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# Synthesis of nano-sized $C_3$-symmetric 2,4,6-triphenyl-1,3,5-*s*-triazine and 1,3,5-triphenylbenzene derivatives via the trimerization followed by Suzuki-Miyaura cross-coupling or O-alkylation reactions and their biological evaluation

Sambasivarao Kotha [a]*, Dhurke Kashinath [a], Manu Lopus [b] & Dulal Panda[b]

[a]Department of Chemistry, Indian Institute of Technology-Bombay, Powai, Mumbai 400 076, India

[b]School of BioSciences and Bioengineering, Indian Institute of Technology-Bombay, Powai, Mumbai 400 076, India

E-mail: srk@chem.iitb.ac.in

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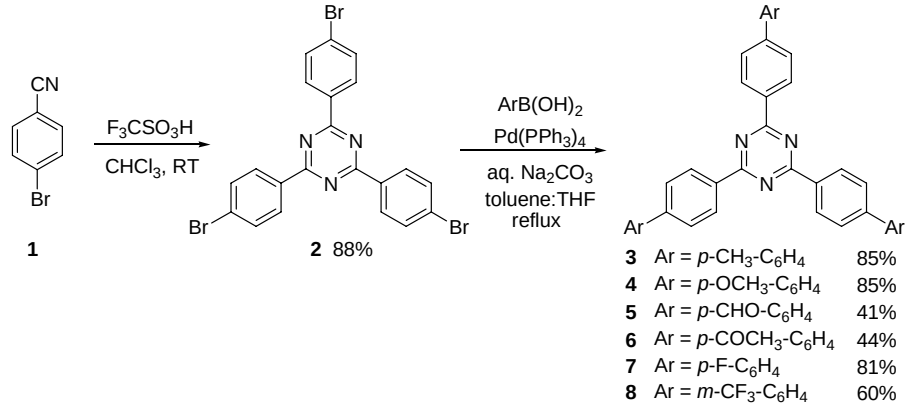
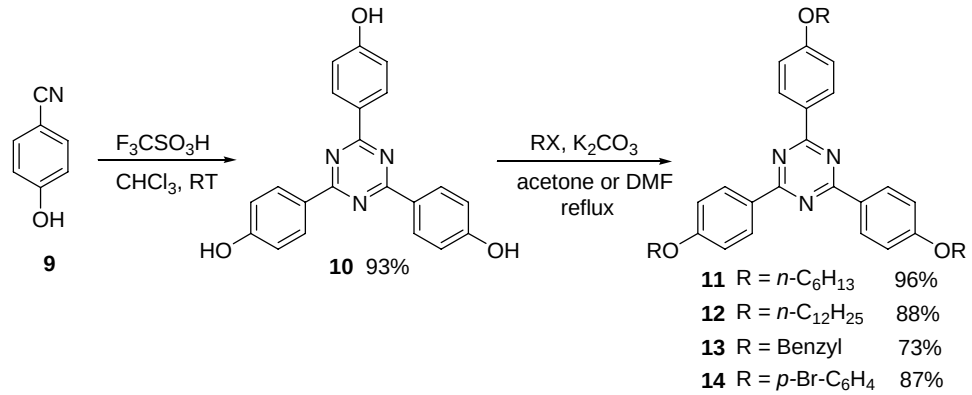
Various $C_3$-symmetric 2,4,6-triphenyl-1,3-5-*s*-triazine and 1,3,5-triphenylbenzene derivatives have been prepared using cyclotrimerization, Suzuki-Miyaura cross-coupling and O-alkylation reactions as key steps. The biological activity of O-alkylated triazine derivatives has been studied towards the HeLa cell proliferation. The resulting $C_3$-symmetric derivatives can also be useful in materials chemistry.

