A New and Direct Synthesis of Chalcones *Via* TFAA-H_3PO_4 Mediated C-C Bond Forming Reaction

Kavitha Kankanala[a,b], Lingam Venkata Reddy[a], Vangala Ranga Reddy[c], Khagga Mukkanti[a] and Sarbani Pal*[,b]

[a]*JNT University, Kukatpally, Hyderabad – 500072, India*

[b]*Department of Chemistry, MNR Degree and PG College, Kukatpally, Hyderabad – 500072, India*

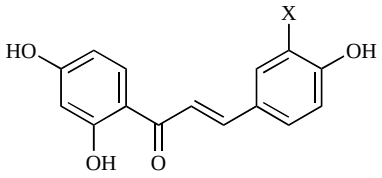
[c]*Dr. Reddys Laboratories Limited, Integrated Product Development, Bachupally, Hyderabad-500055, India*

Received June 13, 2010: Revised September 17, 2010: Accepted October 13, 2010

Abstract: A number of *α,β*-unsaturated carboxylic acids were reacted with electron rich arenes or heteroarene in the presence of trifluoroacetic anhydride (TFAA) and H_3PO_4 at room temperature to give a variety of chalcone derivatives in good to excellent yields. The methodology was used to prepare novel compounds of potential pharmacological significances.

Keywords: Chalcones, TFAA, *α,β*-unsaturated carboxylic acids, arenes.

Chalcones and their derivatives display a range of pharmacological properties [1] such as anti-inflammatory [2], antimitotic [3], anticancer [4-6] or antimicrobial [7] activities. Butein and isoliquiritigenin (Fig. **1**) that belong to this class are known activators of sirtuin and are reported to be beneficial for the treatment of obesity and diabetes *via* exerting their anti-aging effects [8]. Sirtuins are an evolutionarily conserved class of proteins that regulate a variety of cellular functions such as genome maintenance, longevity, and metabolism [9]. Chalcones are also valuable synthetic precursors of a large number of natural products based on flavonoids, isoflavonoids, neoflavonoids and aurones [10]. A number of methods have been reported for the synthesis of chalcones (Fig. **2**). These include Aldol condensation (or Claisen Schmidt reaction) between aromatic aldehyde possessing no alpha hydrogens and ketone containing at least two alpha hydrogens in the presence of a base [11] or iodine [12] or $SOCl_2$/EtOH [13] or simply by grinding under a solvent free condition [14]. An efficient synthesis of chalcones was achieved by Suzuki reaction [15, 16] between cinnamoyl chlorides and phenylboronic acids or between aroyl chlorides and arylvinylboronic acids. The other methods include $SnCl_4$-mediated Friedel Crafts alkylation of *β*-chlorovinyl ketones [17] or elimination of bromine from ArCHBrCHBrCOAr [18]. Chalcones can also be prepared *via* one-pot palladium-mediated hydrostannylation-coupling reaction sequence[19] or gold nano particle catalysed tandem oxidation and crossed Aldol rection [20]. All these methods however involved the use of particular type of ketones/aldehydes or environmentally harmful and moisture sensitive acid/alkyl chlorides or expensive transition metal catalysts. Moreover, preparation of starting materials is cumbersome in some of the cases. Due to our interest in the preparation of drug-like small molecules of potential pharmacological importance we required an easy access to various chalcones that could eventually help us to build a diversity-based compound library. Herein we report a new, one-pot and simple synthesis of chalcones directly from *α,β*-unsaturated aromatic acids *via* a C-C bond forming reaction (Scheme **1**).



A (X = OH; Butein)
B (X = H; isoliquiritigenin)

Fig. (1). Chalcone derivatives as sirtuin activators.

The use of TFAA/H_3PO_4 as an efficient catalyst system for C-C bond forming reaction between a carboxylic acid and arenes has been studied earlier [21-23]. Accordingly, we have reported TFAA/H_3PO_4-mediated smooth C-acylation of arenes and heteroarenes [24, 25] and O-acylation of phenols [26]. Notably, a variety of carboxylic acids [21-23] (including naproxen [22]) has been used for C-acylation earlier except cinnamic acid. This prompted us to examine the reaction of *α,β*-unsaturated aromatic acids with (hetero)arenes in the presence of TFAA/H_3PO_4. Cinnamic acid (**1**) was initially chosen as an acid partner for the present dehydrative acylation of arenes (**2**). Results of this study are summarized in Table **1**. Thus, the acid **1** (1.0 mol) was reacted with anisole **2a** (1.0 mol) in the presence of commercially available 85% H_3PO_4 (0.1 mol) and TFAA (4.0 mol) at room temperature. Yields of the product i.e. 1-(4-methoxyphenyl)-3-phenylprop-2-en-1one (**3a**) was examined at different interval of time and was found to be 76, 88 and 95% after 5, 15 and 60 min, respectively (entries

*Address correspondence to this author at the Department of Chemistry, MNR Degree and PG College, Kukatpally, Hyderabad 500 072, India; Tel: 90-40-23041488; Fax: 04023067380; E-mail: sarbani277@yahoo.com

