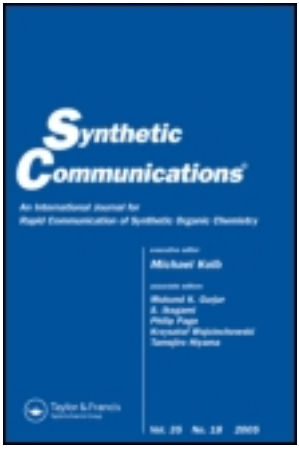

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Synthesis of Chiral 2,4-Chiral 2,4-Dichloro-6-menthoxy-1,3,5-triazines and 2-Chloro-4, 6-Dimenthoxy-1,3,5-triazines as Enantiodifferentiating Coupling Reagents. An X-ray Study on 2,4,6-Trimenthoxy-1,3,5-triazine

Zbigniew J. Kamiński [a] , Stanislaw W. Markowicz [a] , Beata Kolesińska [a] , Dariusz Martynowski [b] & Marek L. Główka [b]

[a] Institute of Organic Chemistry, Technical University of Łódź (Lodz), ul. Żwirki 36, 90-924, Łódź, Poland

[b] Institute of General and Ecological, Chemistry, Technical University of Łódź (Lodz), ul. Żwirki 36, 90-924, Łódź, Poland

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SYNTHESIS OF CHIRAL 2,4-DICHLORO-6-MENTHOXY-1,3,5-TRIAZINES AND 2-CHLORO-4,6-DIMENTHOXY-1,3,5-TRIAZINES AS ENANTIODIFFERENTIATING COUPLING REAGENTS. AN X-RAY STUDY ON 2,4,6-TRIMENTHOXY-1,3,5-TRIAZINE

Zbigniew J. Kamiński*, Stanisław W. Markowicz, Beata Kolesińska

Institute of Organic Chemistry,
Technical University of Łódź (Lodz), ul. Żwirki 36, 90-924 Łódź, Poland.

Dariusz Martynowski, Marek L. Główka

Institute of General and Ecological. Chemistry,
Technical University of Łódź (Lodz), ul. Żwirki 36, 90-924 Łódź, Poland.

ABSTRACT: Chiral mono- di- and trimenthoxy-1,3,5-triazines ware obtained from natural menthol and cyanuric chloride and applied as enantioselective coupling reagents in the synthesis of dipeptides.

Introduction

The increased demand for enantiomerically homogeneous substrates stimulate intensive efforts in asymmetric synthesis and search for new efficient reagents and new processes enabling chiral discrimination[1]. Opening an access to both enantiomers is of particular value in the syntheses involving unnatural substrates[2] which often are less compliant to resolution *via* enzymatic processes.

* to whom correspondence should be addressed

The presence of three chlorine atom prone to substitution reaction makes the cyanuric chloride an interesting template for simultaneous attachment of reactant and chiral auxiliary with the third functionality remaining for tuning the activity of the two former or alternatively, for bounding the chiral template to the polymer carrier. Unexpectedly, this advantage of triazine has been explored in very limited extend[3,4].

The aim of this paper is to present the route to triazine condensing reagents[5] bearing chiral alkoxyl substituent derived from natural menthol. It is expected, that presence of chiral substituent in the triazine ring will induce effective control over the admittance of reactants to nitrogen atoms of triazine ring, which has been recognised as crucial factor for intramolecular catalysis of acylation by „superactive triazine esters"[6]. Moreover, 1,3,5-triazines substituted with chiral alkoxy group would be excellent substrates in the synthesis of non-linear optics materials[7], intermolecular interactions with directional preferences[8], in studies on the mechanism of O→N alkyl group migration[9] and others.

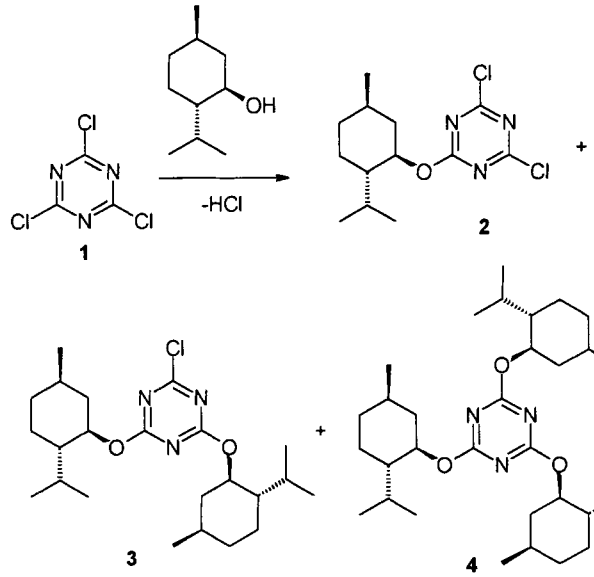
Although a broad variety of primary alcohols easily reacts with cyanuric chloride, the secondary alcohols bearing centre of chirality close to triazine ring were found less prone to react and the previous attempts to obtain triazines substituted with chiral alkoxy groups[10] failed.

