Pergamon

Tetrahedron Letters, Vol. 35, No. 38, pp. 6967-6970, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01484-1

Ritter Reaction on Terpenoids. III. Stereospecific Preparation of Bicyclic [3.3.1] Substituted Piperidines.‡

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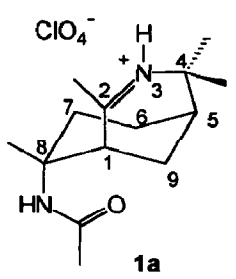
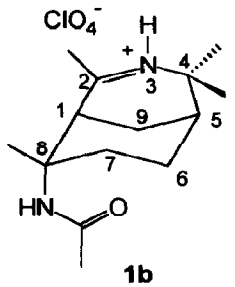
Abstract: Treatment of chiral monoterpenes with different nitrile compounds in the presence of perchloric acid affords (1S,5R,8R) 8-alkyl(aryl)-2-alkyl(aryl)-2,4,4,8-tetramethyl-3-azabicyclo[3.3.1]non-2-ene or the corresponding (1R,5S,8S) enantiomer. The respective free imines yield optically pure piperidine derivatives when treated with reducing agents ($NaBH_4$, $NaCNBH_3$).

We have reported that reaction of (+)-limonene and (-)-β-pinene with acetonitrile and perchloric acid constitutes a good approach to obtain enantiospecifically 3-aza-bicyclo[3.3.1]non-2-ene systems of predictable configuration[1] affording compound **1a** and its antipode **1b**, respectively. There is tantalizing evidence to believe that the first step in the reaction mechanism is the Ritter reaction.[2-4] The absolute stereochemistry of these compounds was unambiguously determined by X-ray analysis of the free imino compound,[5] which was obtained by alkaline hydrolysis of the corresponding perchlorate salt. These iminium salts presented remarkable resistance to hydrolysis in acidic conditions,[6] and even the free imines showed great stability on standing. Thus, this approach could be exploited for the synthesis of piperidine alkaloid analogues employing this 3-azabicyclic frames as precursors and further transformation to the desired alkaloids Ritter reaction has also been employed to prepare 3-azatricyclo[5.3 $1.0^{4,9}$]undecane systems[7,8] but not from readily available starting materials. Therefore, we studied the reactivity of several monoterpenes with nitriles under Ritter-type conditions in order to know the reliability of this method. The reactions were carried out according to the general procedure.[9] The results are presented in Table 1 and they indicated that starting from chiral terpenes, optically pure 3-



1a



1b

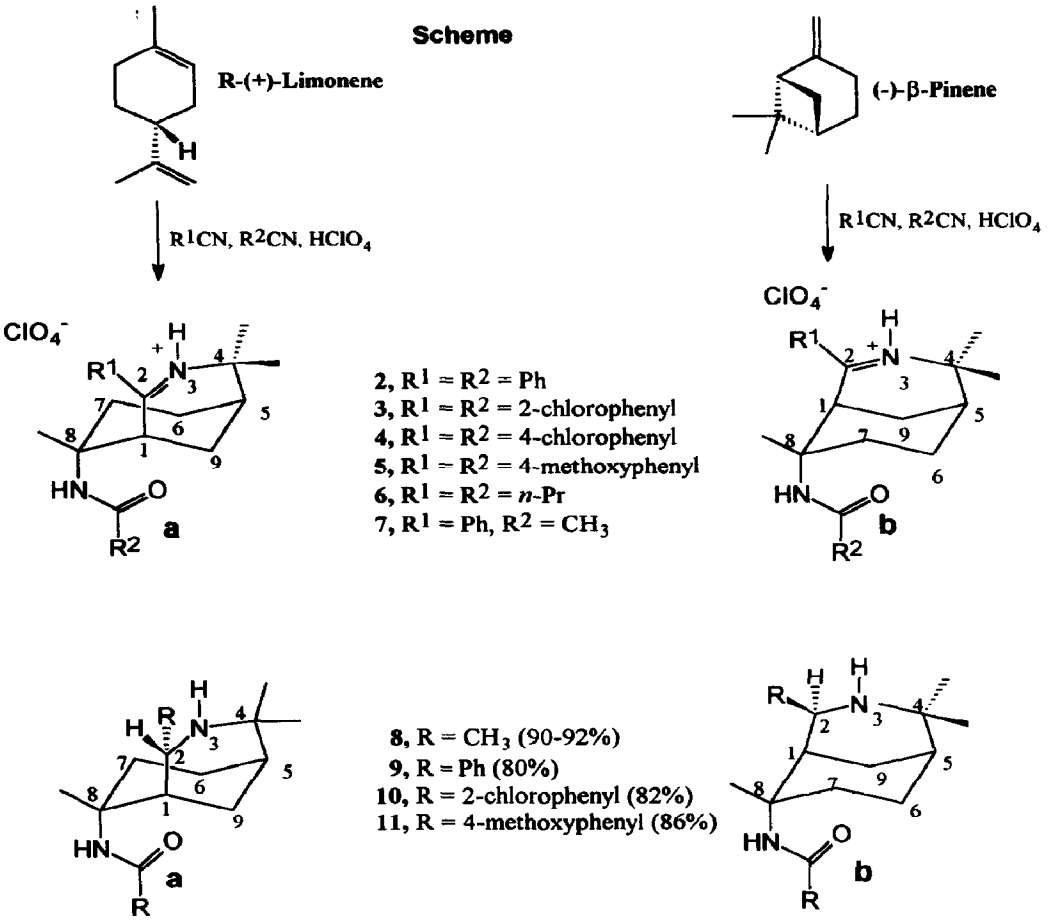
aza-bicyclic compounds were obtained. (+)-Limonene led to the **a** series while α- and β-pinene to the **b** series. It is surprising that the rest of monoterpenes tested afforded the same skeleton.