1570-1786/11 $58.00+.00

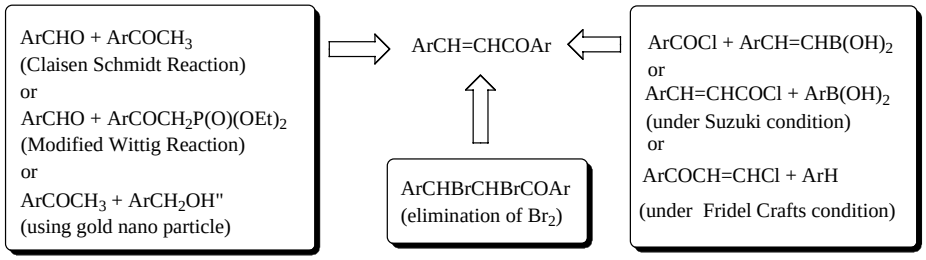
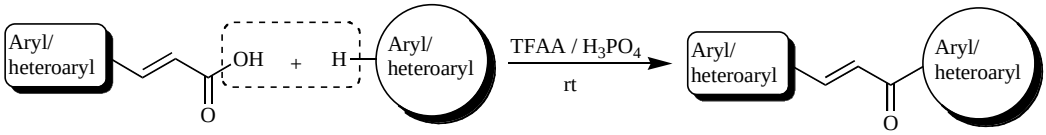
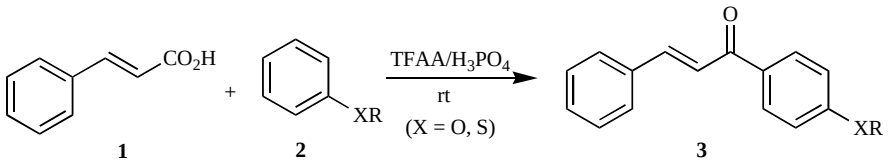


Fig. (2). Summary of various methods reported for the synthesis of chalcones.

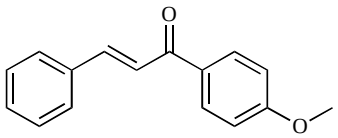
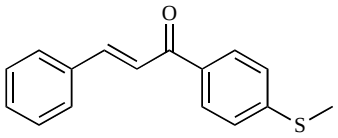
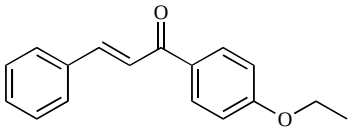
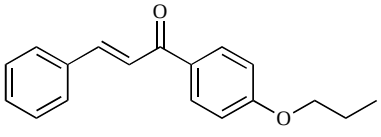
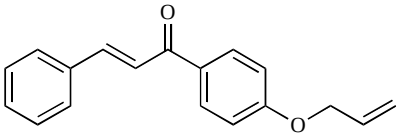


Scheme 1. Preparation of chalcones from *α,β*-unsaturated carboxylic acids and (hetero)arenes.

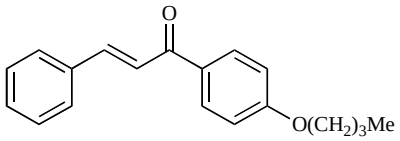
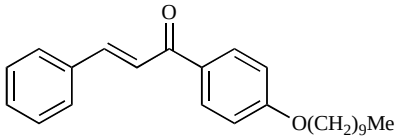
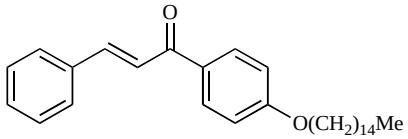
Table 1. TFAA/H_3PO_4–Mediated Synthesis of Chalcones (3) from Cinnamic Acid (1) and Aryl (thio)ethers (2)[a]



1 **2** **3**

Entry	Aryl (thio)ethers (2)	Products (3)	Time	%Yield[b]
1	PhOMe **2a**	 **3a**	5 min	76
2	**2a**	**3a**	15 min	88
3	**2a**	**3a**	30 min	95
4	PhSMe **2b**	 **3b**	10 min	88
5	PhOEt **2c**	 **3c**	45 min	82
6	$PhOCH_2CH_2CH_3$ **2d**	 **3d**	45 min	80
7	$PhOCH_2CH{=}CH_2$ **2e**	 **3e**	1 h	75

(Table 1). Contd…..

Entry	Aryl (thio)ethers (2)	Products (3)	Time	%Yield[b]
8	PhO^nBu **2f**	 **3f**	45 min	79
9	$PhO(CH_2)_9CH_3$ **2g**	 **3g**	3h	83
10	$PhO(CH_2)_{14}Me$ **2h**	 **3h**	3 h	90

[a]All the reactions were carried out using acid **1** (1.0 mol), arene **2** (1.0 mol), 85% H_3PO_4 (0.1 mol) and TFAA (4.0 mol) at room temperature.
[b]Isolated yield.

