



The umpolung of substituent effect in nucleophilic aromatic substitution. A new approach to the synthesis of *N,N*-disubstituted melamines (triazine triskelions) under mild reaction conditions

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ARTICLE INFO

Article history:

Received 28 November 2008
Received in revised form 15 February 2009
Accepted 6 March 2009
Available online 11 March 2009

Keywords:

Triazine
Melamine
Nucleophilic aromatic substitution
Cyanuric chloride

ABSTRACT

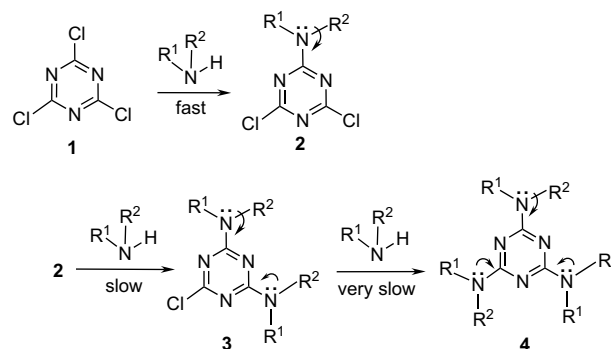
By the umpolung of substituent effect 1,3,5-triazines substituted with three dialkylamino groups were prepared under mild reaction conditions by treatment of cyanuric chloride with tertiary amines. Quaternary *N*-triazinylammonium salts were identified as reactive intermediates activating the triazine ring and strongly promoting the persubstitution of all chlorine atoms. The final degradation of intermediate *N*-triazinylammonium chlorides proceeded at room temperature or in boiling dichloromethane spontaneously within irreversible evolution of appropriate chloroalkane.

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1. Introduction

Recently, it has been found that relatively simple *N*-substituted melamine derivatives interfere with the replication/transcription system as highly active inhibitors of DNA topoisomerase,¹ telomerase,² and histone deacetylase.³ As potent cytotoxic agents targeting the G2/M phase of the cell cycle,⁴ inhibitors of phosphatidylinositol 3-kinase,⁵ matrix metalloproteinase,⁶ tyrosine kinase,⁷ and inhibitors of angiogenesis,⁸ melamine derivatives are some of the most promising anticancer,⁹ antiviral, antitripanozoma,¹⁰ and antiprotozoal agents.

The availability of more complex melamine analogues is, however, severely limited due to harsh reaction conditions necessary for the substitution of the potentially most versatile substrate,^{3,11} which is cyanuric chloride. In the described procedures substituted melamine is prepared from cyanuric chloride by treatment with ammonia, primary or secondary amines. It is already well known¹² that the accumulation of electron donating amine substituents gradually decreases the reactivity of the triazine ring. Therefore, every subsequent substitution proceeds steadily less readily than the preceding one (Scheme 1). Thus, the exhaustive substitution usually proceeds under harsh reaction conditions^{13,14} excluding the application of reagents with labile functional groups or fragments. Expecting that the incorporation of sensitive DNA (RNA) or peptidic



Scheme 1. Classic pathway to substituted melamines 4.

fragments into the triazine ring would be very valuable for further systematic studies of the therapeutic potential of triazine derivatives, herein we propose a general and expedient method of transformation of cyanuric chloride (**1**) into substituted melamine derivatives under mild reaction conditions.

