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2-Alkyl-4,6-dialkylamino-1,3,5-triazines via Grignard Alkylation of Cyanuric Chloride: An Aged Reaction Revisited

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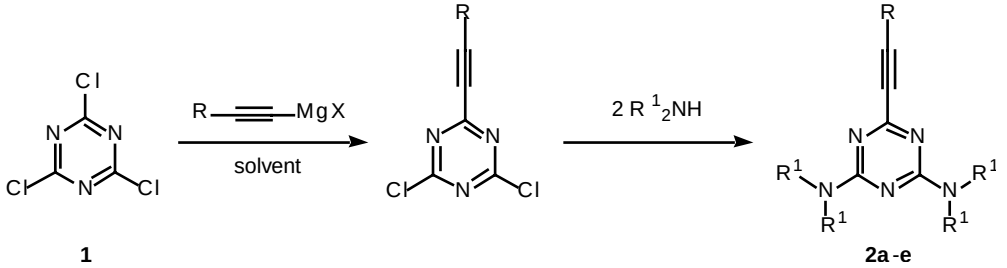
Abstract—Suitable one-pot reaction conditions are suggested to prepare, in good overall yields, some 2-(alk-1′-ynyl)- and 2-alkyl-4,6-dialkylamino-1,3,5-triazines via reaction of cyanuric chloride with Grignard reagents followed by amination.

In our studies[1] concerning the protection of paper against pathogenic fungi, we found that 2-(alk-1′-ynyl)-4,6-dimethoxy-1,3,5-triazines showed an appreciable biostatic activity.[2] Taking into account that alkylamino derivatives of 1,3,5-triazine are generally better biostatic agents than alkoxy derivatives,[1] preparation of 2-(alk-1′-ynyl)-4,6-dialkylamino-1,3,5-triazines was necessary in order to compare their antifungal activities with those of 2-(alk-1′-ynyl)-4,6-dimethoxy-1,3,5-triazines. As repeated attempts to convert the easily available[3] 2-chloro-4,6-dimorpholino-1,3,5-triazine into the corresponding 2-(alk-1′-ynyl)-derivatives by the Pd(0) mediated cross-coupling with alk-1-ynes[4] always resulted in low (15–21%) yields, Grignard alkynylation of cyanuric chloride (**1**, CAUTION) followed by amination (Scheme 1) was attempted, since the alkylation[5] as well as the alkynylation[6] of **1** by organomagnesium reagents and, to a lesser extent, by lithium derivatives,[5m,5q–s,7] has been known, to the best of our knowledge, since 1910.[5a]

Moreover, the same protocol might also be used for the preparation of 2-alkyl-4,6-diheteroalkyl-1,3,5-triazines, which was planned in our investigation.

The reaction between a benzene (CAUTION) solution of **1** and a THF solution of alk-1′-ynylmagnesium halides has been reported to afford 2-(alk-1′-ynyl)-4,6-dichloro-1,3,5-triazines in 50–60% yield.[6a] Since the purification of these intermediates might have caused an appreciable loss of the product owing to the well known[8] reactivity of the C–Cl bonds and the treatment of the crude products with nucleophiles would have lead to complex mixtures of compounds, the reaction between **1** and hex-1-ynylmagnesium bromide was carried out under the experimental conditions recently described[5w] for the nearly quantitative conversion of **1** into 2-(2′,6′-dichlorobenzyl)-4,6-dichloro-1,3,5-triazine with the suitable Grignard reagent: hex-1-ynylmagnesium bromide (0.8 M, Et_2O) was slowly added to a cooled (5°C) benzene solution of **1** ([RMgBr]/[**1**]=1/1 molar ratio); unfortunately, under these conditions, only a 30% (glc)[9] conversion of **1** into 2-(hex-1′-ynyl)-4,6-dichloro-1,3,5-triazine (**2a**, glc-mass) was achieved, even after refluxing the mixture for 50 h. Further experiments were carried out in order to improve the conversion of **1** into **2a**: the best results were obtained, independently of the solvent (THF, Et_2O or THF/Et_2O mixtures) used for the



Scheme 1.

Keywords: 2,4,6-trichloro-1,3,5-triazine; Grignard reagents; alkynylation; alkylation; nucleophilic substitution.

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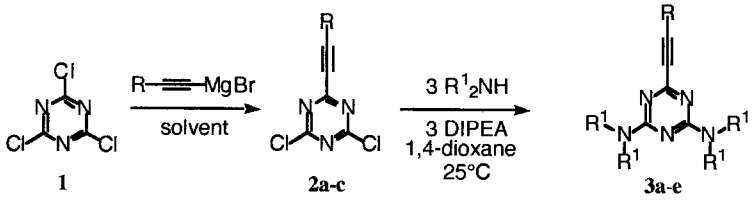
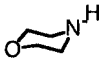
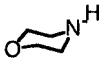
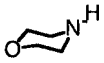
Table 1. Synthesis of 2-(alk-1′-ynyl)-4,6-dialkyl(aryl)amino-1,3,5-triazines (**3a–e**) (In all cases, a solution of the Grignard reagent was added to a solution of **1** in THF at 0°C; a [RMgX]/[**1**]=1/1 molar ratio was used if not otherwise stated (see Experimental))



1 **2a-c** **3a-e**

Entry	R	**2**	Solvent	R^1_2NH	**3** (% yield)[a]
1	*n*-Bu	**a**	Et_2O		**a** (82)
2	*n*-Bu	**a**	Et_2O	Et_2NH	**b** (66)
3	*t*-Bu	**b**	THF/Et_2O[b]		**c** (75)
4	*t*-Bu	**b**	THF/Et_2O[b]		**d** (60)
5	Ph[c]	**c**	THF/Et_2O[d]		**e** (51)

[a] Evaluated on isolated, chemically pure compounds.
[b] 5.5/1 v/v.
[c] An excess of phenylethynylmagnesium chloride (1.5 molar equivalents) was used to obtain the maximum conversion (60%) of **1** into **2c**.
[d] 1/2 v/v.

preparation and/or the solubilization of the Grignard acetylenic reagent, when a THF solution of **1** was used.[10] It is noteworthy that, under our experimental conditions, no appreciable formation of the feared disubstituted byproducts[6a] was observed.