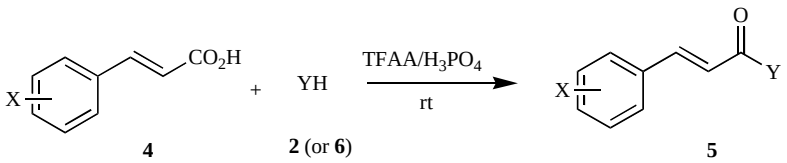
1-3, Table **1**). Further increase in time did not improve the product yield. The use of lower quantity of TFAA and H_3PO_4 was also examined and found to be less productive as the progress of the reaction was slow and the product yield was decreased significantly. The product **3a** isolated was well characterized by NMR, IR and MS. Thus appearance of a signal at 1654 cm^{-1} in the IR spectra and 188.7 ppm in ^{13}C NMR confirmed the presence of a carbonyl group. The geometry of the double bond was confirmed as "*E*" based on the observed "*J*" value (~ 15.0 Hz). Notably, the present C-C bond forming reaction was found to be highly regioselective as no *ortho* product was obtained from the reaction mixture. Having established the optimum reaction condition and the identity of the product we then decided to examine the reaction of **1** with other aryl (thio)ethers (**2,** X = O and S).

A number of aryl ethers were reacted with cinnamic acid to give a variety of chalcones possessing an alkoxy group at the *p*-position of aroyl ring (entries 5-10, Table **1**). Apart from small and long chain alkyl moiety, the alkoxy group may contain an alkenyl moiety (entry 7, Table **1**) and was well tolerated. The reaction was also found to be effective when thioanisole was used (entry 4, Table **1**) in place of arylether. In general, duration of these reactions varied from 30 min to 3.0 h providing good to excellent yields of products. In order to expand the generality and scope of this process we examined the reaction of cinnamic acid possessing various substituents on the benzene ring with a number of aryl ethers or heteroarenes. The results of this study are summarized in Table **2**.

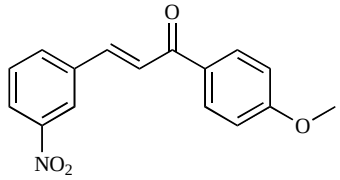
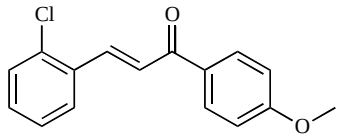
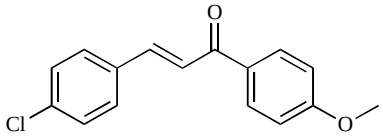
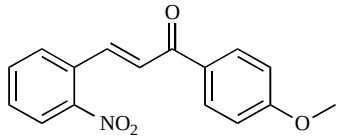
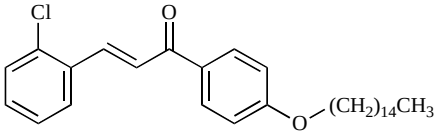
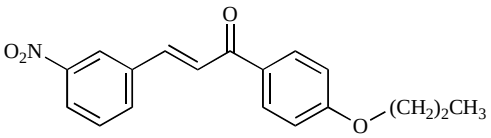
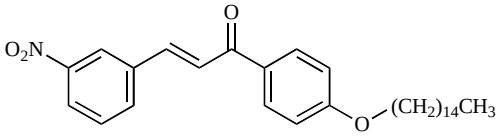
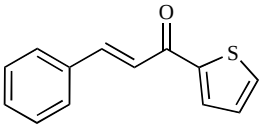
Both electron withdrawing and donating groups such as nitro (entries 1, 4, 6, 7 and 9, Table **2**) and chloro (entries 2, 3, 5 and 10, Table **2**), respectively present in the reactant cinnamic acid (**4**) was well tolerated and provided the desired chalcone (**5**) in good yields. The use of thiophene (**6**) in place of arylether also provided the expected chalcone derivatives in good yields (entries 8-10, Table **2**). The reaction was completed within 5 min in these cases. The use of heteroaryl substituted acrylic acid e.g. (*E*)-3-(2-chloroquinolin-3-acylic acid **6c** (prepared from **6a** *via* 2-chloroquinolin-3-aldehyde **6b**) [27, 28] was also examined in the present C-C bond forming reaction. The corresponding chalcone derivative **7** and **8** was obtained when **6c** was reacted with arylether **2a** or thiophene **6**, respectively (Scheme **2**). Some of the chalcones synthesized were converted to novel heterocyclic compounds of potential biological interest. For example, chalcone **3b** on treating with urea in the presence of HCl in n-butanol at 120 ºC for 4h provided corresponding 4,5-diaryl-5,6-dihydropyrimidinone derivative **9** [29] the methanesulfanyl group of which was then oxidized to the corresponding sulfone **10** (Scheme **3**) [30].