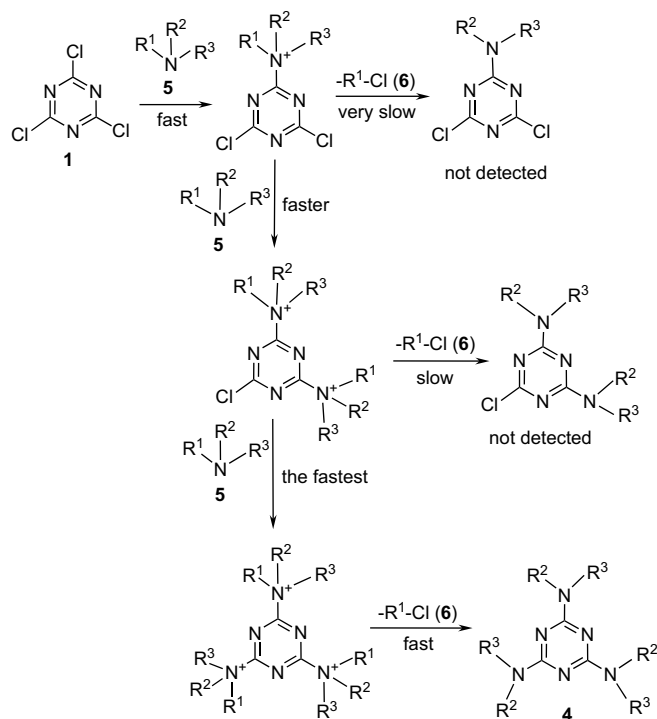
2. Results and discussion

The proposed method is based on the amine substituent umpolung effect from electron donating to electron withdrawing, anticipating a fundamental change in the reactivity of triazine in

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this multistage process. It has been assumed that deactivation of triazine ring is caused by fast deprotonation of triazinylammonium intermediate salts **2–4**, which are formed as intermediates in the reaction of chlorotriazines with amines bearing N–H bond. It has been hypothesized that oppositely directed electron withdrawing effect of ammonium substituent should increase reactivity of triazine in aromatic nucleophilic reaction and facilitate formation of multisubstituted products (see Scheme 2) and reduce the contamination of the final product with triazines partially substituted with alkylamino groups.



Scheme 2. Synthesis of per-substituted melamines by treatment of cyanuric chloride with tertiary amine in DCM solution at room temperature. Intermediate triazinylammonium salts were not isolated.

In order to verify this hypothesis, we used tertiary amines **5** instead of primary or secondary ones in the reaction and observed fast, complete substitution of all three chlorine atoms. Any attempts to isolate intermediates were unsuccessful due to intensive degradation during the purification procedures. Therefore, the progress of the reaction was monitored by the colorimetric method based on the reaction with 4-(4-nitrobenzyl)pyridine (NBP). The strong red coloration characteristic of reaction of NBP with chlorine atoms attached to the triazine ring disappeared with the formation of a strongly polar intermediate reacting substantially less readily with NBP. The subsequent dealkylation of the intermediate to tris-*N,N*-dialkylamino-1,3,5-triazines proceeded after all cyanuric chloride was consumed. It has to be added that substitution of all chlorine atoms in **1** proceeds with stoichiometric amount of amines **5a–i** at low temperature. Whereas under more vigorous conditions degradation of intermediate, partially substituted triazines proceeded vigorously yielding chloro-1,3,5-triazines only partially substituted with *N,N*-dialkylamino groups.¹⁵ For more reactive amines, dealkylation proceeded spontaneously after warming up the reaction mixture to room temperature. For less reactive amines, an additional heating of the primary substitution product in methylene chloride completed the dealkylation process leading to tris-*N,N*-dialkylamino-1,3,5-triazines (Table 1).

In the case of tertiary amines **5** with different substituents at the nitrogen atom ($R_1 \neq R_2 \neq R_3$), it was found that groups, which were

Table 1

Synthesis of *N,N*-disubstituted melamines **4a–i** by *N,N*-dialkylation of cyanuric chloride (**1**) with tertiary amines **5a–i**

Entry	Tertiary amines 5a–i	2,4,6-Tris-(<i>N,N</i> -dialkylamino)-1,3,5-triazines (4a–i)	
		Yield [%]	Mp [°C] (lit. mp)
1	4-Methylmorpholine (5a)	96	264–266 (263–264) ¹⁴
2	1-Methyl-pyrrolidine (5b)	95	175–177 (176–179) ¹⁴
3	1-Methyl-piperidine (5c)	94	216–217 (215–216) ¹⁴
4	Triethylamine (5d)	99	44–47 (46–47) ¹⁶
5	Tri- <i>n</i> -propylamine (5e)	98	68–70 (75) ¹⁷
6	Tri- <i>n</i> -butylamine (5f)	96	112 (112) ¹⁴
7	<i>N,N</i> -Dimethylaniline (5g)	76	113–115 (117.5) ¹⁸
8	<i>N,N</i> -Dimethylbenzylamine (5h)	90	168–171 (172–174) ¹⁹
9	(1-Methyl-pyrrolidin-2-yl)-morpholin-4-yl-methanone (5i)	81	Oil

