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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, and antimicrobial evaluation of novel trichalcones containing core *s*-triazine moiety

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Abstract A series of ten new trichalcones containing core *s*-triazine moiety were synthesized. The intermediate 2,4,6-tris(*p*-formylphenoxy)-1,3,5-triazine was synthesized by the reaction of cyanuric chloride with sodium salt of *p*-hydroxy benzaldehyde using phase-transfer catalyst. Thus, the prepared 2,4,6-tris(*p*-formylphenoxy)-1,3,5-triazine has been subsequently treated with various acetophenones to afford title compound in excellent yields. The structures of intermediate and newly synthesized trichalcones were confirmed by physical and spectral analysis. All the trichalcones were evaluated for antibacterial and antifungal activities. Selected trichalcones showed good to excellent antibacterial and antifungal activities with reference to the well-established standards.

Keywords 2,4,6-Trichloro-1,3,5-triazine (TCT) · 2,4,6-Tris(*p*-formylphenoxy)-1,3,5-triazine · Trichalcones · Antibacterial activity · Antifungal activity

Introduction

Research on new substances possessing antibacterial activity has attracted considerable attention owing to the continuous increase in bacterial resistance (Witte, 1999). Further, infection caused by various microorganisms possesses a serious challenge to the medical community and need for an effective therapy has led to the research for novel antibacterial agents (Akbas and Ismet, 2005). 1,3,5-Triazine derivatives have been known for long time. They have found widespread applications in the pharmaceutical, textile, plastic, and rubber industries and are used as pesticides, dyestuffs, optical bleaches, explosives, and surface active agents. The chemistry of this group of compounds has been studied intensively and has been the subject of many reviews (Smolin and Rapopart, 1959; Mur, 1964; Quirke, 1984; Bartholomew, 1996; Comins and O'Conner, 1988; Giacomelli *et al*., 2004). The *s*-triazine scaffold provides the basis for the design of biologically relevant molecules with widespread application as therapeutics and herbicides (LeBaron *et al*., 2008). Numerous 1,3,5-triazine containing compounds are recognized to be powerful chelating agents and have been used for the preparation of metal complexes (Gamez *et al*., 2003) and liquid crystals (Lai *et al*., 2008). *s*-Triazine derivatives have been employed in combinatorial and supramolecular chemistry (Giacomelli *et al*., 2004). *s*-Triazine derivatives have been successfully utilized as reagents in the conversion of functional groups (Blotny, 2006). More recently, triazine derivatives are involved in new developments in the field of dendrimers (Steffensen *et al*., 2006).

The reactivity of functional groups on the substituents attached to the 1,3,5-triazine ring system also has drawn considerable interest. Recently, the reactivity of peripheral functional groups on the aryl substituents appended on *s*-triazine AB_2 type monomer structural units is utilized in the synthesis of hyperbranched polymers (Kim *et al*., 1996; Cho *et al*., 2001). Though the synthesis of 2,4,6-tris(4-formylphenoxy)-1,3,5-triazine is reported, (Deborah *et al*., 1994; Hongdong Duan *et al*., 2011) the reactivity of its peripheral trifunctional groups is not much more explored. We are

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interested in the studies of three reactive aldehyde groups of 2,4,6-tris(4-formylphenoxy)-1,3,5-triazine for the formation of trichalcone which later used for biological applications.

The *s*-triazine-based chalcones and their derivatives are found to be effective as local anesthetics (Daukshas *et al*., 1984), antibacterial (Bremner and Meyer, 1998; Nielsen *et al*., 2004), antimalarial (Kenyon *et al*., 1995; Liu *et al*., 2001; Go *et al*., 2004), antiprotozoal (*Zhai et al*., 1999; Lunardi *et al*., 2003), antitubercular (Lin *et al*., 2002;), anticancer (Modzelewska *et al*., 2006; Rao *et al*., 2004), and antifungal agents (Svetaz *et al*., 2004; Nowakowska, 2007).

Based on the above observations and earlier investigations, here we are reporting the synthesis of various trichalcones containing core *s*-triazine ring and evaluation of their antibacterial and antifungal activity.

