Synthesis of Triaryl Pyridinium Derivatives under Silica Supported Approach and Their Applications

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Abstract: Substituted triaryl pyridinium salts are synthesized by one pot multiple components reaction under conventional/solid phase routes. Triaryl pyridinium salts showed effective photo responsive properties in alkaline medium. We have examined the catalytic activities of synthesized pyridinium salt for preparation of quinoline and its derivative under conventional/solid supported approach.

Keywords: Multiple approch, Photo response, Solid phase, One pot reaction, Optimization, Hantzsch reaction.

INTRODUCTION

One pot multicomponent reactions are become manifest as an efficient and important tool in drug discovery with rapid creation of several multiple bond with minimal waste [1, 7]. Beginelli and Hantzsch reactions played crucial role in medicinal organic chemistry owing to their pharmacological applications [8]. Some of the polyhydroquinoline are used as an antiatherosclerotic, antitumor, hepatoprotective, geroprotective and tyrosine kinase inhibitors [9, 18]. Simple and substituted pyridine ring systems are very important precursors due to their multiple applications such as anaesthetic, anticonvulsant, antimalarial and vasodilator [19, 20].

Some of the triaryl pyridine derivatives are acted as new therapeutic drug because of their π-staking aligns with H-bonding ability [21, 24]. Recent studies mentioned that, 3, 4, 5- triaryl pyridine system showed special medicinal interest due to its structural coincidence to the acceptable photodynamic cell and thiopyrylium cancer therapeutic moieties [26]. Substituted triaryl pyridine derivative are acted as novel materials for the conversion of solar energy into chemical reaction [27, 28].

Pravin and coworkers reported the synthesis of triaryl pyridine derivatives under solvent free condition by using heavy metal derivative such as bismuth triflate, which is used as a catalyst [25].

Herein, we wish to report the synthesis of *N*-alkylated triaryl pyridine derivatives under conventional and solvent free methodologies. We have examined the photo physical and chemical behaviors of synthesized triaryl pyridinium salts under different medium. We have studied the catalytic response of synthesized triaryl pyridinium salt for the preparation of quinoline derivatives under conventional/solid phase routes.

EXPERIMENTAL SECTION

Preparation of 2-methoxy-4-(2, 6-diphenylpyridin-4-yl) phenol 1

3.0g of 4-hydroxy-3-methoxy benzaldehyde (1.971×10^{-2} mmol; 1.0 equiv.) 4.97 g of acetophenone (4.140×10^{-2} mmol; 2.0equiv.) and 10g of NH_4OAc are dissolved (4.140×10^{-2} mmol; 1.0equiv.) in 50mL of acetic acid (4.140×10^{-2} mmol; 2.0equiv.) under refluxing condition for 3 h. to give 2-methoxy-4-(2, 6-diphenylpyridin-4-yl) phenol **1** in qualitative yield. Yield: 7.82g, (98%); Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 3.98 (s, 3H), 7.09 (s, 1H), 7.11-7.24 (d, 2H), 7.44 (s, 2H), 7.96-8.24 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 56.1, 109.7, 115.2, 116.7, 120.5, 127.1, 128.5, 129.0, 133.1, 137.1, 146.9, 150.1, 157.4; MS: m/e: 353.14; Anal. Calcd for: $C_{24}H_{19}NO_2$: C: 81.55; H: 5.38; N: 3.96; Found: C: 81.48; H: 5.30; N: 3.88.

General Procedure of *N*-Alkylation Reaction

2-methoxy-4-(2, 6-diphenylpyridin-4-yl) phenol **1** (7.158×10^{-3} mmol; 1.0 equiv.) is treated with benzyl bromide/4-nitro benzyl bromide (7.516×10^{-3} mmol; 1.05 equiv.) in the presence of 20 mL of dry acetonitrile under refluxing condition for 9-10 hours to give *N*-alkylated product of compound **2a**/**3a**.

