Pergamon

Tetrahedron Vol. 51, No. 31, pp. 8605-8612, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00475-0

Ring Opening of the Isoxazolidine System: a New Synthesis of 3-Amino-2(5H)furanones

Francesco Casuscelli,[a] Ugo Chiacchio,[b] Maria R. Di Bella,[a] Antonio Rescifina,[b] Giovanni Romeo,[a] Roberto Romeo[a] and Nicola Uccella[c]

[a]Dipartimento Farmaco-Chimico, Universita' di Messina 98168, Italy

[b]Dipartimento di Scienze Chimiche, Universita' di Catania 95125, Italy

[c]Dipartimento di Chimica, Universita' di Arcavacata di Rende 87036, Italy

Abstract: A new ring opening reaction of isoxazolidine nucleus is reported, which is based on the treatment of 3-carboxyalkyl-substituted derivatives with NaH. The process results in a new and general synthetic pathway towards the formation of 3-methylamino-2(5H)furanones.

Unsaturated five-membered lactones, butenolides, are often the central skeletons of naturally occurring oxygen heterocycles[1]. Moreover, they occur, as intermediates, in the synthesis of many products of biological interest;[2] for instance, butenolides have been used as synthons in the formation of 4,5-dihydroxy-D-threo-L-norvaline and derivatives, valuable precursors of clavalanine, a clavam antibiotic isolated from Streptomices clavuligerus[3].

Among the numerous reported syntheses of 2-butenolides[4], the route based on the β-elimination reaction of 2-hydroxy- or 2-halo-butanolides is not familiar, since availability of the starting lactones is quite narrow.[5]

The pericyclic reaction of suitable 1,3-dipoles to alkenes has been also usefully exploited:[6] in a previous report we have described a new general synthetic approach to α,γ-butenolides by cycloaddition of suitable nitrones to alkenes, followed by hydrogenolytic ring cleavage of the obtained isoxazolidines.[7]

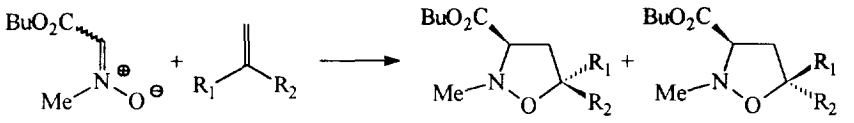
The present paper reports the extension of the 1,3-dipolar cycloaddition approach in the direction of providing a new and direct entry to 3-amino-2(5H)furanones, which represent versatile synthons for the obtainment of β-lactams:[8] the designed reaction scheme is based on a new rearrangement pathway of the isoxazolidine nucleus.

RESULTS AND DISCUSSION

The pericyclic reaction of C-carbobutoxy-N-methylnitrone **1**[9] with alkenes **2-8**, in toluene at 80° C for 48 h, afforded a mixture of the epimeric isoxazolidines **9-15** (**68-80** % yield). The epimeric ratio was evaluated by ^{1}H NMR analysis of the crude reaction mixture; *trans* isomers are generally the major products (Table 1).

The rationalization of the obtained product distribution is based on the evaluation of the different stabilization effects, which operate in the transition states leading to two diastereomeric *cis* and *trans* cycloadducts, as well as on the consideration that the nitrone **1** exists as a mixture of *E* and *Z* isomers (*E*/*Z* ratio = 6.3:1),[10] with the isomer *E* predominating.

Table 1. Reaction of Nitrone **1** with Alkenes **2-8**.



1 **2-8** **9a-15a** **9b-15b**

Alkene	R_1	R_2	Isoxazolidine	Yield (%)	Epimeric ratio *trans/cis*
2	C_4H_9	H	**9**	70	6.1:1
3	C_5H_{11}	H	**10**	70	6.4:1
4	C_6H_{13}	H	**11**	72	6.4:1
5	C_3H_7	CH_3	**12**	68	1.3:1
6	C_6H_{11}	H	**13**	74	6.1:1
7	-$(CH_2)_5$-		**14**	60	
8	CH_2OH	H	**15**	80	3.5:1

The half life of this rearrangement is 65 h at 100 °C; the rate of isomerization is an order of magnitude slower than its rate of disappearance.[11] Thus, in the adopted experimental conditions, the preferential formation of *trans* cycloadducts **9a-11a** and **13a**, in the reaction of **1** with **2-4** and **6** respectively, explainable on the basis of an *exo* transition state, sterically preferred, reflects the relative distribution of *E/Z* forms of the reacting nitrone (*trans/cis* cycloadducts ratio = 6/1).