We have shown that electron rich arenes or heteroarene participated well in TFAA/H_3PO_4 mediated C-C bond forming reaction with α,β-unsaturated aromatic acids. The use of other arene e.g. toluene and benzene was examined and found to be less reactive or inert, respectively in the present reaction highlighting the key role played by the electron donating groups. The reactivity order thus may be presented for arene e.g. ArZ as Z = alkoxy, thioalkyl > alkyl >> hydrogen. The use of some other unsaturated carboxylic acid such as acrylic acid was also examined. While the reaction proceeded well in this case, the product isolated was found to be 1,3-bis(4-methoxyphenyl)propan-1-one (i.e. *p*-$MeOC_6H_4CH_2CH_2COC_6H_4OMe$-p) instead of desired 1-(4-methoxyphenyl)prop-2-en-1-one (i.e. CH_2=$CHCOC_6H_4$ OMe-*p*) as indicated by the spectral data. Perhaps the desired product formed underwent a further Michael-type reaction with the unreacted anisole present in the reaction mixture. The present methodology therefore appeared to be effective for the β-substituted α,β-unsaturated acids. A probable mechanism for TFAA/H_3PO_4 mediated reaction of α,β-

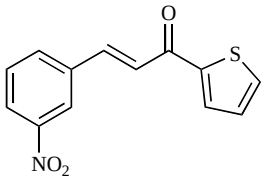
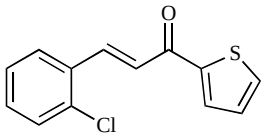
Table 2. TFAA/H_3PO_4–Mediated Synthesis of Chalcones (5) from Substituted Cinnamic Acids (4) and (hetero)arenes (2)[a]



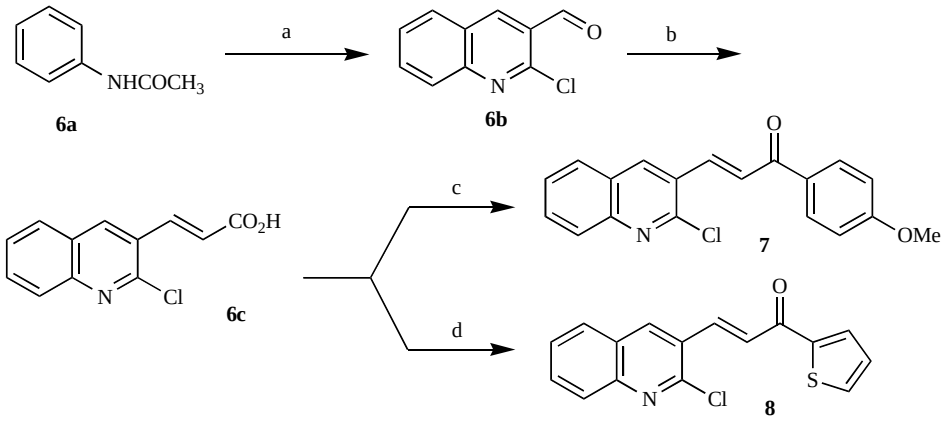
4 **2** (or **6**) **5**

Entry	4; X =	Aryl ether (2 or 6)	Product (5)	Time	% yield[b]
1	NO_2-*m* **4a**	PhOMe **2a**	 **5a**	30 min	85
2	Cl-*o* **4b**	**2a**	 **5b**	3h	86
3	Cl-*p* **4c**	**2a**	 **5c**	3h	95
4	NO_2-*o* **4d**	**2a**	 **5d**	30 min	90
5	**4b**	**2h**	 **5e**	3h	86
6	**4a**	**2d**	 **5f**	30 min	88
7	**4a**	**2h**	 **5g**	3h	81
8	**1**	 **6**	 **5h**	5 min	76

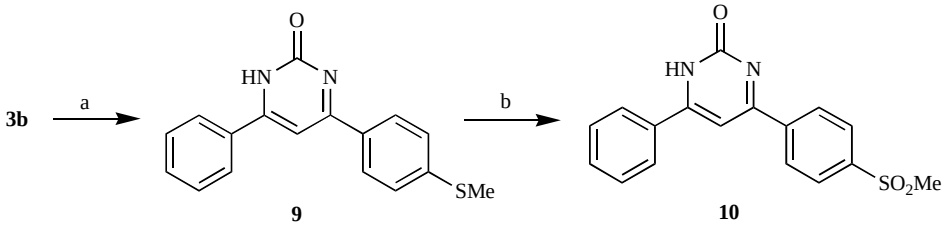
(Table 2). Contd…..

Entry	4; X =	Aryl ether (2 or 6)	Product (5)	Time	% yield[b]
9	**4a**	**6**	 **5i**	5 min	67
10	**4b**	**6**	 **5j**	5 min	77

[a]All the reactions were carried out using acid **4** or **1** (1.0 mol), arene **2 or 6** (1.0 mol), 85% H_3PO_4 (0.1 mol) and TFAA (4.0 mol) at room temperature.
[b]Isolated yield.



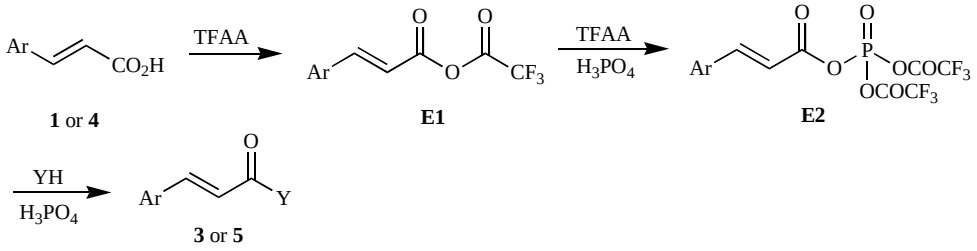
Scheme 2. Preparation and reaction of heteroaryl substituted acrylic acid with arenes; *Reagents and conditions*: (a) $POCl_3$, DMF, reflux, 4h, 83%; (b) $CH_2(CO_2H)_2$, pyridine, reflux, 2h, 72%; (c) **2a**, TFAA/H_3PO_4, room temperature, 3h, 77%; (d) **6**, TFAA/H_3PO_4, room temperature, 0.5h, 72%.