Results and discussion

We found that treatment of cyanuric chloride and (1R,2S,5R)-(-) menthol in THF solution with 2,4,6-collidine gave mixture of products **2-4** (Scheme 1). The products ware separated on silicagel column[11] and eluted in a gradient hexane-toluene or hexane-chloroform mixture. Three major fractions were collected yielding 2,4-dichloro-6-menthoxy-1,3,5-triazine (**2**), 2-chloro-4,6-dimenthoxy-1,3,5-triazine (**3**) and 2,4,6-trimenthoxy-1,3,5-triazine (**4**).

The structures of triazines **2-3** has been confirmed by elemental analysis and ^{1}H-NMR spectroscopic data. The structure of **4** was determined by X-ray diffraction study[12]. Strong downfield shift of CH-O hydrogen in menthol from 3.40 ppm to 5.21 ppm in **2**, 5.06 ppm in **3**, and 5.04 ppm in **4** respectively, caused by deshilding effect of triazine ring, we have found the most characteristic feature for **2-4**.

Of particular interest is the preparation of triazine **4** with relatively hindered three menthoxy substituents, because in opposite to the earlier apprehension[10], this result expand the scope of substitution also on sterically hindered secondary alcohols.



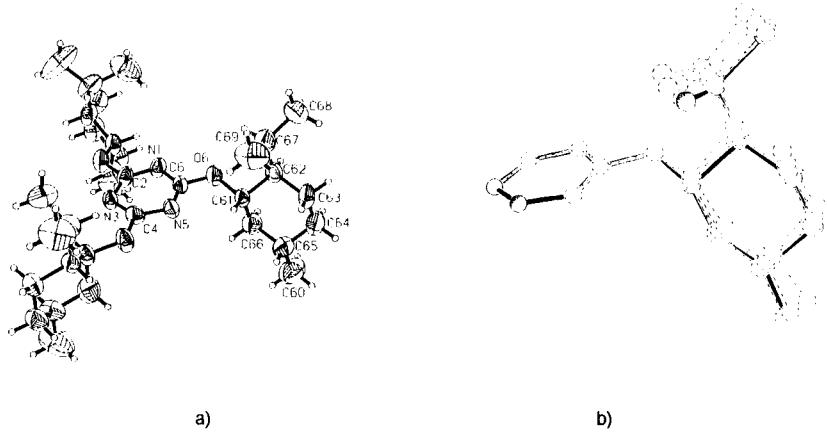


Figure 1. a). General view and numbering system in 2,4,6-trimanthoxy-1,3,5-triazine structure. Only one independent molecule is shown. The other molecule has very similar conformation. b). Orientations of six menthoxy substituents in the two crystallographically independent molecules of **4** in relation to *s*-triazine ring. The fragments are superimposed on *s*-triazine ring.

The most crucial finding of crystal structure **4** is approximately threefold symmetry (not crystallographic) of the two independent molecules bearing all three menthoxy group oriented in the same direction which resulted in strong differentiation of triazine ring faces.

The reasons for the uniformity of spatial arrangement of menthoxyl substituents of triazine ring are: (*i*) rigidity of menthol ring due to three equatorial substituents in the observed form, and (*ii*) conjugation of *s*-triazine π-electrons with oxygen lone pairs[13], which forced the same orientation of the three alkoxy substituents, observed in other symmetrical trialkoxy-1,3,5-triazines[14].

More convenient synthetic procedure leading to **3** was based on our observation that 2-monochloro-4,6-disubstituted-1,3,5-triazines are stable in the presence of triethylamine, but 2,4-dichloro-4-alkoxy-1,3,5-triazines reacts rapidly yielding appropriate quarterly ammonium salts, which were found very prone to decomposition in the presence of water. Thus, we were able to prepare homogeneous sample of **3** by removing **2** from the mixture of products obtained by classic procedure involving the treatment of menthol and cyanuric chloride with sodium bicarbonate[15].

