BIFC and QFC Promoted Rapid and Cleaner Aromatization of 1,4-Dihydropyridines under Solvent-free Condition

Vajiravelu Sivamurugan,[a,b]* Ajayan Vinu,[c] Valiyaveettil Suresh,[b] Muthaiyahpillai Palanichamy[b] and Velayutham Murugesan[a]

[a]Department of Chemistry, Anna University, Sardar Patel Road, Chennai 600025, India
[b]Department of Chemistry, National University of Singapore, 3 Science drive 3, 117 543, Singapore
[c]ICYS Fellow, National Institute for Materials Science, 1-2-1, Tsukuba, Ibaraki305 0047, Japan
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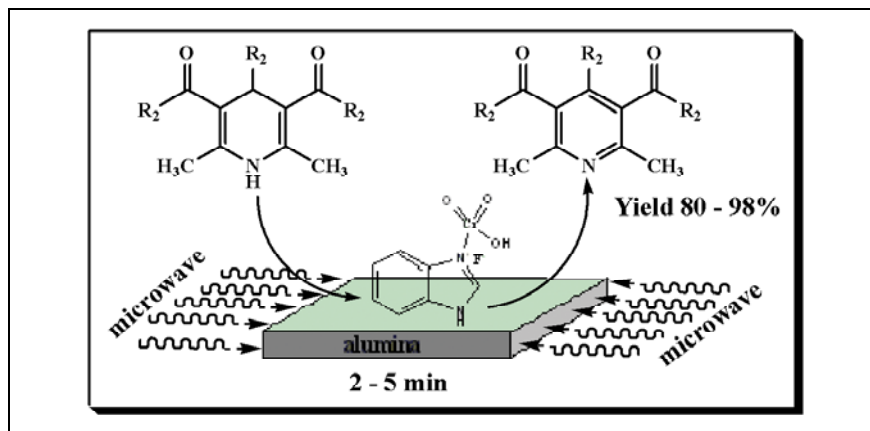
This communication expresses aromatisation of 1,4-dihydropyridines to pyridine derivatives with the help of alumina supported benzimidazolium fluorochromate (BIFC) and quinolinium fluorochromate (QFC) as oxidants under solvent-free microwave irradiation. Moderate to excellent yield (80-98%) of pyridine derivatives were achieved by this methodology.

INTRODUCTION

The oxidation of Hantzsch 1,4-dihydropyridines (1,4-DHPs) has attracted much attention because of its chemical and biological importance. In the human body, 1,4-DHPs are oxidised to corresponding pyridine derivative by Cytochrome P-450 present in the liver [1]. In addition 1,4-DHPs act as NADH mimics and serve as an active bio-redox system for unsaturated conjugated systems as well as carbonyl groups present in living organisms [2]. Furthermore, 1,4-DHPs are easily accessible raw materials for the preparation of libraries of pyridine derivatives [3].

During the past two decades numerous reagents, catalysts and methods have been developed for the aromatisation of 1,4-DHPs [4]. Even in recent years several groups have reported various methods for aromatisation including bismuth nitrate [5], barium manganate [6], ferric chloride [7], peroxydisulphate [8], iodobenzene diacetate (IBD) [9], zirconium nitrate [10], cobalt acetate assisted with H_2O_2 [11], urea nitrate and peroxydisulphate [12], potassium permanganate [13], nitric oxide [14], manganese dioxide [15], manganese triacetate [16], free-radical reagents [17], cobalt catalysed