Materials and methods

All reagents were obtained from commercial suppliers, Merk Pvt. Ltd., Sd Fine Chemicals Mumbai, Aldrich USA and used without further purification. Melting points were determined in an open glass capillaries and are uncorrected. The purity of compounds was checked by TLC. The IR spectra of all compounds were recorded in KBr on Shimadzu FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra (DMSO) were recorded on a Brucker Avance 400 MHz spectrometer using tetramethylsilane (TMS, $\delta = 0$ ppm) as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer.

Synthesis of 2,4,6-tris (4-formyl phenoxy)-1,3,5-triazine(**III**)

A solution of sodium hydroxide (1.6 g, 0.04 mol) and *p*-hydroxybenzaldehyde (4.88 g, 0.04 mol) equivalent amount was prepared in 50 mL distilled water and taken in a 250 mL round-bottom flask at room temperature. To this solution, cyanuric chloride (1.84 g, 0.01 mol) in 50 mL dichloromethane and tetrabutyl ammonium bromide (TBAB) (0.020 g, 6.5×10^{-5} mol) as phase-transfer catalyst were added with constant stirring. The stirring was continued further at the same temperature for 24 h. After the completion of reaction as monitored by TLC, the two layers were separated. The organic layer was then well washed with (10 %) NaOH (3×25 mL) and distilled water (2×20 mL). It was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure to yield white powdered product. It was further purified by recrystallization from ethyl acetate to afford the white fluffy precipitate (Scheme 1).

Yield (%)-90, m.p($^{\circ}$C)-174, IR (KBr) in cm^{-1}: 2830, 2739 (C–H str. aldehyde), 1702 (C=O), 1566 (C=N str.), 840 (C–N, *s*-triazine).; ^{1}H NMR ($CDCl_3$): δ 7.32 (d, 6HAr-H), 7.92 (d, 6HAr-H), 10.00 (s, 3H –CHO) ppm. ^{13}C NMR ($CDCl_3$): δ 121.95 (C-3), 130.79 (C-4), 133.88 (C-5), 155.36 (C-2), 172.63 (C-1), 190.61(C-6) ppm.; EIMS (*m*/*z*, %): 442 ($M^+ + 1$); Anal. Calcd. for $C_{24}H_{15}N_3O_6$: C, 65.31; H, 3.43; N, 9.52 %. Found: C, 65.29; H, 3.41, N, 9.48 %.

General procedure for the synthesis of 2,4,6-tris[4′-{1″(phenyl)-2″-propenone-3″-yl}-phenoxy]-1,3,5-triazine**V**(**a**–**j**)

2,4,6-Tris(4-formyl phenoxy)-1,3,5-triazine(**III**) (4.42 g, 0.01 mol) was dissolved in DMF (30 mL) and unsubstituted acetophenone(**IV**) (3.6 g, 0.03 mol) was added to it. Then, solution of KOH (5 mL of 40 %) was added to reaction mixture with constant stirring at room temperature. After completion of reaction (monitored by TLC, 24 h), the reaction mixture was poured into crushed ice and neutralized with dil. HCl. The product was precipitated out. It was separated, washed with water, and dried. It was purified by recrystallization from the mixture of acetic acid:water (9:1) to give **Va**. The same general procedure was followed for the compound **Vb**–**Vj** (Table 1).

Biological activity

The antimicrobial activities of the synthesized trichalcones **Va–j** were determined by disc diffusion method (Biljana and Niko, 2010). The compounds were evaluated for

Scheme 1 2,4,6-Tris (4-formyl phenoxy)-1,3,5-triazine

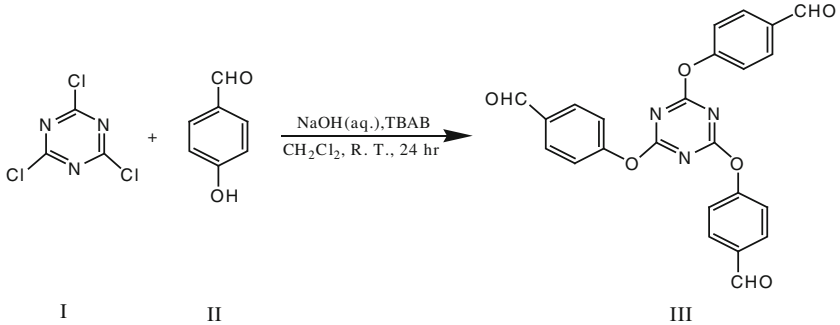

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Table 1 Synthesis of trichalcones