As expected, the reaction of **1** with 2-methyl-1-pentene **5**, performed in the same experimental conditions, showed a poor stereoselectivity,[12] linked to the slight difference in the energies of two alternative *E-exo* transition states leading to *cis* and *trans* stereoisomers.

The reaction of **1** with **8** gave rise to a 3.5:1 mixture of the *trans* and *cis* isomers **15a** and **15b**. The increased amount of the *cis* isomer, with respect to isoxazolidines **2-4** and **6**, is rationalizable on the basis of an intramolecular hydrogen bonding,[13] involving the oxygen atom of the 1,3-dipole and the hydroxylic functionality of the dipolarophile. This bond slightly shifts the process through the *E-endo* approach, leading to *cis* isomer, even if steric effects, which favour the *E-exo* transition state leading to *trans* adduct, continue to maintain a predominant control on the reaction course.

The stereochemical assignments to the obtained cycloadducts have been performed on the basis of spectrometric parameters.

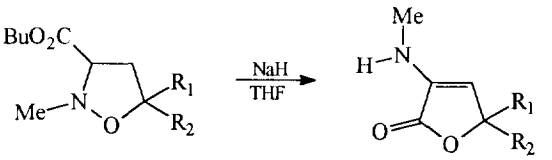
The ^{1}H NMR spectrum of **9a**, taken as model compound, shows two multiplets centred at 2.10 and 2.50 δ; the downfield resonance corresponds to the C_4 proton in a *cis* position with respect to the substituent at C_3 , because of the deshielding effect exerted by the carboxybutyl group on the same side of the pentatomic ring.

Furthermore, H_3 and H_5 protons resonate as doublets of doublets centred at 3.18 δ (J_{cis} = 8.8 Hz and J_{trans} = 6.4 Hz) and 3.97 δ (J_{cis} = 10.7 Hz and J_{trans} = 7.7 Hz) respectively.

The configurational assignment has been confirmed by NOEDS spectroscopy. The positive NOE observed for H_5 on irradiating the H_3 proton is clearly indicative of their *cis* relationship.

Isoxazolidines **9-15**, as epimeric mixtures, were reacted with an equivalent amount of NaH in dry THF at room temperature, until t.l.c. showed the disappearance of the starting material (3-5 h). After the usual work-up, 3-methylamino-2-(5H)furanones **16-22** have been obtained in satisfactory yields (73-85%) (Table 2).

Table 2. Formation of Furanones **16-22**.



9-15 **16-22**

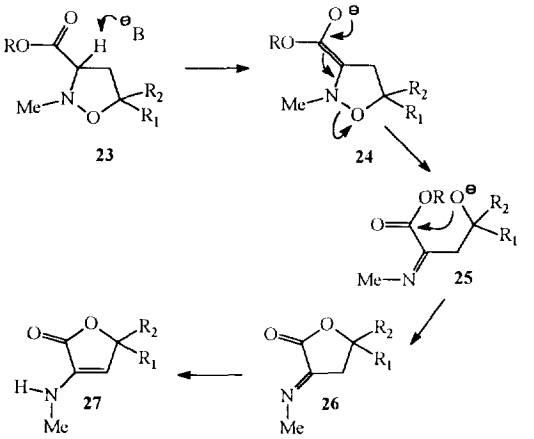
Isoxazolidines	R_1	R_2	Furanones	Yield (%)
9	C_4H_9	H	**16**	75
10	C_5H_{11}	H	**17**	80
11	C_6H_{13}	H	**18**	84
12	C_3H_7	CH_3	**19**	85
13	C_6H_{11}	H	**20**	99
14	-(CH_2)-		**21**	79
15	CH_2OH	H	**22**	59

The structures of the isolated products have been assigned on the basis of analytical and spectroscopic data, as reported in the experimental section.