autooxidation [18], bismuth subnitrate [19], methane sulfonic acid [20], *N*-hydroxyphthalimide/air [21], Mn-complex/H_2O_2 [22], $Tl(NO_3)_3$ [23], SeO_2 [24], $KBrO_3/SnCl_4$ [25], $Fe(ClO_3)_3/CH_3COOH$ [26], $BiCl_3$/zeolite [27], UV irradiation [28] and heterogeneous conditions [29-31]. The versatile synthetic utility of chromium reagents for oxidation in organic synthesis is still in practice. Some of the chromium reagents reported for the oxidation of 1,4-DHPs include pyridinium chlorochromate [32], carboxy-pyridinium chlorochromate [33], Magtrieve [34], tetrakis-pyridine cobalt(II)dichromate [35] and nicotinium dichromate [36]. The aromatisation of 1,4-DHPs using heterocyclic fluorochromates under solvent-free condition has not been developed so far. After a few initial steps [37,38], we report herein microwave promoted aromatisation of 1,4-DHPs using alumina supported quinolinium fluorochromate (QFC) and benzimidazolium fluorochromate (BIFC) under solvent-free condition.

The heterocyclic fluorochromates, QFC and BIFC, were prepared according to our earlier reported procedure [39-41]. The alumina supported chromium reagents were readily prepared by adding alumina to a solution of chromium reagents in acetone. After the addition, excess solvent was removed under reduced pressure [39]. The

alumina supported reagents so-obtained were dried at 100°C and stored in an air-tight container. The advantages of solid supported catalytic system provide easier workup and separation of products. In addition the solid support acts as an *in situ* adsorbent of the reduced chromium species lead to formation of products with acceptable purity.

The derivatives of 1,4-DHP were synthesized and characterized by our recent report [42,43]. In all the reactions 5 mmol of 1,4-DHP (**1 - 16**) was treated with 5.2 mmol of alumina supported QFC or BIFC and irradiated in household microwave oven (Scheme 1). The progress of the reaction was monitored by TLC analysis. After completion of reaction the reaction mixture was subjected to a short column of silica gel (5 cm) (100 – 200 mesh;

spectra which was due to the attachment of hydrogen at C-4 of pyridine ring. All other 1,4-DHPs were smoothly aromatized to the corresponding pyridine derivatives with excellent yield (98%). The electro positive or negative character of substituents has little effect on the reactivity of BIFC and QFC with only marginal differences in the yields was observed. This is a general trend in the oxidation of 1,4-DHP proceeding by the abstraction of hydrogen substituted in the fourth position of 1,4-DHP.

Table 2 shows the reactivity of BIFC and QFC supported over various inorganic solids. In order to evaluate the effect of solid supports on the reactivity of reagents, reaction of 5 mmol of 1,4-DHP (entry 6) and 5.2 mmol of BIFC or QFC on various inorganic supports under microwave irradiation was carried out. Alumina

Scheme 1
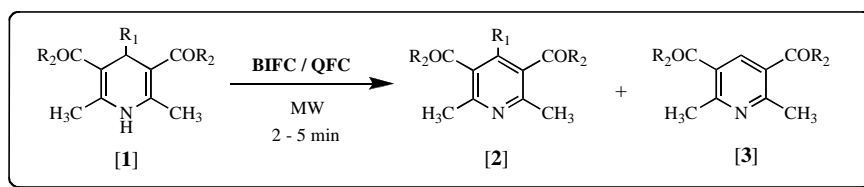
eluent: *n*-hexane:ethyl acetate 80:20) and the products were obtained with high purity. The results (Table 1) reveal that dealkylation also occurs in addition to aromatization when 1,4-DHP bears secondary alkyl group (entry 2) or benzyl group (entry 3) which are susceptible to form stable carbocation [32-34,36]. It was identified by the presence of a singlet at 9.4 ppm of the proton nmr

(neutral), silica gel, celite, montmorrilinite K10 (clay), zeolite (NaY) and Si-MCM-41 were used as solid supports in this study. The results convey that montmorrilonite, alumina and zeolite were found to be more active supports for the aromatisation of 1,4-dihydropyridines. This is due to high surface area and good adsorption capacity of these supports. Table 3 shows