Entry	Product	R	R_1	R_2	R_3	R_4
1.	**Va**	H	H	H	H	H
2.	**Vb**	H	H	Cl	H	H
3.	**Vc**	H	H	Br	H	H
4.	**Vd**	H	H	NO_2	H	H
5.	**Ve**	H	NO_2	H	H	H
6.	**Vf**	H	H	OCH_3	H	H
7.	**Vg**	OCH_3	H	H	OCH_3	H
8	**Vh**	H	OCH_3	OCH_3	H	H
9.	**Vi**	H	OCH_3	OCH_3	OCH_3	H
10.	**Vj**	H	H	CH_3	H	H

antibacterial activity against *Proteus vulgaris*, *Staphylococcus aureus*, *Xanthomonas citri*, and *Erwinia cartovora.* The antifungal activity was evaluated against *Alternaria and Curvularia lunata*. The test compounds **V(a–j)**, in measured quantities, were dissolved in dimethyl sulphoxide (DMSO) to get the final concentration 200 µg/mL. The bacterial (24 h) and fungal (48 h) cultures from the slants were diluted with sterile distilled water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were spread on solidified agar (NA-nutrient agar for bacteria and PDA-potato dextrose agar for fungi) medium. The filter paper disks prepared by only DMSO (as a negative control) and with solutions of test compounds **V(a–j)** as well as standard compounds (Penicillin and Nystatin as positive control) were carefully placed over the spread cultures and incubated at 37 °C for 24 h for bacteria and at 28–30 °C for 48 h for fungi. After the incubation period, the plates were examined for the zone of inhibition. The diameters for the zone of inhibitions were measured (in mm) including the diameter of the disk also. All determinations were made in triplicate for each of the compound and the average value was taken. The antibacterial and antifungal activity was evaluated against *P. vulgaris*, *S. aureus*, *X. citri*, *E. cartovora*, *Alternaria*, and *C. lunata.* The outcomes of mean values and standard deviation are shown in Table 2.

Spectroscopic data of selected compounds

2,4,6-Tris[4′-{1′′-(phenyl)-2′′-propenone-3′′-yl}-phenoxy]-1,3,5-triazine(**Va**)

Yield(%)-85, m.p.(°C)-180, IR (KBr) in cm^{-1}:1643 (C=O), 1602 (C=N str.), 1579 (–CH=CH–, str.), 831 (C–N, *s*-triazine).; ^{1}H NMR (DMSO- d_6): δ 6.80 to 6.83 (d, 3H, –CO–CH=), 7.03–7.72 (m, 27 Ar–H), 8.09 to 8.13 (d, 3H, Ar–CH =) ppm.; ^{13}C NMR (DMSO- d_6) δ 115.73 (C-3) 118.73 (C-3), 125.49 (C-4), 127.96 (C-10), 128.26 (C-5), 130.33 (C-12), 132.23 (C-9), 137.99 (C-6), 144.52 (C-2), 160.05 (C-1), 189.16 (C-8) ppm.; Anal. Calcd. for $C_{48}H_{33}N_3O_6$: C, 77.10; H, 4.45; N, 5.62 %. Found: C, 77.05; H, 4.41, N, 5.58 %.

2,4,6-Tris[4′-{1′′-(4′′′-chlorophenyl)-2′′-propenone-3′′-yl}-phenoxy]-1,3,5-triazine(**Vb**)

Yield(%)-89, m.p.(°C)-230, IR (KBr) in cm^{-1}: 1688 (C=O), 1599 (C=N str.), 1500 (–CH=CH–, str.), 817 (C–N,

Table 2 Antibacterial and antifungal activities of synthesized trichalcones compounds using disc diffusion method(**Va–j**)

