A New Facile Synthesis of 2-Substituted 4,6-Diphenyl-1,3,5-triazines

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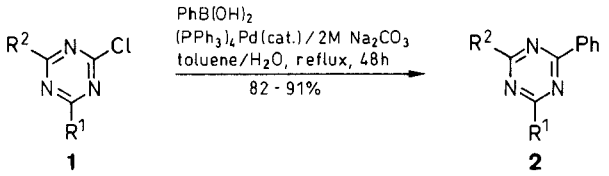
A new efficient synthesis of symmetrically and unsymmetrically 2-substituted 4,6-diphenyl-1,3,5-triazines **2** by palladium-catalyzed cross coupling reaction of 2-substituted 4,6-dichloro-1,3,5-triazines **1** with phenylboronic acid is described.

2,4,6-Triaryl-1,3,5-triazines are generally available by cyclotrimerisation of aromatic nitriles under various conditions.[1-3] But this method is only useful for the preparation of 1,3,5-triazines having three identical aryl substituents. The Grignard[4] and Friedel–Crafts[5] reactions with cyanuric halides are limited to those substituents that will not react either with the organometallic reagent or under the highly acidic conditions required in the latter case. Unsymmetrically substituted 2,4,6-triaryl-1,3,5-triazines can be prepared in good to moderate yield by ring formation using synthetic intermediates like imido compounds.[6-8]

In 1981 Suzuki and co-workers reported on the synthesis of biaryls by the palladium-catalysed cross coupling reaction of phenylboronic acid with haloarenes.[9] This procedure has widely been used for the synthesis of phenylenes[10] and polyphenylenes[11] and for the (hetero)arylation of various heterocycles including pyridines,[12] thiophenes,[13] thiazoles,[14] furanes,[14,15] pyrazines[16] or pyrimidines,[17] respectively. Nothing is known about the suitability of this method of C,C-coupling for the preparation of 2,4,6-triaryl-1,3,5-triazines.

Herein we describe that 2-substituted 4,6-diphenyl-1,3,5-triazines **2** can be easily obtained in high yields by palladium(0)-catalyzed reaction of the corresponding chloro-1,3,5-triazines **1** with phenylboronic acid.

If one equivalent of the 2-substituted 4,6-dichloro-1,3,5-triazines **1a–d** containing alkoxy or a phenoxy substituent, respectively, was stirred and refluxed for several hours with 2 equivalents phenylboronic acid in toluene/2 M sodium carbonate using tetrakis(triphenylphosphine)palladium(0) as catalyst, the 2-alkoxy(phenoxy)-4,6-diphenyl-1,3,5-triazines **2a–d** were obtained in high yield. Using the same reaction conditions 2,4,6-triphenyl-1,3,5-triazine[2] **(2e)** could be prepared starting from cyanuric chloride **1e**.



1 **2**

1	R^1	R^2	2	R^1	R^2
a	OMe	Cl	**a**	OMe	Ph
b	OC_3H_7	Cl	**b**	OC_3H_7	Ph
c	$OC_{10}H_{21}$	Cl	**c**	$OC_{10}H_{21}$	Ph
d	OPh	Cl	**d**	OPh	Ph
e	Cl	Cl	**e**	Ph	Ph

Taking into account the possibility of successive chlorine exchange of cyanuric chloride and considering that Suzuki's cross coupling tolerates a variety of functional groups like alkoxycarbonyl,[9] nitro,[19] formyl[19,20] or carboxamido[21] substituents, this synthetic approach can be useful for the preparation of highly functionalized 2,4,6-triaryl-1,3,5-triazines as excellent intermediates for organic synthesis.

All reagents were of commercial quality. Phenylboronic acid was purchased from Aldrich Chemical Co. $(Ph_3P)_4Pd$ was received from Janssen Chimica. Silica gel 60, 230–400 mesh, (E. Merck) and TLC on silica gel 60 F-254 plates were used for flash and analytical chromatography. Melting points were determined with a BOETIUS micro melting point apparatus and are uncorrected. IR spectra were obtained using a Specord M 80 spectrophotometer (Carl Zeiss Jena).

