Direct diastereoselective introduction of *l*-menthol residue into 1,2,4-triazin-5(4*H*)-one

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The reaction of 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) with *l*-menthol in the presence of aliphatic acid anhydrides results in (6*S*)- and (6*R*)-1-acyl-6-(*l*-menht-3-yl)-1,6-dyhydro-3-phenyl-1,2,4-triazin-5(4*H*)-ones. The reaction is diastereoselective with predominant formation of (6*S*)-isomers. The reaction diastereoselectivity increases with enhancement of the steric hindrance in the vicinity of the reaction center of the azine.

Key words: 3-phenyl-1,2,4-triazin-5(4*H*)-one, *l*-menthol, diastereoselectivity, acetic anhydride, isobutyric anhydride, 1-acyl-6-(*l*-menth-3-yloxy)-3-phenyl-1,6-dyhydro-1,2,4-triazin-5(4*H*)-ones, nucleophilic addition.

In the series of π-deficient (hetero)aromatic compounds, nucleophilic substitution reactions of hydrogen (S_N^H) cover an extensive group of two-step processes whose common feature is the formation of nucleophilic addition products (σ^H-adducts) in the first step.[1]

After the formation of these adducts, the prochiral carbon atom in the azine ring acquires sp^3-hybridization and becomes asymmetrical. Thus, in most cases, σ^H-adducts exist as mixtures of *R*- and *S*-enantiomers which are usually difficult to identify by conventional physicochemical methods.[2] In the presence of two or more asymmetric carbon atoms in the substrate and/or nucleophile, σ^H-adducts are produced as diastereomers. Moreover, the asymmetric carbon atom introduced in the substrate molecule either directly or indirectly (for example, by *in situ* acylation) is expected to determine the stereochemistry of the addition product, *i.e.,* to induce the stereoselective formation of a new asymmetric center upon the attack of an achiral nucleophile. In the ideal case, this may result in the predominance of only one stereoisomer in the nucleophilic addition product. Thus Lewis acid- or copper(I)-catalyzed addition of Grignard reagents or allylsilanes to homochiral *N*-acylium salts of pyridin-4-ones, prepared *in situ* on treatment with optically active chloroformates, has been reported.[3—8] In these transformations, the introduction of optically active fragments into acyl groups allows one to attain a high degree of asymmetric induction (*de* 88—98%), and the corresponding substituted pyridones are formed in high yields.[9—11]

An example of transformation in which the product stereochemistry is determined by participation of an optically active acylating agent is provided by *S*-proline-catalyzed asymmetric addition of aliphatic ketones to 9-tosyl-3,4-dihydrocarboline, resulting in the corresponding C-adducts with high degrees of optical purity.[12]

The stereoselective formation of a new asymmetric center in the achiral azine substrate upon the attack by an optically active nucleophile is represented by only few examples. For example, in the presence of silver triflate or chlorate, chiral allylsilanes add enantioselectively to activated *N*-acylquinolinium ions obtained from the corresponding achiral quinolines and isoquinolines.[13,14] The stereoselective introduction of the *l*-menthol residue into substituted azoles has been reported.[15] We have briefly described the reaction of *l*-menthol with 1,2,4-triazin-5(4*H*)-one.[16]

This communication describes a detailed study of the influence of the nature of acylating agents, namely, carboxylic acid anhydrides, on the stereochemistry of the products of *l*-menthol addition to 3-phenyl-1,2,4-triazin-5(4*H*)-one.

Results and Discussion

It was found that the reaction of 1,2,4-triazinone **1** with *l*-menthol carried out in acetic anhydride for 6—12 h at room temperature proceeds diastereoselectively, resulting in the predominant formation of (6*S*)-1-acetyl-6-

