Acta Biochimica Polonica

Vol. 48 No. 4/2001

1143–1146

QUARTERLY

Communication

Synthesis and application of chiral triazine condensing reagents prepared from esters of amino acids★✪

Zbigniew J. Kamiński✉, Krzysztof J. Zając and Konrad Jastrząbek

Institute of Organic Chemistry, Technical University of Łódź, 90-924 Łódź, Poland

Received: 26 September, 2001; accepted: 20 November, 2001

Key words: enantioselective reagent, coupling reagent, peptide synthesis, chiral triazines

Treatment of cyanuric chloride with chiral amines or esters of chiral amino acids gave chiral 2,4-dichloro-6-alkylamino-1,3,5-triazines (2–5) in 49–69% yield, which were found useful as coupling reagents. Enantioselective activation and enantioselective aminolysis in the presence of 2–5 was observed.

Chiral triazines have been found very efficient enantioselective condensing reagents [1, 2]. Their application enables the synthesis of optically active products from racemic substrates with enantiomeric excess exceeding 98% and Kagan's coefficient "s" exceeding 100 [3].

The advantage of triazine enantioselective reagents is an easy access to a broad spectrum of analogues obtained by modification of the leading structure of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT). In our previous studies, a chiral auxiliary derived from terpenic alcohol [1–2] was successfully introduced into the triazine reagent and applied in the enantioselective syntheses of peptides, esters and carboxylic acid anhydrides.

Successful condensations involving achiral triazines **1a–b** and achiral immobilized triazines [4, 5] encouraged us to develop a new group of chiral triazine condensing reagents using amines as chiral auxiliaries. An advantage of this approach is an easy access to a broad spectrum of inexpensive chiral amines and amino-acids precursor. The risk accompanying this approach is a consequence of the well known effect caused by the presence of alkylamino group in the triazine ring result-

★Presented at the XVI Polish Peptide Symposium, September 1–4, 2001, Jagiellonian University, Kraków, Poland.

✪The study was supported by the State Committee for Scientific Research (KBN, Poland) under the Project 3 T09A 029 16.

✉phone: (48 42) 631 3151; e-mail: kaminsz@ck-sg.p.lodz.pl

Abbreviations: CDMT, 2-chloro-4,6-dimethoxy-1,3,5-triazine; THF, tetrahydrofurane.

ing in a decrease of the reactivity of triazine. Usually, the deactivation of triazine caused by alkylamino group is substantial, therefore in the case of 2-alkylamino-4,6-dichloro-1,3,5-triazines only one chlorine is expected to be substituted under mild reaction conditions [4]. On the other hand, in the presence of two alkylamino groups, substitution of chlorine proceeds slowly even under vigorous conditions.

MATERIALS AND METHODS

Treatment of cyanuric chloride with primary or secondary amines in the presence of sodium bicarbonate gave 2-alkylamino-4,6-dichloro-1,3,5-triazines **1–5** (see Scheme 1) in 49–98% yield under phase transfer conditions (Table 1).

We found that formation of the peptide bond by means of triazines **1–5** proceeds under mild reaction conditions in three subsequent stages: In the first step the condensing agent is preactivated by treatment with a tertiary amine, usually 4-methylmorpholine; affording triazinylammonium chloride **6**.