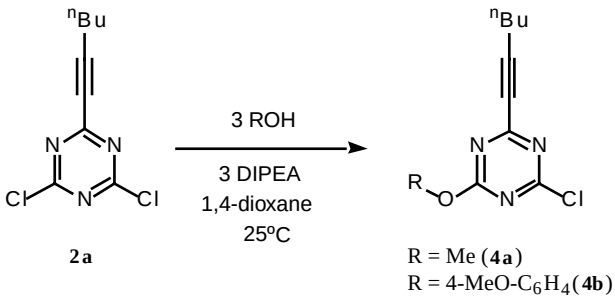
The nearly quantitative (glc)[11] alkynylation of **1** prompted us to attempt the in situ treatment of **2a** with *N*-nucleophiles according to the reaction conditions described for the conversion of 2-(2′,6′-dichlorobenzyl)-4,6-dichloro-1,3,5-triazine into the corresponding 2-(2′,6′-dichlorobenzyl)-4,6-diarylamino-1,3,5-triazines.[5w] The chemoselectivity of the reaction was not predictable, since it has been reported that the acetylenic bond, activated by an heterocyclic ring, easily undergoes conjugate addition.[6c,12]

The direct treatment of **2a** with an excess (3 molar equivalents) of morpholine in the presence of diisopropylethylamine (DIPEA, 3 molar equivalents)[5w] afforded 2-(hex-1′-ynyl)-4,6-dimorpholino-1,3,5-triazine (**3a**) in very good yield (82%, Table 1, entry 1) and no conjugate addition byproducts were detected. The syntheses of the other 2-(alk-1′-ynyl)-4,6-dialkyl(aryl)amino-1,3,5-triazines (**3b–e**) were therefore carried out under the one-pot experimental protocol used for **3a** (Table 1, entries 2–5).

Although the preparation of 2-(alk-1′-ynyl)-4,6-dimethoxy-1,3,5-triazines can be effectively carried out by a Pd(0) catalyzed cross-coupling,[4] the described easy conversion of 2-(trimethylsilylethynyl)-4,6-dichloro-1,3,5-triazine into the corresponding 4,6-dimethoxy derivative by reaction with absolute methanol[6b] suggested the attempt to convert **2a** into the corresponding 2-(hex-1′-ynyl)-4,6-dimethoxy-1,3,5-triazine by the same procedure. In our hands this approach failed: when a large excess (3 molar equivalents) of absolute methanol was added to **2a**, only a 40% yield of 2-(hex-1′-ynyl)-4-chloro-6-methoxy-1,3,5-triazine (**4a**) was obtained (Scheme 2); even worse results were obtained when the nucleophilic substitution was attempted both in the presence of *t*-BuOK[13] and under the phase-transfer conditions,[1b,14] which always allowed us to react **1** with both *O*- and *N*-nucleophilic reagents. On the other hand, a nearly quantitative yield (98%) of 2-(hex-1′-ynyl)-4-chloro-6-(4″-methoxyphenoxy)-1,3,5-triazine (**4b**) was obtained when **2a** was treated with an excess of 4-methoxyphenol (Scheme 2). The absence, also in this case, of any traces of disubstitution products, could be rationalized by assuming that the alk-1′-ynyl substituent shows a deactivating effect comparable to that shown by an alkoxy substituent: 2,4,6-trialkoxy-1,3,5-triazines are prepared from the corresponding dialkoxy precursors only under suitable reaction conditions.[1b,8,13,14a]

The satisfactory results obtained in the synthesis of **3a–e** suggested using a similar one-pot procedure also for the preparation of 2-alkyl-4,6-dialkylamino-1,3,5-triazines.

As already stated for acetylenic derivatives, several studies concerning the alkylation of **1** by Grignard reagents[5] are available which, however, do not succeed in exhaustively describing the reactivity of **1** towards these organometallics.



Scheme 2.

A recent patent[5w] deals with 2,4-dialkylamino-1,3,5-triazines bearing, in the C_6 position a further C–C bonded substituent (R). While the systems characterized by a benzyl moiety (R=2-chloro, 2,4- and 2,6-dichlorobenzyl) have been prepared by the reaction of **1** with the suitable Grignard reagent, other derivatives bearing substituents (R=C_1–C_{10} alkyl, C_3–C_{10} alkenyl, C_3–C_{10} alkynyl, C_3–C_7 cycloalkyl and phenyl) which theoretically might have been introduced by the same approach have been synthesized via rather time consuming multistep approaches. On the other hand, although the procedure reported by Hirt[5d] is usually cited for the Grignard alkylation of **1**, it has to be said that Hirt adopted in fact the Barbier[15] protocol.[16] Moreover, no clear information is available about the conditions suitable to selectively convert **1** into its monoalkylderivatives.

