbonate effectively catalyzed the reaction in good to excellent yields. Using this catalyst, the reactions could be carried out in a short period of time with very good yield of triaryl pyridines, up to 98% under solvent free condition. This catalyst is cheapest and readily available.

Key words: Triaryl pyridines, Solvent free condition, Ammonium Carbonate, Yield.

I. Introduction

One-pot multicomponent coupling reactions (MCRs), where several organic moieties are coupled in one step, for carbon-carbon and carbon-heteroatom bond formation is an attractive synthetic strategy for the synthesis of small-molecule libraries with several degrees of structural diversities[1]. Multiaryl substituted pyridine derivatives are recently reported as electron transport materials[2]. The highly substituted pyridine derivatives, like 2-amino-4-aryl-3,5-dicyano-6-sulfanylpyridines have significant and diverse medicinal utility. Essentially, these compounds serve as high potency agonists for the human adenosine receptors and act as potential therapeutic agents for the treatment of Creutzfeldt-Jacob disease, Parkinson's disease, hypoxia, asthma, cancer, kidney disease and prion disease[3-5]. Due to their π-stacking ability, some pyridines are used in supramolecular chemistry[6-8]. Previously, 2,4,6-triarylpyridines have been prepared by the condensation of 1,5-diketones with formamide-formic acid[9], reaction of (aroylmethylene) isoquinolinium ylide with α, β-unsaturated ketones[10-11], and reaction of N-phenacylpyridinium salts with α, β-un-saturated ketones in the presence of ammonium acetate[12]. More recently, many improved methods for preparation of 2,4,6-triaryl pyridines have been reported such as reaction of α-ketoketene dithioacetals with methyl ketones in the presence of ammonium acetate[13], reaction of N-phosphinylethanimines with aldehydes[14], addition of lithiated β-enaminophosphonates to chalcones[15], condensation of acetophenones, benzaldehydes and NH_4OAc in the presence of NaOH under solvent free condition[16], one pot reaction of acetophenones, benzaldehydes and NH_4OAc without catalyst under micro-wave irradiation[17]etc, a one-pot solvent free synthesis of 2,4,6 tri substituted pyridines by condensation of various aldehydes, ketones and ammonium carbonate in water under sealed condition have been attempted.

II. Experimental section

General procedure: To a mixture of P(substituted)- acetophenone**(I)** (4mmol) and P(substituted)-benzaldehyde **(2)** (2mmol), and$(NH_4)_2CO_3$ (4mmol)was refluxed in water at 150^0C under sealed conditions(seal tube). After the completion of reaction the reaction mixture is cooled to room temperature and poured in crushed ice, r 2,4,6-Tri(P-substituted Phenyl)pyridine yield (98%) is obtained as a crystalline solid (Scheme-1) the purity was checked by HPLC.

Synthesis of 2,4,6-Tri(P-hydroxy Phenyl)pyridine(3c): To a mixture of P-OH benzaldehyde**(II)** (2mmol), P-OH acetophenone**(I)** (4mmol) and$(NH_4)_2CO_3$ (4mmol)was refluxed in water for 6 hours at 150^0C under sealed conditions(seal tube). After the completion of reaction the reaction mixture is

cooled to room temperature and poured in crushed ice, yellow colour 2,4,6-tri(P-hydroxy Phenyl)pyridine yield (98%) is obtained as a yellow crystalline solid (Scheme-1), and its structure was confirmed by IR,^{1}H NMR,^{13}C NMR and Mass spectral data. m.p: >300^{0}C above.

IR($\nu_{max,}$ KBr):3472 ,1600,1583,1472,1440,1204,1162,1125,925,763,677; ^{1}H NMR (DMSO/ TMS, 90 MHZ) :6.84-6.94(6H,d), 7.76-8.15(8H,m), 9.80(1H,S) (Fig.1); ^{13} C NMR (DMSO/ TMS,22.5 MHz): 113.5, 115.5,115.9, 128.3, 128.7, 130.3, 144.9, 149, 156.3, 158.2 (Fig.2), Mass ion(m/e) :370.1[M^{+}] (Fig.3).