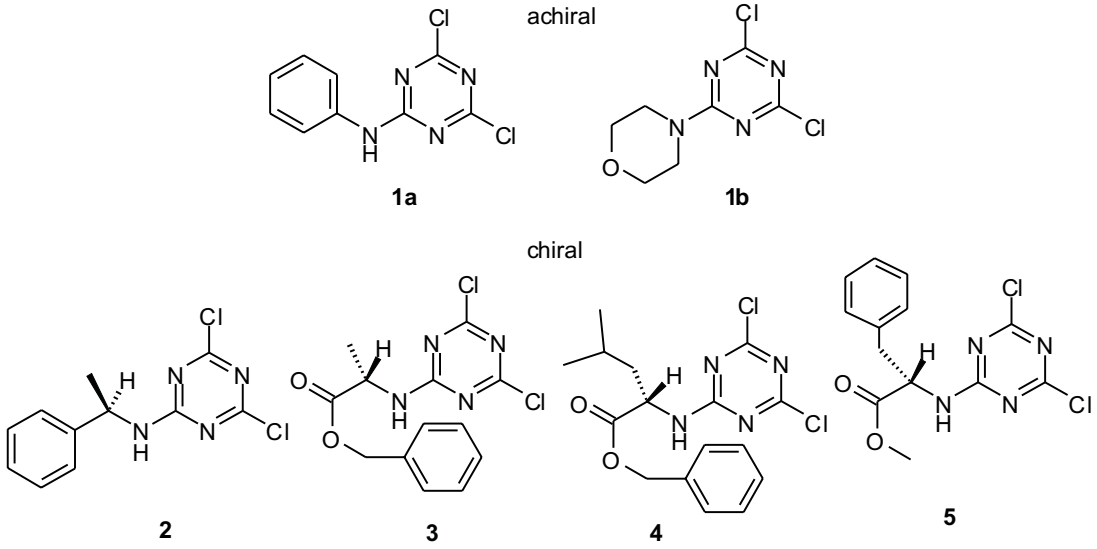
The next stage involves activation of the carboxylic group by substitution of the quaternary triazinylammonium salt with a carboxylic moiety. Due to the chirality of the alkylamino group (–NH-R), the activation proceeds enantioselectively yielding enantiomerically enriched triazine ester **7** and unreacted carboxylic component **8**.

The third stage, aminolysis, also proceeds enantioselectively due to the presence of a chiral alkylamino group (–NH-R) in ester **7**.

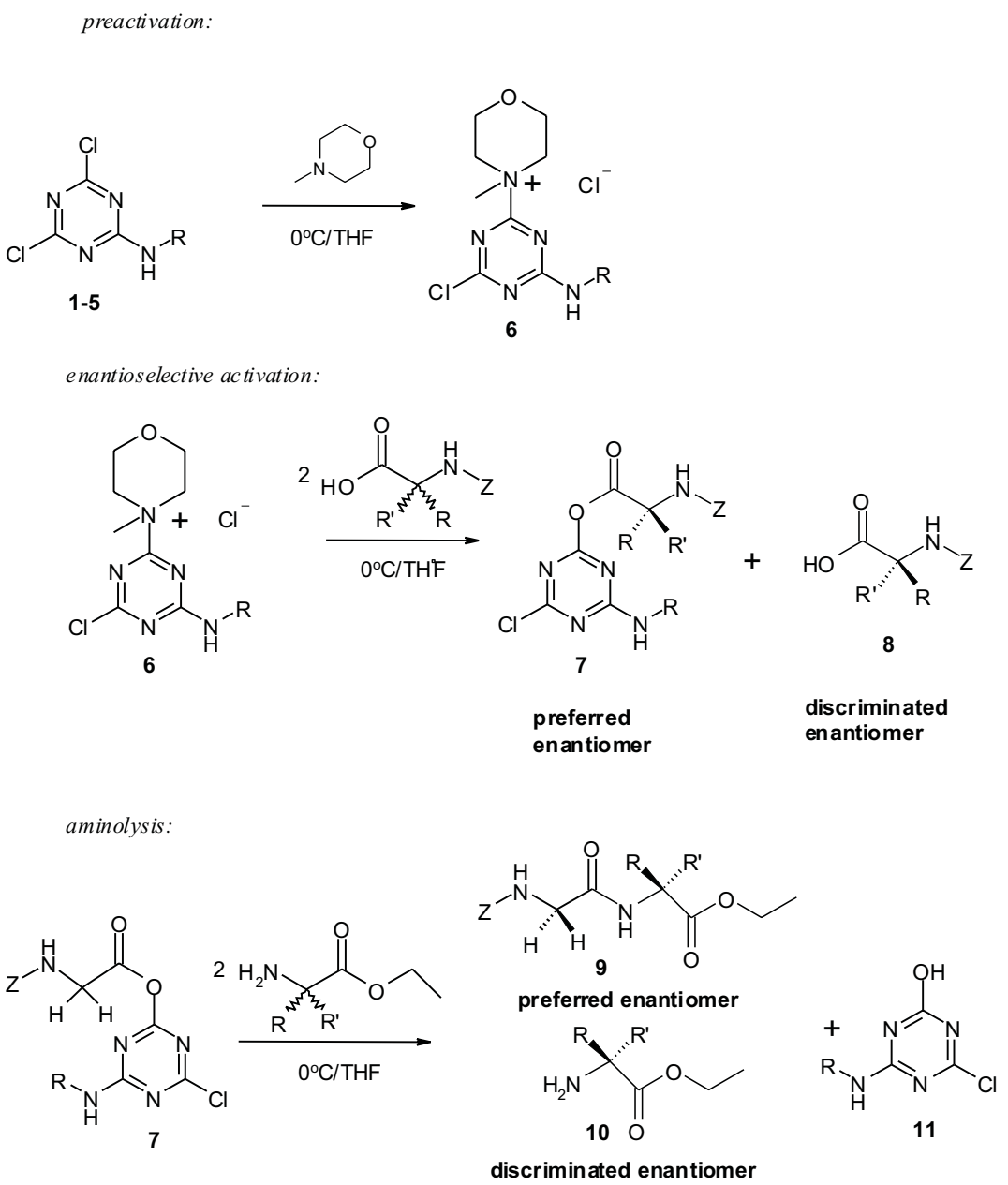
In order to avoid diastereomeric interaction, in all the condensations only a single racemic substrate was reacted with an appropriate achiral glycine derivative.

