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Green Synthesis of 2-(4-Cinnamoylphenylamino)-3-(4-Trifluoromethylphenyl)-1,8-Naphthyridines as possible Antibacterial Agents

K. Mogilaiah*, K. Shiva Kumar, S. Kavitha and A. Nageswara Rao

Department of Chemistry, Kakatiya University, Warangal 506 009, India

***Corres. Author: kaleru.mogilaiah@gmail.com**
Mobile No:09963353295

Abstract: A simple, highly efficient and eco-friendly synthesis of 2-(4-cinnamoyl phenylamino)-3-(4-trifluoromethylphenyl)-1,8-naphthyridines **4** is described by grinding 1-[4-({3-[4-(trifluoromethyl) phenyl] [1,8]naphthyridin-2-yl}aminophenyl]-1-ethanone **3** with various aromatic aldehydes in the presence of solid KOH in a mortar with pestle. The yields are good and purity is high. The structures of newly synthesized compounds **3** and (**4a-j**) have been established by their elemental analyses and spectral (IR, ^{1}H NMR and MS) data. The compounds (**4a-j)** were screened for their antibacterial activity against Gram-negative *Escherichia coli* and Gram-positive *Bacillus subtilis.* Compound **4d** and **4e** showed significant antibacterial activity against both the organisms.

Keywords: Claisen-Schmidt condensation, α, β-unsaturated ketones,1,8-naphthyridine, solid KOH, antibacterial activity.

Introduction

1,8-Napthtyridine derivatives have attracted considerable attention owing to their effective biological activity and extensive use[1-3]. Chalkones, more generally α, β-unsaturated ketones are widely recognized as versatile synthons for a verity of organic transformations.[4-6] In recent years considerable interest has developed in the study of organic reactions in solvent-free (solid state) conditions. Many such reactions have been studied because of their interesting chemistry and commercial importance. For instance, a large number of organic reactions are typically carried out under anhydrous conditions, using volatile organic solvents like benzene, which are the cause of environmental problems and are also potentially carcinogenic. Hence, it is required to develop safe, practical and environment friendly processes. The pioneering work of Toda *et al.*[7,8] has shown that many exothermic reactions, can be accomplished in high yield by just grinding solids together using mortar and pestle, a technique known as 'Grindstone Chemistry' which is one of the 'Green Chemistry Techniques'. Reactions are initiated by grinding, with the transfer of very small amount of energy through friction[9]. In addition to being energy efficient Grindstone Chemistry also results in high reactivity and less waste products. In view of this, and in continuation of our interest on solvent-free reactions of 1,8-naphthyridine derivatives[10-12], herein is reported the Claisen-Schmidt condensation under solvent-free conditions using solid KOH as catalyst.