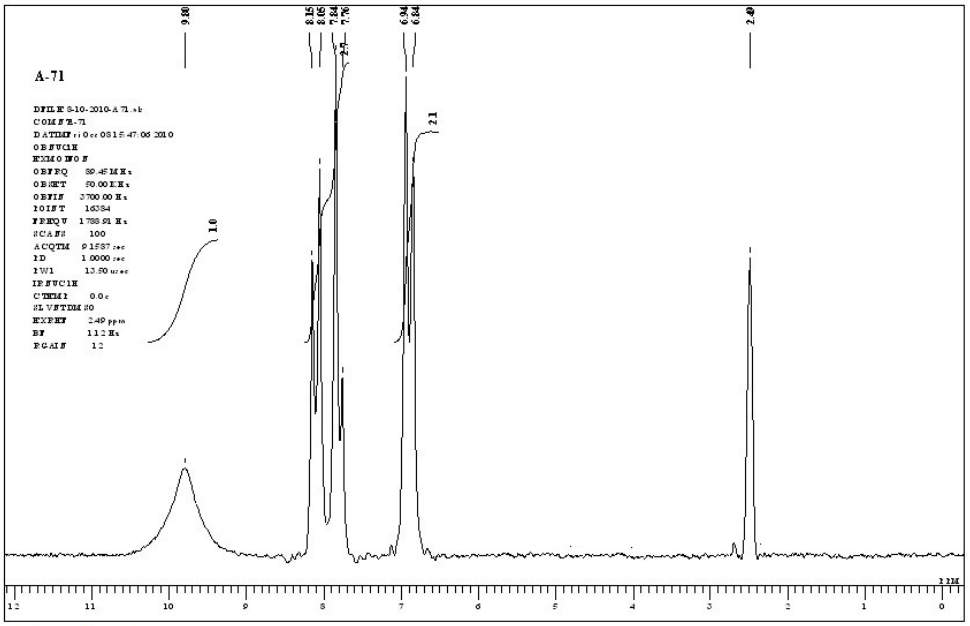


Fig.1 ^{1}H NMR Spectrum of compound 3c

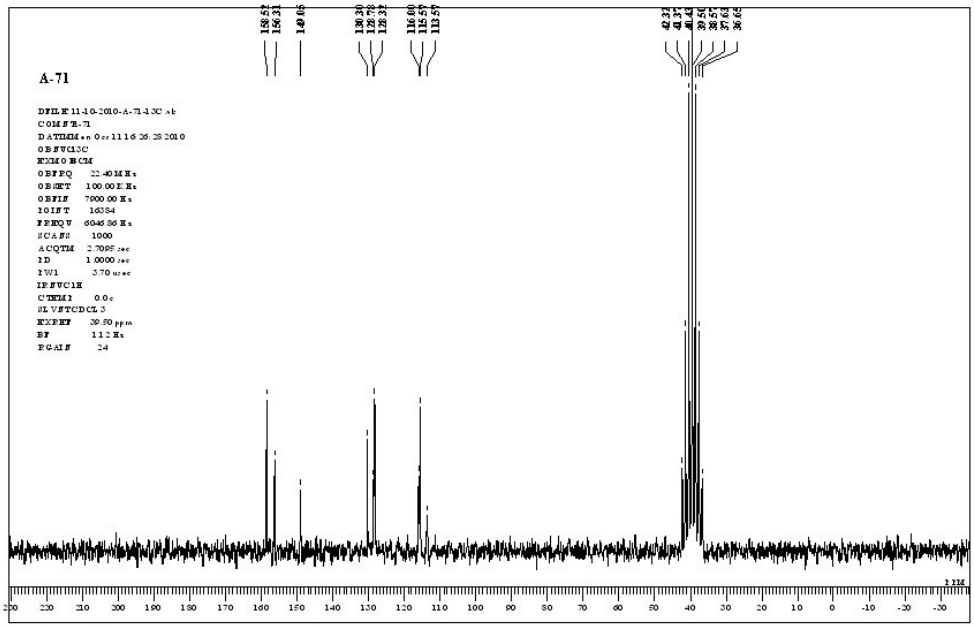


Fig.2 ^{13}c NMR Spectrum of compound 3c.