Scheme 3. Synthesis of 4,5-diaryl-5,6-dihydropyrimidinone; *Reagents and conditions*: (a) Urea, HCl, *n*-BuOH, 120 ºC, 4h, 66%; (b) Oxone^{TM}, acetone-H_2O (2:1), room temperature, 1h, 58%.

unsaturated aromatic acids with (hetero)arenes can be proposed (Scheme **4**) [21-23]. Thus, phosphoric acid that plays the role of a covalent catalyst leads to the generation of acyl bis(trifluoroacetyl)phosphate **E2** from the acylation precursor acyl trifluoroacetate **E1** generated *in situ* [22]. The acyl bis(trifluoroacetyl)phosphate **E2** then acetylates the (hetero)arene ring in the presence of phosphoric acid to afford the products **3** and **5**. A strong electron donating group present on the arene ring therefore facilitates the acylation step greatly after activation of **E2** by phosphoric acid as a proton source. It is mention worthy that excess of TFAA and TFA (trifluoroacetic acid generated during the reaction) can be removed by distillation during a large scale synthesis [31] of chalcone and the recovered TFA can be converted back to TFAA *via* dehydration thereby eliminating the acid waste.

In conclusion, a new and regioselective synthesis of chalcones has been achieved *via* TFAA/ H_3PO_4 mediated C-C bond forming reaction between cinnamic acids and electron rich (hereto)arenes. This is the first example that



Scheme 4. Probable mechanism for TFAA/H_3PO_4 mediated reaction of α,β-unsaturated aromatic acids with (hetero)arenes.

involves the direct use of α,β-unsaturated aromatic acid in TFAA/ H_3PO_4 mediated aromatic acylation process. The present one-pot method being simple and straightforward is easy to handle and does not involve the use of unstable/moisture sensitive cinnamoyl chlorides or expensive reagents/catalysts. The generality and scope of this methodology has been demonstrated in synthesizing a variety of chalcone derivatives. The methodology though works with electron rich (hetero)arenes is certainly superior to the classical Friedel-Crafts acylation technique (which is uncommon in the literature perhaps due to the requirement of unstable cinnamoyl halides) and other multistep synthesis. The methodology was used to prepare novel compounds of potential pharmacological significances.

EXPERIMENTAL

General method for the preparation of compound **3:** A slurry of cinnamic acid (1.0 mol) and 85% orthophosphoric acid (0.1 mol) and aryl (thio)ethers (1.0 mol) was stirred under a normal and open atmosphere. To this mixture was added TFAA (4.0 mol) dropwise and the resulting mixture was allowed to stir at room temperature according to the time indicated in the Table **1** (the progress of the reaction was monitored by TLC). After completion the reaction mixture was poured into crushed ice (50 g) and extracted with diethyl ether (3 x 30 mL). The organic layers were collected, combined, washed with 10% Na_2CO_3 solution (1 x 25 mL) followed by brine solution (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue obtained was purified by column chromatography followed by re-crystallization to give the desired chalcone.

Spectral and Analytical Data of Selected Compounds

Compound **3a**: White solid; ^{1}HNMR ($CDCl_3$, 400 MHz): δ 3.89 (s, 3H), 6.99 (d, 2H, *J* = 8.8 Hz), 7.41 (m, 3H), 7.54 (d, 1H, *J* = 15.4 Hz), 7.65 (m, 2H), 7.80 (d, 1H, *J* = 15.7 Hz), 8.04 (d, 2H, *J* = 8.8 Hz); ^{13}CNMR ($CDCl_3$) δ 55.4 (*p*-OCH_3), 113.0 (aromatic C), 121.9 (aromatic C), 128.3 (aromatic C), 128.9 (aromatic C), 130.3 (aromatic C), 130.8 (aromatic C), 131.1 (aromatic C), 135.1 (aromatic C), 143.9 (=CH), 163.4 (=CH), 188.7 (CO); IR (KBr) ν_{max}/cm^{-1}: 1654 (CO), 1600 (C=C), 1572 (C=C), 1259 (C-O), 973, 829, 762; Mass (ESI) 239.10 (M+1, 100%); Anal. calcd for $C_{16}H_{14}O_2$ C 80.65; H 5.92; found C 80.61; H 5.83.

