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An efficient synthesis of 2,4,6-triaryl pyridines and their biological evaluation

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ABSTRACT

A simple and efficient synthesis of 2,4,6-triaryl pyridines with different substituents at 2- and 6-positions were described by one-pot condensation of 4,4'-difluoro chalcone, substituted acetophenones and ammonium acetate in glacial acetic acid. The newly synthesized compounds were characterized by elemental analysis, LCMS, FT-IR, and NMR spectroscopic data. All the compounds were evaluated for their antimicrobial and antioxidant activities.

Keywords: 4,4'-Difluoro chalcone, substituted acetophenones, ammonium acetate, antimicrobial activity, antioxidant activity.

INTRODUCTION

Pyridine derivatives play an important role in biological systems. The pyridyl heterocyclic nucleus is a widespread sub-unit in numerous natural products resembling B_6-vitamin pyridoxine, pyridoxal, pyridoxamine and coa decarboxylase [1, 2]. Pyridines display variety of biological activities such as antimalarial, antioxidant, anticonvulsant, anesthetic, antioxidant, antibacterial and antiparasitic properties [3, 4]. They are also used as fungicides, pesticides, herbicides, dyes, additives and in qualitative and quantitative analysis [5-7]. Due to their π-stacking ability, some pyridines are used as versatile ligands in coordination and supramolecular structures [8, 9].

Several methods have been reported for the synthesis of pyridine with 2,4,6-triaryl substitution pattern (Krohnke pyridines) [10]. Successful synthesis of Krohnke type pyridines is reported through the reaction of N-phenacylpyridinium salts with α, β-unsaturated ketones in the presence of ammonium acetate [11]. However, the pyridinium salts have to be synthesized first, so this method is relatively expensive. Some of the other methods for the synthesis of 2,4,6-triaryl pyridines include, the one-pot reaction of acetophenones, benzaldehydes and NH_4OAc without catalyst under microwave irradiation [12], addition of lithiated β -enaminophosphonates to chalcones [13], reaction of a-ketoketene dithioacetals with methyl ketones in the presence of NH_4OAc [14], one pot condensation of acetophenones, benzaldehyde, ammonium acetate and solid sodium hydroxide in polyethylene glycol (PEG- 400) as green reaction solvent [15] and reaction between chalcones and ammonium acetate under solvent-free condition [16].

However, in most of the established methodologies, same substituent present in the 2- and 6-positions of pyridine or some expensive reagents were used for the preparation of pyridine with different substituents in the 2- and 6-positions. In view of the chemical and pharmacological importances of the 2,4,6-triarylpyridines and in continuation of our work on the synthesis of different derivatives of 4,4'-difluoro chalcone [17-22], it was planned to synthesize a series of 2,4,6-triarylpyridines with different substituents at 2- and 6-positions starting from 4,4'-difluoro chalcone by a new route.

