International Journal of Technical Innovation in Modern Engineering & Science (IJTIMES)
Impact Factor: 5.22 (SJIF-2017), e-ISSN: 2455-2585
Volume 4, Issue 7, July-2018

Efficient synthesis of 3-aryl-1-(4-{[3-(3-methoxyphenyl)- [1,8]naphthyridin- 2-yl]amino}phenyl)-2-propen-1-ones

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Abstract-

Interaction of 2-chloro-3-(3-methoxyphenyl)[1,8]naphthyridine 48 with 4-aminoacetophenone 49 in the presence of K_2CO_3 in the solid state grinding conditions at RT furnished 1-(4-{[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]-amino}-phenyl)-1-ethanone 51 in 95% yield. Claisen-Schmidt condensation of 1-(4-{[3-(3-methoxyphenyl)-[1,8]naphthyridin-2-yl]amino}phenyl)-1-ethanone 51 with various aromatic aldehydes in the presence of pTSA(p-toluenesulphonic acid) in solvent-free grinding conditions at RT afforded the corresponding 3-aryl-1-(4-{[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]amino}phenyl)-2-propen-1-ones52 by Claisen-Schmidt condensation (Chalcones or α, β-unsaturated ketones) (Scheme I). Reactions are not time consuming and the yields of the products are very good. The reaction did not proceed at all when performed without PTSA. The process is environmentally benign and the experimental procedure is very simple. The Whatman filter paper discs (6 mm diameter) with different compounds were placed aseptically on seeded nutrient agar plates with different bacteria and incubated for 72 hr at 37 ± 1°C. The presence of substituents especially methyl, chloro, fluoro and dimethoxy groups when attached to phenyl ring increases the anti bacterial activity notably. Zone of inhibition was screened in mm.

Keywords- Claisen-Schmidt condensation, [1,8]naphthyridines, anti bacterial activity, inhibition.

INTRODUCTION

1,8-Naphthyridines have gained considerable attention because of their wide biological and pharmacological activities[1-4]. Nalidixic acid (1-ethyl-3-carboxy-7-methyl-1,8-naphthyridin-4-one) has been found to be particularly effective against Gram-negative bacteria found in chronic urinary tract infections.[5]

Claisen-Schmidt condensation is one of the most important preparating methods for carbon-carbon bond formation, which is pivotal process in organic synthesis[6,7]. Chalcones (α,β—unsaturated ketones) are useful synthons in synthesis of a large number of bioactive heterocyclic compounds[8-10]. Compounds with the chalcone backbone have been shown to possess various biological activities.[11-13]

In recent years organic reactions in the solid state (solvent-free) have been attracting the chemists because of their simplicity and synthetic value[14-15]. Compared to traditional methods, many reactions proceed more efficiently in the solid state (solvent-free). Reactions have many advantages like reduced pollution, low cost and simplicity in processing and handling.

The pioneering work of Toda *et al.*[16-17] has shown that many organic 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[18]. In addition to being energy efficient Grindstone Chemistry also results in high reactivity and less waste products. Further, 1,8-naphthyridine is the core structural moiety in synthetic organic compounds possessing a variety of important biological activities[19].

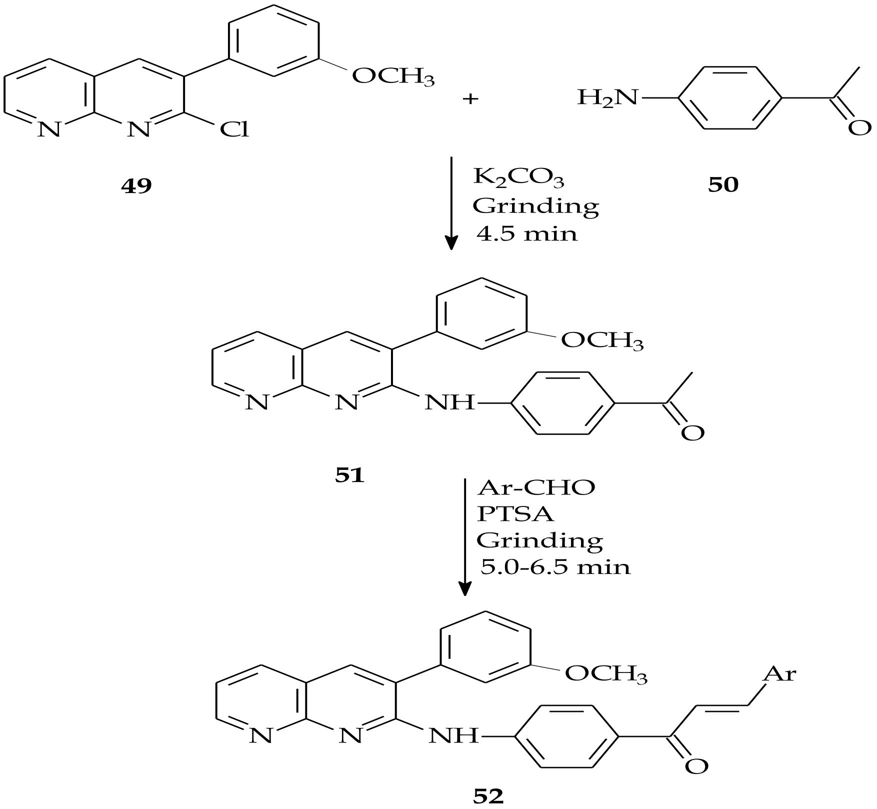
Motivated by the above observations, we herein report a convenient, practical and efficient PTSA catalyzed Claisen-Schmidt condensation in solvent-free conditions.