Table 1

Oxidation of Hantzsch 1,4-Dihydropyridine Derivatives

Entry	R_1	R_2	QFC Time[a] (min)	QFC Yield[b,c] (%)	BIFC Time[a] (min)	BIFC Yield[b,c] (%)
1	CH_3	OC_2H_5	4	80	4	84
2	$(CH_3)_2CH^*$	OC_2H_5	4	78	3	80
3	$C_6H_5CH_2^*$	OC_2H_5	5	85	4	89
4	$4-NO_2C_6H_4$	OC_2H_5	3	90	2.5	93
5	$3-NO_2C_6H_4$	OC_2H_5	4	86	3	90
6	$3(OCH_3)4(OH)C_6H_3$	OC_2H_5	3	93	2.5	96
7	$3,4(OCH_3)_2C_6H_3$	OC_2H_5	3	92	3	98
8	2-Furyl	OC_2H_5	4	90	4	96
9	3-Indolyl	OC_2H_5	5	85	5	90
10	C_6H_5	OCH_3	3	86	2.5	93
11	$4-NO_2C_6H_4$	OCH_3	4	90	3	93
12	$3-NO_2C_6H_4$	OCH_3	4	88	3	90
13	$3(OCH_3)4(OH)C_6H_3$	OCH_3	4	90	3.5	95
14	$3,4(OCH_3)_2C_6H_3$	OCH_3	4	88	4	96
15	2-Furyl	OCH_3	5	85	4	88
16	3-Indolyl	OCH_3	5	85	4	90

[a]Reaction time monitored by TLC analysis; [b]Isolated yield after column chromatography; [c]The products were confirmed by comparison of FTIR and MS spectral analysis, and melting points and elemental analysis with reported literature; *Dealkylated product [3] was obtained

a comparative study of present methodology with earlier reports. The results reveal that the present methodology readily oxidises 1,4-DHPs and offers easier separation of products with acceptable purity in excellent yield of pyridine derivatives in comparison with other reports.

stage apparatus and are uncorrected. The FTIR spectra of the products were recorded on a Nicolet 360 FTIR as KBr pellets. The elemental analysis of the derivatives was carried out in a Heraeus CHNO rapid analyser. The mass spectra of products were recorded on a Finnigan Mat 8230MS spectrometer.

Oxidation of Hantzsch 1,4-dihydropyridines. A mixture of

Table 2

Effect of Solid Support

S. No	Support[a]	Reaction time[b] (min)		Yield[c] (%)	
		BIFC	QFC	QFC	BIFC
1.	Alumina	4	4	93	95
2.	Silica gel	4	4	90	94
3.	Celite	4	4	86	90
4.	Si-MCM-41	4	4	85	85
5.	NaY	4	4	90	93
6.	K10	4	4	89	93

[a]Model reaction: 5 mmol of entry 6 with 5.2 mmol of BIFC/QFC under MW irradiation; [b]Reaction time monitored by TLC analysis; [c]Isolated yield after column chromatography

Table 3

A Comparative Study of BIFC and QFC with other Oxidising Reagents

S. No	Oxidising agent*	Reaction Time (h)	Yield (%)	Ref.
1.	Quinolinium fluorochromate (QFC)	3 min	90	Present Work
2.	Benzimidazolium fluorochromate (BIFC)	3 min	95	Present Work
3.	$KMnO_4$ / Ultrasonics	5	80	14
4.	NO / C_6H_6	8	85	15
5.	MnO_2 / CH_2Cl_2 / Ultrasonics	5 min	90	16
6.	Magtrieve / $CHCl_3$ / reflux	3	90	35
7.	3-Carboxypyridinium chlorochromate (CPCC)/ CH_3CN / reflux	3	92	34
8.	Potassium peroxodisulphate / CH_3CN / reflux	1	90	9
9.	$Mg(HSO_4)_2$ / $NaNO_2$ / CH_2Cl_2 / r.t	15	80	32
10.	Nicotinium dichromate / CH_3CN / reflux	6.5	97	37
11.	$NaNO_2$ / $C_2H_2O_4$ / CH_2Cl_2	1.5	90	30
12.	Co-naphthenate / O_2 / $CHCl_3$ / reflux	17	91	19
13.	$BaMnO_4$ / C_6H_6 / reflux	2	92	7
14.	HNO_3 / bentonite / MW	4	87.8	38
15.	NH_4NO_3 / HNO_3 / bentonite / MW	5	80	30