In summary, since no general procedure was available, the experimental conditions to selectively and completely convert **1** into the corresponding monoalkylation products by aliphatic (primary, secondary, α-branched primary), benzyl and phenyl Grignard reagents had to be sought.

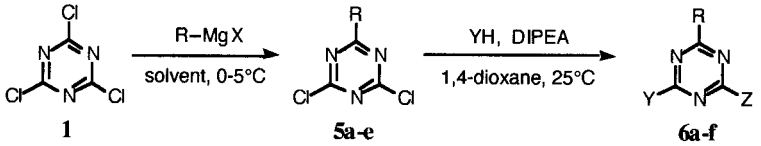
On an analytical scale, the reaction of **1** with 2-phenylethylmagnesium bromide was attempted under the experimental conditions recently reported.[5w] When complete conversion of **1** (3 h, glc, see Ref. 9) into **5a** was achieved, diethylamine and DIPEA were added,[5w] and the corresponding 2-(2′-phenylethyl)-4-(*N*,*N*-diethylamino)-6-chloro-1,3,5-triazine (**6a**) was formed (glc-mass) in nearly quantitative (glc) yield. On a preparative scale **6a** was recovered in good (78%) overall yield (Table 2, entry 1).

Under comparable experimental conditions, the reaction of benzylmagnesium chloride with **1** was not so satisfactory: the addition of a 0.78 M Et_2O solution of benzylmagnesium chloride to **1** resulted in the formation of a deep red mixture from which, after treating with diethylamine, **6b** was recovered in a poor (37%) yield (Table 2, entry 2). In a further experiment, in order to avoid the formation of the coloured and uneluable byproducts, the reaction was attempted by using a much more diluted (0.13 M) solution of the Grignard reagent and a more nucleophilic amine for the conversion of **5b** into **6c** (Table 2, entry 3). Under these conditions an almost colourless solution was obtained after adding the Grignard reagent and the following reaction with morpholine gave **6c** in satisfactory (75%) yield (Table 2, entry 3). Similar results were obtained, under comparable reaction conditions, in all the other cases tested (Table 2, entries 4–6), although the reaction between **1** and (*S*)-2-methylbutylmagnesium chloride was rather peculiar. When 1.2 molar equivalents of the Grignard reagent were used, the conversion of **1** into **5d** was 60% and the following treatment with morpholine gave **6e** in a poor (47%) overall yield (see Ref. 11). It has to be underlined, however, that no reduction products were observed. The nearly complete conversion of **1** into **5d** was achieved only when an excess (2.2 molar equivalents) of the Grignard reagent was used; under these conditions chemically pure **6e** was finally isolated in satisfactory yield (78%, Table 2, entry 5).

An attempt to convert **5a** into the corresponding dimethoxy derivative was also carried out. The reaction of intermediates **5** with *O*-nucleophiles is, in principle, more interesting than that of intermediates **2**, since 2-(alk-1′-ynyl)-4,6-dialkoxy-1,3,5-triazines are readily available by the Pd(0) catalysed cross-coupling.[4]

The conversion of 2-alkyl-4,6-dichloro-1,3,5-triazines into the corresponding dialkoxy derivatives by reaction with alcohols has been reported too;[5k,m] when we reacted **5a** with absolute methanol, in the presence of DIPEA, only a 42% yield of 2-(2′-phenylethyl)-4-methoxy-6-chloro-1,3,5-triazine (**7**) was recovered and attempts to force the nucleophilic substitution always resulted in the formation of complex deep coloured mixtures containing appreciable amounts of 2-(2′-phenylethyl)-4(*N*,*N*-isopropylethylamino)-6-chloro-1,3,5-triazine[17] but no trace of the desired compounds.

Table 2. Synthesis of 2-alkyl-1,3,5-triazine derivatives (**6a**–**f**) (A benzene solution of **1** was used; in each case the complete conversion of the precursor into **5a**–**e** (glc) was reached; a **1**/[RMgX]/[YH]=1/1.2/3 molar ratio was used, if not otherwise stated)



1 **5a-e** **6a-f**

Entry	RMgX (Molarity)[a]	**5**	Y, Z	**6** (% yield)[b]
1	Ph⁄⁄MgBr (0.68)	**a**	Y=Et_2N,[c] Z=Cl	**a** (78)
2	Ph⁄⁄MgCl (0.78)	**b**	Y=Z=Et_2N	**b** (37)
3	Ph⁄⁄MgCl (0.13)	**b**	Y=Z=morpholino	**c** (75)
4	⁄⁄MgCl (0.29)[d]	**c**	Y=Z=morpholino	**d** (79)
5	(S) ⁄⁄MgCl (0.23)[e]	**d**	Y=Z=morpholino	**e** (78)
6	PhMgBr (0.22)[d]	**e**	Y=Z=morpholino	**f** (73)

[a] In diethyl ether, if not otherwise stated.
[b] Isolated yield of recovered, chemically pure compounds.
[c] 1.1 molar equivalents were used.
[d] In a 1/1 Et_2O/THF mixture.
[e] The quantitative conversion of **1** into **5d** was achieved only when 2.2 molar equivalents of the Grignard reagent were used.