EXPERIMENTAL SECTION

Melting points were recorded with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU FTIR-8400. NMR spectra were recorded on advance DPX 300 MHz FT-NMR spectrometer using trimethylsilane (TMS) as the internal reference. Mass spectra were recorded on ESQUIRE 3000 Mass spectrometer. All the reagents used were purchased from Aldrich and used without further purification. All the reactions were monitored by thin layer chromatography using pre-coated silica gel plates (Merck). Visualization of the plates was done under UV illumination at 254 nm for UV active materials and further visualization was achieved in iodine chamber and H2SO4-anisaldehyde stain. All microwave reactions were carried out in a Synthon 3000 microwave reactor. The multitude microwave has a twin magneton with maximum output power of 1400 W. The output power can be controlled in unpulsed control mode over whole power range which is adjustable in 1 W increment. A Motorola 68xxx series microprocessor system control is used to measure the temperature, pressure, time and power on the progress of the reaction. The temperature and the pressure were monitored throughout the reaction by an infrared detector.

Antibacterial activity

The antibacterial activity of the compounds**52a-j** thus prepared was evaluated by the filter paper disc technique of Vincent and Vincent[14]. The bacteria used in the present study were *Escherichia coli*, (Gram-negative) and *Bacillus subtilis* (Gram-positive). The compounds were dissolved in acetone and tried at two different concentrations (250 and 500 g/disc). The Whatman filter paper discs (6 mm diameter) with different compounds were placed aseptically on seeded nutrient agar plates with different bacteria and incubated for **72** hr at 37 ± 1°C. At the end of the incubation period, the diameter of the growth inhibition zones was measured. At least 10 paper discs were observed and repeated twice.



	Ar		Ar
a,	C_6H_5	**f,**	$4\text{-}FC_6H_4$
b,	$4\text{-}CH_3C_6H_4$	**g,**	$2\text{-}NO_2C_6H_4$
c,	$4\text{-}CH_3OC_6H_4$	**h,**	$3\text{-}NO_2C_6H_4$
d,	$2\text{-}ClC_6H_4$	**i,**	$4\text{-}NO_2C_6H_4$
e,	$4\text{-}ClC_6H_4$	**j,**	$3,4\text{-}(OCH_3)_2C_6H_3$

The synthetic route to these compounds is depicted in **Scheme I**.

RESULTS AND DISCUSSION

Table I IR and mass spectral data of 3-Aryl-1-(4-{[3-(3-methoxyphenyl)- [1,8]naphthyridin-2-yl]amino}phenyl)-2-propen-1-ones **52**

Compd	Ar	$_{max}$ in cm^{-1}				MS (ESI) (M$^+$) *m/z*
		NH	C=O	C=N	HC=CH (*trans*)	
52a	C_6H_5	3370	1699	1611	983	457.30
52b	4-$CH_3C_6H_4$	3418	1659	1614	981	471.39
52c	4-$CH_3OC_6H_4$	3412	1668	1615	985	487.26
52d	2-ClC_6H_4	3430	1667	1612	984	491.19
52e	4-ClC_6H_4	3433	1660	1608	982	491.19
52f	4-FC_6H_4	3443	1665	1604	985	475.17
52g	2-$NO_2C_6H_4$	3455	1658	1609	984	502.52
52h	3-$NO_2C_6H_4$	3448	1660	1606	985	502.52
52i	4-$NO_2C_6H_4$	3452	1662	1608	985	502.52
52j	3,4-$(OCH_3)_2C_6H_3$	3404	1664	1610	982	517.20