S. no.	Zone of inhibition (mm)					
	P. vulgaris	*S. aureus*	*X. citri*	*E. cartovora*	*Alternaria*	*C. lunata*
Va	7.83 ± 0.28	10.03 ± 0.15	6.96 ± 0.15	7.93 ± 0.20	5.10 ± 0.10	6.16 ± 0.15
Vb	14.00 ± 0.10	12.06 ± 0.20	10.06 ± 0.11	8.06 ± 0.05	8.03 ± 0.15	7.20 ± 0.20
Vc	11.86 ± 0.23	9.96 ± 0.05	11.10 ± 0.17	13.00 ± 0.10	6.16 ± 0.28	10.13 ± 0.11
Vd	5.90 ± 0.17	4.93 ± 0.11	6.10 ± 0.10	6.96 ± 0.05	7.00 ± 0.10	8.20 ± 0.17
Ve	10.03 ± 0.05	7.13 ± 0.15	7.96 ± 0.05	6.00 ± 0.10	7.96 ± 0.15	6.96 ± 0.05
Vf	6.96 ± 0.05	7.86 ± 0.23	8.86 ± 0.32	8.06 ± 0.11	10.23 ± 0.20	13.16 ± 0.15
Vg	7.86 ± 0.23	9.10 ± 0.10	10.03 ± 0.15	9.10 ± 0.17	12.16 ± 0.20	12.23 ± 0.20
Vh	12.26 ± 0.25	9.90 ± .0.17	11.13 ± 0.15	12.16 ± 0.20	12.13 ± 0.15	12.13 ± 0.15
Vi	11.06 ± 0.11	13.03 ± 0.05	10.10 ± 0.17	12.26 ± 0.25	13.20 ± 0.20	14.13 ± 0.05
Vj	10.03 ± 0.06	7.93 ± 0.11	10.06 ± 0.11	8.03 ± 0.15	5.16 ± 0.05	6.96 ± 0.05
Penicillin (Std.)	15	15	15	15	NA	NA
Nystatin (Std.)	NA	NA	NA	NA	15	15
DMSO −ve control	–	–	–	–	–	–

P. vulgaris Proteus vulgaris, *S. aureus Staphylococcus aureus*, *X. citri Xanthomonas citri*, *E. cartovora Erwinia cartovora*, *C. lunata Curvularia lunata*, *NA* not applicable

(−) No zone of inhibition, values are means of three replicates, ± Standard deviation

s-triazine).; ^{1}H NMR (DMSO-d_6): δ 7.3 (d, 3H, –CO–CH=), 7.6–8.0 (m, 24Ar-H), 8.1 to 8.2 (d, 3H, Ar–CH=) ppm.;^{13}C NMR (DMSO- d_6) δ 121.65 (C-3), 121.92 (C-7), 128.48 (C-4), 129.63 (C-11), 129.80 (C-5), 132.49 (C-10), 135.89 (C-9), 138.41 (C-12), 139.02 (C-6), 143.06 (C-2), 168.39 (C-1), 187.82 (C-8) ppm.; Anal. Calcd. for $C_{48}H_{30}Cl_3N_3O_6$: C, 67.74; H, 3.55; N, 4.94 %. Found: C, 67.70; H, 3.50., N, 4.52 %.

2,4,6-Tris[4′-{1″-(4‴-bromophenyl phenyl)-2″-propenone-3″-yl}-phenoxy]-1,3,5-triazine(**Vc**)

Yield(%)-88, m.p.(°C)-195, IR (KBr) in cm^{-1}: 1688 (C=O), 1602 (C=N str.), 1599 (–CH=CH–, str.), 817 (C–N, *s*-triazine).; ^{1}H NMR (DMSO- d_6): δ 6.57–6.60 (d, 3H, –CO–CH=), 7.04–7.73 (m, 24 Ar–H), 7.83–7.86 (d, 3H, Ar–CH=) ppm.;^{13}C NMR (DMSO- d_6) δ 114.96 (C-3) 121.65 (C-7), 127.93 (C-4), 129.42 (C-11), 131.37 (C-5), 131.48 (C-10), 132.49 (C-9), 135.33 (C-12), 138.41 (C-6), 139.02 (C-2), 155.57 (C-1), 197.29 (C-8) ppm.; Anal. Calcd. for $C_{48}H_{30}Br_3N_3O_6$: C, 58.56; H, 3.07; N, 4.27 %. Found: C, 58.52; H, 3.02., N, 4.22 %.