In particular, the molecular formula of furanones follow from an exact mass determination. The IR absorptions of the carbonyl group at 1720 cm^{-1} are in accord with γ-lactones.

The ^1H NMR spectra show the H_4 protons as doublets in the range of 5.5 δ, while H_5 protons resonate at 5.0 δ; moreover, the *N*-methyl groups resonate as doublets (J = 4.0 Hz) at 2.7 δ.

The chemical conversion of 3-carboxyalkyl-substituted isoxazolidines into 3-methylamino-2-(5H)furanones can be rationalized on the basis of a sequence of steps: the electron-withdrawing group CO_2Bu improves the acidity of the hydrogen atom at C_3, so promoting its abstraction by basic attack of NaH. The obtained enolate ion **24** evolves, via ring-opening, towards the formation of the anion **25**, which affords the lactone **27** by a straightforward intramolecular nucleophilic acyl substitution (Scheme 1).



Scheme 1

The driving force for the transformation is represented by the low critical energy required to induce a carbanionic centre at the position 3 of the *N,O*-heterocycles.

Conversely, the use of nucleophilic reagents promotes a different reaction pattern. Treatment of isoxazolidine **9** with $LiAlH_4$ led to the formation of 3-hydroxymethyl isoxazolidine **28**, which arises from the nucleophilic attack of the hydride ion to the ester functionality (Scheme 2).

9 **28**

Scheme 2

In conclusion, the ring-opening reaction of 3-carboxyalkyl-substituted isoxazolidines, induced by treatment with NaH, constitutes a general and quite easy synthetic entry to variously substituted 2-(5H)-3-aminofuranones, with overall high yields. The results summarized in Table 2 show that the outlined two step sequence, starting from nitrone **1**, is an excellent alternative to the previously reported synthetic approaches.

The amino function present in compounds **16-22** offers the possibility of usefull synthetic manipulations directed towards the synthesis of natural compounds.

EXPERIMENTAL

M.p.s. are uncorrected. Elemental analyses were performed on a Carlo Erba 1106 Elemental Analyzer. Infrared spectra were recorded in nujol on a Perkin Elmer Model 257 spectrophotometer. Mass spectra were obtained on a Varian Mat CH-5 DF and GC-MS HP 5859 A instruments. The ^1H NMR spectra were measured on a Bruker WP 200 SY; chemical shifts are reported in ppm from internal Me_4Si and refer to $CDCl_3$ solutions. NOE measurements were performed by the FT difference method on carefully degassed $CDCl_3$ solutions: the data were obtained by the PAPS sequence. Reaction mixtures were analyzed by t.l.c. on silica gel GF 254 (Merck) and the spots were detected under UV light (254 nm). Flash chromatography was carried out with Kieselgel 60 (Merck).

The *N*-methyl-*C*-carbobutoxynitrone **1** used has been synthesized as reported.[9]

Preparation of isoxazolidines 9-15.

General procedure. A solution of *N*-methyl-*C*-carbobutoxynitrone **1** (2.50 mmol) and alkenes **2-8** (25 mmol) in anhydrous toluene (10 ml) was heated at 80 °C, under stirring, until t.l.c. showed the disappearance of the starting nitrone. The solvent was removed at room temperature and the residue subjected to flash chromatography on silica gel column with hexane-ether 60:40 as eluent.