Compound **3b**: white solid; ^{1}HNMR ($CDCl_3$, 400 MHz) : δ 2.54 (s, 3H), 7.32 (d, 2H, *J* = 8.5 Hz), 7.43 (m, 3H), 7.52 (d, 1H, *J* = 15.8 Hz), 7.65 (m, 2H), 7.81 (d, 1H, *J* = 15.4 Hz), 7.96 (d, 2H, *J* = 8.6 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 14.7 (*p*-SCH_3), 121.7 (aromatic C), 124.9 (aromatic C), 128.3 (aromatic C), 128.9 (aromatic C), 130.4 (aromatic C), 134.3 (aromatic C), 134.9 (aromatic C), 144.4 (=CH), 145.6 (=CH), 189.0 (CO); IR (KBr) ν_{max}/cm^{-1}: 1655 (CO), 1600 (C=C), 1572 (C=C), 1220 (C-O), 1184, 1092, 824, 767, 697 (bending); Mass (ESI) 255.10 (M+1, 100%); Anal. calcd for $C_{16}H_{14}OS$ C 75.55; H 5.55, found C 75.50; H 5.44.

Compound **3c**: white solid; ^{1}HNMR ($CDCl_3$, 400 MHz) : δ 1.44 (t, 3H, *J* = 7.0 Hz), 4.12 (q, 2H, *J* = 7.0 Hz), 6.97 (d, 2H, *J* = 8.8 Hz), 7.41 (m, 3H,), 7.54 (d, 1H, *J* = 15.8 Hz), 7.65 (m, 2H), 7.80 (d, 1H, *J* = 15.8 Hz), 8.04 (d, 2H, *J* = 8.8 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 14.7 (CH_3), 63.7 (OCH_2), 114.2 (aromatic C), 121.9 (aromatic C), 128.3 (aromatic C), 128.9 (aromatic C), 130.3 (aromatic C), 130.8 (aromatic C), 135.1 (aromatic C), 143.8 (=CH), 162.8 (=CH), 188.6 (CO); IR (KBr) ν_{max}/cm^{-1}: 1656 (CO), 1601 (C=C), 1574 (C=C), 1254 (C-O), 1184, 1092, 824, 767, 697 (bending); Mass (ESI) 253.20 (M+1, 100%); Anal. calcd for $C_{17}H_{16}O_2$ C 80.93; H 6.40, found C 80.76; H 6.44.

Compound **3d**: light orange solid; ^{1}HNMR ($CDCl_3$, 400 MHz): δ 1.06 (t, 3H, *J* = 7.3 Hz), 1.86 (sextet, 2H, *J* =7.3 Hz), 4.01 (t, 2H, *J* = 6.6 Hz), 6.98 (d, 2H, *J* = 7.0 Hz), 7.43 (m, 3H), 7.54 (d, 1H, *J* = 15.8 Hz), 7.65 (m, 2H), 7.80 (d, 1H, *J* =15.8 Hz), 8.04 (dd, 2H, *J* = 6.6 Hz, 4.9 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 10.5 (CH_3), 22.5 (CH_2), 69.7 (OCH_2), 114.3 (aromatic C), 121.9 (aromatic C), 128.3 (aromatic C), 128.9 (aromatic C), 130.2 (aromatic C), 130.8 (aromatic C), 135.1 (aromatic C), 143.8 (=CH), 163.0 (=CH), 188.6 (CO); IR (KBr) ν_{max}/cm^{-1}: 1656 (CO), 1601 (C=C), 1574 (C=C), 1254 (C-O), 1184, 1092, 824, 767, 697 (bending); Mass (ESI) 267.20 (M+1, 100%); Anal. calcd for $C_{18}H_{18}O_2$ C 81.17; H 6.81; Found C 80.44; H 6.76.

Compound **3e**: pale yellow oil; ^{1}HNMR ($CDCl_3$, 400 MHz): δ 3.34 (d, 2H, *J* = 6.6 Hz), 5.05 (dd, 2H, *J* = 12.2 & 1.5 Hz), 5.97-5.87 (1H, m), 6.64 (1H, *J* = 15.8 Hz), 7.10-7.60 (9H, m), 7.86 (d, 1H, *J* = 16.1 Hz); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 34.6 (CH_2), 116.2 (aromatic C), 117.1 (aromatic C), 122.4 (aromatic C), 126.1 (aromatic C), 127.4 (aromatic C), 128.3 (aromatic C), 128.9 (aromatic C), 130.3 (aromatic C), 130.7 (aromatic C), 132.0 (aromatic C), 134.1 (aromatic C), 135.8 (aromatic C), 146.6 (=CH), 148.9 (aromatic C), 165.2 (=CH), 189.4 (CO); Mass (ESI) 265.30 (M+1, 100%); Anal calcd for $C_{18}H_{16}O_2$ C 81.17; H 6.10; Found C 80.84; H 6.17.

Compound **3f**: ^{1}HNMR ($CDCl_3$, 400 MHz): δ 0.99 (t, 3H, *J* = 7.3 Hz), 1.50 (m, 2H), 1.81 (m, 2H), 4.01 (t, 2H, *J* = 6.5 Hz), 6.97 (d, 2H, *J* = 8.8 Hz), 7.41 (m, 3H), 7.54 (d, 1H, *J* = 15.8 Hz), 7.69 (m, 2H), 7.80 (d, 1H, *J* = 15.7 Hz), 8.03 (d,

2H, *J* = 8.8 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 13.8, 19.2, 31.1, 67.9 (OCH_2), 34.6 (CH_2), 114.2 (aromatic C), 121.9 (aromatic C), 128.3 (aromatic C), 128.5 (aromatic C), 128.8, 129.2, 130 130.3 (aromatic C), 130.2 (aromatic C), 130.3, 131.3, (aromatic C), 135.1 (aromatic C), 143.8 (=CH), 163.0 (=CH), 188.6 (CO); IR (KBr) v_{max}/cm^{-1}: 2957, 1655 (CO), 1600 (C=C), 1572 (C=C), 1256 (C-O), 829, 764, (bending); Mass (ESI) 281.20 (M+1, 100%); Anal. calcd for $C_{19}H_{20}O_2$ C 81.40; H 7.19; Found C 81.14; H 7.11.