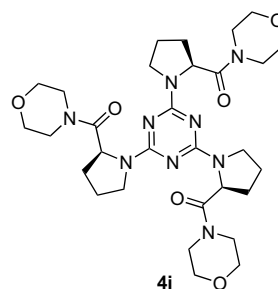


Figure 1.

most prone to substitution were those affording the most reactive halides (benzyl > allyl > methyl > alkyl); however, substitution involving the phenyl group was never detected.²⁰

Therefore, in the case of sterically extended substituents at the nitrogen atom, the best results were obtained in syntheses where tertiary amines with at least one *N*-methyl group were used as the most suitable substrates. This procedure was found effective in the synthesis of the chiral artificial receptor based on triazine triple-substituted with a proline derivative **4i** (Fig. 1).

Based on our previous studies,²¹ we postulate for the intermediate products structure of tris-quaternary *N*-triazinylammonium salts **7a–i**. It was proved that appropriate alkyl halides were formed as by-products. When quaternization proceeded in toluene, which is less volatile, instead of methylene chloride, it was possible to isolate appropriate alkyl chlorides **6a–i** in high yields and to confirm their structure. In the case of highly volatile methyl chloride (**6a**), the product was trapped in ice-cold deuterated chloroform and the structure was confirmed by the presence of a 3.71 ppm signal in the NMR spectrum.

3. Conclusions

To conclude, the classic rule predicting a gradually decreasing reactivity has been reversed by the modification of the substrate structure and the substituent umpolung effect. By using tertiary amines, relatively stable electron withdrawing quaternary ammonium substituents were incorporated into the triazine ring and, due to the accumulation of positive charge, the substitution of every subsequent reactive centre in the triazine ring proceeded more vigorously than the preceding one. Consequently, due to the umpolung of substituent effect, which strongly reduces the amount of partially substituted products and favors the substitution of all the chlorine atoms, a new expedient and convenient procedure has been found. The procedure has a wide range of applications and leads to obtain melamine derivatives, which are otherwise hard to synthesize.

4. Experimental

4.1. General

Melting points were determined on a Büchi apparatus, model 510. IR spectra were recorded as KBr pellets or film on an Infracord 137 E spectrometer. Intensities of signals were estimated as vs=very strong, s=strong, m=medium, w=weak, br=broad. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 250 (250 MHz) spectrometer. Chemical shifts (ppm) are relative to TMS used as an internal standard. The multiplicity were marked as s=singlet, d=doublet, t=triplet, q=quartet, qu=quintet, sext=sextet, m=multiplet.

4.2. Synthesis of 2,4,6-tris-(morpholin-4-yl)-1,3,5-triazine (4a). Typical procedure

The vigorously stirred solution of cyanuric chloride (**1**) (0.37 g, 2 mmol) in dichloromethane (5 ml) was cooled to 0 °C, NMM (**5a**) (0.66 mL, 6 mmol) was added dropwise and stirring was continued for additional 30 min until evolution of gases was ceased. The solution was diluted with dichloromethane (20 mL) and then washed with water, 1 M aqueous KHSO_4 , water, dried with MgSO_4 , filtered, and concentrated to dryness yielding 2,4,6-tris-(morpholin-4-yl)-1,3,5-triazine (**4a**) (1.29 g, yield 96%), mp=264–266 °C, lit.¹⁴ mp=263–264 °C. ^1H NMR (CDCl_3): δ =3.71 (t, J =5.5 Hz, 12H), 3.76 (t, J =5.5 Hz, 12H). ^{13}C NMR (CDCl_3): δ =43.5, 66.7, 165.2. IR (film/NaCl): ν =2970, 2900, 2860, 1560, 1515, 1495, 1460, 1440, 1360, 1250, 1240, 1230, 1115 [cm^{-1}]. Anal. for $\text{C}_{15}\text{H}_{24}\text{N}_6\text{O}_3$ (336.4). Calcd: C, 53.56%; H, 7.19%; N, 24.98%. Found: C, 53.55%; H, 7.24%; N, 24.99%. The evolved gas was absorbed in ice-cold CDCl_3 and then identified as chloromethane (**6a**) by ^1H NMR (CDCl_3): δ =3.71 (s, CH_3Cl).