**Keywords**: 2,4,6-Triphenyl-1,3-5-*s*-triazine, 1,3,5-triphenylbenzene, cyclotrimerization, Suzuki-Miyaura cross-coupling, O-alkylation

Triazine derivatives are useful building blocks in organic chemistry and well known in the literature for their chelating properties[1]. These compounds show diverse biological properties and extensively used in the cosmetic industry. Particularly, the alkyloxy derivatives of triphenyl *s*-triazines act as UV protectants and useful in the preparation of cosmetic materials related to skin and hair of human and animals[2]. Along with these, simple triazine derivatives show biological activity towards various types of bacteria, virus, fungi[3] glucocerebrocisidase inhibition and Gaucher disease[4] and useful in catalysis, analytical and coordination chemistry[5]. They are used extensively for the manufacturing of polymer fibers, plasticizers, thermoplastic resin blends[6], in preparing melamine-formaldehyde resins[7]. Recently the focus has been shifted towards the synthesis of higher generation of $C_3$-symmetric 2,4,6-triphenyl-1,3,5-*s*-triazine derivatives especially with materials applications. In this regard, a new class of disc-shaped molecules with mesophase properties, liquid-crystalline materials have been synthesized using 2,4,6-triphenyl-1,3,5-*s*-triazine as center core[8]. Organic-light-emitting-devices (OLEDs) has attracted a great deal of attention due to their promising applications as electroluminescent devices[9]. Star shaped organic molecules containing 1,3,5-triphenyl benzene and 2,4,6-triphenyl-1,3,5-*s*-triazine units acts as effective emitters or electron transport materials in OLEDs. Therefore, a series of neutral, π-conjugated star shaped organic molecules containing 1,3,5-triazine unit have been synthesized and their chemilumenescent properties have been studied[10]. Triazine unit was also used as host for synthesizing self assembly supramolecular (2-5 nm) networks[11], poly-catenane 2D networks[12] and molecular octupoles which shows off-resonance third order optical nonlinearities[13]. In addition, triazine molecules forms layered structures and useful in crystal engineering[14]. Although several methods are available for the synthesis of triazine skeleton[15], and its derivatives[16], limited methods are reported for the synthesis of $C_3$-symmetric biphenyl-based and trialkoxy derivatives of triazine molecules[17]. Moreover, some of these methods are based on Friedal-Crafts alkylation or Grignard reactions[18]. In view of the importance of triazine derivatives and in continuation of our interest in $C_3$-symmetric molecules[19], herein, a simple and general methodology for the synthesis of biphenyl-based and alkyloxy *s*-triazine derivatives using Lewis acid mediated cyclotrimerizaton followed by Suzuki-Miyaura cross-coupling[20] or O-alkylation reactions as key steps has been reported.