RESULTS AND DISCUSSION

Easily available 2-alkylamino-4,6-dichloro-1,3,5-triazines **1–5** were found to be useful coupling reagents, although less reactive than their analogues substituted with alkoxy groups. In the presence of triazines **2–5** bearing a chiral alkylamino group enantioselective activation as well as enantioselective aminolysis were observed. Enantioselectivities, however, were found to be substantially lower than previously reported for condensations mediated by triazines substituted with a chiral alkoxy group [1, 2] or chiral leaving groups [3].



Scheme 1



Scheme 2

Table 1. Synthesis of achiral 1a–b and chiral triazine based condensing reagents 2–5 from cyanuric chloride and amines or optically active esters of amino acids

Condens. reagent	Amine	React. time /solvent [h]	Yield [%]	m.p. [°C]	α_D^{20} [c = g/100 ml]
1a	Morpholine	0.5/acetone	88	106	–
1b	Aniline	0.5/acetone	98	103	–
2	L-1-phenylethylamine	3/THF	69	179–181	
3	H-L-Ala-OBzl	24/THF	49	133–134	–38.6 (c = 0.5, $CHCl_3$)
4	H-L-Leu-OBzl	24/THF	66	oil	2.9 (c = 0.5, $CHCl_3$)
5	H-L-Phe-OMe	24/THF	63	57–61	–7.5 (c = 0.5, $CHCl_3$)

Table 2. Enantioselective activation and enantioselective aminolysis by means of chiral coupling agents 3–5

Substrates	Peptide	Coupling reagent	Yield [%]	Preferred config.	Enantiomer ratio
2 *rac*-Z-Ala-OH + H-Gly-OMe	Z-Ala-Gly-OMe	**3**	62	L	52:48[a]
Z-Gly-OH + 2 *rac*-H-Ala-OMe	Z-Gly-Ala-OMe	**3**	91	D	45:55[a]
Z-Gly-OH + 2 *rac*-H-Phe-OMe	Z-Gly-Phe-OEt	**3**	40	D	38:62[b]
Z-Gly-OH + 2 *rac*-H-Leu-OMe	Z-Gly-Leu-OMe	**3**	29	D	49:51[b]
Z-Gly-OH + 2 *rac*-H-Ala-OMe	Z-Gly-Ala-OMe	**4**	86.6	D	45:55[a]
2 *rac*-Z-Ala-OH + H-Gly-OMe	Z-Ala-Gly-OMe	**5**	59	D	44:56[a]
Z-Gly-OH + 2 *rac*-H-Ala-OMe	Z-Gly-Ala-OMe	**5**	92	D	42:58[a]

[a]Enantiomer ratio by GC on ChirasilVal; [b]photopolarimetric method.

REFERENCES

1. Kamiński, Z.J., Markowicz, S.W., Kolesińska, B., Martynowski, D. & Główka, M.L. (1998) *Synth. Commun.* **28**, 2689–2696.

2. Kamiński, Z.J., Kolesińska, B., Markowicz, S.W. & Pokrzeptowicz, K. (1999) *Pol. J. Chem.* **73**, 1965–1968.

3. Kamiński, Z.J., Kolesińska, B., Kamińska, J.E. & Góra, J. (2001) *J. Org. Chem*. **66,** 6276–6281.

4. Masala, S. & Taddei, M. (1999) *Org. Lett*. **1**, 1355–1357.

5. Kamiński, Z.J. (2000) *Biopolymers* **55,** 140–165.