Pergamon

Tetrahedron Letters 42 (2001) 2393–2395

TETRAHEDRON LETTERS

Direct diastereoselective addition of *l*-menthol to activated 1,2,4-triazin-5(4*H*)-one†

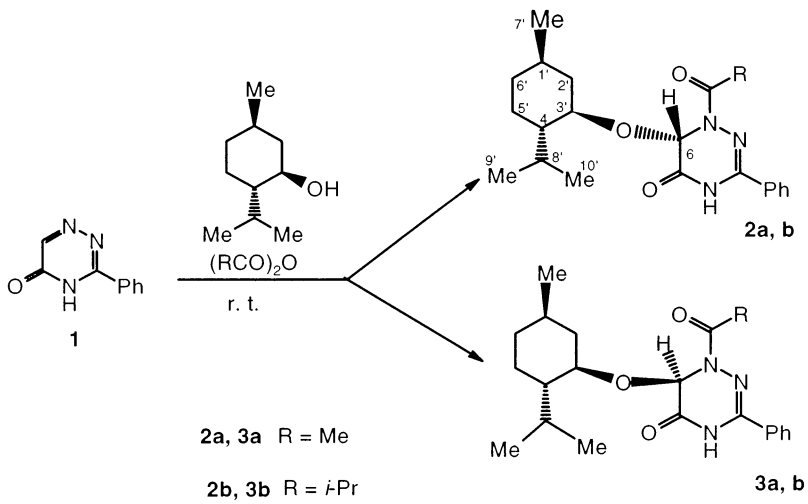
Oleg N. Chupakhin,[a,*] Grigory V. Zyryanov,[b] Vladimir L. Rusinov,[b] Victor P. Krasnov,[a] Galina L. Levit,[a] Marina A. Korolyova[a] and Michael I. Kodess[a]

[a]*Institute of Organic Synthesis, 20, S. Kovalevskaya St., Ekaterinburg 620219, Russia*
[b]*Urals State Technical University, 19, Mira St., Ekaterinburg 620002, Russia*

Received 15 November 2000; revised 16 January 2001; accepted 25 January 2001

Abstract—For the first time in a triazine series it has been found that addition of a chiral *O*-nucleophile, *l*-menthol, to the C^6-unsubstituted atom of 3-phenyl-1,2,4-triazin-5(4*H*)-one **1** activated by aliphatic acid anhydrides proceeds diastereoselectively to form a mixture of 1-acyl-6-[(1′*R*,3′*R*,4′*S*)-menthyl-3′)]-3-phenyl-(6*S*)-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **2** and 1-acyl-6-[(1′*R*,3′*R*, 4′*S*)-menthyl-3′)]-3-phenyl-(6*R*)-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **3** in which the diastereomers **2** predominate. The diastereoselectivity of the process improves as the size of the N^1-acyl substituent increases. © 2001 Published by Elsevier Science Ltd.

The development of new methods for the synthesis of potentially biologically active azaheterocycles as individual stereoisomers is of considerable interest.[1] A variety of the reported synthetic methods are concerned with copper(I) compounds or Lewis acid-promoted addition reactions of aliphatic Grignard reagents or allylsilanes to homochiral *N*-acyl salts of pyridin-4-ones generated in situ under the action of optically active chloroformates.[2] A high degree of asymmetric induction (88–98% de) was achieved in these processes when chiral auxiliaries were incorporated into the acylating groups, and the appropriate substituted pyridones were formed in high yields. The diastereoselective addition of achiral *N*- and *S*-nucleophiles to optically active *N*-substituted pyridin-2-ones (thiones) or pyridin-4-ones resulting in appropriate tetrahydropyridones has been reported.[3]



Scheme 1. Synthesis of compounds **2** and **3**.

* Corresponding author. E-mail: ca@ios.uran.ru

† This work is dedicated to Professor Hans Neunhoeffer on the occasion of his 65th birthday.