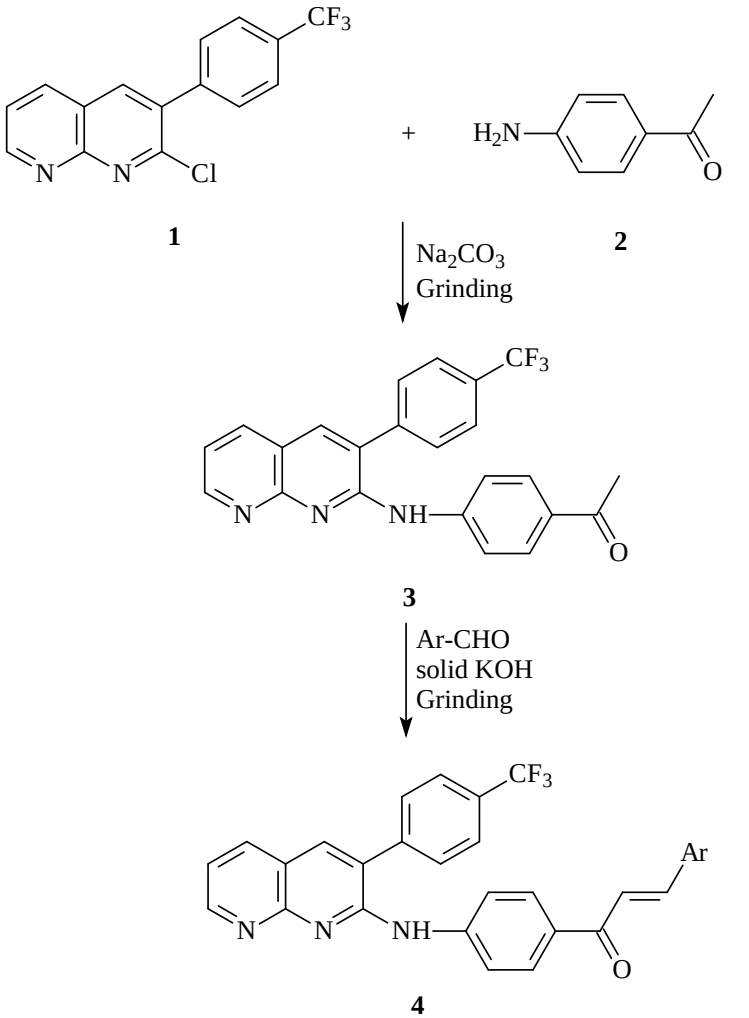
Results And Discussion

Interaction of 2-chloro-3-(4-trifluoromethylphenyl)-1,8-naphthyridine **1** with 4-aminoacetophenone **2** in the presence of Na_2CO_3 in the solid state at room temperature furnished 1-[4-({3-[4-(trifluoromethyl) phenyl][1,8]naphthyridin-2-yl}aminophenyl]-1-ethanone **3** in 95% yield with m.p. 264^{o}C. The structure of the compound **3** has been determined by its spectral and analytical data.

Claisen-Schmidt condensation of **3** with various aromatic aldehydes in the presence of solid KOH in combination with grinding at room temperature in the absence of solvent resulted in the formation of 2-(4-cinnamoylphenylamino)-3 -(4-trifluoromethylphenyl)-1,8-naphthyridines (**4a-j)** (chalkones or α, β-unsaturated ketones) (Scheme 1) in good yields. The reactions were clean, efficient and convenient. The products were obtained with a high degree of purity. The process is environmentally benign. The experimental procedure is very simple.

In a typical case, an equimolar mixture of **3,** benzaldehyde and solid KOH was ground in a mortar by pestle at room temperature for 4.5 min. Work-up of the reaction mixture afforded **4a** (Ar = C_6H_5) in 92% yield, m.p. 248°C. The reaction is of general applicability and the various and different 2-(4-cinnamoylphenylamino)-3-(4-trifluoromethylphenyl)-1,8-naphthyridines (**4a-j)** synthesized are given in Table 1.

The structures of the compounds (**4a-j)** were confirmed by their spectroscopic (IR, ^{1}H NMR and MS) and analytical data. The short reaction period, enhanced reaction rates, cleaner product, cheapness and availability of reagent, easy set-up and work-up are advantages of this procedure.



	Ar
a,	C_6H_5
b,	4-$CH_3C_6H_4$
c,	4-$CH_3OC_6H_4$
d,	2-ClC_6H_4
e,	4-ClC_6H_4

	Ar
f,	4-FC_6H_4
g,	3-$NO_2C_6H_4$
h,	4-$NO_2C_6H_4$
i,	4-$(CH_3)_2NC_6H_4$
j,	3,4-$(CH_3O)_2C_6H_3$

Scheme-1

Table 1. Characterization data of 2-(4-Cinnamoylphenylamino)-3-(4-trifluoromethylphenyl)-1,8-naphthyridines (4a-j)

Compd	Reaction	m.p.	Yield	Mol. formula	Found (%) (Calcd)		
	Time (min)	°C	(%)		C	H	N
4a	4.5	248	92	$C_{30}H_{20}N_3OF_3$	72.88 (72.72	4.10 4.07	8.54 8.48)
4b	5.5	254	95	$C_{30}H_{20}N_3OF_3$	73.23 (73.08	4.40 4.35	8.32 8.25)
4c	6.0	220	93	$C_{31}H_{22}N_3O_2F_3$	70.98 (70.85	4.25 4.22	8.06 8.00)
4d	7.0	245	92	$C_{30}H_{19}N_3OF_3Cl$	68.15 (67.99	3.65 3.61	7.99 7.93)
4e	6.5	250	95	$C_{30}H_{19}N_3OF_3Cl$	68.16 (67.99	3.64 3.61	7.98 7.93)
4f	6.5	260	91	$C_{30}H_{19}N_3OF_4$	70.34 (70.17	3.77 3.73	8.25 8.18)
4g	4.5	252	88	$C_{30}H_{19}N_4O_3F_3$	66.84 (66.67	3.58 3.54	10.43 10.37)
4h	4.0	265	92	$C_{30}H_{19}N_4O_3F_3$	66.83 (66.67	3.57 3.54	10.42 10.37)
4i	5.5	258	93	$C_{32}H_{25}N_4OF_3$	71.43 (71.37	4.71 4.68	10.48 10.40)
4i	6.5	256	92	$C_{32}H_{24}N_3O_3F_3$	69.36 (69.18	4.39 4.35	7.64 7.56)

Experimental

All melting points were determined on a Cintex melting point apparatus and are uncorrected. Homogeneity of the compounds was checked by precoated TLC plates (Merck, 60F-254). IR spectra were recorded in KBr on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer; ^{1}H NMR spectra on a Varian Gemini 400 MHz spectrometer using TMS as internal standard and mass spectra on Finnigan MAT-1020 instrument. Elemental analyses were performed on a Perkin-Elmer 240 CHN analyser.