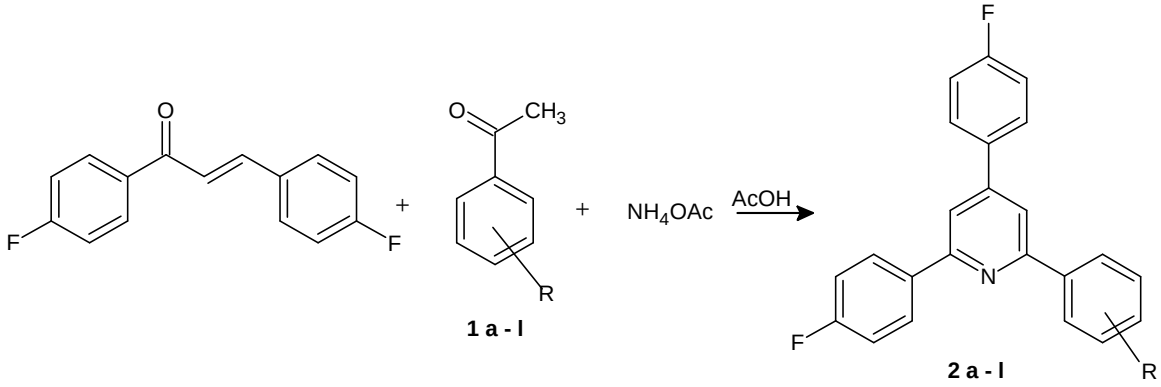
MATERIALS AND METHODS

2.1 Chemistry

Reagent grade chemicals were used without further purification. The substrates and solvents were used as received. Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds confirmed by thin layer chromatography using Merck silica gel 60 F_{254} coated aluminium plates. IR spectra were recorded on Shimadzu-FTIR Infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^1H(400 MHz) NMR spectra were recorded on a Bruker AMX 400 spectrometer, with 5mm PABBO BB -1H TUBES and ^{13}C (100 MHz) NMR spectra were recorded for approximately 0.03 M solutions in DMSO-d6 at 100 MHz with TMS as internal standard. LCMS were obtained using Agilent 1200 series LC and Micromass zQ spectrometer. Elemental analysis was carried out by using VARIO EL-III (Elementar Analysensysteme GmBH).

2.1.1 Procedure for the synthesis of 2, 4, 6-triaryl pyridines (2a-l)

A mixture of substituted acetophenone **1a-l** (10 mmol) and ammonium acetate (0.8 g, 11 mmol) was dissolved in 20 ml glacial acetic acid and refluxed for 1 hr. A solution of 4,4'- difluoro chalcone (2.44 g, 10 mmol) in 10 ml glacial acetic acid was added to the reaction mixture and further refluxed for 6 hrs. The reaction mixture was cooled to room temperature and the crude solid obtained was recrystallized from *N, N* - dimethyl formamide. The physical characteristics of the synthesized compounds were recorded in Table **1**.



Scheme 1: Synthesis of 2,4,6-triarylpyridines 2a-l

2.1.2 Spectroscopic data of synthesized compounds

(2a): IR(KBr): γ = 1601, 1506 (Pyridine ring), 1221(C-F), 822(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 7.34 (m, 5H, ArH), 7.48 (m, 2H, ArH), 8.11(q, 2H, ArH), 8.18 (s, 2H, Py-H), 8.31, 8,37 (2 × m, 4H, ArH). ^{13}C NMR (100.64 MHz, DMSO): δ = 164.27 (C-F), 161.82 (C-F), 156.51, 155.47 (PyC-Ar), 148.61, 148.54, 138.67 (ArC-Py), 135.16, 135.13, 134.07, 134.00, 129.74, 129.66, 129.30,129.24, 129.16, 128.74, 126.98, 116.40, 116.32, 116.23, 116.02, 115.81, 115.67, 115.46 (Ar-C). LCMS: m/z = 345.3 (M^++2).

(2b): IR(KBr): γ = 1602, 1504 (Pyridine ring), 1219(C-F), 819(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 7.34 (m, 4H, ArH), 7.52 (m, 2H, ArH), 8.12(m, 2H, ArH), 8.18 (s, 2H, Py-H), 8.34 (m, 4H, ArH). LCMS: m/z = 362.3 (M^++1).

Table 1. Characterization data of 2,4,6 triaryl pyridines (2a-l)