Table # 1. Reactions conditions and $[\alpha]_D$ of the piperidine alkaloid precursors.

Terpene	Nitrile	Compound	$[\alpha]_D$ MeOH	m.p. (°C)	React Temp (°C)
(+)limonene	PhCN	**2a**	-231.5 c 0.9	210-212	r.t
(-)β-pinene	PhCN	**2b**	+243.4 c 0.9	214	r.t.
(-)α-pinene	PhCN	**2b**	+225.3 c 0 9	210-211	r.t
nerol	PhCN	**2a,b**	0	242	r.t.
α-terpineol	PhCN	**2a,b**	0	230	r.t.
terpinolene	PhCN	**2a,b**	0	241	r.t
1,8-cineole	PhCN	**2a,b**	0	245	r.t
linalool	PhCN	**2a,b**	0	246	r.t
(+)limonene	2-ClPhCN	**3a**	-123.0 c 0.9	231 (d)	60-70
(-)β-pinene	2-ClPhCN	**3b**	+136.0 c 1.2	239	60-70
(-)α-pinene	2-ClPhCN	**3b**	+118 0 c 0.8	231	60-70
nerol	2-ClPhCN	**3a,b**	0	231-232	60-70
(+)limonene	4-ClPhCN	**4a**	-198.0 c 1.0	177	100-110
(-)β-pinene	4-ClPhCN	**4b**	+264.0 c 0.1	243-245	100-110
(+)limonene	4-MeOPhCN	**5a**	-132.0 c 0.3	241 (d)	60-70
(-)β-pinene	4-MeOPhCN	**5b**	+128.0 c 1.0	242 (d)	60-70
(-)α-pinene	4-MeOPhCN	**5b**	+142 0 c 1 1	243 (d)	60-70
α-terpineol	4-MeOPhCN	**5a,b**	0	236 (d)	60-70
(-)β-pinene	*n*-PrCN	**6b**	+85.0 c 1.0	183	r.t
(-)α-pinene	*n*-PrCN	**6b**	+81.0 c 1.0	183-184	r.t.
(-)β-pinene	PhCN+MeCN	**7b**	+173.0 c 0.1	270-271	r.t.

All of these compounds were fully characterized on the basis of their spectroscopic and physical properties as can be seen in compound **2a** taken as a prototype.[10] A very interesting result was observed when β–pinene was treated with two nitriles (aceto and benzonitrile) to afford compound **7b** No other product was isolated. In this case, phenyl group stabilizes the carbonium ion formed in the first step better than the methyl group [1]

Scheme



Compounds **8a, 8b,9a, 9b, 10b and 11b** were easily prepared by hydrolytic reduction of **1, 2, 3** and **5**, respectively, employing aqueous NaOH followed by treatment with $NaBH_4$ or $NaBH_3CN$ [11] Yields are indicated in the Scheme.