Reaction of **1** *with 1-hexene* **2**. Reaction time 48 h. *Trans/cis* cycloadducts ratio 6.1:1. Major component: (*3R,5S*) and (*3S,5R*)-2-methyl-3-carbobutoxy-5-butyl-isoxazolidine **9** (70% yield). Light yellow oil; ν_{max} 2960, 2860, 1750, 1380, 1270, 1190, 1060 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.60-1.80 (m, 16H, $-(CH_2)_2CH_3$ and $5-C_4H_9$), 2.10 (ddd, 1H, H_4, J = 6.4, 10.7 and 12.4 Hz), 2.62 (ddd, 1H, H_4, J = 7.7, 8.8 and 12.4 Hz), 2.75 (s, 3H, $N-CH_3$), 3.18 (dd, 1H, H_3, J = 6.4 and 8.8 Hz), 3.97 (dd, 1H, H_5, J =7.7 and 10.7 Hz), 4.10 (t, 2H, $O-CH_2$, J = 7.2 Hz); MS: *m/z* 243 (M^+, 8%), 143 (12), 142 (100), 84 (12), 70 (16), 69 (12), 57 (40), 56 (28), 55 (44), 44 (16), 43 (28). (Found: C, 64.25; H, 10.32; N, 5.72%. Calcd. for $C_{13}H_{25}NO_3$: C, 64.19; H, 10.28; N, 5.76%).

Reaction of **1** *with 1-heptene* **3**. Reaction time 48 h. *Trans/cis* cycloadducts ratio 6.4:1. Major component: (*3R,5S*) and (*3S,5R*)-2-methyl-3-carbobutoxy-5-pentyl-isoxazolidine **10** (70% yield). Light yellow oil; ν_{max} 2960, 2860, 1750, 1470, 1360, 1270, 1190, 1060 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.80-1.75 (m, 18H, -$(CH_2)_2CH_3$ and 5-C_5H_{11}), 2.10 (ddd, 1H, H_4, J = 6.3, 10.6 and 12.3 Hz), 2.55 (ddd, 1H, H_4, J = 7.4, 8.6 and 12.3 Hz), 2.77 (s, 3H, N-CH_3), 3.28 (dd, 1H, H_3, J = 6.3 and 8.6 Hz), 4.06 (m, 1H, H_5), 4.14 (t, 2H, O-CH_2, J = 7.2 Hz); MS: *m/z* 257 (M^+, 9%), 157 (34), 156 (100), 86 (9), 84 (14), 57 (43), 55 (37), 43 (25). (Found: C, 64.25; H, 10.32; N, 5.72%. Calcd. for $C_{14}H_{27}NO_3$: C, 64.19; H, 10.28; N, 5.76%).

Reaction of **1** *with 1-octene* **4**. Reaction time 48 h. *Trans/cis* cycloadducts ratio 6.4:1. Major component: (*3R,5S*) and (*3S,5R*)-2-methyl-3-carbobutoxy-5-hexyl-isoxazolidine **11** (72% yield). Light yellow oil; ν_{max} 2960, 2860, 1750, 1470, 1360, 1250, 1180, 1040 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.60-1.80 (m, 20H, -$(CH_2)_2CH_3$ and 5-C_6H_{13}), 2.08 (ddd, 1H, H_4, J = 6.3, 10.6 and 12.4 Hz), 2.56 (ddd, 1H, H_4, J = 7.4, 8.6 and 12.4 Hz), 2.75 (s, 3H, N-CH_3), 3.15 (dd, 1H, H_3, J = 6.3 and 8.6 Hz), 3.95 (m, 1H, H_5), 4.20 (t, 2H, O-CH_2, J = 7.1 Hz); MS: *m/z* 271 (M^+, 5%), 171 (26), 170 (100), 99 (11), 71 (27), 69 (15), 58 (18), 57 (93), 43 (48). (Found: C, 66.36; H, 10.77; N, 5.22%. Calcd. for $C_{15}H_{29}NO_3$: C, 66.42; H, 10.70; N, 5.17%).

Reaction of **1** *with 2-methyl-1-pentene* **5**. Reaction time 48 h. Flash chromatography gave a not resolved mixture of epimeric *trans* and *cis* 2,5-dimethyl-3-carbobutoxy-5-propyl-isoxazolidines **12a** e **12b** in 68% yield. The epimeric ratio was 1.3:1. Light yellow oil; ν_{max} 2970, 2880, 1750, 1460, 1380, 1270, 1190, 1070, 900 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.80-1.80 (m, 14H, -$(CH_2)_2CH_3$ and 5-C_3H_7), 1.23 (s, 3H, 5-CH_3, *trans*), 1.33 (s, 3H, 5-CH_3, *cis*), 2.21-2.40 (m, 2H, H_4), 2.73 (s, 3H, N-CH_3), 3.11-3.39 (m, 1H, H_3), 4.15 (t, 2H, O-CH_2, J = 7.1 Hz); MS: *m/z* 243 (M^+, 7%), 143 (11), 142 (100), 104 (8), 57 (15), 43 (9), 42 (14).