*Model reaction: Aromatisation of 1,4-DHP derivative (Entry 4) with reported oxidising agents

Conclusions. The present investigation concludes that BIFC and QFC are valuable oxidising agents for aromatization of 1,4-dihydropyridines. The reactions are readily promoted by QFC and BIFC assisted with MW irradiation. The reactions afford more yield (up to 98%) than earlier reports. BIFC is found to be an active reagent for the oxidation compare to QFC. The alumina supported BIFC or QFC provides easier separation of products, process simplicity and products were obtained with excellent purity.

EXPERIMENTAL

Materials and Methods. All the materials used in this study were of high purity and purchased from E-Merck (Germany). The melting point of the products was determined on Raga hot

5 mmol of Hantzsch 1,4-DHPs (1 - 16) and 5.2 mmol of BIFC or QFC was thoroughly mixed and adsorbed on alumina (neutral). The alumina supported mixture was taken in an open Erlenmeyer flask (100 mL) and irradiated using a household microwave oven (model: IFB 17PM 1S) with a power range of 325 W and a pulse of 10 seconds. The progress of the reaction was monitored by TLC (silica gel precoated plate; *n*-hexane:ethyl acetate ratio = 80:20). After completion of the reaction, the mixture was diluted with dichloromethane and the product was seperated by column chromatography (*n*-hexane:ethyl acetate ratio = 80:20) and recrystallised from ethanol. The same procedure was adopted for all the reactions. The reaction time and yield are presented in Table 1.

Spectral and Analytical Characterisation of Pyridine Derivatives

Diethyl-2,6-dimethyl pyridine-3,5-dicarboxylate (2 & 3). FTIR spectrum (KBr, cm⁻¹): 3010 - 2975 (alkyl C-Hstr), 1730

(ester C=Ostr), 1615 (C=Nstr), 1535(aromatic C=C). m/z: 251 (100.0%), 252 (14.8%), 253.1 (1.8%). $C_{13}H_{17}NO_4$ (251.1): Calcd.: C, 62.14; H, 6.82; N, 5.57; O, 25.47. Found: C, 62.10; H, 6.78; N, 5.50; O, 25.42

Diethyl-2,6-dimethyl-4(4-hydroxy-3-methoxyphenyl)-pyridine-3,5-dicarboxylate (6). FTIR spectrum (KBr, cm^{-1}): 3025 - 2980 (alkyl C-Hstr), 1733 (ester C=Ostr), 1630 (C=Nstr), 1530 (aromatic C=C). m/z: 373 (100.0%), 374 (22.1%). $C_{20}H_{23}NO_6$ (373.15) Calcd.: C, 64.33; H, 6.21; N, 3.75; O, 25.71. Found. C, 64.30; H, 6.15; N, 3.70; O, 25.68.

Diethyl-2,6-dimethyl-4(3,4-dimethoxyphenyl)pyridine-3,5-dicarboxylate (7). FTIR spectrum (KBr, cm^{-1}): 3015 - 2980 (alkyl C-Hstr), 1725 (ester C=Ostr), 1620 (C=Nstr), 1525 (aromatic C=C). m/z: 387 (100.0%), 388 (23.6%). $C_{21}H_{25}NO_6$ (387.17) Calcd.: C, 65.10; H, 6.50; N, 3.62; O, 24.78. Found: C, 65.05; H, 6.45; N, 3.50; O, 24.60.