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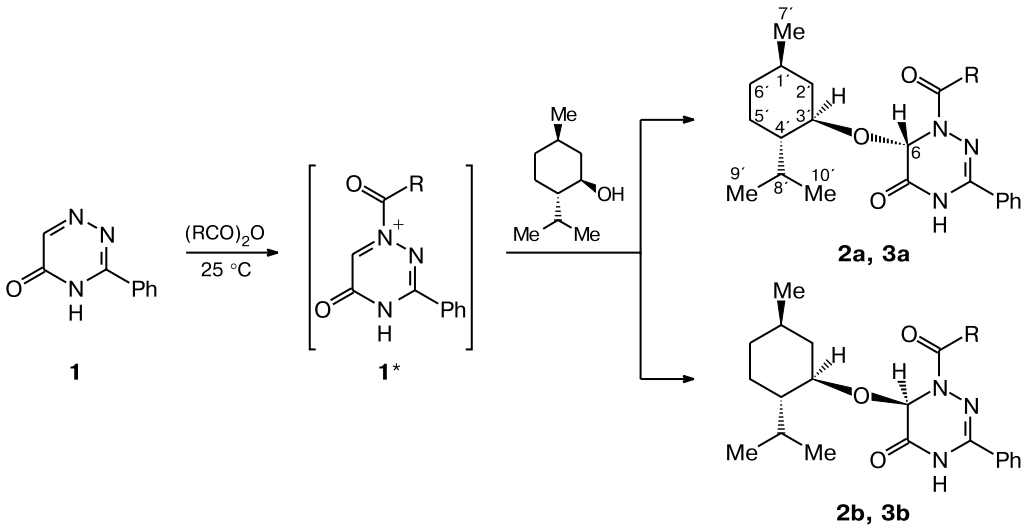
Scheme 1



R = Me (**2a,b**), Pr^i (**3a,b**)

([1′*R*,3′*R*,4′*S*]-menth-3-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**2a**) (molar ratio **2a** : **2b** = 60 : 40) (Scheme 1).

Diastereomers **2a,b** were identified in the mixture based on ^{1}H NMR data (Table 1). In particular, the C(6)H protons in products **2a** and **2b** are responsible for singlets at δ 5.99 and 5.90, respectively. The C(3′)H protons of the menthol fragment are manifested at δ 3.28—3.38 and 3.42—3.52 as resolved multiplets with an overall intensity corresponding to one proton.

The chromatographic behaviors of diastereomers **2a** and **2b** are different, which is favorable for their separation. The stereoisomer **2a** formed predominantly was separated by flash chromatography (*de* 94% based on HPLC data). The absolute configuration of diastereomer **2a**, in particular, the mutual arrangement of the hydrogen atom

Table 1. Spectral characteristics of products **2a,b** and **3a,b** (400 MHz, $CDCl_3$)

Product	^{1}H NMR, δ (*J*/Hz)									
	1,2,4-Triazinone		COR R	*l*-Menthol						
	NH	C(6)H		C(2′)H_AH_B	C(3′)H	C(4′)H	C(7′)H_3	C(8′)H	C(9′)H_3	C(10′)H_3
2a	9.56 (s, 1 H)	6.34 (s, 1 H)	2.46 (s, 3 H, Me)	0.95, 2.37 (both m, 1 H each, CH_A, CH_B)	3.51 (td, 1 H, *J* = 10.6, *J* = 4.3)	1.15 (m, 1 H)	0.94 (d, 3 H, *J* = 6.6)	1.88 (sept.d, *J* = 7.0, *J* = 2.5)	0.75 (d, 3 H, *J* = 7.1)	0.65 (d, 3 H, *J* = 6.9)
2b	9.48 (s, 1 H)	6.24 (d, 1 H, *J* = 0.8)	2.47 (s, 3 H, Me)	0.89, 2.10 (both m, 1 H each, CH_A, CH_B)	3.51 (td, 1 H, *J* = 10.6, *J* = 4.3)	1.19 (m, 1 H)	0.90 (d, 3 H, *J* = 6.5)	2.11 (m, 1 H)	0.84 (d, 3 H, *J* = 7.1)	0.80 (d, 3 H, *J* = 6.9)
3a	9.51 (s, 1 H)	6.32 (d, 1 H, *J* = 0.8)	1.18, 1.28 (both d, 3 H each, Me, *J* = 6.9); 3.63 (m, 1 H, CH)	0.92, 2.41 (both m, 1 H each, CH_A, CH_B)	3.54 (td, 1 H, *J* = 10.5, *J* = 4.2)	1.12 (m, 1 H)	0.96 (d, 3 H, *J* = 6.6)	1.88 (sept.d, 1 H, *J* = 7.0, *J* = 2.5)	0.75 (d, 3 H, *J* = 7.1)	0.63 (d, 3 H, *J* = 6.9)
3b	9.45 (s, 1 H)	6.26 (d, 1 H, *J* = 0.8)	1.20, 1.29 (both d, 3 H each, Me, *J* = 6.9); 3.63 (m, 1 H, CH)	0.84, 2.02 (both m, 1 H each, CH_A, CH_B)	≈3.62 [a]	1.15 (m, 1 H)	0.87 (d, 3 H, *J* = 6.6)	2.15 (m, 1 H)	0.85 (d, 3 H, *J* = 7.1)	0.84 (d, 3 H, *J* = 6.9)

[a] The signals are superimposed by the signals of the predominant isomer.