Compound **3g**: Pale yellow solid; ^{1}HNMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J* = 7.0 Hz), 1.26-1.48 (m, 14H), 1.81 (m, 2H), 4.04 (t, 2H, *J* = 6.6 Hz), 6.96 (d, 2H, *J* = 8.8 Hz), 7.41 (m, 3H), 7.54 (d, 1H, *J* = 15.8 Hz), 7.64 (m, 2H), 7.80 (d, 1H, *J* = 15.7 Hz), 8.03 (d, 2H, *J* = 8.8 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 14.1 22.6, 26.0, 31.9, 68.2 (OCH_2), 114.2 (aromatic C), 121.8 (aromatic C), 128.3 (aromatic C), 128.4 (aromatic C), 128.8, 129.3 (aromatic C), 130.2 (aromatic C), 130.7, 135.1 (aromatic C), 143.8 (=CH), 163.0 (=CH), 188.6 (CO); IR (KBr) v_{max}/cm^{-1}: 2922, 2850, 1656 (CO), 1606 (C=C), 1575 (C=C), 1273 (C-O), 829, 764 (bending); Mass (ESI) 365.30 (M+1, 100%); Anal. calcd for $C_{25}H_{32}O_2$ C 82.37; H 8.85; Found C 82.06; H 8.94.

ACKNOWLEDGEMENT

The authors (K. K. and S. P.) thank Mr. M. N. Raju, the chairman of MNR Educational Trust for constant support and encouragement.

REFERENCES

[1] Dhar, D.N. *Chemistry of Chalcones and Related Compounds*: Wiley & Sons: New York, **1981**.

[2] Bhat, B.A.; Dhar, K.L.; Puri, S.C.; Saxena, A.K.; Shanmugavel, M.; Qazi, G.N. Synthesis and biological evaluation of chalcones and their derived pyrazoles as potential cytotoxic agents. *Bioorg. Med. Chem*., **2005**, *15*, 3177-3180.

[3] Edwards, M.L.; Stemerick, D.M.; Sunkara, P.S. Chalcones: a new class of antimitotic agents. *J. Med. Chem.*, **1990**, *33*, 1948-1954.

[4] Jarvill-Taylor, K.J.; Anderson, R.A.; Graves, D.J. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. *J. Am. Coll. Nutr.*, **2001**, *20*, 327-336.

[5] Bombardelli, E.; Mancuso, S.; Delle Monache, F. US Patent Application US5808137, Sep. 15, 1998.

[6] De Vincenzo, R.; Scambia, G.; Benedetti, P. P.; Ranelletti, F.O.; Bonanno, G.; Ercoll, A.; Delle Monache, F.; Ferrari, F.; Piantelli, M.; Mancuso, S. Effect of synthetic and naturally occurring chalcones on ovarian cancer cell growth: structure-activity relationships. *Anticancer Drug Des.*, **1995**, *10*, 481-490.

[7] Li, R.; Chen, X.; Gong, B.; Selzer, P. M.; Li, Z.; Davidson, E.; Kurzban, G.; Miller, R.E.; Nuzum, E.O.; McKerrow, J.H.; Fletterick, R.J.; Gillmor, S.A.; Craik, C. S.; Kuntz, I. D.; Cohen, F. E.; Kenyon, G. L. Structure-based design of parasitic protease inhibitors. *Bioorg. Med. Chem.*, **1996**, *4*, 1421-1427.

[8] Milne, J. C.; Denu, J. M. The Sirtuin family: therapeutic targets to treat diseases of aging. *Curr. Opin. Chem. Biol*., **2008**, *12*, 11-17.

[9] Yamamoto, H.; Schoonjans, K.; Auwerx, J. Sirtuin functions in health and disease. *J. Mol. Endocrinol.*, **2007**, *21*, 1745-1755.

[10] Heller, W.; Forkmann, G. In: The Flavonoids: Advances in Research since 1985; Harborne, J.B. Ed.; Chapmann & Hall: London, **1994**; pp. 499-535.

[11] Toda, F.; Tanaka, K.; Hamai, K. Aldol condensation in the absence of solvent: Acceleration of the reaction and enhancement of the stereoselectivity. *J. Chem. Soc. Perkin Trans. I.*, **1990**, 3207-3209.

[12] Wang, H.; Zeng, J. Iodine-catalyzed efficient synthesis of chalcones by grinding under solvent-free conditions. *Can. J. Chem.*, **2009**, *87*, 1209-1212.