Table 1. Compounds **2** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a] or Lit. mp (°C)	IR (KBr) ν (cm^{-1})	MS *m/z* (%)
2a	82	110–112 (hexane)	$C_{16}H_{13}N_3O$ (263.3)	1550, 1530, 1380, 1360	263(M^+, 84), 233(49), 130(45), 104(70), 103(100), 77(31)
2b	91	104–106 ($AcOH/H_2O$)	$C_{18}H_{17}N_3O$ (291.1)	1540, 1530, 1450, 1380, 1360, 780	291(M^+, 68), 290(100), 248(79) 233(35), 130(35), 104(87), 103(69), 77(41)
2c	83	51–53[b] ($AcOH/H_2O$)	$C_{25}H_{31}N_3O$ (389.6)	1540, 1530, 1450, 1380, 1350, 780	389(M^+, 15), 388(19), 312(11), 250(39), 210(32), 208(100), 104(31)
2d	86	144–146 (AcOH)	$C_{21}H_{15}N_3O$ (325.4)	1550, 1520, 1490. 1360, 1210, 770	325(M^+, 60), 181(17), 180(100), 129(29), 77(37)
2e	87	240–242 (AcOH)	232[2]	1520, 1370, 745	309 (M^+, 67), 228(62), 159(32), 130(10), 103(100), 89(17), 77(10)

[a] Satisfactory elemental analyses obtained: C ± 0.33, H ± 0.18, N ± 0.15.
[b] Purification was carried out by flash chromatography using petroleum ether/EtOAc (30 : 1) as eluent.

Table 2. NMR Data of the Triazines **2**

Product	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
2a	4.02 (s, 3H), 7.34–7.45 (m, 6H), 8.45–8.50 (m, 4H)	55.0 (q, 1C), 128.6 (d, 4C), 129.1 (d, 4C), 132.7 (d, 2C), 135.7 (s, 2C), 171.9 (s, 1C), 173.6 (s, 2C)
2b	1.12 (t, 3H, J = 7.5), 1.96 (qt, 2H, J = 7.5, 7.0), 4.58 (t, 2H, J = 7.0), 7.51–7.62 (m, 6H), 8.62–8.67 (m, 4H)	10.45 (q, 1C), 22.0 (t, 1C), 69.58 (t, 1C), 128.4 (d, 4C), 128.9 (d, 4C), 132.5 (d, 2C), 135.6 (s, 2C), 171.4 (s, 1C), 173.3 (s, 2C)
2c	0.92 (t, 3H, J = 7.0), 1.35 (m, 12H), 1.57 (tt, 2H, J = 7.5), 1.96 (tt, 2H, J = 7.5, 6.5), 4.65 (t, 2H, J = 6.5), 7.50–7.70 (m, 6H), 8.63–8.78 (m, 4H)	14.1 (q, 1C), 22.6 (t, 1C), 25.95 (t, 1C), 28.8 (t, 1C), 29.3 (t, 1C), 29.4 (t, 1C), 29.5 (t, 2C), 31.9 (t, 1C), 68.2 (t, 1C), 128.5 (d, 4C), 129.0 (d, 4C), 132.6 (d, 2C), 135.8 (s, 2C), 171.6 (s, 1C), 173.5 (s, 2C)
2d	7.31–7.61 (m, 11H), 8.54–8.58 (m, 4H)	121.7 (d, 2C), 125.6 (d, 1C), 128.5 (d, 4C), 129.0 (d, 4C), 129.3 (d, 2C), 132.8 (d, 2C), 135.2 (s, 2C), 152.1 (s, 1C), 171.6 (s, 1C), 173.9 (s, 2C)
2e	7.55–7.66 (m, 9H), 8.76–8.82 (m, 6H)	128.6 (d, 6C), 129.0 (d, 6C), 132.5 (d, 3C), 136.3 (s, 3C), 171.7 (s, 3C)

^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM 400 and a Bruker WH 270 spectrometer, respectively. Mass spectra were performed with a Varian MAT 711 (70 eV) spectrometer. The 2-alkoxy(phenoxy)-4,6-dichloro-1,3,5-triazines **1a–d** were prepared from cyanuric chloride and the appropriate aliphatic alcohol or phenol, respectively, according to known procedures.[4,18]

2-Methoxy-4,6-diphenyl-1,3,5-triazine (2a); Typical Procedure:
2-Methoxy-4,6-dichloro-1,3,5-triazine (**1a**; 1.79 g, 10.0 mmol), phenylboronic acid (2.44 g, 20 mmol) and $(PPh_3)_4Pd$ (57.8 mg, 0.05 mmol) were added to a heterogeneous mixture of toluene (50 mL) and a solution of Na_2CO_3 (8.48 g, 80 mmol) in H_2O (40 mL). The mixture was stirred and refluxed under a N_2 atmosphere for 48 h. After cooling to r.t., the organic layer was seperated and the aqueous solution was extracted with toluene (2 × 50 mL). The combined organic solutions were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Recrystallization of the residue from hexane afforded compound **2a** as a white solid (Tables 1 and 2).

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