Reaction of **1** *with vinylcyclohexene* **6**. Reaction time 72 h. *Trans/cis* cycloadducts ratio 6.1:1. Major component: (*3R,5S*) and (*3S,5R*)-2-methyl-3-carbobutoxy-5-cyclohexyl-isoxazolidine **13** (63.5% yield). Light yellow oil; ν_{max} 2940, 2850, 1750, 1470, 1270, 1190, 1070 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.70-2.00 (m, 18H, -$(CH_2)_2CH_3$ and 5-C_6H_{11}), 2.14 (ddd, 1H, H_4, J = 6.8, 10.5 and 12.4 Hz), 2.55 (ddd, 1H, H_4, J = 7.3, 8.4 and 12.4 Hz), 2.75 (s, 3H, N-CH_3), 3.22 (dd, 1H, H_3, J = 6.8 and 8.4 Hz), 3.85 (ddd, 1H, H_5,, J =7.3, 7.3 and 10.5 Hz), 4.15 (t, 2H, O-CH_2, J = 6.8 Hz); MS: *m/z* 269 (M^+, 9%), 169 (33), 168 (100), 122 (13), 121 (12), 104 (13), 95 (32), 86 (11), 84 (11), 83 (12), 67 (19), 57 (31), 55 (37), 42 (40). (Found: C, 66.95; H, 10.14; N, 5.18%. Calcd. for $C_{15}H_{27}NO_3$: C, 66.91; H, 10.04; N, 5.20%).

Reaction of **1** *with methylenecyclohexane* **7**. Reaction time 72 h. First fractions gave 2-methyl-3-carbobutoxy-5-spirocyclohexanisoxazolidine **14** (60% yield). Light yellow oil; ν_{max} 2940, 2850, 1750, 1450, 1350, 1270, 1190, 1070, 950, 840 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.80-1.85 (m, 17H, -$(CH_2)_2CH_3$ and spirocyclohexyl), 2.14-2.37 (m, 2H, H_4,), 2.73 (s, 3H, N-CH_3), 3.25 (dd, 1H, H_3, J = 7.8 and 9.0 Hz), 4.15 (t, 2H, O-CH_2, J =7.0 Hz); MS: *m/z* 255 (M^+, 30%), 160 (45), 155 (54), 154 (100), 147 (31), 104 (70), 86 (21), 81 (30), 57 (33), 42 (59). (Found: C, 65.80; H, 9.75; N, 5.53%. Calcd. for $C_{14}H_{25}NO_3$: C, 65.88; H, 9.80; N, 5.49%).

Reaction of **1** *with allyl alcohol* **8**. Reaction time 48 h. Flash chromatography gave a not resolved mixture of epimeric *trans* and *cis* 2,5-dimethyl-3-carbobutoxy-5-hydroxymethyl-isoxazolidines **15a** e **15b** in 80% yield. The epimeric ratio was 3.5:1. Yellow oil; ν_{max} 3600-3100, 2960, 2870, 1750, 1460, 1390, 1190, 1050, 840 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.80-1.80 (m, 7H, -$(CH_2)_2CH_3$), 2.25-2.65 (m, 2H, H_4), 2.80 (s, 3H, N-CH_3), 3.25-3.85 (m, 3H,

H_3 and CH_2OH), 4.05-4.60 (m, 1H, H_5), 4.15 (t, 2H, O-CH_2, J= 7.1 Hz); MS: *m/z* 217 (M^+, 11%), 117 (31), 116 (100), 99 (11), 98 (12), 72 (12), 70 (38), 58 (21), 43 (15), 42 (76).

Preparation of substituted 3-methylamino-2-5(H)furanones 16-22.