Compound	Mol. formula	R	Yield (%)	m.p. (ºC)	Elemental Analysis %, Found (Calculated)		
					C	H	N
2a	$C_{23}H_{15}F_2N$	4-H	86	175	80.23 (80.45)	4.39 (4.40)	4.01 (4.08)
2b	$C_{23}H_{14}F_3N$	4-F	84	205	76.40 (76.45)	3.89 (3.91)	3.81 (3.88)
2c	$C_{23}H_{14}ClF_2N$	4-Cl	85	225	73.05 (73.12)	3.74 (3.73)	3.70 (3.71)
2d	$C_{23}H_{14}BrF_2N$	4-Br	83	197	65.33 (65.42)	3.31 (3.34)	3.28 (3.32)
2e	$C_{24}H_{17}F_2NO$	4-OCH_3	79	214	77.11 (77.20)	4.54 (4.59)	3.72 (3.75)
2f	$C_{23}H_{14}F_2N_2O_2$	4- NO_2	81	272	71.10 (71.13)	3.61 (3.63)	7.16 (7.21)
2g	$C_{23}H_{16}F_2N_2$	4-NH_2	78	205	77.12 (77.08)	4.45 (4.50)	7.79 (7.82)
2h	$C_{23}H_{15}F_2NO$	4- OH	80	242	76.83 (76.87)	4.23 (4.21)	3.84 (3.90)
2i	$C_{23}H_{15}F_2NO$	3-OH	79	210	76.85 (76.87)	4.17 (4.21)	3.87 (3.90)
2j	$C_{23}H_{15}F_2NO_2$	2,4-$(OH)_2$	76	215	73.55 (73.59)	3.98 (4.03)	3.69 (3.73)
2k	$C_{23}H_{13}Cl_2F_2N$	2,4- $(Cl)_2$	82	173	66.96 (67.01)	3.14 (3.18)	3.32 (3.40)
2l	$C_{25}H_{21}F_2N$	3,4-$(CH_3)_2$	84	246	80.37 (80.41)	5.62 (5.67)	3.71 (3.75)

(2c): IR(KBr): γ = 1603, 1502 (Pyridine ring), 1223(C-F), 824(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 7.34 (m, 3H, ArH), 7.59 (m, 3H, ArH), 8.12(m, 2H, ArH), 8.19 (s, 2H, Py-H), 8.35(m, 4H, ArH). ^{13}C NMR (100.64 MHz, DMSO): δ = 164.24, 161.80 (C-F), 155.53, 155.27, 155.18 (PyC-Ar), 148.63, 137.41, 137.34 (ArC-Py), 135.05 (C-Cl), 134.17, 133.86, 129.70, 129.62, 129.20, 129.12, 128.96, 128.69, 116.70, 116.54, 116.34, 116.18, 115.97, 115.76, 115.62, 115.41 (Ar-C). LCMS: m/z = 379.1 (M^++2).

(2d): IR(KBr): γ = 1601, 1504 (Pyridine ring), 1224(C-F), 816(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 7.34 (m, 4H, ArH), 7.54 (m, 2H, ArH), 8.11(m, 2H, ArH), 8.18 (s, 2H, Py-H), 8.36 (m, 4H, ArH). LCMS: m/z = 425.3 (M^++3).

(2e): IR(KBr): γ = 2837 (-OCH_3), 1600, 1503 (Pyridine ring), 1216(C-F), 817(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 3.29 (s, 3H, OCH_3), 7.34 (m, 6H, ArH), 8.11(m, 2H, ArH), 8.19 (s, 2H, Py-H), 8.37(m, 4H, ArH). LCMS: m/z = 374.1 (M^++1).

(2f): IR(KBr): γ = 1600, 1506 (Pyridine ring), 1549 (NO_2), 1226(C-F), 811(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 7.34 (m, 4H, ArH), 7.56 (m, 2H, ArH), 8.09(m, 2H, ArH), 8.19 (s, 2H, Py-H), 8.29 (m, 4H, ArH). LCMS: m/z = 389.4 (M^++1).

(2g): IR(KBr): γ = 3310 (NH_2), 1740 (NH bending), 1604, 1507 (Pyridine ring), 1220(C-F), 821(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 7.34 (m, 4H, ArH), 7.52 (m, 2H, ArH), 8.09(m, 2H, ArH), 8.18 (s, 2H, Py-H), 8.37 (m, 4H, ArH), 12.21 (s, 2H, NH_2). LCMS: m/z = 359.3 (M^++1).

(2h): IR(KBr): γ = 3162 (OH), 1604, 1509 (Pyridine ring), 1224(C-F), 829(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 3.28 (s, 1H, OH), 7.34 (m, 6H, ArH), 8.11(m, 2H, ArH), 8.18 (s, 2H, Py-H), 8.36 (m, 4H, ArH). LCMS: m/z = 360.4 (M^++1).