**Scheme I** — Preparation of the biphenyl-based triazines **3**-**8**

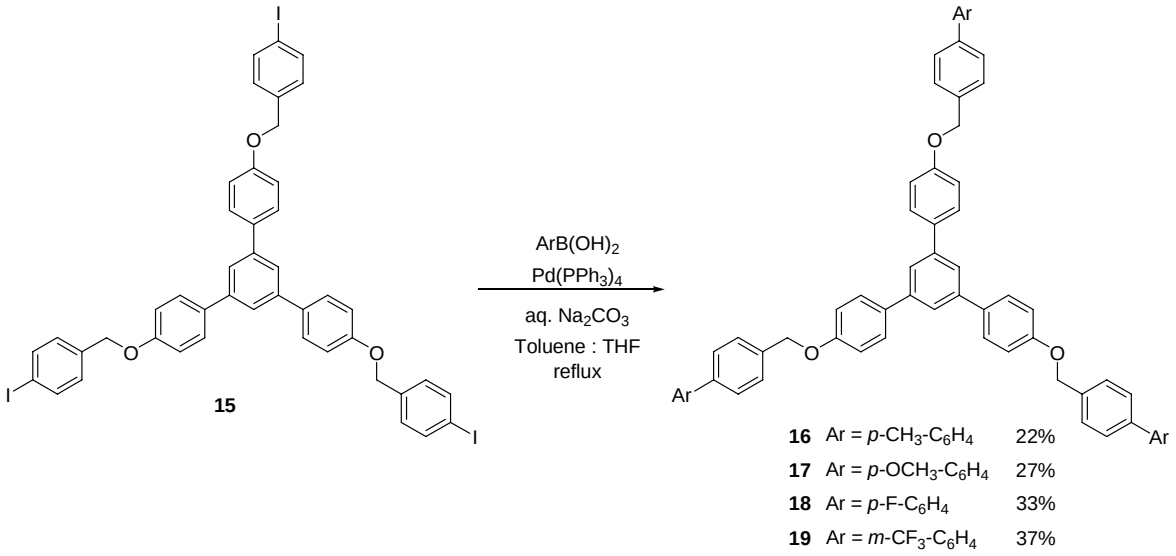



**Scheme II** — Preparation of the O-alkylated triazines **11**-**14**

In this regard, initially 2,4,6-tris(4-bromophenyl)-1,3,5-*s*-triazine **2** was prepared according to literature procedure[21]. The cyclotrimerization of 4-bromobenzonitrile **1** in presence of trifluoromethanesulfonic acid gave bromo derivative **2** in 88% yield. Then bromo derivative **2** was coupled with various aryl boronic acids under Suzuki-Miyaura cross-coupling conditions. To this end, the bromo derivative **2** was refluxed (in Toluene:THF, 1:1) with various arylboronic acids in the presence of tetrakistriphenylphosphine palladium(0) [$Pd(PPh_3)_4$] and base (aq. $Na_2CO_3$) to give the corresponding cross-coupling products **3**-**8** in moderate to good yields (40-85%) (**Scheme I**). All the cross-coupling products were characterized based on their complimentary spectral data. Physical properties of Suzuki coupling products were studied using Transmission Electron Microscopy which indicates the formation of flakes with 200-300 nm widths for biphenyl-based derivatives. This may be due to π-π stacking between the molecules[22].

After preparing the biphenyl-based triazine derivatives **3**-**8**, attention was turned towards the synthesis of triphenoxy derivatives of 1,3,5-*s*-triazine under phase transfer-catalysis (PTC) conditions. To achieve this, the trihydroxy compound **10** was prepared from 4-cyanophenol[23]. The treatment of 4-cyanophenol **9**, with trifluoromethane sulfonic acid gave the trimerized product **10** in 93% yield (**Scheme II**). Next, **10** was treated with different alkyl/aryl bromides under PTC conditions to generate alkyloxy/aryloxy derivatives **11**-**14** in good yields (73-96%).

The halogen functionality present in the compound type **14** can be used further for the preparation of biphenyl derivatives of higher generation using Suzuki-Miyaura cross-coupling reaction. To test this idea, the compound **15** (prepared by the trimerization of *p*-hydroxyacetophenone followed by *O*-alkylation with *p*-iodobenzyl bromide) was treated with different arylboronic acids under palladium-catalyzed Suzuki-Miyaura cross-coupling reaction and as expected, the cross-coupling products **16**-**19** in 22-38% yields were obtained (**Scheme III**)[28]. The low yields are due to the poor solubility of the coupling products in common solvents and practical difficulties associated with the




**Scheme III** — Preparation of the compounds **16-19**

column chromatography. As an extension of this strategy, liquid crystalline materials based on 1,3,5-triphenylbenzene and 2,4,6-triphenyl-1,3,5-*s*-triazine were also synthesized[24].

It is clear from the introduction part that the triazine compounds show diverse biological activity. Considering this, our attention was turned towards the biological activity of resulting compounds. Towards this, *O*-alkylated derivatives were tested for the HeLa cell proliferation (**Table I**).

**Table I —** Cell proliferation data for the compounds **10-14**

| Conc. (μ*M*) | % Cell proliferation of triphenoxy derivatives | | | | |
|---|---|---|---|---|---|
| | **10** | **11** | **12** | **13** | **14** |
| 0 | 100 | 100 | 100 | 100 | 100 |
| 1 | 98 | 96.5 | 97.6 | 99.9 | 97.5 |
| 3 | 97.5 | 98.2 | 95.5 | 98.65 | 98.7 |
| 10 | 98.1 | 9.3 | 98.3 | 99 | 95.3 |
| 20 | 97.9 | 96.6 | 97.44 | 98 | 96 |

## Experimental Section

**General Procedure for the Suzuki–Miyaura cross-coupling reaction**: A mixture of tribromo compound **2** (1 equiv), arylboronic acid (6-7 equiv), $Pd(PPh_3)_4$ (8-10 mol%), $Na_2CO_3$ (6 equiv) in water and solvent THF and toluene (1:1) was heated at 90°C under $N_2$. At the conclusion of reaction (TLC monitoring), the mixture was diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water, brine and dried ($MgSO_4$). The solvent was evaporated and the crude product obtained was charged on a silica gel column. Elution of the column with EtOAc-hexane gave the desired cross-coupling product.