Preliminary experiments of condensations confirmed that **2-3** are efficient coupling reagents for the peptide synthesis (see Table 1).

The presence of chiral substituent in the triazine ring without any doubts determines enantioselectivity of triazine ester formation as well as its aminolysis. The e.e. vary significantly with the structure of substrates used in the condensation. In the favorite cases, e.e. reaches 93 - 100%, but considering the ratio of racemic substrate used in experiments, the efficiency of the reagents **2-3** is sufficiently high for application in preparation of optically pure products.

Experimental

*Synthesis of 2,4-dichloro-6-menthoxy-1,3,5-triazine (**2**), 2-chloro-4,6-dimenthoxy-1,3,5-triazine (**3**) and 2,4,6-trimenthoxy-1,3,5-triazine (**4**).*

To the vigorously stirred solution of cyanuric chloride (7.4 g; 40 mmol) and (-) menthol (12.48 g; 80 mmol) in chloroform (50 ml), collidine (8.8 ml; 80 mmol) was added dropwise in such a rate to keep temperature below 30°C. The stirring was continued for 2 days at room temperature until all cyanuric chloride was consumed. The resulting brown suspension was filtered and filtrate was washed with water, 1M

Table 1. Synthesis of dipeptides involving triazine **2** or **3** as chiral condensing reagent

	Peptide, (substrate ratio)	Coupling reagent	Yield [%]	α_D^{20}	e.e[a]. or d.e. (preferred configuration)
1.	Z-Gly-OH + D,L-Ala-OEt (1:2)	**2**	87	(-)22.1 (c=1, EtOH)	93 (L)
2.	Z-Gly-OH + D,L-Phe-OMe (1:2)	**2**	72	(+)16.4 (c=1, AcOEt)	48 to 100 (L)
3.	Z-D,L-Ala-OH + Gly-OEt (2:1)	**2**	86	(-)24.8 (c=1, EtOH)	100 (L)
4.	Z-D,L-Ala-OH + L-Leu-OMe (2:1)	**2**	72	(-)34.8 (c=1, EtOH)	100 (L,L)
5.	Z-D,L-Ala-OH + L-Phe-OEt (2:1)	**2**	75	(-)35.8 (c=1, etanol)	100 (L)
6.	Z-Gly-OH + D,L-Ala-OEt (1:2)	**3**	72	(-)24.8 (c=1, EtOH)	100 (L)
7	Z-Gly-OH + D,L-Phe-OEt (1:2)	**3**	77	(-)10.5 (c=1, EtOH)	79 (L)

[a)] calculated by comparing optical rotation measured with average value of appropriate literature data[16].

$NaHSO_4$ solution, water, dried with $MgSO_4$ and than concentrated under reduced pressure. The oily residue was separated on Silicagel H column (15 x 5 cm). Product was eluted with light petroleum (250 ml), than with mixture of light petroleum-toluene (gradient increased from 5% to 50% toluene). Fractions (10 ml) ware collected and separation was monitored by TLC (Merck F-254; toluene-cyclohexane 1:1; visualization by spraying with 4-(4-nitrobenzyl)pyridine 1% solution in ethanol).

*2,4-Dichloro-6-menthoxy-1,3,5-triazine (**2**)*

Fractions 1-32 ware collected and evaporated to dryness affording yellow oil (4.13 g; 34%) R_f=0.45, α_D^{20} = - 76.4 (c=1.4, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ= 0.773, (d, 3H, J=7Hz, CH_3-CH), 0.858 (d, 3H, J_1=7Hz, CH_3-C-CH_3); 0.951 (d, 3H, J_1=7Hz, CH_3-C-CH_3); 1.05-1.50 (m, 4H, CH_2-CH_2); 1.50-2.00 (m, 4H, CH-C, CH_2-C-O); 2.18 (dh, 1H, J_1=11Hz, J_2=4Hz, CH-C-O); 5.21 (dt, 1H, J_1=11Hz, J_2= 5Hz, CH-O).

$C_{13}H_{19}N_3OCl_2$ (304.22) calc. C 51.33; H 6.30; N 13.81; found: C 50.95; H 6.15; N 14.20.