2,4,6-Tris[4′-{1″-(4‴-nitrophenyl)-2″-propenone-3″-yl}-phenoxy]-1,3,5-triazine(**Vd**)

Yield(%)-85, m.p.(°C)-200, IR (KBr) in cm^{-1}: 1697 (C=O), 1598 (C=N str.), 1521 (–CH=CH–, str.), 817 (C–N, *s*-triazine).; ^{1}H NMR (DMSO- d_6): δ 7.49–7.52 (d, 3H, –CO–CH=), 7.8–8.29 (m, 24 Ar–H), 8.31–8.32 (d, 3H, Ar–CH=)ppm.;^{13}C NMR (DMSO- d_6) δ 121.65 (C-3), 121.92 (C-7), 128.48 (C-4), 129.63 (C-11), 129.80 (C-5), 132.49 (C-10), 135.89 (C-5), 138.41 (C-10), 139.02 (C-9), 143.06 (C-12), 168.39 (C-1), 187.82 (C-8) ppm.; Anal. Calcd. for $C_{48}H_{30}N_6O_{12}$: C, 65.31; H, 3.43; N, 9.52 %. Found: C, 65.25; H, 3.40., N, 9.48 %.

2,4,6-Tris[4′-{1″-(4‴-methoxyphenyl)-2″-propenone-3″-yl}-phenoxy]-1,3,5triazine(**Vf**)

Yield(%)-86, m.p.(°C)-250, IR (KBr) in cm^{-1}: 1643 (C=O), 1602 (C=N str.), 1577 (–CH=CH–, str.), 1166 (C–O) 829 (C–N, *s*-triazine).; ^{1}H NMR (DMSO- d_6): δ 3.8 (s, 9H, OCH_3) 6.79–6.83 (d, 3H, –CO–CH=), 7.03–7.96 (m, 24 Ar–H), 8.09–8.13 (d, 3H, Ar–CH=)ppm.;^{13}C NMR (DMSO- d_6) δ 55.14 (C-13), 113.3 (C-11), 121.97 (C-3), 122.17 (C-7), 129.33 (C-4), 130.18 (C-5), 130.48 (C-9), 133.05 (C-10), 141.65 (C-6), 151.38 (C-2), 161.11 (C-12), 163.06 (C-1), 187.35 (C-8) ppm.; Anal. Calcd. for $C_{51}H_{39}N_3O_9$: C, 73.11; H, 4.69; N, 5.02 %. Found: C, 73.05; H, 4.66., N, 5.05 %.

2,4,6-Tris[4′-{1″-(3‴,4‴,5‴-trimethoxyphenyl)-2″-propenone-3″-yl}-phenoxy]-1,3,5-triazine(**Vi**)

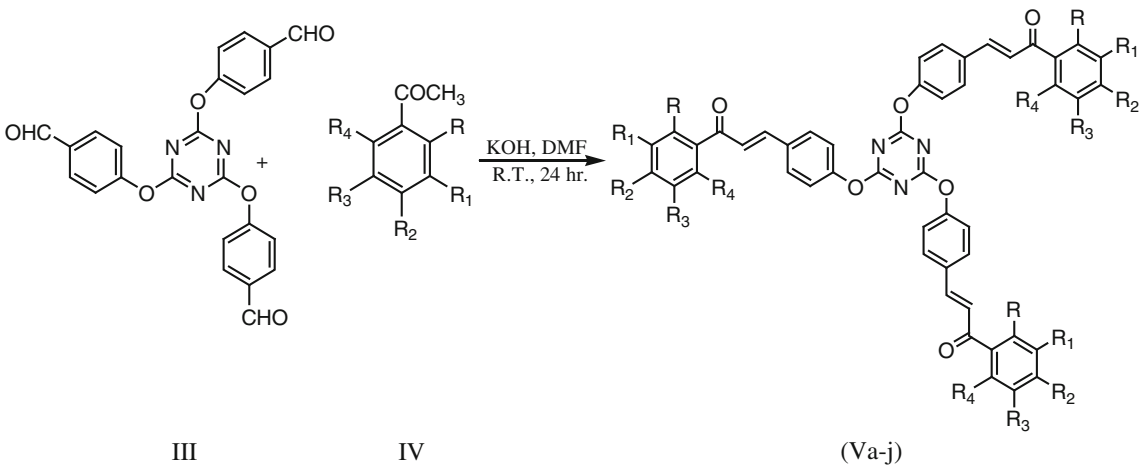
Yield(%)-84, m.p.(°C)-210, IR (KBr) in cm^{-1}: 1647 (C=O), 1604 (C=N str.), 1570 (–CH=CH–, str.), 1163 (C–O), 829 (C–N, *s*-triazine).;^{1}H NMR (DMSO- d_6): δ 3.7 (s, 9H, OCH_3),3.8 (s, 18 H 2 × OCH_3), 6.89–6.92 (d, 3H, –CO–CH=), 7.20–7.89 (m, 18Ar-H), 8.007–8.10 (d, 3H, Ar–CH=) ppm.;^{13}C NMR (DMSO- d_6): δ 55.79 (C-13), 60.12 (C-14,) 105.51 (C-4), 115.11 (C-3), 121.01 (C-8), 129.11 (C-7), 130.28 (C-10), 130.69 (C-9), 139.36 (C-6), 142.92 (C-11), 152.90 (C-2), 161.94 (C-1), 187.19 (C-8). ppm.; Anal. Calcd. for $C_{57}H_{51}N_3O_{15}$: C, 67.25; H, 5.05; N, 4.13 %. Found: C, 67.23; H, 5.01., N, 4.09 %.