[13] Rateb, N.M.; Zohdi, H.F. Atom-efficient, solvent-free green synthesis of chalcones by grinding. *Synth. Commun.*, **2009**, *39*, 2789-2794.

[14] Palleros, D.R. Solvent-free synthesis of chalcones. *J. Chem. Educ*., **2004**, *81*, 1345-1347.

[15] Eddarir, S.; Cotelle, N.; Bakkour, Y.; Rolando, C. An efficient synthesis of chalcones based on the Suzuki reaction. *Tetrahedron Lett*., **2003**, *44*, 5359-5363.

[16] Urawa, Y.; Nishiura, K.; Souda, S.; Ogura, K. A convenient method for preparing aromatic α,β-unsaturated ketones from α,β-unsaturated acyl chlorides and arylboronic acids via suzuki-miyaura type coupling reaction. *Synthesis*, **2003**, 2882-2885, doi: 10.1055/S-2003-44347.

[17] Belyaev, V.F. A synthesis of cjalcones and their thiophene analogs based on β-carbonyl ketones. *Chem. Heterocycl. Compounds*, **1965**, *1*, 141-143.

[18] Bickel, C.L. The debromination of α,β-dibromo ketones by bases. *J. Am. Chem. Soc.*, **1950**, *72*, 349-350.

[19] Kerr, D.J.; Hamel, E.; Jung, M.K.; Flynn, B.L. The concise synthesis of chalcone, indanone and indenone analogues of combretastatin. *Bioorg. Med. Chem.*, **2007**, *15*, 3290-3298.

[20] Kim, S.; Bae, S. W.; Lee, J. S.; Park, J. Recyclable gold nanoparticle catalyst for the aerobic alcohol oxidation and C–C bond forming reaction between primary alcohols and ketones under ambient conditions. *Tetrahedron*, **2009**, *65*, 1461-1466.

[21] Gali, C. Acylation of arenes and heteroarenes with *in situ* generated acyl trifluoroacetates. *Synthesis*, **1979**, 303-304, doi: 10.1055/S-1979-28661.

[22] Smyth, T.P.; Corby, B.W. Toward a clean alternative to friedel−crafts acylation: in situ formation, observation, and reaction of an acyl bis(trifluoroacetyl)phosphate and related structures. *J. Org. Chem.*, **1998**, *63*, 8946-8951.

[23] Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. R. A high speed parallel synthesis of 1,2-diaryl-1-ethanones via a clean-chemistry C–C bond formation reaction. *Tetrahedron*, **2003**, *59*, 3283-3290.

[24] Pal, S.; Bindu, P.; Venna, P. R.; Dubey, P. K. Novel naproxen derivatives: lewis acid/transition-metal free synthesis via C-C bond forming reaction. *Lett. Org. Chem.*, **2007**, *4*, 292-295.

[25] Pal, S.; Khan, M. A.; Bindu, P.; Dubey, P. K. Transition-metal/Lewis acid free synthesis of acyl benzothiophenes via C-C bond forming reaction. *Beilstein J. Org. Chem.*, **2007**, *3*, 35, doi:10.1186/1860-5397-3-35.

[26] Kavitha, K.; Reddy, V. R.; Mukkanti, K.; Pal, S. A TFAA–H_3PO_4-mediated direct, metal-free and high-speed synthesis of aryl carboxylate esters from phenols. *J. Fluorine Chem.*, **2009**, *130*, 505-508.

[27] For preparation of 2-chloroquinolin-3-aldehyde, see: Meth-Cohn, O.; Narine, B.; Tarnowski, B. A versatile new synthesis of quinolines and related fused pyridines. *Part II. Tetrahedron Lett*., **1979**, *20*, 3111-3114.

[28] The (E)-3-(2-chloroquinolin-3-acylic acid was prepared according to a similar procedure reported in the literature, see for example: Brown, T.H.; Blakemore, R.C.; Blurton, P.; Durant, G.J.; Ganellin, C.R.; Parsons, M.E.; Rasmussen, A.C.; Rawlings, D.A.; Walker, T.F. Isocytosine H_2-receptor histamine antagonists II. Synthesis and evaluation of biological activity at histamine H_1-and H_2-receptors of 5-(heterocyclyl) methylisocytosines. *Eur. J. Med. Chem.*, **1989**, *24*, 65-72.

[29] Kidwai, M.; Misra, P. Ring closure reactions of chalcones using microwave technology. *Synth. Comm.*, **1999**, *29*, 3237-3250.

[30] Compounds possessing 1,3-diaryl substitution pattern with methanesulfonyl group at p-position of one of the aryl ring are reported to show promising cyclooxygenase-2 (COX-2) inhibitory properties, see for example: Zarghi, A.; Kakhgi, S.; Hadipoor, A.; Daraee, B.; Dadrass, O.G.; Hedayati, M. Design and synthesis of 1,3-diarylurea derivatives as selective cyclooxygenase (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 1336-1339.

[31] Smyth, T.P.; Corby, B.W. Industrially viable alternative to the friedel−crafts acylation reaction: tamoxifen case study. *Org. Process Res. Dev. Chem.*, **1997**, *1*, 264-267.