*2-Chloro-4,6-dimenthoxy-1,3,5-triazine (**3**)*

Fractions 47-52 after evaporation under reduced pressure to dryness gave **3** as yellow oil (5.65 g, 33.3%). R_f=0.20, α_D^{20} = - 48.8 (c=1.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ= 0.788 (d, 3H, J = 7Hz); 0.929 (dd, 6H, J_1 = 7 Hz, J_2 = 4 Hz); 1.095 (q, 2H, I = 12 Hz); 1.40-1.60 (m, 3H); 1.70 (broad d, 2H, J =14.5 Hz); 2.051 (dh, 1H, J_1=13 Hz, J_2= 4 Hz); 2.10-2.20 (m, 1H); 5.071 (dt, 1H, J_1 = 14 Hz, J_2 = 4.5 Hz).

$C_{23}H_{38}N_3O_2Cl$ (424.03) calc. C 65.15; H 9.03; N 9.91; found: C 65.28; H 8.97; N 9.79

*2-Chloro-4,6-dimenthoxy-1,3,5-triazine (**3**), procedure B.*

The suspension of $NaHCO_3$ (5.5 g, 60 mM,) in THF (40 ml) was vigorously stirred and treated with cyanuric chloride (3.68 g; 20 mmol) and (-) menthol (6.25 g; 40 mmol. The stirring was continued for 3 days at room temperature until all cyanuric chloride was consumed. The suspension was filtered and filtrate was evaporated to dryness. The residue was dissolved dichloromethane and washed with water, 1M $NaHSO_4$, water, 2M aqueous solution of triathylamine (4x10 ml), again water, 1M $NaHSO_4$, than dried with $MgSO_4$ and concentrated under reduced pressure to gave **3** as yellow oil (4.05 g, 48%). R_f=0.20, α_D^{20} = - 32.2 (c=1.5, $CHCl_3$);

*2,4,6-Trimenthoxy-1,3,5-triazine (**4**)*

From fractions 53-63 after evaporation under reduced pressure to dryness, **4** was isolated as colorless crystals (2.5 g, 17.2%) m.p.116-119°C. R_f = 0.15, α_D^{20} = - 99 (c=0.7, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ= δ= 0.774 (d, 3H, J = 7Hz); 0.942 (dd, 6H, J_1 = 7 Hz, J_2 = 4 Hz); 1.105 (m, 2H,); 1.55 (m, 2H); 1.75 (d, J=14Hz, 2H); 1.955 (dh, J_1= 7 Hz, J_2= 2.5 Hz, 1H); 2.152 (broad d, J= 14 Hz, 1H); 5.071 (dt, 1H, J_1 = 14 Hz, J_2 = 4.5 Hz).

Crystallography:

$C_{33}H_{57}N_3O_3$, M=543.84 Monoclinic, a=16.848(3), b=10.843(2), c=19.376(4) Å, β=103.60(3)°; V=3435.96 Å^3 (cell constants were determined by least-squares refinement of 20 reflections with high θ angles, λ=1.54178 Å). Space group $P2_1$ (No. 4), Z=4, Dx=1.051 g/cm^3, μ(CuKα)=0.0052 cm^{-1}. Colorless plates, measured crystal size 0.4x0.2x0.2 mm, KM4 diffractometer (30 kV, 34 mA), room temperature, graphite monochromated CuKα radiation, $2\theta/\omega$ scan mode, scan width=1.30+0.38 tanθ, a total 9033 reflections in range $2<\theta<75°$ measured.

The structure was solved by direct methods and refined by full-matrix least-squares method with anisotropic thermal parameters for non-hydrogen atoms. An hydrogen atoms, although easily found in the difference Fourier syntheses, were added in calculated geometrical positions and refined in riding positions. 2626 reflections with $F \geq 3\sigma(F_o)$ were used in refinement of 817 parameters. The two independent molecules were refined alternatively (as blocks) to improve data to parameter ratio. The weighting scheme $w^{-1}=\sigma^2 (F_o^2)+(0.0868 P)^2$ with $P=[Max(F_o^2,0)+2F_c^2]/3$ was used. Goodness of fit was 1.047, average shift/error 0.019, $\Delta\rho_{max}$ and $\Delta\rho_{min}$ were 0.25 and -0.31e $Å^{-3}$ and the final R=0.0588. All calculations were performed on a Pentium computer with SHELX93[17].

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12. The coordinates, bond distances and angles are deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, Cambridge, UK, and can be obtained as a standard cif file from one of the authors (MLG) at the e-mail adress marekglo@ck-sg.p.lodz.pl.

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