Table 2. Energy characteristics of (6*S*)-1-acetyl-6-([1′*R*,3′*R*,4′*S*]-menth-3′-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (**2a**) and (6*R*)-1-acetyl-6-([1′*R*,3′*R*,4′*S*]menth-3-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (**2b**)

Product	E_{tors}	E_{total}	ΔH_f	E_{HOMO}	E_{LUMO}	ΔE*
	kcal mol^{-1}			eV		
2a	7.173	−99242.3	−85.244	−9.063	−0.739	8.324
2b	49.212	−99237.5	−72.893	−9.118	−0.296	8.822

* $\Delta E = E_{LUMO} - E_{HOMO}$.

Table 3. Transformation of diastereomers **2a,b** in a DMSO-d_6 solution at 140 °C (according to ^{1}H NMR data)

τ/min	Contents of stereoisomers (mol %)		Molar ratio **2a** : **2b**
	2a	**2b**	
0	50	50	1.0
12	40	30	0.75
15	35	25	0.71
20	30	20	0.66
25	27	18	0.66
35	25	17	0.68

Table 4. Transformation of diastereomers **2a,b** in a $CDCl_3$ solution in the presence of TFA (according to ^{1}H NMR data)

τ/min	Contents of stereoisomers (mol %)		Molar ratio **2a** : **2b**
	2a	**2b**	
0	50	50	1.0
12	47	53	0.88
18	42	51	0.82
20	44	54	0.81
22	39	55	0.71
24	37	53	0.69
26	35	53	0.66
28	33	52	0.63
30	34	53	0.64
32	26	47	0.55
34	29	48	0.60
36	23	45	0.51
38	22	44	0.50
40	15	39	0.38
50	19	41	0.46
60	14	35	0.40
70	13	33	0.39
80	7	27	0.25
105	3	21	0.14
165	2.5	18	0.13

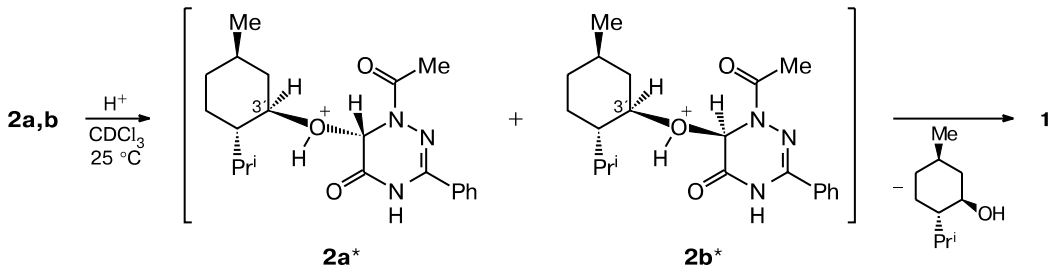
and the menthol fragment at the sp^3-hybridized C(6) atom and the position of the acetyl group were determined by X-ray diffraction taking into account the known absolute configuration of *l*-menthol.[16]

The asymmetric course of this synthesis is directly related to the fact that diastereomers **2a,b** possess different energies and, therefore, they are produced at different rates. The energy, the charge, and orbital characteristics of products **2a,b** were calculated using the semiempirical quantum-chemical PM3 method (Table 2). The calculations confirm that the predominant formation of diastereomer **2a** is due to its higher thermodynamic stability. As a consequence, this isomer has a lower torsion energy (E_{tors}), total energy (E_{total}), and heat of formation (ΔH_f).

This is supported by the data obtained by NMR monitoring of thermolysis of an equimolar mixture of diastereomers **2a** and **2b** in DMSO-d_6 carried out in a NMR tube (Table 3). The thermal dissociation of isomer **2a** is less intensive, which may be due to the partial formation of this compound from thermodynamically less stable **2b**.