(2i): IR(KBr): γ = 3167 (-OH), 1604, 1509 (Pyridine ring), 1224(C-F), 829(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 3.29 (s, 1H, OH), 7.34 (m, 6H, ArH), 8.11(m, 2H, ArH), 8.19 (s, 2H, Py-H), 8.37(m, 4H, ArH). LCMS: m/z = 360.5 (M^++1).

(2j): IR(KBr): γ = 3173 (-OH), 1602, 1504 (Pyridine ring), 1220(C-F), 823(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 3.29 (s, 2H, OH), 7.34 (m, 6H, ArH), 8.11(m, 2H, ArH), 8.18 (s, 2H, Py-H), 8.37(m, 4H, ArH). LCMS: m/z = 376.1 (M^++1).

(2k): IR(KBr): γ = 1601, 1506 (Pyridine ring), 1226(C-F), 817(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 7.34 (m, 4H, ArH), 7.54 (m, 2H, ArH), 8.09(m, 2H, ArH), 8.18 (s, 2H, Py-H), 8.28 (m, 4H, ArH). LCMS: m/z = 413.2 (M^++1).

(2l): IR(KBr): γ = 3067 (-CH_3), 1601, 1506 (Pyridine ring), 1226(C-F), 817(*p*- disbstituted aryl ring) cm^{-1}. ^1H NMR(400.23 MHz, DMSO): δ = 2.72 (s, 3H, CH_3), 2.88(s, 3H, CH_3), 7.32 (m, 3H, ArH), 7.76-8.57(m, 10H, ArH). LCMS: m/z = 372.4 (M^++1).

2.2 Biological Evaluation

2.2.1 Antimicrobial activity

The antimicrobial activity of synthesized compounds **2a-l** was carried out using agar well diffusion method [23-25]. The *in vitro* antimicrobial activity was carried out against 24 h culture of four bacterial strains Gram positive *Bacillus subtilis, streptococcus haemolytius* Gram negative**,** *Pseudomonas aeruginosa, Klebsiella pneumoniae.* Two fungal strains were *aspergillus niger and candida albicans*. The compounds were tested at 40 µg/mL concentration against both bacterial and fungal strains. DMSO was used as a vehicle. Ciprofloxacin and Fluconazole were used as standard drugs for comparison of antibacterial and antifungal activities respectively. The zone of inhibition was compared with standard drug after 24 h of incubation at 37 ^oC for antibacterial activity and 72 h at 25 ^oC for antifungal activity.

The MIC of all synthesized compounds **2a-l** was determined by a micro dilution method [25, 26]. The respective clinical strain was spread separately on the medium. The wells were created using a stainless steel sterilized cork borer under aseptic conditions. The synthesized compounds at different concentrations viz. 10, 20, 30, 40 and 50 µg were dissolved respectively in 25, 50, 75, 100 and 125 µL of DMSO and later loaded into corresponding wells. The zone of inhibition was compared with standard drugs after 24 h of incubation at 37 ^oC for antibacterial activity and 72 h at 25 ^oC for antifungal activity.

2.2.2 Total antioxidant capacity

The total antioxidant capacity of the synthesized compounds was evaluated by phosphomolybdenum method [27]. About 1 mL of compound solutions in DMSO (20 µg) was combined with 1 mL of reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate and 4mM ammonium molybdate). The tubes were capped and incubated in a boiling water bath at

95^0C for 90 min. After the samples cooled to room temperature, the absorbance of each solution was measured at 695 nm against reagent blank using spectrophotometer. The results were expressed in μM of ascorbic acid equivalent per mg of the sample.

2.2.3 DPPH radical scavenging activity

The scavenging effects of three synthesized compounds **2h, 2i** & **2j**, which have the phenolic –OH group, on the DPPH free radical, were evaluated by the reported methods [28, 29]. Compounds of different concentrations were prepared in DMSO, 1 mL of each compound solutions having different concentrations (20 μg, 40 μg, 60 μg, 80 μg and 100 μg) were taken in different test tubes; 4 mL of a 0.1 mM ethanol solution of DPPH was added and shaken vigorously. The tubes were then incubated in the dark room at room temperature for 20 min. A DPPH blank was prepared without compound, and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm was measured using a UV-visible spectrophotometer and the remaining DPPH was calculated. The percent of decrease in the absorbance was recorded for each concentration, and percent quenching of DPPH was calculated on the basis of the observed decrease in absorbance of the solution. The radical scavenging activities were expressed as the inhibition percentage and were calculated using the formula:

$$\text{Radical scavenging activity (\%)} = [(A_0 - A_1 / A_0)\times 100]$$

Where A_0 was the absorbance of the control (blank, without compound) and A_1 was the absorbance of the compound. The radical scavenging activity of ascorbic acid was also measured and compared with that of the different synthesized compounds. For all the compounds and standards, half inhibition concentration (IC_{50}) was calculated graphically.

RESULTS AND DISCUSSION

3.1 Chemistry

2,4,6-Triarylpyridines with different substituents in 2- and 6-positions were synthesized by the condensation of 4,4'-difluoro chalcone, substituted acetophenone and ammonium acetate in glacial acetic acid (Scheme **1**). The structures of the isolated products, **2a–l,** were confirmed by IR, NMR (^{1}H and ^{13}C), LCMS and elemental analysis.

Mechanistically, it is reasonable to assume that the reaction pathway may involve the initial condensation of ammonia with a molecule of acetophenone to form imine. Michael addition of the imine to the chalcone molecule leading to an adduct which was on cyclisation by intra molecular Michael addition reaction followed by aromatization to form 2,4,6-triarylpyridine.

The IR spectra of all the compounds showed stretching frequency near 1600 and 1500 cm^{-1} confirming the formation of pyridine moiety. In the ^{1}H NMR spectra of 2, 4, 6-triaryl pyridines, all the protons appeared in the aromatic region for halo substituted products. LCMS and ^{13}C-NMR spectral data supported the formation of **2a-l**. Elemental analysis also gave satisfactory results for all the compounds.

3.2 Biological evaluation

3.2.1 Antimicrobial studies

The synthesized 2,4,6-triaryl pyridines **2a-l**, were assayed for their antimicrobial activities against four bacterial strains Gram positive, *Bacillus subtilis, Streptococcus haemolytius;* Gram negative, *Pseudomonas aeruginosa, Klebsiella pneumoniae.* The compounds were also tested against two fungal strains *Aspergillus niger, Candida albicans* using agar well diffusion

method [23-25]. Further, their MIC values were determined against these organisms by micro dilution method [25, 26] using DMSO as a solvent. Ciprofloxacin and Fluconazole were used as standard antibiotics. All the tested compounds were emerged as active against all tested microorganisms (Table **2, 3**).

Table 2. Anti-microbial activity of synthesized compounds

Zone of inhibition in (mm)						
Compound	***S.aureus***	***B.subtilis***	***S.typhi***	***E.coli***	***A.niger***	***C.albicans***
	Antibacterial strains				**Antifungal Strains**	
2a	19	20	21	22	22	22
2b	19	19	21	22	22	21
2c	22	20	20	21	19	22
2d	19	19	18	19	19	20
2e	20	23	19	22	19	20
2f	20	22	18	21	21	18
2g	20	22	19	21	22	18
2h	22	20	21	20	21	18
2i	22	20	20	18	20	22
2j	22	19	20	19	20	22
2k	19	21	19	21	21	21
2l	21	22	19	22	22	21
Ciprofloxacin	22	23	21	22	-	-
Fluconazole	-	-	-	-	22	23
Control	0	0	0	0	0	0

Table 3. Minimum Inhibitory Concentration (MIC) of Synthesized compounds

MIC (µg/µL)						
Compound	***S.aureus***	***B.subtilis***	***S.typhi***	***E.coli***	***A.niger***	***C.albicans***
10-50 (µg)	**Antibacterial strains**				**Antifungal Strains**	
2a	30	30	30	40	40	30
2b	30	40	30	30	30	30
2c	30	30	30	40	30	30
2d	30	30	40	30	30	30
2e	20	30	30	30	30	40
2f	40	40	30	40	40	30
2g	30	20	30	40	30	40
2h	30	40	40	30	40	40
2i	40	40	40	40	30	40
2j	20	30	40	20	20	40
2k	30	40	40	40	20	30
2l	40	20	20	30	40	20
Control DMSO	0	0	0	0	0	0

The different substitutions on the triaryl pyridines moiety almost equally contribute to the antimicrobial activity comparable with that of standard drugs tested. However, based on this promising observation, it is immature to arrive at the conclusion on structure activity relationship aspect of these molecules and further evaluation is needed to use them for clinical use.