General Method:

The title compounds were prepared in the following steps:

Synthesis of 1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino phenyl]-1-ethanone **3**

A mixture of 2-chloro-3-(4-trifluoromethylphenyl)-1,8-naphthyridine **1** (0.01 mol), 4-aminoacetophenone **2** (0.01 mol) and Na_2CO_3 (0.01 mol) was ground in a mortar by pestle at room temperature for 4.5 min. On completion of reaction, as monitored by TLC, the reaction mixture was treated with chilled water. The separated solid was filtered, washed with water and purified by recrystallization from methanol to give **3,** yield 95%, m.p. 264°C. Anal. Calcd for $C_{23}H_{16}N_3OF_3$: C, 67.81; H, 3.96; N, 10.31. Found : C, 67.96; H, 4.00; N, 10.38%; IR (KBr): 3404 , 1656 , 1605 cm^{-1}; ^{1}H NMR (DMSO-d_6) : δ 2.55 (s, 3H, CH_3), 7.82 (m, 1H, C_6-H), 7.95 (m, 2H, C_4-H, C_5-H), 8.62 (m, 1H, C_7-H), 7.15-7.72 (m, 8H, Ar-H), 10.45 (s, 1H, NH); MS (ES$^+$): m/z 408[M+H]$^+$

Synthesis of 2-(4-Cinnamoylphenylamino)-3-(4-trifluoromethylphenyl)- 1,8-naphthyridines **(4a-j)**

A mixture of **3** (0.01 mol), aromatic aldehyde (0.01 mol) and solid KOH (0.01 mol) was ground by pestle and mortar at room temperature for the period indicated in Table 1. After completion of the reaction as indicated by TLC, the reaction mixture was digested with cold water. The solid that precipitated was filtered, washed with water and purified by recrystallization from methanol to afford **(4a-j**) (Table 1).

(*E*)-3-phenyl-1-[4-({3-[4-(trifluoromethyl)phenyl] [1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4a**

IR (KBr): 3398, 1652 , 1600, 982 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ 6.60 (d, 1H, olefinic C_α-H), 8.18 (m, 2H, C_4-H, C_5-H), 8.50 (m, 1H, C_7-H), 7.20-7.92 (m, 15H, olefinic C_β-H, C_6-H, 13 Ar-H), 12.32 (s, 1H, NH); MS (ES$^+$): m/z 496[M+H]$^+$

(*E*)-3-(4-methylphenyl)-1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4b**
IR (KBr): 3357, 1655, 1592. 980 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 6.62 (d, 1H, olefinic C_α-H), 8.10 (m, 2H, C_4-H, C_5-H), 8.62 (m, 1H, C_7-H), 7.20-7.95 (m, 14H, olefinic C_β-H, C_6-H, 12 Ar-H), 12.28 (s, 1H, NH); MS (ES^+): m/z 510$[M+H]^+$

(*E*)-3-(4-methoxyphenyl)-1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4c**
IR (KBr): 3416, 1655, 1605. 976 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 6.85 (d, 1H, olefinic C_α-H), 7.98 (m, 2H, C_4-H, C_5-H), 8.55 (m, 1H, C_7-H), 7.10-7.92 (m, 14H, olefinic C_β-H, C_6-H, 12 Ar-H), 12.30 (s, 1H, NH); MS (ES^+): m/z 526$[M+H]^+$

(*E*)-3-(2-chlorophenyl)-1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4d**
IR (KBr): 3404, 1654, 1595. 982 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ 6.65 (d, 1H, olefinic C_α-H), 8.20 (m, 2H, C_4-H, C_5-H), 8.55 (m, 1H, C_7-H), 7.30-7.98 (m, 14H, olefinic C_β-H, C_6-H, 12 Ar-H), 12.40 (s, 1H, NH); MS (ES^+): m/z 530$[M+H]^+$