4.3. Synthesis of 2,4,6-tris-(pyrrolidin-1-yl)-1,3,5-triazine (4b)

Starting materials: cyanuric chloride (**1**) (1.84 g, 10 mmol), 1-methyl-pyrrolidine (**5b**) (2.89 mL, 30 mmol), dichloromethane (20 mL). Product: 2,4,6-tris-(pyrrolidin-1-yl)-1,3,5-triazine (**4b**) was obtained (2.74 g, yield 95%), mp=175–177 °C, lit.¹⁴ mp=176–179 °C. ^1H NMR (CDCl_3): δ =1.70 (qu, J =8.0 Hz, 12H), 3.52 (t, J =8.0 Hz, 12H). ^{13}C NMR (CDCl_3): δ =24.7, 44.2, 165.2. IR (film/NaCl): ν =2938, 2866, 2568, 2512, 2408, 2152, 1536, 1504, 1434, 1399, 1375, 1320, 1216, 1161, 1121, 1055 [cm^{-1}]. Anal. for $\text{C}_{15}\text{H}_{24}\text{N}_6$ (288.4). Calcd: C, 62.47%; H, 8.39%; N, 29.14%. Found: C, 62.45%; H, 8.35%; N, 29.11%.

4.4. Synthesis of 2,4,6-tris-(piperidin-1-yl)-1,3,5-triazine (4c)

Product: 2,4,6-tris-(piperidin-1-yl)-1,3,5-triazine (**4c**) was obtained (3.11 g, yield 94%), mp=216–217 °C, lit.¹⁴ mp=215–216 °C. ^1H NMR (CDCl_3): δ =1.49–1.69 (m, 12H), 1.81–1.98 (m, 6H), 3.70 (t, J =6.5 Hz, 12H). ^{13}C NMR (CDCl_3): δ =20.7, 23.5, 50.0, 163.2. IR (film/NaCl): ν =3015, 2942, 2857, 2737, 1617, 1530, 1481, 1446, 1376, 1298, 1272, 1233, 1217, 1127, 1064, 1025 [cm^{-1}]. Anal. for $\text{C}_{18}\text{H}_{30}\text{N}_6$ (330.5). Calcd: C, 65.42%; H, 9.15%; N, 25.43%. Found: C 65.45%; H 9.12%; N 25.41%.

4.5. Synthesis of 2,4,6-tris-(*N,N*-diethylamino)-1,3,5-triazine (4d)

Starting materials: cyanuric chloride (**1**) (1.84 g, 10 mmol), *N,N,N*-triethylamine (**5d**) (4.18 mL, 30 mmol), dichloromethane (10 mL). Evolved gaseous products passed through the condenser were trapped in ice-cold washer. After ceasing of gas evolution, residue was diluted with dichloromethane (10 mL), cooled to room temperature, washed with 1 M aqueous KHSO_4 (10 mL) then water (10 mL), dried with MgSO_4 , and evaporated yielding 2,4,6-tris-(*N,N*-

diethylamino)-1,3,5-triazine (**4d**) (2.92 g, yield 99%), mp=44–47 °C, lit.¹⁶ mp=46–47 °C. ^1H NMR (CDCl_3): δ =1.40 (q, J =7.0 Hz, 18H), 3.55 (t, J =7.0 Hz, 12H). ^{13}C NMR (CDCl_3): δ =13.4, 40.8, 164.6. IR (film/NaCl): ν =2970, 2940, 2650, 2610, 2500, 1610, 1540, 1485, 1440, 1375, 1340, 1295, 1245, 1190 [cm^{-1}]. Anal. for $\text{C}_{15}\text{H}_{30}\text{N}_6$: (294.5). Calcd: C, 61.19%; H, 10.27%; N, 28.54%. Found: C, 61.17%; H, 10.30%; N, 28.57%.