**Spectral data for 2,4,6-Tris-(4′-methyl-biphenyl-4-yl–[1,3,5]triazine 3**: m.p. 184-186°C; $^1$H NMR (400 MHz $CDCl_3$): δ 2.42 (s, 9H, Ar-$CH_3$), 7.29 (d, *J* = 7.2 Hz, 6H), 7.59 (d, *J* = 7.2 Hz, 6H), 7.76 (d, *J* = 8.4 Hz, 6H), 8.80 (d, *J* = 7.2, 6H, Ar-H attached to triazine ring); $^{13}$C NMR (100.5 MHz $CDCl_3$): δ 21.28 (Ar-$CH_3$), 127.13, 127.18, 129.51, 129.72, 135.02, 137.57, 137.98, 145.10, 171.37; EI Mass (QToF): 580.2760 (M+1).

**2,4,6-Tris-(4′-methoxy-biphenyl-4-yl–[1,3,5]triazine 4**: m.p. 182-184°C; $^1$H NMR (300 MHz $CDCl_3$): δ 3.87 (s, 9H), 7.02 (d, *J* = 8.22 Hz, 6H), 7.64 (d, *J* = 8.79 Hz, 6H), 7.74 (AB part of AA′BB′ system, *J* = 8.42 Hz, 6H), 8.80 (A′ B′ part of AA′BB′ system, *J* = 8.42 Hz, 6H); $^{13}$C NMR (75.4 MHz $CDCl_3$): δ 55.46, 114.43, 126.79, 128.41, 129.53, 132.91, 134.70, 144.70, 159.78, 171.33. EI-HRMS: Calcd. for : $C_{45}H_{33}N_3O_3$ : 627.2522; Found: 628.2611 (M+1).

**2,4,6-Tris-(4’-fluoro-biphenyl-4-yl–[1,3,5]triazine 7**: m.p. 228-230°C; $^1$H NMR (300 MHz $CDCl_3$): δ 7.16-7.22 (m, 6H), 7.65-7.69 (m,6H), 7.84 (d, *J* = 8.42 Hz, 6H), 8.84 (d, *J* = 8.42 Hz, 6H); EI Mass (QToF) : 592.2000.

**2,4,6-Tris-(3′-trifluoromethyl-biphenyl-4-yl-[1,3,5]-triazine 8**: m.p. 222-224°C; $^1$H NMR (400 MHz $CDCl_3$): δ 7.60-7.71 (d, *J* = 8 Hz, 3H), 7.66 (d, *J* = 7.6 Hz, 3H), 7.80 (d, 3H), 7.86 (d, *J* = 7.2

6H), 8.86 (d, *J* = 8.4 Hz, 6H); $^{13}$C NMR (100.4 MHz $CDCl_3$): δ 124.05 ( *J* = 4.2 Hz), 124.15 (*J* = 271.88 Hz), 127.44, 129.46, 129.70, 130.55, 131.43 ( *J* = 31.72 Hz), 135.82, 141.16, 143.70, 171.29. EI-HRMS: Calcd. for: $C_{42}H_{24}N_3F_9$: 742.1904; Found: 742.1915 (M+1).

**General procedure for *O*-alkylation reaction**: A mixture of trihydroxy compound 10 (1.4 mmoles), $K_2CO_3$ (6.3 mmoles) and alkyl/aryl halide (6.3 mmoles) in dry acetone (10 mL) was refluxed for 7-12 hr. At the conclusion of reaction (TLC monitoring), the reaction mixture was cooled to RT, diluted with water and extracted with Ethyl acetate (3 × 10 mL). The combined organic extracts were washed with water, brine and dried ($MgSO_4$). The solvent was evaporated and the crude product obtained was charged on a silica gel column. Elution of the column with EtOAc-petroleum ether gave the desired *O*-alkylated product.