In summary, in order to prepare 2-(alk-1′-ynyl)- and 2-alkyl-4,6-dialkylamino-1,3,5-triazines (**3a–e** and **6a–f**, respectively) in good, overall yields, by the one-pot protocol described (see Experimental), the following points should be considered: (1) the almost quantitative alkynylation of **1** by acetylenic Grignard reagents can be carried out only if a THF solution of **1** is used; (2) similarly good results can be achieved in the alkylation of **1** only if a benzene solution of the precursor is used; (3) in the concentration range we used for Grignard reagents, no trace of dialk-1′-ynyl- or dialkyl derivatives arises; (4) when *N*-nucleophiles are used in the second step of the process no problems subsist; (5) only monosubstitution products are obtained, at least under the conditions reported, when dichloro intermediates are reacted with *O*-nucleophiles.

Experimental

Materials and instruments

Diethyl ether, benzene (CAUTION), tetrahydrofuran (THF) and 1,4-dioxane were purified by standard methods[18] and distilled from Na before use. *N*,*N*-Diethylamine (bp 56°C), morpholine (bp 128°C) and *N*,*N*-diisopropylethylamine (DIPEA, bp 127°C) were distilled from KOH under nitrogen before use. Methanol was dried according to a reported procedure.[18] 4-Methoxyphenol (mp 55°C) and 4-methoxyaniline (mp 58°C) were recrystallized from light petroleum ether[19] and a 1/1 mixture of diethyl ether/hexane, respectively. 2,4,6-Trichloro-1,3,5-triazine (**1**, CAUTION) was recrystallized from anhydrous CCl_4 and stored under nitrogen.[18] Alk-1-ynes were stored over 4 Å molecular sieves and distilled immediately before use. Benzylmagnesium chloride (1.5 M in diethyl ether) was purchased from Aldrich, while ethylmagnesium, 2-phenylethylmagnesium and phenylmagnesium bromides, as well as (*S*)-2-methylbutylmagnesium and isopropylmagnesium chlorides were prepared from the corresponding alkyl halides according to reported procedures.[20] Acetylenic Grignard reagents were prepared from the corresponding alk-1-ynes and the suitable alkylmagnesium halide according to reported procedures.[20] Glc analyses were performed on a Perkin–Elmer 8500 instrument (a DB1, 15 m×0.32 mm capillary column was used) equipped with a flame ionization detector and a split–splitless injector, with He carrier gas. TLC analyses were performed on silica gel 60 plates (Fluka) and flash chromatography[21] purifications were carried out on silica gel 60 (Fluka, 230–400 mesh) using the solvent eluting mixtures reported for each case. Melting points were determined using a Koffler hot-stage apparatus and are not corrected. Optical rotatory powers were measured by a Perkin–Elmer 142 polarimeter equipped with a temperature control device (±0.1°C). ^{1}H and ^{13}C NMR (200 and 50 MHz, respectively) spectra were recorded on a Varian Gemini 200 spectrometer; all NMR data were obtained using $CDCl_3$ solutions if not otherwise stated. Chemical shifts (δ ppm) are referred to tetramethylsilane (TMS) (^{1}H NMR) or $CDCl_3$ (^{13}C NMR) as internal standard. Mass spectra (*m*/*z*, I%) were recorded on a Perkin–Elmer Q-Mass 910 instrument; IS mass spectra, acquired in MCA mode by summing 10 scans, were acquired on a Perkin–Elmer–Sciex API III mass spectrometer (Sciex Co., Thornhill, Ontario, Canada).

General procedure for the preparation of 2-(alk-1′-ynyl)-4,6-dichloro-1,3,5-triazine intermediates (2a–c)

A 0.1 M solution (diethyl ether or diethyl ether/THF) of the suitable acetylenic Grignard reagent was slowly added to a cooled (5°C), mechanically stirred THF solution (0.1 M) of **1** (**1**/Grignard reagent=1/1 molar ratio if not otherwise stated); the mixture was cooled to 0°C and, after 2 h, the temperature was raised to 25°C and stirring was continued until the maximum conversion of the substrate (glc) was reached. For each case the Grignard acetylenic reagent used and the solvent used for the addition, the conversion (time, h) and the glc-mass characterization of the intermediate are reported:

2-(Hex-1′-ynyl)-4,6-dichloro-1,3,5-triazine (2a). Hex-1-ynylmagnesium bromide, diethyl ether, 100% (3); *m*/*z* (I%): 229 ($M^{+\cdot}$, 1.1), 228 (11.5), 214 (68.7), 200 (30.1), 187 (74.4), 163 (7.5), 139 (11.4), 126 (9.0), 106 (24.2), 92 (23.8), 87 (100), 77 (19.4), 64 (43.7), 51 (14.0), 43 (19.3), 39 (10.7).

2-*t*-Butylethynyl-4,6-dichloro-1,3,5-triazine (2b). *t*-Butylethynylmagnesium bromide, THF/diethyl ether 5.5/1 v/v, 100% (15); *m*/*z* (I%): 229 ($M^{+\cdot}$, 1.6), 228 (15.0), 214 (36.0), 106 (25.9), 92 (100), 87 (35.6), 62 (18.7).

2-Phenylethynyl-4,6-dichloro-1,3,5-triazine (2c). Phenylethynylmagnesium chloride, THF/diethyl ether 1/2 v/v, 85% (110);[22] *m*/*z* (I%): 249 ($M^{+\cdot}$, 100), 153 (27.9), 127 (25.89), 100 (11.4), 75 (5.7), 87 (37.9), 61 (11.3), 52 (3.7).