General procedure. A suspension of 1.0 mmol of isoxazolidines **9-15** and 1.2 mmol of NaH in 50 ml of anhydrous THF was stirred at room temperature under N_2 for 5 h. The solution was then washed with saturated aqueous NH_4Cl solution, extracted with chloroform, dried over $MgSO_4$ and evaporated. The residue was subjected to silica gel chromatography using a ether/hexane 40:60 mixture as eluent.

3-Methylamino-5-butyl-2-(5H)furanone **16**. Reaction time 5h; 75% yield. Light yellow oil; ν_{max} 3460-3320, 3070, 2950, 2870, 1750, 1670, 1500, 1460, 1340, 1170, 1030, 790 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.70-1.85 (m, 9H, -$(CH_2)_3CH_3$), 2.70 (d, 3H, N-CH_3, *J* = 4.0 Hz), 3.65-4.30 (m, 1H, NH), 4.80-5.05 (m, 1H, H_5), 5.50 (d, 1H, H_4, *J* =2.0 Hz); MS: *m/z* 169 (M^+, 15%), 124 (65), 123 (27), 111 (100), 109 (15), 96 (29), 84 (29), 83 (97), 67 (22), 57 (57), 56 (25). (Found: C, 63.70; H, 8.80; N, 8.22%. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.27%).

3-Methylamino-5-pentyl-2-(5H)furanone **17**. Reaction time 5 h; 80% yield. Light yellow oil; ν_{max} 3460-3320, 2950, 2870, 1750, 1670, 1500, 1460, 1340, 1170, 1030, 760 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.80-1.95 (m, 11H, -$(CH_2)_4CH_3$), 2.70 (d, 3H, N-CH_3, *J* =3.5 Hz), 3.65-4.10 (m, 1H, NH), 4.80-5.05 (m, 1H, H_5), 5.55 (d, 1H, H_4, *J*=2.5 Hz); MS: *m/z* 183 (M^+, 14%), 138 (47), 111 (100), 110 (55), 98 (29), 83 (89), 70 (29), 57 (37), 56 (67), 55 (36). (Found: C, 65.70; H, 9.22, N, 7.60%. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64%).

3-Methylamino-5-hexyl-2-(5H)furanone **18**. Reaction time 4 h; 84% yield. Light yellow oil; ν_{max} 3460-3320, 2950, 2870, 1740, 1680, 1510, 1460, 1340, 1160, 1040, 750 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.70-1.95 (m, 13H, -$(CH_2)_5CH_3$), 2.80 (d, 3H, N-CH_3, *J* =4.5 Hz), 3.75-4.20 (m, 1H, NH), 4.80-5.00 (m, 1H, H_5), 5.50 (d, 1H, H_4, *J*=2.0 Hz); MS: *m/z* 197 (M^+, 3%), 152 (16), 151 (11), 123 (12), 111 (100), 100 (30), 83 (48), 66 (10). (Found: C, 66.88; H, 9.80, N, 7.06%. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10%).

3-Methylamino-5-methyl-5-propyl-2-(5H)furanone **19**. Reaction time 4 h; 85% yield. Light red oil; ν_{max} 3460-3320, 3070, 2960, 2870, 1745, 1670, 1510, 1460, 1310, 1210, 1020, 780 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.75-1.95 (m, 10H, CH_3 and -$(CH_2)_2CH_3$), 2.75 (d, 3H, N-CH_3, *J* =4.0 Hz), 3.55-4.10 (m, 1H, NH), 5.50 (s, 1H, H_4); MS: *m/z* 169 (M^+, 9%), 126 (100), 125 (12), 110 (9), 98 (64), 70 (17), 58 (83), 57 (11), 56 (60), 55 (24), 54 (15). (Found: C, 63.98; H, 8.82, N, 8.17%. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.27%).