The calculated LUMO and HOMO energies for the obtained diastereomers indicate that the electron transitions should be substantially easier in the molecule of **2a**, suggesting a higher reactivity for this isomer. The ^{1}H NMR monitoring of the hydrolysis of an equimolar mixture of stereoisomers **2a,b** (1% concentration) in $CDCl_3$ in the presence of a catalytic amount of TFA at room temperature (Scheme 2) shows that dissociation of (3′*R*,6*S*)-stereoisomer **2a** into the starting compounds proceeds faster than that of **2b** (Table 4). The difference between the dissociation rates of compounds **2a,b** should be deter-

Scheme 2



mined by the stability of the protonated species **2a*** and **2b*** they form.

Due to the higher steric accessibility of the oxygen atom, protonated form **2a*** is formed more easily, but its subsequent heterolytic dissociation into the starting compounds also proceeds faster. In turn, the formation of the less reactive protonated form **2b***, which is a secondary process, accounts for the lower rate of decomposition of **2b** in acid media.

In view of the spatial structure of products **2a,b**, we suggested that the enhancement of steric crowding near the reaction center should have a pronounced effect on the process stereoselectivity.

Indeed, the reaction of 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) with *l*-menthol in the presence of isobutyric anhydride at room temperature results in the predominant formation of (6*S*)-1-isobutyryl-6-([1′*R*,3′*R*,4′*S*]-menth-3-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**3a**) (Table 5), which was also isolated in the enantiopure state (*de* 94% based on HPLC data).

The diagnostic parameters that would allow one to identify products **3a,b** as either (3′*R*,6*S*)- or (3′*R*,6*R*)-diastereomers, by analogy with compounds **2a,b**, are provided by ^{1}H NMR spectroscopy (see Table 1). Indeed, the ^{1}H NMR signals for the C(6)H protons of diastereomers **3a** and **3b** occur at δ 5.92 and 5.87, respectively. Similarly, the C(3′)H protons of the menthol fragment are responsible for signals at δ 3.25—3.38 and 3.42—3.55.

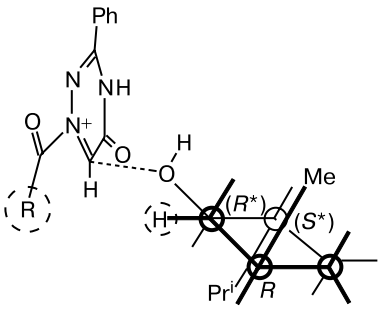
Thus, the steric pathways of the reactions proved to be qualitatively similar; in both cases, (3′*R*,6*S*)-diastereomers predominated and the reaction diastereoselectivity increased when sterically more crowded acylating reagent was used.

Analysis of the results obtained leads to the conclusion that the stereochemistry of the reaction between 3-phenyl-1,2,4-triazin-5(4*H*)-one and *l*-menthol is determined in the step of formation of the *N*-acylium salt **1***, which is postulated for these reactions. Subsequently, this salt is attacked by the chiral nucleophile. Probably, the axial nucleophilic attack of the azine ring, which is preferred from the stereoelectronic standpoint, results in a

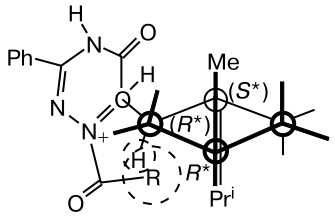
Table 5. Ratio of (6*S*)-1-acyl-6-([1′*R*,3′*R*,4′*S*]-menth-3′-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **2a**, **3a** and (6*R*)-1-acyl-6-([1′*R*,3′*R*,4′*S*]-menth-3′-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **2b**, **3b** in the reaction mixture (according to ^{1}H NMR data)

Compound	Acyl	Ratio of stereoisomers (mol %)		*de* (%)*
		(3′*R*,6*S*)	(3′*R*,6*R*)	
2	Ac	60	40	20
3	Pr^{i}CO	85	15	70

* Diastereomeric yield of (3′*R*,6*S*)-isomer **2a** or **3a**.



I



II

Fig. 1. Newman projections for the transition state of *l*-menthol addition to *N*-acylium salts of 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**): **I** is synclinal structure (preferred), **II** is antiperiplanar structure (less favorable).

synclinal transition state **I**, which precedes the formation of thermodynamically more stable adducts **2a** and **3a** with the *S*-configuration of the C(6) atom in the azine ring. Meanwhile, the structure of the antiperiplanar type transition state **II**, resulting from the equatiorial nucleophilic attack, corresponds to less stable (3′*R*,6*R*)-adducts **2b** and **3b** (Fig. 1).