The liquid in the cold trap was identified as chloroethane (**6d**) (0.88 g, 68%) bp=12 °C (determined by capillary method), lit.²² bp=12 °C; n_D^{20} =1.3751. ^1H NMR (CDCl_3): δ =1.49 (t, J =7.2 Hz, 3H), 3.50 (q, J =7.2 Hz, 2H).

4.6. Synthesis of 2,4,6-tris-(*N,N*-dipropylamino)-1,3,5-triazine (4e)

Product: 2,4,6-tris-(*N,N*-dipropylamino)-1,3,5-triazine (**4e**) (3.71 g, yield 98%), mp=68–70 °C, lit.¹⁷ mp=75 °C. ^1H NMR (CDCl_3): δ =0.87 (t, J =7.0 Hz, 18H), 1.62 (m, 12H), 3.44 (m, 12H). ^{13}C NMR (CDCl_3): δ =13.8, 21.2, 50.3, 165.4. IR (film/NaCl): ν =2960, 2925, 2870, 1655, 1590, 1510, 1500, 1430, 1395, 1330, 1230, 1200 [cm^{-1}]. Anal. for $\text{C}_{21}\text{H}_{42}\text{N}_6$: (378.6). Calcd: C, 66.62%; H, 11.18%; N, 22.20%. Found: C, 66.61%; H, 11.19%; N, 22.22%.

By repeating these synthesis in toluene (20 mL), 1-chloropropane (**6e**) (1.41 g, 90%) was isolated from the distillate collected in the cold trap, bp=45–48 °C, lit.²³ bp=46–47 °C; n_D^{20} =1.3875. ^1H NMR (CDCl_3): δ =1.23 (t, J =7.0 Hz, 3H), 1.80 (br sext, J =7.0 Hz, 2H), 3.51 (t, J =6.5 Hz, 2H).

4.7. Synthesis of 2,4,6-tris-(*N,N*-dibutylamino)-1,3,5-triazine (4f)

Product: 2,4,6-tris-(*N,N*-dibutylamino)-1,3,5-triazine (**4f**) was obtained (4.44 g, yield 96%), mp=112 °C, lit.¹⁴ mp=112 °C. ^1H NMR (CDCl_3): δ =0.92 (t, J =7.5 Hz, 18H), 1.32 (m, 12H), 1.56 (m, 12H), 3.46 (m, 12H). ^{13}C NMR (CDCl_3): δ =13.6, 19.7, 29.9, 51.9, 165.4. IR (film/NaCl): ν =2970, 2930, 2880, 1675, 1575, 1540, 1500, 1425, 1375, 1340, 1240, 1205 [cm^{-1}]. Anal. for $\text{C}_{27}\text{H}_{54}\text{N}_6$: (462.8). Calcd: C, 70.08%; H, 11.76%; N, 18.16%. Found: C, 70.05%; H, 11.75%; N, 18.21%.

From the distillate, 1-chlorobutane (**6f**) was isolated (1.50 g, 81%); bp=77 °C, lit.²⁴ bp=74–77 °C; n_D^{20} =1.4025. ^1H NMR (CDCl_3): δ =0.94 (t, J =7 Hz, 3H), 1.47 (sext, J =7 Hz, 2H), 1.76 (q, J =7 Hz, 2H), 3.54 (t, J =7 Hz).