3-Methylamino-5-cyclohexyl-2-(5H)furanone **20**. Reaction time 4 h; 99% yield. Light red oil; ν_{max} 3460-3320, 3070, 2930, 2860, 1750, 1670, 1510, 1460, 1340, 1170, 1040, 780 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.80-2.00 (m, 11H, cyclohexyl), 2.75 (d, 3H, N-CH_3, *J* =4.0 Hz), 3.60-4.20 (m, 1H, NH), 4.60-4.75 (m, 1H, H_5), 5.55 (d, 1H, H_4, *J* =2.0 Hz); MS: *m/z* 195 (M^+, 15%), 169 (25), 152 (20), 114 (100), 113 (86), 99 (44), 85 (47), 57 (28), 56 (42), 42 (39). (Found: C, 67.78; H, 8.82, N, 7.20%. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17%).

3-Methylamino-5-spirocyclohexan-2-(5H)furanone **21**. Reaction time 3h; 79% yield. White solid, m.p. 106-8 °C; ν_{max} 3460-3320, 3070, 2930, 1750, 1670, 1500, 1430, 1310, 1220, 1130, 1040, 980, 790 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.60-2.05 (m, 10H, $(CH_2)_5$), 2.95 (d, 3H, N-CH_3, *J* =4.0 Hz), 3.95-4.25 (m, 1H, NH), 5.85 (s, 1H, H_4); MS: *m/z* 181 (M^+, 37%), 138 (100), 136 (20), 112 (36), 55 (24), 41 (22). (Found: C, 66.37; H, 8.42, N,

7.80%. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.72%).

3-Methylamino-5-(1-hydroxymethyl)-2-(5H)furanone **22**. Reaction time 3 h; 59% yield. Brown oil; ν_{max} 3600-3100, 2960, 2870, 1750, 1670, 1500, 1440, 1340, 1170, 1040, 730 cm^{-1} ; ^1H NMR: δ ($CDCl_3$) 2.80 (d, 3H, N-CH_3, *J* =6.0 Hz), 3.40-4.40 (m, 4H, NH and CH_2OH), 4.90-5.20 (s, 1H, H_5); 5.45 (m, 1H, H_4, *J* =2.0 Hz); MS: *m/z* 143 (M^+, 4%), 142 (12), 128 (12), 112 (12), 98 (40), 84 (13), 57 (35), 56 (100), 55 (24). (Found: C, 50.46; H, 6.42, N, 9.80%. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.78%).

Reaction of isoxazolidine 9 with $LiAlH_4$.. A suspension of 1 mmol of isoxazolidine **9** and 1.2 mmol of $LiAlH_4$ in 50 ml of anhydrous THF was stirred at room temperature under N_2 for 2 h. The solution was then washed with saturated NH_4Cl solution, extracted with chloroform, dried over $MgSO_4$ and evaporated. The residue was subjected to silica gel column chromatography, using a ether/hexane 40:60 mixture as eluent, to give *3-(1-hydroxymethyl)-5-butyl-isoxazolidine* **28** as a light yellow oil; 72% yield; ν_{max} 3580-3100, 2950, 2860, 1460, 1380, 1047, 760 cm^{-1} ; ^1H NMR: δ ($CDCl_3$) 0.75-1.70 (m, 9H, 5-C_4H_9), 1.80-2.45 (m, 2H, 4-CH_2), 2.70 (s, 3H, N-CH_3), 2.80-3.00 (m, 1H, H_3); 3.40 (s, 1H, OH), 3.60 (d, 2H, CH_2OH, *J* =8.5 Hz), 3.65 -4.15 (m, 1H, H_5); MS: *m/z* 173 (M^+, 10%), 142 (100), 72 (8), 57 (8). (Found: C, 50.46; H, 6.42, N, 9.80%. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.78 %).

ACKNOWLEDGEMENTS

Authors are grateful to the Italian M. U. R. S. T. and C. N. R. for partial financial support.