General procedure for the preparation of 2-(alk-1′-ynyl)-4,6-diheteroalkyl-1,3,5-triazines (3a–e)

A 1,4-dioxane solution of the suitable nucleophile and DIPEA was slowly added to the stirred solution of the 1,3,5-triazine intermediate (**2a–c**) at room temperature (nucleophile/DIPEA/**2a–c**=3/3/1 molar ratio); stirring was continued until the complete conversion of intermediates was achieved (glc, TLC), solvents were removed at reduced pressure and the residue was triturated and hydrolyzed with 0.6 M HCl; organic products, extracted with $CHCl_3$, were washed with water and dried over anhydrous Na_2SO_4. The removal of the solvent at reduced pressure and the purification by flash chromatography afforded the chemically pure compounds. For each case the starting intermediate, the nucleophile used, the time necessary to achieve the complete conversion of the intermediate, the mixture of solvents (v/v) used for the flash chromatography, the yield, the chemical–physycal and the spectroscopic characterization are reported:

2-(Hex-1′-ynyl)-4,6-dimorpholino-1,3,5-triazine (3a). 2a; Morpholine; 15 h; hexane/ethyl acetate 60/40; 82%; white solid, mp 92–93°C; *m*/*z* (I%): 331 ($M^{+\cdot}$, 12.6), 301 (18.4), 286 (25.5), 274 (30.6), 113 (4.4), 81 (5.0), 55 (100); IS mass: $[M+1]^+$=332, $[M+23]^+$=354; ^{1}H NMR: 3.90–3.60 (m, 16H), 2.42 (t, *J*=7.16 Hz, 2H, C≡C–CH_2CH_2), 1.69–1.40 (m, 4H, $CH_2CH_2CH_3$), 0.93 (t, *J*=7.16 Hz, 3H,

CH_2CH_3); ^{13}C NMR: 164.2, 159.4, 89.5, 79.8, 66.7, 43.5, 30.0, 22.1, 19.0, 13.5. Found: C, 61.4; H, 7.4; N, 21.2. $C_{17}H_{25}N_5O_2$ requires C, 61.6; H, 7.6; N, 21.1%.

2-(Hex-1′-ynyl)-4,6-di(*N*,*N*-diethylamino)-1,3,5-triazine (3b). 2a; diethylamine; 40 h; hexane/ethyl acetate 90/10; 66%; viscous liquid; *m/z* (I%): 303 ($M^{+\cdot}$, 72.6), 288 (16.2), 274 (100), 260 (19.78), 232 (4.1), 99 (5.2); IS mass: $[M+1]^+$=304, $[M+23]^+$=326; ^1H NMR (DMSO-d_6, 60°C): 3.50 (q, *J*=7.15 Hz, 8H, N–CH_2CH_3), 2.45 (t, *J*=7.06 Hz, 2H, C≡C–CH_2CH_2), 1.61–1.32 (m, 4H, CH_2CH_2–CH_3), 1.09 (t, *J*=7.16 Hz, 12H, N–CH_2CH_3), 0.93 (t, *J*=7.16 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR: 163.2, 158.3, 87.0, 80.6, 40.3, 40.0, 29.5, 21.2, 17.7, 12.9. Found: C, 67.5; H, 9.5; N, 23.0. $C_{17}H_{29}N_5$ requires C, 67.3; H, 9.6; N, 23.1%.

2-*t*-Butylethynyl-4,6-dimorpholino-1,3,5-triazine (3c). 2b; Morpholine: 8 h; diethyl ether/hexane 80/20; 75%; white solid, mp 226–227°C; *m/z* (I%): 331 ($M^{+\cdot}$, 11.9), 301 (16.0), 286 (26.8), 274 (23.1), 179 (4.2), 113 (14.8), 92 (12.1), 81 (20.1), 69 (13.7), 55 (100); IS mass: $[M+1]^+$=332, $[M+23]^+$=354; ^1H NMR: 3.85–3.68 (m, 16H), 1.34 (s, 9H, CH_3); ^{13}C NMR: 164.3, 159.5, 96.6, 78.5, 66.7, 43.5, 30.4, 27.7. Found: C, 61.8; H, 7.6; N, 20.9. $C_{17}H_{25}N_5O_2$ requires C, 61.6; H, 7.6; N, 21.1%.

2-*t*-Butylethynyl-4,6-di(4′-methoxyanilino)-1,3,5-triazine (3d). 2b; 4-Methoxyaniline; 45 h; benzene/chloroform/ethyl acetate 47.5/43/9.5; 60%; white solid, mp 204–205°C; *m/z* (I%): 403 ($M^{+\cdot}$, 100), 388 (32.4), 380 (5.5), 280 (4.6), 207 (6.3), 197 (4.8), 133 (20.1), 89 (4.4), 52 (10.0); IS mass: $[M+1]^+$=404, $[M+23]^+$=426; ^1H NMR: 8.10 (bs, 2H, N*H*), 7.47 (d, *J*=8.95 Hz, 4H, H_{arom}), 6.85 (d, *J*=8.95 Hz, 4H, H_{arom}), 3.80 (s, 6H, O–CH_3), 1.19 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR: 163.7, 156.3, 130.9, 122.9, 113.9, 113.0 (2C), 99.0, 55.5, 30.1, 27.7. Found: C, 68.2; H, 6.4; N, 17.6. $C_{23}H_{25}N_5O_2$ requires C, 68.5; H, 6.2; N, 17.4%.