**Spectral data for compound 2,4,6-Tris-(4-*n*-hexyloxyphenyl)-[1,3,5]triazine 11**: m.p. 55-57ºC; $^1$H NMR (400 MHz $CDCl_3$): δ 0.90-0.94 (t, *J* = 6.9 Hz, 9H), 1.33-1.39 (m, 12H), 1.45-1.58 (heptet, *J* = 6.6 Hz, 6H), 1.79-1.88 (quintet, *J* = 6.6 Hz, 6H), 4.07 (t, *J* = 6.6 Hz, 6H), 7.03 (d, *J* = 8.1 Hz, 6H), 8.68 (d, *J* = 8.1 Hz, 6H); $^{13}$C NMR (100.5 MHz $CDCl_3$): δ 14.13, 22.69, 25.81, 29.83, 31.70, 68.32, 114.46, 128.91, 130.84, 162.85, 170.77.

**2,4,6-Tris-(4-*n*-dodecyloxyphenyl)-[1,3,5]triazine 12**: m.p. 45-47ºC; $^1$H NMR (400 MHz $CDCl_3$): δ 0.87 (t, *J* = 6 Hz, 9H, terminal $CH_3$), 1.27 (bs, 48H, alkyl $CH_2$-), 1.48 (triplet, *J* = 8 Hz, 6H, alkyl $CH_2$-), 1.79-1.86 (quintet, *J* = 6.8 Hz, 6H, Ar-O-$CH_2$-$CH_2$-), 4.04-4.07 (t, *J* = 6.4 Hz, 6H, Ar-O-$CH_2$-$CH_2$-), 7.02 (d, *J* = 8.8 Hz, 6H, Ar-H), 8.68 (d, *J* = 8.8 Hz, 6H, Ar-H); $^{13}$C NMR (100.5 MHz $CDCl_3$): δ 14.13, 22.71, 26.07, 29.25, 29.38, 29.44, 29.61, 29.63, 29.67, 29.69, 31.94, 68.22, 114.36, 128.87, 130.72, 162.76, 170.70.; EI-HRMS (MicroToF): 862.6750.

**2,4,6-Tris-(4-benzyloxy phenyl)-[1,3,5]triazine 13**: m.p. 84-86ºC; $^1$H NMR (400 MHz $CDCl_3$ + DMSO-$d_6$): δ 5.18 (s, 6H), 7.12 (d, *J* = 8.8 Hz, 6H), 7.33-7.48 (m, 15H), 8.69 (d, *J* = 8.8 Hz, 6H); $^{13}$C NMR (100.5 MHz $CDCl_3$+DMSO-$d_6$): δ 70.15, 114.79, 127.56, 128.16, 128.68, 129.21, 130.83, 136.53, 162.36, 170.64.

**Spectral data for Tris-1,3,5[4-(4-methylphenyl)-benzyloxyphenyl]benzene 16**: m.p. 226-230ºC; $^1$H NMR (400 MHz $CDCl_3$): δ 2.40 (s, 9H, Ar-$CH_3$), 5.16 (s, 6H, Ar-O-$CH_2$-Ar), 7.10 (d, *J* = 8.00 Hz, 6H, Ar-H), 7.25 (m, 6 H), 7.49-7.53 (t, *J* = 7.2 Hz, 12H, Ar-H), 7.60-7.64 (t, 12H, *J* = 6.8 Hz, Ar-H), 7.66 (s, 3H, Ar-H of central benzene ring); $^{13}$C NMR (100.6 MHz $CDCl_3$): δ 21.13 (Ar-$CH_3$), 69.98 (Ar-O-$CH_2$-Ar), 115.25, 123.95, 127.03, 127.27, 128.07, 128.46, 129.59, 134.16, 135.67, 137.26, 137.96, 141.03, 141.86, 158.58; EI-HRMS: Calcd. for: $C_{66}H_{54}O_3$ : 894.4072; Found: 894.5940.