2-Methoxy-4-(2,6-diphenyl-l-methyl benzyl pyridiniumbromide-4-yl) phenol 2a

Yield: 3.77g, (97%); Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 3.94 (s, 3H), 4.52 (s, 2H), 6.08 (s, 1H), 6.96-

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7.12 (d, 2H), 7.39-7.51 (m, 5H) 7.49 (s, 2H), 7.76-8.01 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 56.0, 76.7, 110.1, 114.9, 119.8, 123.4, 127.4, 127.3, 128.4, 128.5, 129.0, 130.1, 132.5, 138.5, 139.4, 145.2, 148.4, 157.4; MS: m/e: 524.45; Anal. Calcd for: $C_{31}H_{26}BrNO_2$: C: 70.93; H: 4.95; N: 2.66; Found: C: 70.85; H: 4.87; N: 2.58.

General Procedure for Anion Exchange Reaction

Triaryl pyridinium bromide **2a/3a** (1.716×10^{-3} mmol; 1.0 equiv.) is treated with various counter anions containing inorganic salt such as $NaBF_4$, K_4PF_6, and $LiCF_3SO_3$ (1.801×10^{-3} mmol; 1.05 equiv.) in the presence of 20 mL of deionized water at room temperature with stirring for 2 h. to give anion exchange product in 92-94% yield. Both metallic bromide and triaryl pyridinium salts are soluble in water. So the separation is not easier. Under these circumstances we have used Soxhlet extraction for separation with dry THF for 1 h under refluxing condition and confirmed by aqueous $AgNO_3$.

2-Methoxy-4-(2,6-diphenyl-l-methylbenzyl pyridinium hexafluorophosphate-4-yl) phenol 2b

Yield: 1.16g; (94%); Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 4.02 (s, 3H), 4.54 (s, 2H), 7.13 (s, 1H), 7.15-7.28 (d, 2H), 7.29-7.40 (m, 5H) 7.48 (s, 2H), 8.00-8.28 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 56.5, 65.0, 110.1, 115.6, 117.1, 120.9, 127.5, 127.7, 128.9, 129.0, 129.4, 130.5, 133.5, 137.5, 139.9, 147.3, 150.5, 157.8 ; MS: m/e: 563.14; Anal. Calcd for: $C_{29}H_{24}F_6NO_2P$: C: 61.79; H: 4.26; N: 2.48; Found: C: 61.71; H: 4.18; N: 2.40.

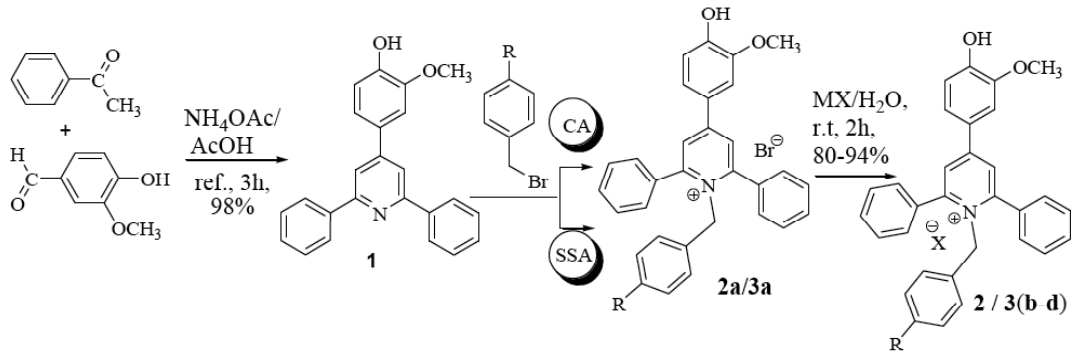
General Procedure for One Pot Preparation of Quinoline Derivatives

Equal molar concentration of 5, 5-dimethylcyclohexadienone (3.856×10^{-3} mmol; 1.05 equiv.), ethylacetoacetate (4.049×10^{-3} mmol; 1.05 equiv.), substituted aryl aldehyde (3.672×10^{-3} mmol; 1.0 equiv.) and NH_4OAc (4.251×10^{-2} mmol; 1.05 equiv.), are mixed in the presence of 1.053×10^{-4} mmol CH_3CN with optimized catalyst concentration of triaryl pyridinium bromide **3a** (1.053×10^{-4} mmol) for 50 minutes under refluxtion to give quinoline derivative **4(a-d)** in 80-96%

RESULTS AND DISCUSSION

Synthesis of substituted triaryl pyridine **1** by treating 4-hydroxy-3-methoxy benzaldehyde (1.971×10^{-2} mmol; 1.0 equi.) with acetophenone (2.0 equi; 4.140×10^{-2} mmol) in the presence of NH_4OAc (4.140×10^{-2} mmol; 1.0 equi.) and dissolved in 50 mL of acetic acid under refluxing condition for 3 hours to give the substituted triaryl pyridine 1 in 98% yield. Compound 1 (1.0 equi; 1.4×10^{-3} mmol) is treated with slight excess amount of benzyl / 4-nitro benzyl bromide in the presence of 20 mL dry CH_3CN under refluxing condition for 9-10 h. to give the *N*-alkylated pyridinium bromide 2a/3a in quantitative yield.