2-Phenylethynyl-4,6-dimorpholino-1,3,5-triazine (3e). 2c; Morpholine; 36 h; hexane/ethyl acetate 50/50; 51%; white solid, mp 193–195°C; *m/z* (I%): 351 ($M^{+\cdot}$, 73.3), 321 (85.4), 306 (100), 294 (96.1), 236 (5.4), 208 (11.4), 204 (8.0), 179 (7.5), 153 (16.7), 81 (14.6), 69 (3.6), 55 (11.9); ^1H NMR: 7.64–7.59 (m, 2H, H_{arom}); 7.39–7.33 (m, 3H, H_{arom}); 3.90–3.60 (m, 16H); ^{13}C NMR: 164.2, 159.4, 132.6, 129.5, 128.2, 121.3, 87.9, 86.5, 66.7, 43.6. Found: C, 65.2; H, 6.1; N, 19.7. $C_{19}H_{21}N_5O_2$ requires C, 64.9; H, 6.0; N, 19.9%.

2-(Hex-1′-ynyl)-4-methoxy-6-chloro-1,3,5-triazine (4a). 2a; Dry methanol; 84 h; hexane/ethyl acetate 90/10; 32%; waxy solid; *m/z* (I%): 225 ($M^{+\cdot}$, 3.2), 210 (13.6), 196 (13.4), 183 (23.7), 106 (5.9), 87 (3.4), 76 (11.1), 64 (11.7), 58 (100), 51 (53.5); IS mass: $[M+1]^+$=226, $[M+23]^+$=248; ^1H NMR: 4.10 (s, 3H, O–CH_3), 2.50 (t, *J*=7.02 Hz, 2H, C≡C–CH_2CH_2), 1.39–1.72 (m, 4H, CH_2CH_2–CH_3), 0.94 (t, *J*=7.16 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR: 172.1, 171.2, 162.4, 97.8, 78.3, 56.1, 29.6, 22.0, 19.1, 13.4. Found: C, 53.4; H, 5.6; N, 18.3; Cl, 15.9. $C_{10}H_{12}ClN_3O$ requires C, 53.2; H, 5.4; N, 18.6; Cl, 15.7%.

2-(Hex-1′-ynyl)-4-(4″-methoxyphenoxy)-6-chloro-1,3,5-triazine (4b). 2a; 4-Methoxyphenol; 44 h; hexane/diethyl ether 70/30 v/v; 98%; pale yellow solid, mp 49–50°C; *m/z* (I%): 317 ($M^{+\cdot}$, 47.6), 282 (5.8), 260 (16.8), 214 (100), 171 (7.3), 147 (6.2), 123 (4.0), 107 (3.1), 87 (11.5), 77 (6.6), 63 (13.1), 52 (63.5); IS mass: $[M+1]^+$=318, $[M+23]^+$=340; ^1H NMR: 7.12–7.07 (m, 2H, H_{arom}), 6.94–6.90 (m, 2H, H_{arom}), 3.80 (s, 3H, O–CH_3), 2.46 (t, *J*=6.98 Hz, 2H, C≡C–CH_2CH_2), 1.69–1.35 (m, 4H, $CH_2CH_2CH_3$), 0.92 (t, *J*=7.20 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR: 172.3, 171.0, 162.7, 157.5, 144.7, 121.8, 114.5, 98.4, 78.2, 55.4, 29.4, 21.8, 19.0, 13.3. Found: C, 60.9; H, 5.0; N, 13.5; Cl, 11.0. $C_{16}H_{16}ClN_3O_2$ requires C, 60.5; H, 5.1; N, 13.2; Cl, 11.2%.

General procedure for the preparation of 2-alkyl-4,6-dichloro-1,3,5-triazine intermediates (5a–e)

A solution (diethyl ether or diethyl ether/THF) of the suitable Grignard reagent was slowly added to a cooled (0–5°C), mechanically stirred benzene solution of **1** (**1**/Grignard reagent=1/1.2 molar ratio if not otherwise stated); the mixture was stirred at 0°C for 3–5 h, the temperature was raised at 25°C and stirring was continued until the complete conversion of the substrate (glc) was obtained. For each case the Grignard reagent, its molarity, the solvent used for the addition, the time necessary to achieve the complete conversion and the glc-mass characterization are reported:

2-(2′-Phenylethyl)-4,6-dichloro-1,3,5-triazine (5a). 2-Phenylethylmagnesium bromide; 0.68; diethyl ether; 3 h; *m/z* (I%): 253 ($M^{+\cdot}$, 16.1), 218 (3.2), 176 (4.2), 157 (3.2), 130 (7.4), 103 (6.5), 91 (100), 87 (7.3), 78 (13.8), 65 (10.9), 62 (9.4).

2-Benzyl-4,6-dichloro-1,3,5-triazine (5b). Benzylmagnesium chloride; 0.78; diethyl ether; 4 h; *m/z* (I%): 239 ($M^{+\cdot}$, 26.8), 238 (36.9), 204 (53.3), 143 (18.7), 117 (100), 91 (55.2), 89 (40.5), 87 (23.3), 77 (10.7), 65 (19.7), 62 (26.0).

2-Isopropyl-4,6-dichloro-1,3,5-triazine (5c). Isopropylmagnesium chloride; 0.29; diethyl ether/THF 1/1 v/v; 3 h; *m/z* (I%): 191 ($M^{+\cdot}$, 3.6), 190 (6.2), 176 (100), 165 (1.2), 163 (2.6), 87 (21.1), 68 (3.6), 62 (16.1), 54 (10.6).