Thus, in the 1,2,4-triazine series, we first demonstrated the possibility of diastereoselective introduction of a chiral O-nucleophile, *l*-menthol, into an achiral azine substrate. It was shown that process diastereoselectivity can be increased by enhancing steric hindrance in the vicinity of the azine reaction center.

Experimental

^{1}H NMR spectra were recorded on Bruker DRX-400 (400 MHz) and Bruker WM-250 (250 MHz) spectrometers in DMSO-d_6 or $CDCl_3$ with Me_4Si as the internal standard. Mass spectra were run on a Varian MAT-311A instrument.

HPLC was carried out on a Milikhrom 4-UV chromatograph using a 64×2 mm column, Silasorb-60 as the sorbent, detection at 230 nm, an eluent velocity of 200 μL min^{-1}, and a 80 : 1 hexane—Pr^{i}OH solvent mixture as the mobile phase. Column chromatography was performed in the flash chromatography mode on a dry column with the Silpearl silica gel (Kavalier). TLC was carried out on Silufol UV plates (Kavalier) in a benzene—AcOEt solvent system (8 : 2). The melting points were measured on a Boetius hot stage and were not corrected.

(6*R*,*S*)-1-Acyl-6-([1´*R*,3´*R*,4´*S*]-menth-3´-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (2a,b, 3a,b). 3-Phenyl-1,2,4-triazin-5(4*H*)-one (**1**) (1 mmol) and *l*-menthol (1.2 mmol) in 3 mL of the corresponding anhydride was kept for 6—24 h. The mixture was concentrated *in vacuo* to dryness. The residue was triturated in ether or benzene, filtered off, and crystallized from methanol.

(6*S*)-1-Acyl-6-([1´*R*,3´*R*,4´*S*]-menth-3´-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (2a, 3a). A mixture of 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) (1 mmol) and *l*-menthol (1.2 mmol) in 3 mL of the corresponding anhydride was kept for 6—24 h and concentrated *in vacuo* to dryness. The residue was dissolved in chloroform and subjected to flash chromatography (AcOEt—benzene, 99 : 1 to 85 : 15), the fraction with $R_f = 0.62$ being collected. The solvent was evaporated *in vacuo* and the precipitate was recrystallized from methanol.

Compound 2a, m.p. 152—153 °C, *de* 94% (HPLC, τ_R = 4.45 min). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 371 $[M]^+$ (4). Found (%): C, 67.90; H, 7.87. $C_{21}H_{29}N_3O_3$. Calculated (%): C, 67.72; H, 7.74.

Compound 3a, oil, *de* 94% (HPLC, τ_R = 3.44 min). Found (%): C, 69.14; H, 8.33. $C_{23}H_{33}N_3O_3$. Calculated (%): C, 69.08; H, 8.22.

Hydrolysis of an equimolar mixture of (6*R*)-1-acetyl-6-([1´*R*,3´*R*,4´*S*]-menth-3´-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (2a) and (6*S*)-1-acetyl-6-([1´*R*,3´*R*,4´*S*]-menth-3´-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (2b). An equimolar mixture of (6*R*)-1-acetyl-6-([1´*R*,3´*R*,4´*S*]-menth-3´-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**2a**) and (6*S*)-1-acetyl-6-([1´*R*,3´*R*,4´*S*]-menth-3´-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**2b**) (0.01 g, 0.027 mmol) were placed in an NMR tube containing 1 mL of $CDCl_3$, and 0.002 mL of TFA was added. The measurements were started 12 min after the addition of TFA and finished after 165 min. The molar content and the molar ratio of the isomers were determined by comparing the integral intensities of the signal of the menthol C(3´)H atom and the residual signal of chloroform-d_1.

Thermolysis of an equimolar mixture of diastereomers 2a and 2b. An equimolar mixture of (6*R*)-1-acetyl-6-([1´*R*,3´*R*,4´*S*]-menth-3´-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**2a**) and (6*S*)-1-acetyl-6-([1´*R*,3´*R*,4´*S*]-menth-3´-yloxy)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**2b**) (0.01 g, 0.027 mmol) were placed in an NMR tube containing 1 mL of DMSO-d_6 and the mixture was heated to 140 °C. The measurements were started 12 min after the temperature was 140 °C and finished 35 min later. The molar content and the molar ratio of the isomers were determined by comparing the integral intensities of the signal of the menthol C(3´)H protons and the residual signal of DMSO-d_6.

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