To reduce the toxicity during the *N*-alkylation reaction, we tried under solvent free silica supported



Compound	2a	2b	2c	2d	3a	3b	3c	3d
R	H	H	H	H	NO_2	NO_2	NO_2	NO_2
Counter anions	$Br^{\ominus}$	$PF_6^{\ominus}$	$BF_4^{\ominus}$	$CF_3SO_3^{\ominus}$	$Br^{\ominus}$	$PF_6^{\ominus}$	$BF_4^{\ominus}$	$CF_3SO_3^{\ominus}$

Reagent and conditions:Conventional approach (CA): MeCN, ref, 10 h,97%; Solid supported approach (SSA): Muffule furnace, 100 ^{0}C, 60-90 min., 94-96%

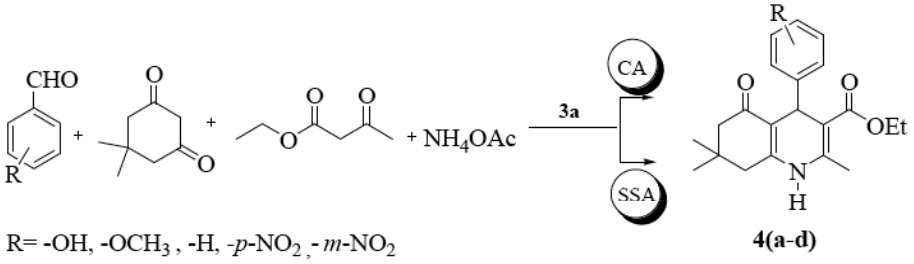
Scheme 1: Synthesis of substituted triaryl pyridinium salts under multiple routes.

method by Muffle furnace at 100 ^{0}C. The reaction is completed in 1 h. to give 96% yield. *N*-alkylation reaction under solid phase method is much superior than conventional method. 4-Nitro benzyl bromide reacts much faster than the benzyl bromide for *N*-alkylation reaction with substituted triaryl pyridines **1** (Scheme **1**).

Properties of ionic liquids differs based on their counter anions. So our interest is to exchange different counter anions from triaryl pyridinium bromide **1** to study their various physiochemical properties. We have carried out the anion exchange reaction with substituted triaryl pyridinium bromide **2a/3a** in the presence of different counter anion containing inorganic salts such as K_4PF_6 , $NaBF_4$ and $LiCF_3SO_3$ in the presence of 10 mL of deionized water under room temperature with stirring for 2 h. to give anion exchange products of compound **2/3(b-d)** in 80-94 % of yield. All synthesized compounds are characterized by both spectral and analytical data.

CATALYTIC ACTIVITIES

Triaryl pyridinium is prepared from easily available starting materials under conventional and solid phase Muffle furnace method. We have tried Hantzsch reaction with catalytic amount of our triaryl pyridinium salts in the presence of solvent and the absence of solvent. 4-Nitrobenzyl substituted triaryl pyridinium bromide **3a** showed excellent catalytic activity than the others derivatives. To optimize the catalyst concentration of triaryl pyridinium salt, the reaction is carried out with various concentrations such as 3.512 × 10^{-5} mmol, 7.024 × 10^{-5} mmol, 1.053 × 10^{-4} mmol and 1.404 × 10^{-4} mmol for quinoline preparation. From the results, we concluded that 1.053 × 10^{-4} mmol is the optimized concentration for preparation of polyhydro quinoline derivatives. While increasing the catalyst concentration from 1.053 × 10^{-2} mmol into 1.404 × 10^{-4} mmol there is no appreciable change. We have prepared various polyhydro quinoline under conventional and solid phase method assisted by different concentrations of triaryl pyridinium salt. The results are summarized in the Table **1** and compared the catalytic efficiency of triaryl pyridine derivative from available literature reports for Hantzsch reaction [8]. We have used very low concentration of present catalyst to modify the reaction rate (1.053 × 10^{-4} mmol) and the reaction is completed less than 25 min. whereas, same target molecules are prepared with Boehmite-SSA catalyst required greater than 200 min reported by Arash *et al* [29]. From these evidence, to the best of our knowledge compound **3** catalyst is the best to prepare polyhydro quinoline derivatives under non-toxic solid phase method.