2-[(S)-2′-Methylbutyl]-4,6-dichloro-1,3,5-triazine (5d). (*S*)-2-Methylbutylmagnesium chloride;[23] 0.23; diethyl ether; 2 h; *m/z* (I%): 204 ($M^{+\cdot}-CH_3$, 7.5), 192 (19.9), 190 (35.1), 165 (62.8), 163 (100), 87 (14.2), 82 (4.2), 68 (8.3), 62 (18.9).

2-Phenyl-4,6-dichloro-1,3,5-triazine (5e). Phenylmagnesium bromide; 0.22; diethyl ether/THF 1/1 v/v; 3 h; *m/z* (I%): 225 ($M^{+\cdot}$, 100), 129 (44.6), 122 (8.76), 103 (32.1), 87 (27.0), 77 (4.2), 76 (8.0), 62 (1.7).

General procedure for the preparation of 2-alkyl-4,6-diheteroalkyl-1,3,5-triazines (6a–f)

A 1,4-dioxane solution of the suitable nucleophile and DIPEA was slowly added to the stirred solution of 1,3,5-triazine intermediate (**5a**–**e**) at room temperature (nucleophile/DIPEA/**5a**–**e**=3/3/1 molar ratio if not otherwise

stated); stirring was continued until complete conversion of the intermediate was achieved (glc, TLC), solvents were removed at reduced pressure and the residue was worked up according to the procedure described for the preparation of **3a**–**e**. For each case the starting intermediate, the nucleophile used, the time necessary to achieve the complete conversion of the intermediate, the mixture of eluents (v/v) used for the flash chromatography, the yield, the chemical–physical and the spectroscopic characterization are reported:

2-(2′-Phenylethyl)-4-(*N*,*N*-diethylamino)-6-chloro-1,3,5-triazine (6a). 5a, Diethylamine (1.1 molar equivalents); 15 h; 78%, viscous liquid; *m*/*z* (I%): 290 ($M^{+\cdot}$, 100), 275 (16.1), 261 (13.0), 255 (3.4), 213 (9.4), 199 (7.0), 186 (6.1), 171 (5.4), 157 (4.4), 132 (8.5), 99 (18.7), 91 (67.5), 77 (5.6), 72 (5.4), 69 (10.2), 62 (3.5), 55 (9.5); ^{1}H NMR: 7.35–7.10 (m, 5H, H_{arom}), 3.59 (q, J=7.10 Hz, 2H, N–CH_2CH$_3$), 3.50 (q, J=7.06 Hz, 2H, N–CH_2CH$_3$), 3.15–3.04 (m, 2H, CH_2CH$_2$Ph), 3.00–2.91 (m, 2H, CH_2Ph), 1.18 (t, J=7.06 Hz, 3H, CH$_2$CH_3), 1.14 (t, J=7.10 Hz, 3H, CH$_2$CH_3); ^{13}C NMR: 178.8, 169.8, 164.0, 140.9, 128.2, 125.7, 41.9, 41.7, 39.7, 32.9, 12.6. Found: C, 61.8; H, 6.4; N, 19.6; Cl, 12.2. $C_{15}H_{19}ClN_4$ requires C, 62.0; H, 6.6; N, 19.3; Cl, 12.1%.

2-Benzyl-4,6-di(*N*,*N*-diethylamino)-1,3,5-triazine (6b). 5b, Diethylamine; 50 h; hexane/diethyl ether 85/15; 37%; viscous liquid; *m*/*z* (I%): 313 ($M^{+\cdot}$, 33.9), 298 (7.6), 294 (100), 270 (27.0), 254 (3.2), 242 (4.1), 207 (3.5), 91 (6.4), 69 (3.0); IS mass: $[M+1]^+$=314, $[M+23]^+$=336; ^{1}H NMR: 7.45–7.40 (m, 2H, H_{arom}), 7.30–7.19 (m, 3H, H_{arom}), 3.78 (s, 2H, CH_2Ph), 3.48 (q, J=7.02 Hz, 8H, N–CH_2CH$_3$), 1.12 (t, J=7.02 Hz, 12H, CH$_2$CH_3); ^{13}C NMR: 175.5, 164.4, 138.9, 129.5, 127.9, 125.9, 45.8, 41.2, 13.3. Found: C, 69.2; H, 8.6; N, 22.2. $C_{18}H_{27}N_5$ requires C, 69.0; H, 8.7; N, 22.3%.

2-Benzyl-4,6-dimorpholino-1,3,5-triazine (6c). 5b, Morpholine; 15 h; hexane/ethyl acetate 60/40; 75%; glassy solid; *m*/*z* (I%): 341 ($M^{+\cdot}$, 39.1), 311 (64.0), 296 (53.7), 284 (80.7), 207 (28.5), 179 (17.5), 138 (18.9), 118 (28.1), 113 (47.8), 91 (100), 69 (33.7); ^{1}H NMR: 7.39–7.18 (m, 5H, Ph), 3.80–3.65 (m, 18H, Ph–CH_2, N–CH_2–CH_2–O); ^{13}C NMR: 176.4, 164.9, 138.0, 129.3, 128.0, 126.2, 66.7, 45.6, 43.4. Found: C, 63.0; H, 6.6; N, 20.8. $C_{18}H_{23}N_5O_2$ requires C, 63.3; H, 6.8; N, 20.5%.