According to this data we conclude that the Ritter reaction on monoterpenes is a good and simple entry to synthesize bridged heterocyclic systems enantiospecifically. Further studies on this process seem to have a potential usefulness in the synthesis of alkaloid derivatives.[12]

Acknowledgments. We thank UMYMFOR for spectra and CONICET for partial financial support

References and Notes

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9) A mixture of terpene (2 mmol) and nitrile (20 mmol) was warmed until melting was complete (when solid nitriles were employed) with vigorous stirring (starting materials and reaction temperatures are indicated in Table 1). Then, concentrated perchloric acid (0.1 ml) was added dropwise and the reaction mixture was stirred overnight at the same temperature The mixture was allowed to cool and ethyl acetate (10 ml) was added. The white precipitate was filtered off and crystallized from ethanol. Yields fluctuated between 12-36%.

10) *1(S),5(R),8(R)-8-Benzamido-2-phenyl-4,4,8-trymethyl-3-azabicyclo[3.3.1]non-2-ene* (**2a**) mp = 210-212°C. $[\alpha]_D$ = -231.5 (0.9, MeOH). IR (Nujol, cm^{-1}) 3350, 2310, 1635, 1615, 1590, 1100, 735, 700, 620. ^{1}H-NMR (DMSO-d_6) δ 0.88 (s, 3H, CH_3 at C-8), 1.50 (s, 3H, CH_3 at C-4), 1.61 (s, 3H, CH_3 at C-4), 1.70-2.20 (bs, 8H, H-1, H-5, H-6, H-7 & H-9), 5 03 (bs, 1H, C=N$\underline{H}^+$), 7.40-8.16 (m, 10H, aromatic protons). ^{13}C-NMR (DMSO-d_6) δ 21.65 (CH_3 at C-4), 23.26 (CH_3 at C-4), 25.66 (C-7), 28.50 (C-6 and Me at C-8), 31.28 (C-9), 33.51 (C-5), 38.83 (C-1), 56 37 (C-8), 62.13 (C-4), 127.28 (Ph), 127.93 (Ph), 128.89 (Ph), 128.96 (Ph), 129.24 (Ph), 131 03 (Ph), 133.08 (Ph), 133.30 (Ph), 134.35 (Ph), 134.98 (Ph), 167 23 (Ph-$\underline{C}$=O), 183.62 (Ph-$\underline{C}$=N). MS (m/z, %) 360 ({M^+}-$HClO_4$, 13), 345 (3), 239 (17), 212 (10), 198 (14), 184 (12), 105 (PhCO, 100), 103 (PhCN, 22). *Anal.*Calcld for $C_{24}H_{29}N_2O_5Cl.1/6H_2O$ · C 62.08, H 7.02, N 6 07, Cl 7.64. Found C 61.68, H 6.72, N 5.86, Cl 7.77.

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12) These synthetic compounds are closely related to naturally occurring alkaloids, for example, aristoteline, isolated from *Aristotelia serrata*, *Aristotelia peduncularis* and from the leaves and stems of *Aristotelia chilensis* (a) Anderson, B. F., Robertson, G. B.; Avey, H. P.; Donovan, W F., Bick, I. R. C ; Bremner, J B., Finney, A J T.; Preston, N. W.; Gallagher, R. T.; Russell, G. B *J Chem. Soc Chem. Commun.*, **1975**, 511. (b) Kyburz, R., Schöpp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta*, **1981**, *64*, 2555 (c) Bhakuni, D S.; Silva, M.; Matlin, S. A.; Sammes, P. G. *Phytochemistry*, **1976**, *15*. 574; aristotelinona, isolated from *A. serrata* (d) Bick, I. R C., Hai, M. A.; Preston, N. W.; Gallagher, R. T. *Tetrahedron Lett*. **1980**, *21*. 545; tasmanine, isolated from *A. peduncularis*[12b]; serratoline, isolated from *A. serrata* (e) Kyburz, R.; Schöpp, E ; Hesse, M. *Helv. Chim. Acta*, **1984**, *67*, 804; hobartine, isolated from *A. peduncularis* (f) Kyburz, R.; Schöpp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta*, **1979**, *62*, 2539.

(*Received in USA* 27 *April* 1994; *revised* 16 *June* 1994; *accepted* 28 *July* 1994)