Reagent and conditions: CA: CH_3CN/ 3a, ref, 50-120 min,80-96%; SSA: Muffule furnace, 100 ^{0}C, 20-45 min., 84-98%

Scheme 2: Synthesis of substituted quinoline derivative under multiple routes.

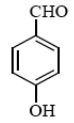
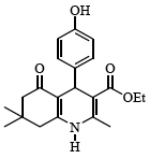
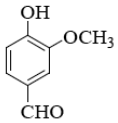
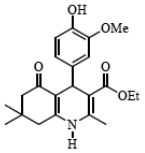
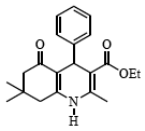
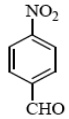
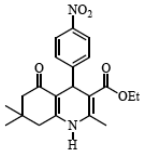
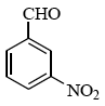
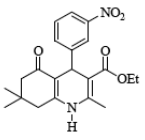
Photophysical Studies

Absorption and emission spectrum of substituted triaryl pyridine **1** is recorded in different medium such as an acidic, alkaline and neutral medium; Figure **1** showed that, in alkaline medium showed maximum intense peak with higher wave length, due to conversion of benzenoid into quinonoid formation and it's observed only under alkaline medium. So, we have extended the absorption and emission studies using strong and weak medium such as CH_3COOH, HCl, H_2O, NaOH and t-BuOK. Among these, photo responsive compound in NaOH solution showed maximum absorption due to effective transformation from benzenoid into quinonoid structure. Neutral and acidic condition does not showed any interesting absorption. Triaryl pyridinium derivatives are sensitive under alkaline medium. So absorption and emission studies are examined with various bases

Table 1: Different Concentration of Triaryl Pyridinium Salts for the Preparation of Quinoline Derivatives 2-3(a-d)

Catalyst	Concentration of triaryl pyridine salt											
	3.512×10^{-5} mmol				7.024×10^{-5} mmol				1.053×10^{-4} mmol			
	CA		SSA		CA		SSA		CA		SSA	
	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
2a	90	88	40	92	80	90	35	94	58	94	30	98
2b	100	86	45	90	95	87	40	91	70	92	35	97
2c	115	84	50	88	105	85	45	89	86	89	35	96
2d	120	80	55	85	110	83	50	87	92	90	45	94
3a	80	88	30	90	65	92	25	95	50	96	20	98
3b	92	83	35	85	77	88	30	90	56	92	25	96
3c	103	86	40	88	83	88	35	89	68	94	30	94
3d	110	84	45	86	75	90	40	91	72	92	35	92

Table 2: Preparation of Various Quinoline Derivatives in the Presence of Optimized Catalyst Concentration of Compound 3

S.No	Aryl Aldehyde	Target	1.053×10^{-4} mmol				M.p. (^{0}C)	
			CA		SSA		(Literature)	Obtained
			Time (min)	Yield (%)	Time (min)	Yield (%)		
1			40	87	20	91	(228-231)[30]	230-232
2			45	84	25	87	(205-206)[31]	203-205
3			50	85	30	90	(217-219)[32]	220-222
4			55	85	35	85	(242-244)[30]	243-245
5			55	82	40	89	(176-179)[33]	175-177

such as t-BuOK, NaOH, $Sr(OH)_2$, $Mg(OH)_2$ and Ag_2CO_3. Among these, NaOH medium showed maximum absorption than the others. Figures **(1 & 2)** showed emission spectrum of photo responsive