Diethyl-2,6-dimethyl-4(2-furyl)pyridine-3,5-dicarboxylate (8). FTIR spectrum (KBr, cm^{-1}): 3010 - 2975 (alkyl C-Hstr), 1730 (ester C=Ostr), 1615 (C=Nstr), 1535 (aromatic C=C). $C_{17}H_{19}NO_5$ (317.13): m/e: 317.13 (100.0%), 318.13 (18.8%), 319.13 (2.7%). Ele. Comp: Calcd. C, 64.34; H, 6.03; N, 4.41; O, 25.21. Found. C, 64.25; H, 6.10; N, 4.35; O, 25.10.

Diethyl-2,6-dimethyl-4(3-indolyl)pyridine-3,5-dicarboxylate (9). FTIR spectrum (KBr, cm^{-1}): 3025 - 2980 (alkyl C-Hstr), 1735 (ester C=Ostr), 1610 (C=Nstr), 1535 (aromatic C=C). $C_{21}H_{22}N_2O_4$ (366.16): m/e: 366.16 (100.0%), 367.16 (23.1%), 368.16 (3.4%). Ele. Comp: Calcd. C, 68.84; H, 6.05; N, 7.65; O, 17.47. Found. C, 68.70; H, 6.15; N, 7.50; O, 17.30.

Dimethyl-2,6-dimethyl-4(4-hydroxy-3-methoxyphenyl)-pyridine-3,5-dicarboxylate (13). FTIR spectrum (KBr, cm^{-1}): 3015 - 2980 (alkyl C-Hstr), 1715 (ester C=Ostr), 1615 (C=Nstr), 1535-1520 (aromatic C=C). $C_{18}H_{19}NO_6$ (345.12): m/e: 345.12 (100.0%), 346.12 (19.8%), 347.13 (3.1%). Ele. Comp: Calcd. C, 62.60; H, 5.55; N, 4.06; O, 27.80. Found. C, 62.50; H, 5.40; N, 4.10; O, 27.65.

Dimethyl-2,6-dimethyl-4(3,4-dimethoxyphenyl)pyridine-3,5-dicarboxylate (14). FTIR spectrum (KBr, cm^{-1}): 3010 - 2985 (alkyl C-Hstr), 1710 (ester C=Ostr), 1620 (C=Nstr), 1525 (aromatic C=C). $C_{19}H_{21}NO_6$ (359.14): m/e: 359.14 (100.0%), 360.14 (21.0%), 361.14 (3.4%). Ele. Comp: Calcd. C, 63.50; H, 5.89; N, 3.90; O, 26.71. Found. C, 63.35; H, 5.75; N, 3.84; O, 26.60

Dimethyl-2,6-dimethyl-4(2-furyl)pyridine-3,5-dicarboxylate (15). FTIR spectrum (KBr, cm^{-1}): 30105 - 2980 (alkyl C-Hstr), 1705 (ester C=Ostr), 1610 (C=Nstr), 1530 (aromatic C=C). $C_{15}H_{15}NO_5$ (289.1): m/e: 289.10 (100.0%), 290.10 (16.6%), 291.10 (2.4%). Ele. Comp: Calcd. C, 62.28; H, 5.23; N, 4.84; O, 27.65. Found. C, 62.15; H, 5.10; N, 4.68; O, 27.54.

Dimethyl-2,6-dimethyl-4(3-indolyl)pyridine-3,5-dicarboxylate (16). FTIR spectrum (KBr, cm^{-1}): 3010 - 2975 (alkyl C-Hstr), 1713 (ester C=Ostr), 1607 (C=Nstr), 1535 – 1520 (aromatic C=C). $C_{19}H_{18}N_2O_4$ (338.13): m/e: 338.13 (100.0%), 339.13 (20.9%), 340.13 (3.0%). Ele. Comp: Calcd. C, 67.44; H, 5.36; N, 8.28; O, 18.91. Found. C, 67.35; H, 5.26; N, 8.15; O, 18.80.

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