(*E*)-3-(4-chlorophenyl)-1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4e**
IR (KBr): 3380, 1655, 1596,976 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ 6.64 (d, 1H, olefinic C_α-H), 8.10 (m, 2H, C_4-H, C_5-H), 8.52 (m, 1H, C_7-H), 7.18-7.80 (m, 14H, olefinic C_β-H, C_6-H, 12 Ar-H), 12.30 (s, 1H, NH); MS (ES^+): m/z 530$[M+H]^+$

(*E*)-3-(4-fluorophenyl)-1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4f**
IR (KBr): 3395,1654,1602,982 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ 6.68 (d, 1H, olefinic C_α-H), 8.08 (m, 2H, C_4-H, C_5-H), 8.50 (m, 1H, C_7-H), 7.15-7.97 (m, 14H, olefinic C_β-H, C_6-H, 12 Ar-H), 12.32 (s, 1H, NH); MS (ES^+): m/z 514$[M+H]^+$

(*E*)-3-(3-nitrophenyl)-1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4g**
IR (KBr): 3386,1655,1601,978 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ 7.15 (d, 1H, olefinic C_α-H), 8.12 (m, 2H, C_4-H, C_5-H), 8.55 (m, 1H, C_7-H), 7.60-7.80 (m, 14H, olefinic C_β-H, C_6-H, 12 Ar-H), 12.30 (s, 1H, NH); MS (ES^+): m/z 541$[M+H]^+$

(*E*)-3-(4-nitrophenyl)-1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4h**
IR (KBr): 3408,1654,1605,986 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ7.18 (d, 1H, olefinic C_α-H), 8.16 (m, 2H, C_4-H, C_5-H), 8.58 (m, 1H, C_7-H), 7.25-7.90 (m, 14H, olefinic C_β-H, C_6-H, 12 Ar-H), 12.35 (s, 1H, NH); MS (ES^+): m/z 541 $[M+H]^+$

(*E*)-3-[4-(dimethylamino)phenyl)]-1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4i**
IR (KBr): 3404,1658,1600,975 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ 3.12 [s, 6H, $N(CH_3)_2$], 6.76 (d, 1H, olefinic C_α-H), 8.00 (m, 2H, C_4-H, C_5-H), 8.65 (m, 1H, C_7-H), 7.25-7.94 (m, 14H, olefinic C_β-H, C_6-H, 12 Ar-H), 12.34 (s, 1H, NH); MS (ES^+): m/z 539$[M+H]^+$

(*E*)-3-(3,4-dimethoxyphenyl)-1-[4-({3-[4-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}amino)phenyl]-2-propen-1-one **4j**
IR (KBr): 3408,1656,1595,985 cm-^{1} ; ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 7.25 (d, 1H, olefinic C_α-H), 8.00 (m, 2H, C_4-H, C_5-H), 8.55 (m, 1H, C_7-H), 7.80-7.96 (m, 14H, olefinic C_β-H, C_6-H, 12 Ar-H), 12.40 (s, 1H, NH); MS (ES^+): m/z 556$[M+H]^+$

Antibacterial Activity:

The antibacterial activity was assayed using filter paper disc method of Vincent and Vincent[13] by measuring the zone of inhibition in mm. All the title compounds **4** were screened *in vitro* for their antibacterial activity against the Gram-negative *Escherichia coli* and Gram-positive *Bacillus subtilis* at 250 and 500 µg/disc concentrations. Known antibiotic Gentamycin was used as standard. The results are summarized in Table 2. The activity data indicate that all the compounds are active against both Gram-negative and Gram-positive bacteria. The activity of the compound depends upon the nature and position of the substituent at the aryl moiety. Compounds **4d, 4e** and **4f** displayed promising antibacterial activity. Other compounds showed either moderate of less activity against these organisms. Introduction of nitro groups at aryl moiety decreases the activity of the compounds. The most active compound of the series was **4e**.

Table 2. Antibacterial activity data of compounds (4a-j)

Compd	Inhibition zone (in mm)			
	E. coli at		*B. subtilis* at	
	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc
4a	8.5	16.0	6.0	9.5
4b	9.5	18.0	7.0	12.0
4c	8.0	15.5	6.0	11.0
4d	10.5	20.0	7.0	13.0
4e	11.5	21.5	7.5	14.0
4f	10.0	19.0	7.0	12.5
4g	5.5	8.5	5.0	7.0
4h	6.5	10.0	5.5	7.5
4i	9.0	17.0	6.5	11.0
4j	9.5	18.5	7.0	11.5
Gentamycin	12.0	22.0	8.0	15.0

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