3.2.2 Evaluation of total antioxidant capacity

The total antioxidant activity for the synthesized compounds was evaluated by using phosphomolybdate method [27]. This assay was based on the reduction of Mo(VI) to Mo(V) in presence of the antioxidant compounds and the subsequent formation of a green

phosphate/Mo(V) complex at acidic pH, which was measured at 695 nm. The antioxidant capacity of the compounds **2a-l** was determined for 20 µg concentration. The antioxidant capacities of the compounds determined by phosphomolybdate method were expressed as µM of ascorbic acid equivalent/mg of the sample. The results were summarized in Table **4**.

From the Table **4**, compound **2d**, **2c, 2a** and **2i** showed moderate antioxidant capacity. Compound **2d** & **2c** reduces Mo(VI) to Mo(V) in better way due to the presence of –Br and –Cl group.

Table 4. Total antioxidant activity of synthesized compounds

Sample No.	**Total Antioxidant activity** (µM equivalent of ascorbic acid per mg of the sample)
2a	5.87±0.067
2b	2.82±0.045
2c	7.46±0.058
2d	8.52±0.042
2e	4.15±0.085
2f	1.63±0.025
2g	1.94±0.036
2h	3.05±0.054
2i	5.83±0.074
2j	3.62±0.028
2k	2.60±0.064
2l	2.47±0.035

3.2.3 DPPH radical scavenging activity

A rapid, simple and inexpensive method to measure antioxidant capacity of substances involves the use of the free radical, 2,2-Diphenyl-1-picrylhydrazyl (DPPH). DPPH is widely used to test the ability of compounds to act as free radical scavengers or hydrogen donors. Antioxidants tested on DPPH were also found extremely effective in cell systems. This simple test further provides information on the ability of a compound to donate electrons during antioxidant action [28, 29]. The radical scavenging mechanism is based on the transfer of H-atom from the phenolic –OH group of 2,4,6-triaryl pyridines to DPPH radical to form DPPH-H.

All the three tested synthesized compounds **2h, 2i** & **2j**, which have the phenolic –OH group, scavenged DPPH radical significantly in a concentration-dependent manner. The phenolic –OH group which can donate hydrogen atom in compounds **2h, 2i** & **2j** may contribute to the radical scavenging activity. 50 % Inhibition concentration (IC_{50}) for the synthesized compounds and the standards were also calculated (Table **5**).

Table 5. DPPH scavenging assay of synthesized compounds

Sample No.	**Mean % DPPH scavenging activity±SD**					**IC_{50} Value (µg/ml)**
	20 µg	**40 µg**	**60 µg**	**80 µg**	**100µg**	
2h	14.8±0.04	19.3±0.02	32.5±0.01	49.7±0.06	72.5±0.02	80.50
2i	12.9±0.06	18.9±0.01	33.8±0.04	50.2±0.02	71.2±0.06	77.94
2j	14.5±0.01	19.7±0.06	34.4±0.02	51.3±0.06	72.7±0.04	78.50
Standard (Ascorbic acid)	43.18±0.06	58.32±0.06	69.12±0.06	89.46±0.01	96.38±0.06	34.38

CONCLUSION

In summary, we have described a simple and efficient method for the synthesis of 2,4,6 triaryl pyridines by the one-pot condensation of 4,4'-difluoro chalcone, substituted acetophenones and ammonium acetate in glacial acetic acid. The newly synthesized compounds are confirmed by the spectral analysis. This method appears to have a broad scope with respect to variation in the 2- and 6-positions of pyridine. Further, the synthesized compounds are evaluated for their antimicrobial and antioxidant activities. The antimicrobial and antioxidant activity reveal that most of the compounds show moderate to good activity.

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