Results and discussion

The starting material 2,4,6-Tris(*p*-formylphenoxy)-1,3,5-triazine(**III**) for the synthesis of trichalcones(**V**) was prepared by the reaction of one equivalent of 2,4,6-trichloro-1,3,5-triazine and three equivalent of sodium salt of *p*-hydroxybenzaldehyde in the presence of TBAB as phase-transfer catalyst in dichloromethane at room temperature for 24 h. Trichalcones(**V**) were synthesized by the reaction of one equivalent of 2,4,6-tris(*p*-formylphenoxy)-1,3,5-triazine(**III**) and variety of acetophenones(**IV**) in the presence of aqueous KOH solution at room temperature for 24 h affording good yield. All the newly synthesized trichalcones were evaluated for their antibacterial and antifungal activity.

We have introduced for the first time the use of TBAB as a phase-transfer catalyst in the synthesis of 2,4,6-tris(*p*-formylphenoxy)-1,3,5-triazine at room temperature affording excellent yield 90 % higher than the published methods which require refluxing (Deborah *et al*., 1994; Hongdong Duan *et al*., 2011). Initially, trichalcone(**Va**) was obtained using synthetic method outlined in Scheme 2 affording good yield. Infrared (IR) indicated the disappearance of aldehyde. Further variety of trichalcones (**Vb**–**Vj**) were synthesized by the similar procedure using array of substituted acetophenones containing electron-withdrawing and -releasing substituent to account the effect of substituent on yield of trichalcone. The electron-withdrawing and -releasing substituent does not show any considerable effect on yield of trichalcone.

In comparison with standard antibacterial penicillin, compounds **Vb** and **Vh** found to be active against *P. vulgaris.* Compounds **Vb** and **Vi** were found to be active against *S. aureus*. As compared with standard antibacterial compounds, **Vb**, **Vc**, **Vh**, **Vi**, and **Vj** were observed as active against *X. citri* and compounds **Vc**, **Vh**, and **Vi** were found to be active against *E. cartovora.* In comparison with



Scheme 2 Synthesis of 2,4,6-Tris[4′-{1′′(phenyl)-2′′-propenone-3′′-yl}-phenoxy]-1,3,5-triazine**V**(**a**–**j**)

standard antifungal nystatine, compounds **Vf**, **Vg**, and **Vh** were found to be active against *Alternaria* and compounds **Vf** and **Vi** were found to be active against *C. lunata.* Compound **Vb** showed highest antibacterial activity whereas compound **Vi** showed highest antifungal activity.

Conclusion

In conclusion, we have developed a new method for the synthesis of intermediate 2,4,6-tris(*p*-formylphenoxy)-1,3,5-triazine(**III**) using phase-transfer catalyst. The reactive terminal aldehyde groups on the side substituents of 2,4,6-tris(*p*-formylphenoxy)-1,3,5-triazine(**III**) could be readily elaborated to the trifunctionalized chalcones by reaction with the various acetophenones. The structures of the newly synthesized trichalcones were confirmed by elemental analysis, FT-IR, ^{1}H and ^{13}C NMR spectroscopy and further screened for their antimicrobial activity. The antibacterial and antifungal activity revealed that most of the compounds showed moderate to good activity.

Efforts on the synthesis, characterization, and antimicrobial activity of trichalcones starting from 2,4,6-tris(4-acetylphenoxy)-1,3,5-triazine are in progress and will be reported in future communications.

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