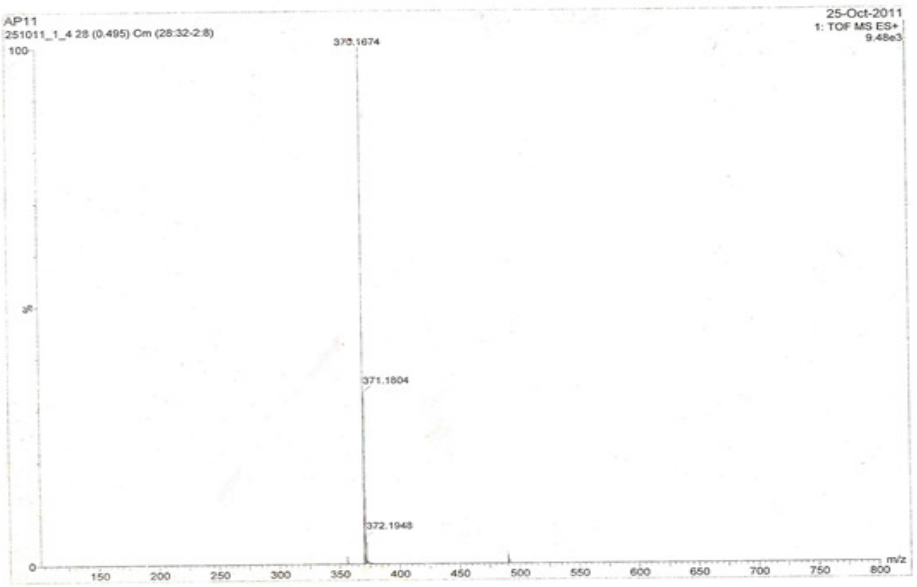
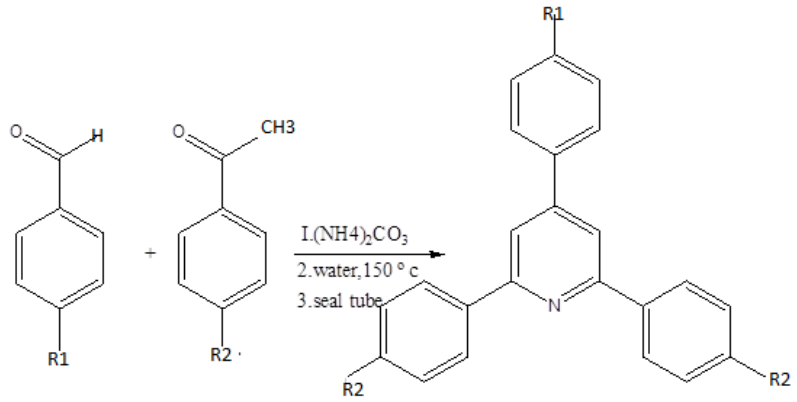


Fig.3 Mass Spectrum of compound 3c.

Scheme-1



(1) (2) 3a-3f

Table.1

Compound	R_1	R_2	Time(h)	Yield (%)	Melting point(^{0}C)(lit)
(3a)	H	H	4	97	134-136(135)[14]
(3b)	Cl	H	4.5	95	127-129(126-129)[14]
(3c)	OH	OH	6	96	>300
(3d)	CH_3	CH_3	5	90	177-178(178-180)[16]
(3e)	OCH_3	H	6	96	99-100(98)[18]
(3f)	Cl	Br	5.5	94	>205
(3g)	NO_2	Br	5	85	>210

III. Results and Discussion

Synthesis of triaryl pyridines by a one pot condensation of aldehyde, ketone and $(NH_4)CO_3$ under solvent free condition (Scheme.1). High yield (97%) was obtained with benzaldehyde and acetophenone. To evaluate the scope and limitations of the methodology, reactions were carried out with various substituted benzaldehydes including both electron donating and electron withdrawing substituents at para position of the aromatic ring (Table 1). The results showed that there is no adverse effect of substituents, either electron donating or electron withdrawing, on the aromatic ring of benzaldehyde or acetophenone on the product yield. In the case of all the aldehydes, very high yields (>85%) were obtained in comparatively less time (4 - 6. h). All the products were characterized by comparing melting points with those of the reported compounds. The reaction conditions such as temperature, time were optimized. Temperature was optimized by varying the temperature from 40˚C - 160˚C, optimum temperature obtained was 150˚C.

The effect of various ammonia sources was studied. Effect of the different ammonia derivatives on yield of the product were checked, maximum, yield was obtained for $(NH4_{)2}CO_3$. The mechanism of triaryl pyridine synthesis is as shown in Scheme 2. First step involves the condensation of ammonia with a molecule of chalcone and Michel addition of ammonia to the second molecule of chalcone leads to the formation of 2,4-diaryl-1-azadiene 3 and the 1:1 adduct 4 probably undergoes a formal [4 + 2] cycloaddition to form tetra hydro pyridine intermediate 5. Dehydration to dihydropyridine intermediate 6 and then oxidative aromatization with removal of the benzyl side chain would yield 2,4,6-triarylpyridine. According the mechanism, the role of $(NH_4)_2CO3$ as nitrogen source and carbonic acid is formed as by product, the reaction is catalyzed by acid.sence

The main advantages of the present method in the synthesis of triarylpyridines are that they are clean reactions without any side product under solvent free condition and workup does not require column chromatography.

IV. Conclusion

A mild, efficient and environmentally friendly approach for the synthesis of 2,4,6-trisubstituted pyridines via cyclo condensation of aromatic ketones with aromatic aldehydes and ammonium carbonate catalyst has been developed. The tri substituted pyridines were produced with 100% selectivity without formation of any other side product. The green context of the reaction is the use of non-corrosive catalyst under solvent free reaction condition and workup procedure does not require column chromatography.

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