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00154-X

There are a few examples of the stereoselective formation of a new asymmetric center in an achiral azine substrate by attack of a chiral nucleophile. For instance, a highly enantioselective addition took place involving a chiral allylsilane in the presence of AgOTf and activated *N*-acylquinolinium ions generated from achiral quinolines and isoquinolines.[4] Another case of the stereoselective addition of *l*-menthol in the azole series has been reported recently.[5]

In this work we wish to report the first case in the triazine series of the diastereoselective addition of the enantiopure *O*-nucleophile, *l*-menthol, to the unsubstituted cyclic carbon of achiral 3-phenyl-1,2,4-triazin-5(4*H*)-one **1**[6] activated with acid anhydrides.

The formation of 1-acyl-6-[(1′*R*,3′*R*,4′*S*)-menthyl-3′)]-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **2a**–**3a** and **2b**–**3b** proceeds smoothly in solution in the anhydride $(RCO)_2O$ (R = Me or *i*-Pr, respectively) at room temperature for 6–12 h (Scheme 1). Evaporation in vacuo and workup gave the diastereomers **2a**–**3a** and **2b**–**3b** as mixtures (90% yield) with the preferred formation of isomer **2a** (**2b**). The structures of all new compounds were established by ^{1}H NMR spectroscopy, mass-spectrometry and microanalytical data.[7]

Products **2a** (**2b**) as individual stereoisomers were isolated from the mixture of **2a**–**3a** (**2b**–**3b**) by flash-chromatography on a dry column[8] (94% de according to HPLC,[9] **2a** mp 152–153°C; **2b** an oil). Assignment of the absolute configuration **2a** became possible on the basis of X-ray crystallography, as shown in Fig. 1. Product **2a** is presented by two crystallographically independent molecules (A and B) with similar geometric parameters. The absolute configuration of the (3′*R*,6*S*)-stereoisomer **2a** was established starting from the known absolute configuration of enantiopure (–)-*l*-menthol. According to X-ray data the asymmetric C^6 and $C^{3'}$ atoms of **2a** exist with the opposite configuration. In the starting *l*-menthol, the $C^{3'}$ atom configuration was *R*, so the C^6 atom of the 1,2,4-triazinone was assigned to be in the *S* configuration.

The diastereomeric composition of **2a**–**3a** and **2b**–**3b** mixtures can be easily determined by both HPLC[9] and ^{1}H NMR[10] data, especially according to the intensities of the C^6H-protons of the triazine moiety and the $C^{3'}$H-proton of the menthyl fragment (Table 1). Most proton NMR peaks of the compounds synthesized were assigned by one-dimensional (1D) and two-dimensional (2D) NMR spectra including COSY and DQF COSY.[10] The stereo-configuration of compounds **2b** and **3b** was determined by comparison of their NMR spectra with those of **2a** and **3a**.

In order to determine the influence of the steric hindrance caused by the COR acyl moiety on the N^1 atom near to the reaction center on the diastereoselectivity we investigated the interaction of stoichiometric quantities of **1** with *l*-menthol in DMSO-d_6 solution at room temperature in the presence of anhydrides $(RCO)_2O$ using ^{1}H NMR techniques.[11] The preferred formation of (3′*R*,6*S*)-diastereoisomers **2a**, **2b** was demonstrated. Thus, after 12 h the molar ratios of the **2a**–**3a** (R = Me) and **2b**–**3b** (R = *i*-Pr) diastereoisomers in the reaction mixture were 60:40 and 85:15, respectively. So the more bulky acylating agent—isobutyric anhydride—improves the reaction stereoselectivity.

Compounds **2a**–**3a** and **2b**–**3b** are very stable, but stirring an equimolar mixture of **2a** and **3a** in deuterochloroform (1% solution) with a few drops of trifluoroacetic acid resulted in the decomposition of both diastereoisomers and, according to ^{1}H NMR data, the rate of degradation of epimer **2a** was higher compared with **3a**.[11] Probably, the preferable formation of stereoisomer **2a** other than **3a** from triazinone **1** and *l*-menthol is due to kinetic factors.