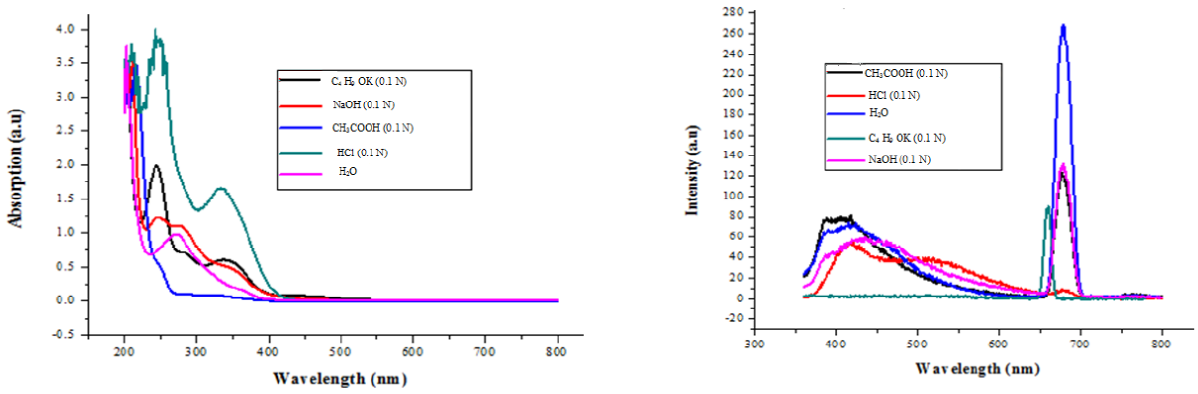


Figure 1: Absorption and emission spectra of triaryl pyridine **1** with different P^H values.

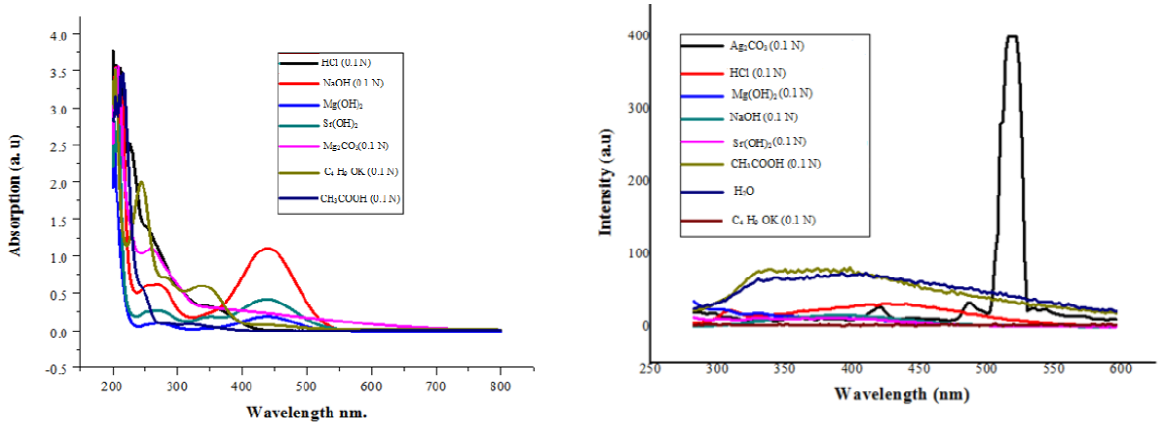


Figure 2: Absorption and emission spectra of triaryl pyridine **2a** with different P^H values.

moieties with different medium and there is no remarkable change of compound **1 & 2a**, where as under NaOH condition both the moieties showed emission peak at 350-450nm. Same concentration of NaOH solution with nitro substituted *N*-alkylated triaryl derivatives **3 (a-d),** there are no appreciable changes. When compared the λmax value between triaryl pyridine **1** and substituted triaryl pyridine **2/3 (a-d)** under NaOH medium, absorption is shifted from 320nm into 450nm; so *N*-alkylated triaryl pyridinium salts are more photo responsive moieties than the triaryl pyridine **1**.

CONCLUSION

We have prepared *N*-alkylated triaryl pyridinium derivatives under conventional and solid phase method. Solid phase method is much more effective than the conventional method due to greener, non-toxic, lesser reaction time with higher yields. Triaryl pyridinium derivatives showed maximum absorption and bathchromic shift in alkaline medium. Benzenoid into quinonoid transformation are studied using various alkali and alkaline earth metal hydroxide. Among these, NaOH showed interesting information. One-pot multicomponent reaction is which carried out in the presence of optimistic concentration of 4-nitrobenzyl triaryl pyridinium bromide **3a** showed excellent catalytic response while compared with available literature data.

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