2-Isopropyl-4,6-dimorpholino-1,3,5-triazine (6d). 5c, Morpholine; 18 h; hexane/ethyl acetate 65/35 v/v; 79%; white solid, mp 112–113°C; *m*/*z* (I%): 293 ($M^{+\cdot}$, 64.3), 278 (14.1), 263 (82.6), 248 (79.8), 236 (100), 218 (18.5), 206 (17.1), 193 (7.5), 179 (8.4), 162 (12.6), 150 (5.4), 113 (10.4), 94 (8.4), 81 (8.1), 69 (7.5), 55 (11.1); ^{1}H NMR: 3.82–3.68 (m, 16H), 2.70 [sept, J=6.88 Hz, 1H, (CH$_3$)$_2$CH], 1.21 (d, J=6.88 Hz, 6H, CHCH_3); ^{13}C NMR: 182.4, 165.1, 66.8, 43.5, 37.0, 20.9. Found: C, 57.5; H, 7.6; N, 24.0. $C_{14}H_{23}N_5O_2$ requires C, 57.3; H, 7.9; N, 23.9%.

2-[(*S*)-2′-Methylbutyl]-4,6-dimorpholino-1,3,5-triazine (6e). 5d, Morpholine; 48 h; hexane/ethyl acetate 70/30; 78%; waxy solid; $[\alpha]_{546}^{25}$=+10.43 (c=0.815, CHCl$_3$); *m*/*z* (I%): 321 ($M^{+\cdot}$, 2.8), 320 (4.8), 306 (17.0), 292 (6.8), 276 (5.1), 265 (100), 234 (9.9), 220 (12.8), 208 (7.3), 179 (4.1), 113 (3.3), 94 (3.2), 69 (2.8), 56 (3.5); ^{1}H NMR: 3.83–3.68 (m, 16H), 2.52 (dd, J=13.74 Hz, J'=6.20 Hz, 1H, Triazine–CHHCH), 2.29 (dd, J=13.74 Hz, J'=7.98 Hz, 1H, Triazine–CHHCH), 2.10–1.93 (m, 1H, CH), 1.48–1.11 (m, 2H, CH_2CH$_3$), 0.91 (d, J=6.63 Hz, 3H, CHCH_3), 0.90 (t, J=7.32 Hz, 3H, CH$_2$CH_3); ^{13}C NMR: 177.8, 164.2, 66.8, 45.9, 43.5, 33.3, 29.4, 19.2, 11.3. Found: C, 60.0; H, 8.2; N, 21.9. $C_{16}H_{27}N_5O_2$ requires C, 59.8; H, 8.5; N, 21.8%.

2-Phenyl-4,6-dimorpholino-1,3,5-triazine (6f). 5e, Morpholine; 15 h; hexane/ethyl acetate 50/50; 73%; white solid, mp 190–191°C; *m*/*z* (I%): 327 ($M^{+\cdot}$, 84.2), 297 (98.8), 296 (87.0), 282 (75.1), 270 (100), 252 (21.9), 240 (20.3), 225 (9.7), 212 (17.0), 207 (23.1), 193 (7.4), 184 (18.3), 179 (10.1), 149 (12.1), 129 (10.9), 104 (18.6), 94 (3.2), 82 (2.5), 56 (4.9); ^{1}H NMR: 8.40–8.36 (m, 2H, H_{arom}), 7.48–7.40 (m, 3H, H_{arom}), 4.05–3.70 (m, 16H); ^{13}C NMR: 170.4, 165.2, 137.3, 131.2, 128.2, 128.0, 66.3, 43.6. Found: C, 62.6; H, 6.5; N, 21.5. $C_{17}H_{21}N_5O_2$ requires C, 62.4; H, 6.5; N, 21.4%.

2-(2′-Phenylethyl)-4-methoxy-6-chloro-1,3,5-triazine (7). 5a, Methanol; 64 h; hexane/ethyl acetate 80/20 v/v; 42%; viscous liquid; *m*/*z* (I%): 249 ($M^{+\cdot}$, 59.7), 234 (62.0), 172 (29.8), 130 (57.0), 105 (29.9), 91 (100), 78 (16.9), 65 (20.2), 58 (10.6); IS mass: $[M+1]^+$=250, $[M+23]^+$=272; ^{1}H NMR: 7.34–7.12 (m, 5H, H_{arom}), 4.06 (s, 3H, CH_3), 3.12 (buried m, 4H, CH_2CH_2); ^{13}C NMR: 182.6, 171.9, 171.2, 140.1, 128.4, 128.2, 126.2, 55.8, 39.9, 32.8. Found: C, 57.9; H, 4.7; N, 16.6; Cl, 14.3. $C_{12}H_{12}ClN_3O$ requires C, 57.7; H, 4.8; N, 16.8; Cl, 14.2%.

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9. Evaluated relative response factor of **1** 8.2924 (internal standard dodecane).

10. Since acetylenic Grignard reagents tend to crystallize from concentrated THF or Et_2O solutions, in each case a 0.2–0.3 M solution of the reagent was used.

11. In preparative scale, the *nearly quantitative conversion* of **1** (see Ref. 9) can afford, after the treatment with *N*-nucleophiles, appreciable (5–15%) amounts of byproducts, the separation of which from the desired final products causes the drop in the overall yields.

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16. One-pot treatment of **1** with alkyl halides and Mg turnings in diethyl ether or diethyl ether/benzene mixture.

17. Identified by its mass spectrum: $[M+1]^+=305$, $[M+23]^+=327$.

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23. Prepared from (*S*)-2-methyl-1-chlorobutane, showing $[\alpha]_{25}^{D}=+1.59$, o.p. 97.5%;[24] 2.2 molar equivalents were used.

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