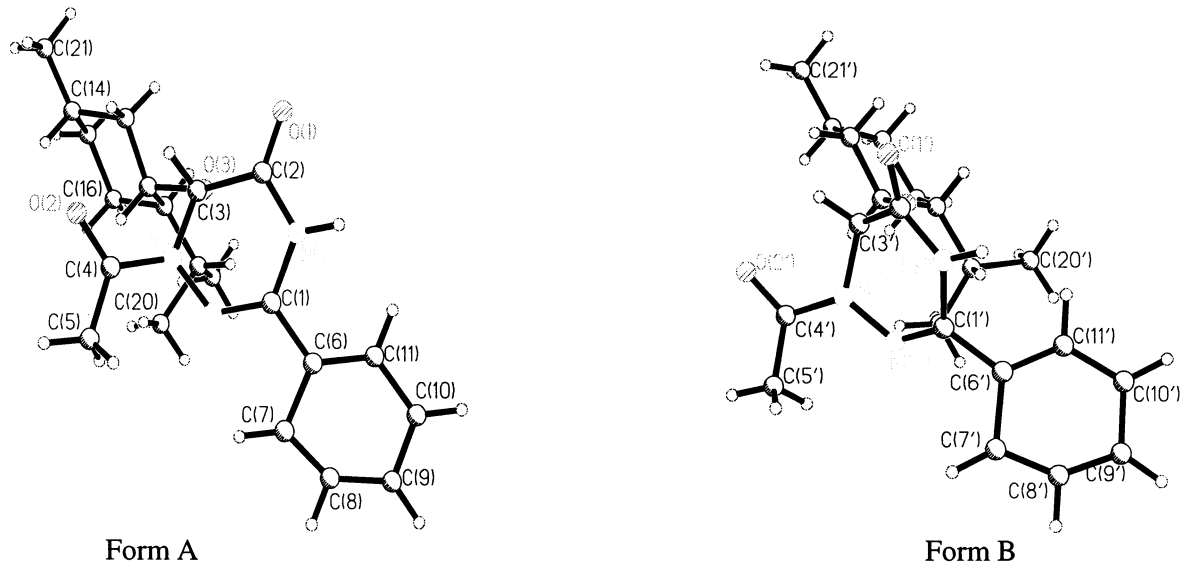


Figure 1. A molecular view of stereoisomer **2a**.

Table 1. Selected ^{1}H NMR data for the compounds studied (400 MHz, $CDCl_3$)[10]

	Chemical shifts, δ (ppm) and coupling constants, J (Hz)									
	1,2,4-Triazinone fragment		Acyl COR	*l*-Menthol fragment						
Compound	NH	C^6H		$C^{2'}H^AH^B$	$C^{3'}H$	$C^{4'}H$	$C^{7'}H_3$	$C^{8'}H$	$C^{9'}H_3$	$C^{10'}H_3$
2a	9.56 s	6.34 s	2.46 s (CH_3)	2.37m (H^A) 0.95 m (H^B)	3.51 t d $J=10.60$ $J=4.26$	1.15 m	0.94 d $J=6.58$	1.88 sp d $J=7.00$ $J=2.50$	0.75 d $J=7.05$	0.65 d $J=6.93$
2b	9.51 s	6.32 d $J=0.80$	3.63 sp (CH) 1.28 d (CH_3) $J=6.90$ 1.18 d (CH_3) $J=6.90$	2.41 m (H^A) 0.92 m (H^B)	3.54 t d $J=10.50$ $J=4.20$	1.12 m	0.96 d $J=6.56$	1.88 sp d $J=7.00$ $J=2.50$	0.75 d $J=7.07$	0.63 d $J=6.94$
3a	9.48 s	6.24 d $J=0.80$	2.47 s (CH_3)	2.10 m (H^A) 0.89 m (H^B)	3.62 t d $J=10.60$ $J=4.27$	1.19 m	0.90 d $J=6.52$	2.11 m	0.84 d $J=7.05$	0.80 d $J=6.95$
3b	9.45 s	6.26 d $J=0.80$	3.63 sp (CH) 1.29 d (CH_3) $J=6.90$ 1.20 d (CH_3) $J=6.90$	2.02 m (H^A) 0.84 m (H^B)	~3.62[a]	1.15 m	0.87 d $J=6.63$	2.15 m	0.85 d $J=7.08$	0.84 d $J=6.92$

[a] Signal is overlapped by signals of a major isomer.