Table II ^{1}H NMR spectral data of 3-Aryl-1-(4-{[3-(3-methoxyphenyl)- [1,8]naphthyridin-2-yl]amino}phenyl)-2-propen-1-ones **52**

Compd	Ar	^{1}H NMR (400 MHz, $CDCl_3$) (ppm)
52a	C_6H_5	3.81 (s, 3H, OCH_3), 6.23 (d, 1H, olefinic C-H), 6.61 (d, 1H, olefinic C-H), 8.57 (m, 2H, C_7-H, C_4-H of naphthyridine), 8.05-8.18 (m, 4H, C_5-H, C_6-H of naphthyridine, 2Ar-H), 7.22-7.85 (m, 11H, Ar-H), 12.52 (s, 1H, NH).
52b	4-$CH_3C_6H_4$	2.49(s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.21 (d, 1H, olefinic C-H), 6.59 (d, 1H, olefinic C-H), 8.49 (m, 2H, C_7-H, C_4-H of naphthyridine), 7.99-8.16 (m, 4H, C_5-H, C_6-H of naphthyridine ,2Ar-H), 7.20-7.83 (m, 10H, Ar-H), 12.38 (s, 1H, NH).
52c	4-$CH_3OC_6H_4$	3.74(s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.21 (d, 1H, olefinic C-H), 6.40 (d, 1H, olefinic C-H), 8.51 (m, 2H, C_7-H, C_4-H of naphthyridine), 7.99-8.15 (m, 4H, C_5-H, C_6-H of naphthyridine, 2Ar-H), 7.19-7.82 (m, 10H, Ar-H), 12.39 (s, 1H, NH).
52d	2-ClC_6H_4	3.79 (s, 3H, OCH_3), 6.25 (d, 1H, olefinic C-H), 6.44 (d, 1H, olefinic C-H), 8.19-8.23 (m, 2H, C_7-H, C_4-H of naphthyridine),8.12-8.25 (m, 4H, C_5-H, C_6-H of naphthyridine, 2Ar-H), 7.24-7.88 (m, 10H, Ar-H), 12.42 (s, 1H, NH).
52e	4-ClC_6H_4	3.75 (s, 3H, OCH_3), 6.21 (d, 1H, olefinic C-H), 6.43 (d, 1H, olefinic C-H), 8.48 (m, 2H, C_7-H, C_4-H of naphthyridine), 8.06-8.19 (m, 4H, C_5-H, C_6-H of naphthyridine, 2Ar-H), 7.24-7.89 (m, 10H, Ar-H), 12.40 (s, 1H, NH). *Contd..*

Table II ^{1}H NMR spectral data of 3-Aryl-1-(4-{[3-(3-methoxyphenyl)- [1,8]naphthyridin-2-yl]amino}phenyl)-2-propen-1-ones **52** *Contd..*

Compd	Ar	^{1}H NMR (400 MHz, $CDCl_3$) (ppm)
52f	4-FC_6H_4	3.79 (s, 3H, OCH_3), 6.29 (d, 1H, olefinic C-H), 6.45 (d, 1H, olefinic C-H), 8.50 (m, 2H, C_7-H, C_4-H of naphthyridine), 7.99-8.14 (m, 4H, C_5-H, C_6-H of naphthyridine, 2Ar-H), 7.21-7.83 (m, 10H, Ar-H), 12.40 (s, 1H, NH).
52g	2-$NO_2C_6H_4$	3.78 (s, 3H, OCH_3), 6.32 (d, 1H, olefinic C-H), 6.49 (d, 1H, olefinic C-H), 8.48 (m, 2H, C_7-H, C_4-H of naphthyridine),8.12-8.14 (m, 4H, C_5-H, C_6-H of naphthyridine, 2Ar-H), 7.25-7.89 (m, 10H, Ar-H), 12.39 (s, 1H, NH).
52h	3-$NO_2C_6H_4$	3.77 (s, 3H, OCH_3), 6.22 (d, 1H, olefinic C-H), 6.42 (d, 1H, olefinic C-H), 8.45 (m, 2H, C_7-H, C_4-H of naphthyridine),8.00-8.19 (m, 4H, C_5-H, C_6-H of naphthyridine, 2Ar-H), 7.22-7.81 (m, 10H, Ar-H), 12.38 (s, 1H, NH).
52i	4- $NO_2C_6H_4$	3.80 (s, 3H, OCH_3), 6.29(d, 1H, olefinic C-H), 6.48 (d, 1H, olefinic C-H), 8.49 (m, 2H, C_7-H, C_4-H of naphthyridine), 8.05-8.18 (m, 4H, C_5-H, C_6-H of naphthyridine, 2Ar-H), 7.25-7.89 (m, 10H, Ar-H), 12.40 (s, 1H, NH).
52j	3,4-$(OCH_3)_2C_6H_3$	3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.19 (d, 1H, olefinic C-H), 6.38 (d, 1H, olefinic C-H), 8.44 (m, 2H, C_7-H, C_4-H of naphthyridine), 7.91-8.08 (m, 4H, C_5-H, C_6-H of naphthyridine, 2Ar-H), 7.15-7.79 (m, 9H, Ar-H), 12.38 (s, 1H, NH).