REFERENCES

1. a) Devon, T.C. and Scott A.I. in "Handbook of Naturally Occurring Compounds", *vol. 1 and 2*, Academic Press Inc., New York, **1975**. b) Culberson , C.F. in " Chemical and Botanical guide to Lichen Products", University of North Carolina Press, Chapel Hill, **1969**. c) Katritzky A. R. in "Comprehensive Heterocyclic Chemistry", Pergamon Press, Oxford, New York, *vol.4*, **1984**, 694.
2. a) Petragnani N., Ferraz H.M.C., Silva G.V.J. *Synthesis*, **1986**, 157. b) Noir V., Sinhababu A.K., *J. Org. Chem.*, **1980**, *43*, 1983. c) Bansai R., Cooper G.F, Corey E.J. *J. Org. Chem.* , **1991**, 56, 1329. d) Schaaf T.K., Bindra J.S., Eggler J.F., Plattern J.J. , Nelson A. J., Johnson M.R., Constantine J.W., Hess H.J., Elger W. *J. Med. Chem.*, **1981**, *24*, 1353. e) Sulser H., De Pizzul J., Buchi W. *J. Food Sci*, **1967**, *32*, 611.
3. De Bernardo S., Tengi J.P., Sasso G.J., Weigele M., *J. Org. Chem.* ,**1985**, *50*, 3457.
4. a) Cory R.M., Ritchie B.M., Shrier A.M. *Tetrahedron. Lett.*, **1990**, *31*, 6789. b) Tsuboi S., Wada H., Muranaka R., Takeda A. *Bull. Soc. Chem. Jpn.*, **1987**, *60*, 2917. c) Ma S. , Lu X., *J. Org. Chem.*, **1993**, *58*, 1245. d) Tsuboi S., Wada H., Mimura S., Takeda A. *Chem. Lett.*, **1987**, 937. e) Baskaran S., Islam.I., Vankar S.P., Chandrasekaran S. *J.C.S. Chem. Commun.*, **1992**, 626. f) Escudier J.M., Baltes M., Gorrichon L., *Tetrahedron Lett.*, **1992**, *33*, 1439. g) Jacobi P.A., Touchette K. H., Selnik. H. G. *J. Org. Chem.*, **1992**, *57*, 6305. h) Burke S.D., Pacofsky G. J., Piscopio A.D. *J. Org. Chem.* **1992**, *57*, 6420. i) Zhang K.J., Bogerding A.J., Carlson R. M., *Tetrahedron Lett.*, **1988**, *29*, 5703.
5. a) Hanessian S., Hodge P. J., Murray J., Sahoo S.P. *J.C.S. Chem. Commun.*, **1986**, 754. b) Garcia G.A., Murray H., Tariz J. *Synth. Commun.*, **1983**, *13*, 569. c) Nakano T., Nagai Y. *J.C.S. Chem. Commun.*, **1981**, 815. d) Brownbridge P., Egert E., Hunt P.G., Kennard O., Warren S., *J.C.S. Perkin*

Trans. 1, **1981**, 2751.

6. a) Kanemasa S., Naragawa N., Suga H., Tsuge O. *Bull. Chem. Soc. Jpn.*, **1989**, *62*, 171. b) Shishido K., Irie O., Shibuya M., *Tetrahedron Lett.*, **1992**, *33*, 4589.
7. Chiacchio U., Di Bella M.R., Rescifina A., Romeo G., Uccella N. *Heterocycles*, **1993**, *36*, 2209.
8. Ariza J., Font J., Ortuno R.M. *Tetrahedron Lett.*, **1991**, *32*, 1979.
9. Belzecki C., Panfil I. *J. Org. Chem.*, **1979**, *44*, 1212.
10. a) Inouye Y., Takaya K., Kakisawa H. *Bull. Chem. Soc. Jpn*, **1983**, *56*, 3541. b) Dicken C.M., DeShong P. *J. Org. Chem.*, **1982**, *47*, 2047.
11. Dicken C.M., DeShong P., Staib R.R., Freyer A.J., Weinreb S.M. *J. Org. Chem.*, *47*, 4397.
12. Inouye Y., Watanabe Y., Takahashi S., Kakisawa H. *Bull. Chem. Soc. Jpn*, **1979**, *52*, 3763.
13. Chiacchio U., Casuscelli F., Corsaro A., Rescifina A., Romeo G., Uccella N. *Tetrahedron*, **1994**, *50*, 6671.

(*Received in UK* 19 *April* 1995; *revised* 14 *June* 1995; *accepted* 16 *June* 1995)