In conclusion, for the first time in the 1,2,4-triazine series the diastereoselectivity of nucleophilic addition during a reaction of achiral 3-aryl-1,2,4-triazin-5-ones with enantiopure *l*-menthol in the presence of acylating agents has been found. It has been shown that the stereoselectivity of the reaction depends on the size of the acyl moiety. Further investigations of the diastereoselectivity of the above process in the presence of other acylating agents are in progress.

Acknowledgements

The authors wish to thank Dr. G. G. Alexandrov for X-ray analysis. This work was supported by the Russian Foundation of Basic Research (Grant No. 00-03-32776 and No. 00-15-97390) and partially by Award No. REC-005 of the US Civilian Research & Development Foundation for the Independent States of the Former Soviet Union (CRDF).

References

1. Daly, J. W.; Garraffo, H. F.; Spande, T. F. In *Alkaloids*; Gordell, D. A., Ed.; Academic Press: San Diego, 1993; Vol. 43, pp. 185–288.
2. (a) Brown, J.; Foley, M.; Comins, D. *J. Am. Chem. Soc.* **1988**, *110*, 7445–7447; (b) Comins, D.; Goehring, R.; Joseph, S.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574–2576; (c) Comins, D.; Hong, H.; Salvador, J. *J. Org. Chem.* **1991**, *58*, 7197–7199; (d) Comins, D.; Hong, H. *J. Org. Chem.* **1993**, *55*, 5035–5036; (e) Comins, D.; Joseph, S.; Goehring, R. *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728; (f) Comins, D.; Killpack, M. *J. Am. Chem. Soc.* **1992**, *114*, 10972–10974; (g) Comins, D.; Dehghani, A. *J. Org. Chem.* **1995**, *60*, 794–795; (h) Comins, D.; LaMunyon, D.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182–8187; (i) Sato, M.; Aoyagi, S.; Yago, S.; Kibayashi, C. *Tetrahedron Lett.* **1996**, *37*, 9063–9066.
3. (a) Soshickij, J.; Jagodzinski, T.; Liebscher, J. *J. Het. Chem.* **1997**, *34*, 643–648; (b) Lakhvich, T.; Lakhvich, O.; Stanishevski, L. *(N.Y.) Chem. Het. Comp.* **1997**, *33*, 448–451.
4. (a) Yamaguchi, R.; Tanaka, M.; Matsuda, T.; Fujita, K.-i. *J. Chem. Soc., Chem. Commun.* **1999**, 2213–2215; (b) Yamaguchi, R.; Tanaka, M.; Matsuda, T.; Okano, T.; Fujita, K.-i.; The 8th International Kyoto Conference on New Aspects of Organic Chemistry, Book of Abstracts, Kyoto, 2000, p. 62.
5. Godfrey, Ch. R. A.; Simpkins, N. S.; Walker, M. D. *Synlett* **2000**, 388–390.
6. Neunhoeffer, H.; Reichel, D.; Cullman, B.; Rehn, I. *Liebigs. Ann. Chem.* **1990**, *776*, 631–640.
7. All new compounds gave satisfactory spectral and analytical data.
8. Silpearl for TLC (Kavalier), benzene–ethyl acetate from 99:1 to 85:15.
9. Determined by HPLC: Silasorb-600, UV 230 nm, 0.2 ml/min, hexane–propanol-2, 80:1, τ_R (**3a**) = 3.70 min, τ_R (**2a**) = 4.45 min; τ_R (**3b**) = 2.80 min, τ_R (**2b**) = 3.44 min.
10. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker DRX-400 instrument.
11. ^{1}H NMR spectra were recorded at 250 MHz on a Bruker WM-250 instrument.