Table III Physical and analytical data of 3-Aryl-1-(4-{[3-(3-methoxy- phenyl)[1,8]naphthyridin-2-yl]amino}phenyl)-2-propen-1-ones **52**

Compd	Ar	Reaction Time (min)	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calcd)		
						C	H	N
52a	C_6H_5	5.0	225	94	$C_{30}H_{23}N_3O_2$	78.89 (78.75	5.08 5.07	9.23 9.18)
52b	4-$CH_3C_6H_4$	5.5	232	96	$C_{31}H_{25}N_3O_2$	79.18 (78.96	5.36 5.34	8.95 8.91)
52c	4-$CH_3OC_6H_4$	6.0	220	93	$C_{31}H_{25}N_3O_3$	76.50 (76.37	5.18 5.17	8.69 8.62)
52d	2-ClC_6H_4	6.5	235	92	$C_{30}H_{22}ClN_3O_2$	73.36 (73.24	4.53 4.51	8.60 8.54)
52e	4-ClC_6H_4	6.0	230	96	$C_{30}H_{22}ClN_3O_2$	73.37 (73.24	4.52 4.51	8.58 8.54)
52f	4-FC_6H_4	6.5	240	94	$C_{30}H_{22}FN_3O_2$	75.92 (75.78	4.68 4.66	8.89 8.84)
52g	2-$NO_2C_6H_4$	6.0	198	90	$C_{30}H_{22}N_4O_4$	71.83 (71.70	4.42 4.41	11.20 11.15)
52h	3-$NO_2C_6H_4$	5.5	242	92	$C_{30}H_{22}N_4O_4$	71.82 (71.70	4.43 4.41	11.19 11.15)
52i	4-$NO_2C_6H_4$	5.0	210	94	$C_{30}H_{22}N_4O_4$	71.84 (71.70	4.42 4.41	11.21 11.15)
52j	3,4-$(OCH_3)_2C_6H_3$	6.0	215	92	$C_{32}H_{27}N_3O_4$	74.40 (74.26	5.28 5.26	8.17 8.12)

Table IV— Antibacterial activity data of 3-Aryl-1-(4-{[3-(3-Methoxy-phenyl)[1,8]naphthyridin-2-yl]amino}phenyl)-2-propen-1-ones **52**

Compd	Ar	Inhibition zone (in mm)			
		E. coli at		*B. subtilis* at	
		250 g/disc	500 g/disc	250 g/disc	500 g/disc
52a	C_6H_5	8.8	13.3	6.3	10.8
52b	4-$CH_3C_6H_4$	9.4	15.3	7.0	11.8
52c	4-$CH_3OC_6H_4$	8.3	12.3	6.0	11.0
52d	2-ClC_6H_4	9.0	18.5	6.8	12.5
52e	*4*-ClC_6H_4	11.5	21.0	7.5	14.5
52f	4-FC_6H_4	10.5	20.5	7.0	14.0
52g	2-$NO_2C_6H_4$	6.0	10.0	5.0	9.5
52h	3-$NO_2C_6H_4$	7.5	12.0	5.5	10.5
52i	4-$NO_2C_6H_4$	9.0	16.0	6.0	11.5
52j	3,4-$(CH_3O)_2C_6H_3$	11.0	19.5	6.5	13.5
	Gentamycin	12.0	22.0	8.0	15.0

CONCLUSION

We have devised a simple and efficient synthesis of chalcones(α,β-unsaturated ketones) by using *p*TSA as catalyst in solvent-free grinding conditions. The experimental simplicity, easily available and cheap catalyst, short reaction times, very good yields, pure products and environmental acceptability are worthy advantages of this method. Some of them exhibited as more potent when compare to that of standard drug gentamycin.

ACKNOWLEDGEMENT

The authors are thankful to the Department of Pharmacy, Kakatiya University, Warangal for helping in the evaluation of antibacterial activity One of them (P K Ch) is grateful to CSIR, New Delhi for the award of Senior Research Fellowship.

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