**Tris-1,3,5[4-(4-methoxyphenyl)benzyloxyphenyl]benzene 17**: m.p. 145-147ºC; $^1$H NMR (400 MHz $CDCl_3$): δ 3.85 (s, 9H, Ar-$OCH_3$), 5.15 (s, 6H, Ar-O-$CH_2$-Ar), 6.98 (d, *J* = 8.4 Hz, 6H, Ar-H), 7.10 (d, *J* = 8.8 Hz, 6H, Ar-H), 7.51 (d, *J* = 8.4 Hz, 6H, Ar-H) 7.54 (d, *J* = 8.8 Hz, 6H, Ar-H), 7.59 (d, *J* = 8.4Hz, 6H, Ar-H), 7.64 (d, *J* = 8.4Hz, 6H, Ar-H), 7.66 (s, 3H, Ar-H of central benzene ring); $^{13}$C NMR (100.6 MHz $CDCl_3$): δ 55.49 (Ar-O-$CH_3$), 70.05 (Ar-O-$CH_2$-Ar), 114.36, 115.32, 124.01, 127.09, 128.17, 128.28, 128.51, 133.43, 134.19, 135.38, 140.75, 141.91, 158.65, 159.35.

**Tris-1,3,5[4-(4-fluoromethylphenyl)benzyloxyphenyl]benzene 18**: m.p. 170-174ºC; $^1$H NMR (300 MHz $CDCl_3$): δ 5.18 (s, 6H, Ar-O-$CH_2$-Ar), 7.10 (d, *J* = 8.4 Hz, 6H, Ar-H), 7.54-7.66 (m, 30 H, Ar-H), 7.77 (d, *J* =7.2 Hz, 3H, Ar-H), 7.84 (s, 3H, Ar-H of central benzene ring); $^{13}$C NMR (75.4 MHz $CDCl_3$): δ 69.90 (Ar-O-$CH_2$-Ar), 115.40, 124.11, 124.24, 127.65, 128.32, 128.61, 129.49, 130.58, 134.36, 137.04, 139.68, 141.74, 141.97, 158.60.

**Tris-1,3,5[4-(3-trifluoromethylphenyl)benzyloxyphenyl]benzene 19**: m.p. 167-170ºC; $^1$H NMR (300 MHz $CDCl_3$): δ 5.18 (s, 6H, Ar-O-$CH_2$-Ar), 7.10 (d, *J* = 8.4 Hz, 6H, Ar-H), 7.54-7.66 (m, 30 H, Ar-H), 7.77 (d, *J* =7.2 Hz, 3H, Ar-H), 7.84 (s, 3H, Ar-H of central benzene ring); $^{13}$C NMR (75.4 MHz $CDCl_3$): δ 69.90 (Ar-O-$CH_2$-Ar), 115.40, 124.11, 124.24, 127.65, 128.32, 128.61, 129.49, 130.58, 134.36, 137.04, 139.68, 141.74, 141.97, 158.60; EI-HRMS: Calcd. for: $C_{66}H_{45}O_3F_9$:1057.3303; Found: 1057.3298 (M+1).

**Cell Culture and Proliferation Assay**: Sulphorhodamine B assay was carried out as follows: HeLa cells were grown in minimal essential medium (Himedia) supplemented with 10% (v/v) fetal bovine serum, kanamycin (0.1 mg/mL), penicillin G (100 units/mL) and sodium bicarbonate (30 mg/mL) at 37ºC in 5% $CO_2$. Cell proliferation was determined in 96-well plates using the sulforhodamine B assay as previously described[25]. In brief, 1 × $10^5$ cells were seeded in each well. Approximately 24 hr later, cells were incubated with different concentrations of each

compounds for an additional 24 hr. Cells were then fixed with 10% trichloroacetic acid and stained with 0.4% sulforhodamine B dissolved in 1% acetic acid. Each assay condition within an experiment was carried out two times, and two replicate experiments were performed. The results are given in the **Table I**.

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