4.8. Synthesis of 2,4,6-tris(*N*-methylphenylamino)-1,3,5-triazine (4g)

2,4,6-Tris(*N*-methylphenylamino)-1,3,5-triazine (**4g**) was obtained (3.01 g, yield 76%), mp=113–115 °C, lit.¹⁸ mp=117.5 °C. ^1H NMR (CDCl_3): δ =3.47 (s, 9H), 7.24–7.61 (m, 15H). ^{13}C NMR (CDCl_3): δ =37.9, 126.1, 126.2, 128.6, 143.5, 164.9. IR (film/NaCl): ν =3062, 3038, 2942, 2794, 1951, 1774, 1679, 1600, 1536, 1481, 1446, 1386, 1320, 1263, 1169, 1098, 1026 [cm^{-1}]. Anal. for $\text{C}_{24}\text{H}_{24}\text{N}_6$ (396.5). Calcd: C, 72.70%; H, 6.10%; N, 21.20%. Found: C, 72.61%; H, 6.15%; N, 21.11%.

4.9. Synthesis of 2,4,6-tris(dimethylamino)-1,3,5-triazine (4h)

To the vigorously stirred solution of cyanuric chloride (**1**) (1.84 g, 10 mmol) in dichloromethane (20 mL), *N,N*-dimethylbenzylamine (**5h**) (4.51 mL, 30 mmol) was added dropwise. Then, the mixture was heated under reflux for additional 30 min and dichloromethane was distilled off. The residue was heated for additional 60 min and benzyl chloride was distilled off. The residue was dissolved in chloroform (30 mL) and then washed with 1 M aqueous KHSO_4 (40 mL) and water (40 mL). The organic layer was dried with Na_2SO_4 , filtered, and concentrated to dryness. After crystallization

from hexane, 2,4,6-tris(dimethylamino)-1,3,5-triazine (**4h**) was obtained (1.89 g, yield 90%), mp=168–171 °C, lit.¹⁹ mp=172–174 °C. ¹H NMR (CDCl₃): δ=3.12 (s, 18H). ¹³C NMR (CDCl₃): δ=36.7, 165.7. IR (film/NaCl): ν=3480, 3016, 2928, 2790, 2480, 2440, 1624, 1544, 1513, 1446, 1393, 1304, 1215, 1113, 1050 [cm⁻¹]. Anal. for C₉H₁₈N₆ (210.3). Calcd: C, 51.41%; H, 8.63%; N, 39.97%. Found: C, 51.44%; H, 8.65%; N, 39.93%.

The distillate was washed with 1 M aqueous KHSO₄ (10 mL) dried with CaCl₂, filtered, and redistilled yielding benzyl chloride (**6h**) (2.33 g, 92%); bp=176 °C, lit.²⁵ bp=174 °C; n_D²⁰=1.5390. ¹H NMR (CDCl₃): δ=4.55 (s, 2H), 7.33 (br s, 5H).

4.10. Synthesis of 2,4,6-tris[(S)-2-(morpholin-4-yl-carbonyl)-pyrrolidin-1-yl]-1,3,5-triazine (**4i**)

Starting materials: cyanuric chloride (**1**) (0.37 g, 2 mmol), 4-(1-methyl-pyrrolidine-2-carbonyl)-morpholine (**5i**) (1.18 g, 6 mmol). Product: 2,4,6-tris[(S)-2-(morpholin-4-yl-carbonyl)-pyrrolidin-1-yl]-1,3,5-triazine (**4i**) was obtained (1.02 g, yield 81%) as a pale oil, [α]_D²⁰ –32.8 (c 1, CHCl₃). ¹H NMR (CDCl₃): δ=1.53–1.82 (m, 6H), 2.01–2.55 (m, 6H), 2.75–3.11 (m, 6H), 3.22–3.35 (m, 3H), 3.40–3.95 (m, 24H). ¹³C NMR (CDCl₃): δ=23.9, 28.3, 43.5, 45.9, 47.7, 66.7, 165.2, 173.2. IR (film/NaCl): ν=2961, 2923, 2857, 1650, 1565, 1531, 1490, 1436, 1400, 1359, 1302, 1270, 1232, 1167, 1029 [cm⁻¹]. Anal. for C₃₀H₄₅N₉O₆ (627.8). Calcd: C, 57.40%; H, 7.23%; N, 20.08%. Found: C, 57.44%; H, 7.25%; N, 20.03%.

Acknowledgements

The study was supported by the Polish State Committee for Scientific Research under the Project PBZ-KBN-126/T09/15.

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