Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: V. Galet , M. P. Vaccher , J. L. Bernier , J. P. Henichart & D. Lesieur (1993) Regioselective Acylation of Benzoselenazolinone, Synthetic Communications, 23:5, 621-629, DOI: 10.1080/00397919308009820

To link to this article: http://dx.doi.org/10.1080/00397919308009820

Published online: 27 Oct 2006.

SYNTHETIC COMMUNICATIONS, 23(5), 621-629 (1993)

REGIOSELECTIVE ACYLATION OF BENZOSELENAZOLINONE

V. Galet†, M.P. Vaccher†, J.L. Bernier♠, J.P. Henichart ♠, D. Lesieur†[1]

† Institut de Chimie Pharmaceutique, 3 rue du Professeur Laguesse, BP 83 F - 5906 Lille Cedex

♠ I.N.S.E.R.M. U 16, place de Verdun, F - 59045 Lille Cedex

Synthetic Communications 1993.23:621-629.

Abstract : Substitutions on benzoselenazolinone were performed by using successively (i) aliphatic or aromatic acids and (ii) acid chlorides in the presence of (i) polyphosphoric acid and (ii) aluminium chloride in dimethylformamide. Regioselective acylation at C_6 position was demonstrated by ^1H NMR using Nuclear Overhauser Effect.

Much of the role of selenium in biology can be attributed to the mammalian enzyme glutathione peroxidase (GSH-Px). This selenoenzyme is one of the major defence of the organism against reactive

[1]To whom correspondence should be addressed

oxygen species (ROS). Indeed, GSH-Px is able to reduce hydroperoxides which are responsible for many deleterious effects in the cell[1]. The active center of the enzyme undergoes a catalytic redox cycle involving the selenium in various oxidation states with versatile activity[2]. Experimental evidences for the role of these different oxidized forms of the selenium moiety have been provided by the use of more simple molecules[3,4]. It has been demonstrated that the formation of an isoselenazolidin-3-one ring system plays a central role in this action and is consistent with the pharmacological activity of related molecules such as ebselen which is the 2-phenyl-1,2-benzoisoselenazol-3 (2H)-one. This molecule was found to exhibit *in vitro* a GSH-Px like activity and to behave as an antioxidant[5-7].

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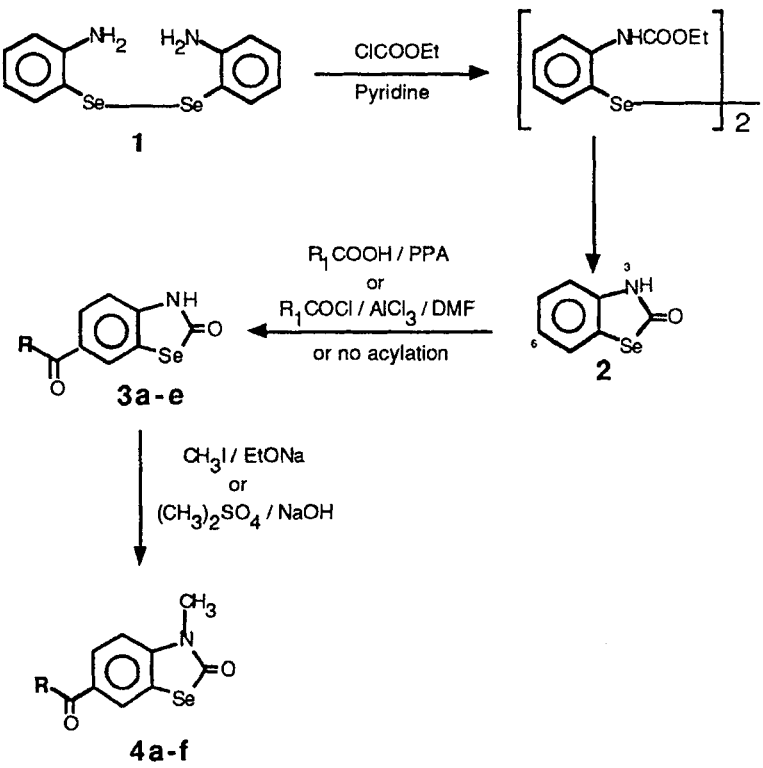
In connection with our investigations concerning the replacement of oxygen by sulfur within active 1,3 benzoxazolinones[8], we thought that the introduction of a selenium moiety in these heterocycles would be evermore favorable for the pharmacological activity. The synthesis of 1,3-benzoselenazol-2-one ring is well documented, nevertheless the electrophilic reactivity of this heterocycle has been poorly investigated. Adopting Bauer's synthesis of the 1,3 benzoselenazolinone[9], we made a serial of compounds as described in scheme 1 in which the heterocycle was acylated by two different methods. The position of acylation was unambiguously assessed by ^{1}H NMR spectra. Then, N-methyl substitution was carried out.

1,3-benzoselenazolinone **2** was most conveniently prepared by reducing bis-o-urethanophenyl diselenide obtained by condensation of bis-o-aminophenyl diselenide **1** with ethyl chloroformate, in the presence of tin and hydrochloric acid.

The acylation of **2** was then performed either in polyphosphoric acid using various aliphatic or aromatic acids (method A), or in dimethylformamide, with aluminum chloride in excess as the catalyst, using aliphatic or aromatic acid chlorides (method B). Method A was



Scheme 1

generally selected except for acetic acid **3a** and nicotinic acid **3e** which both gave better yields with method B. In both methods, the substitution at the C_6 position was ascertained by ^1H NMR 400 MHz using NOE.

For instance, in the ^1H NMR spectrum of **4b**, aromatic protons were assigned as follows: $CDCl_3$ δ (ppm) 3.50 (s, 3H, CH_3), 7.08 (d, 1H, H_4 aromatic, J_1= 8 Hz), 7.92 (dd, 1H, H_5 aromatic, J_1=8 Hz, J_2= 1.7 Hz), 8.12 (d, 1H, H_7, J_2= 1.7 Hz) (see fig. 1A).

The saturation of the N-CH_3 proton resonance (3.5, s, 3H) induced a change in the integrated intensity of the peak at 7.08 ppm consistent with the C_4 assignement for this proton (see fig 1B). The shape of aromatic

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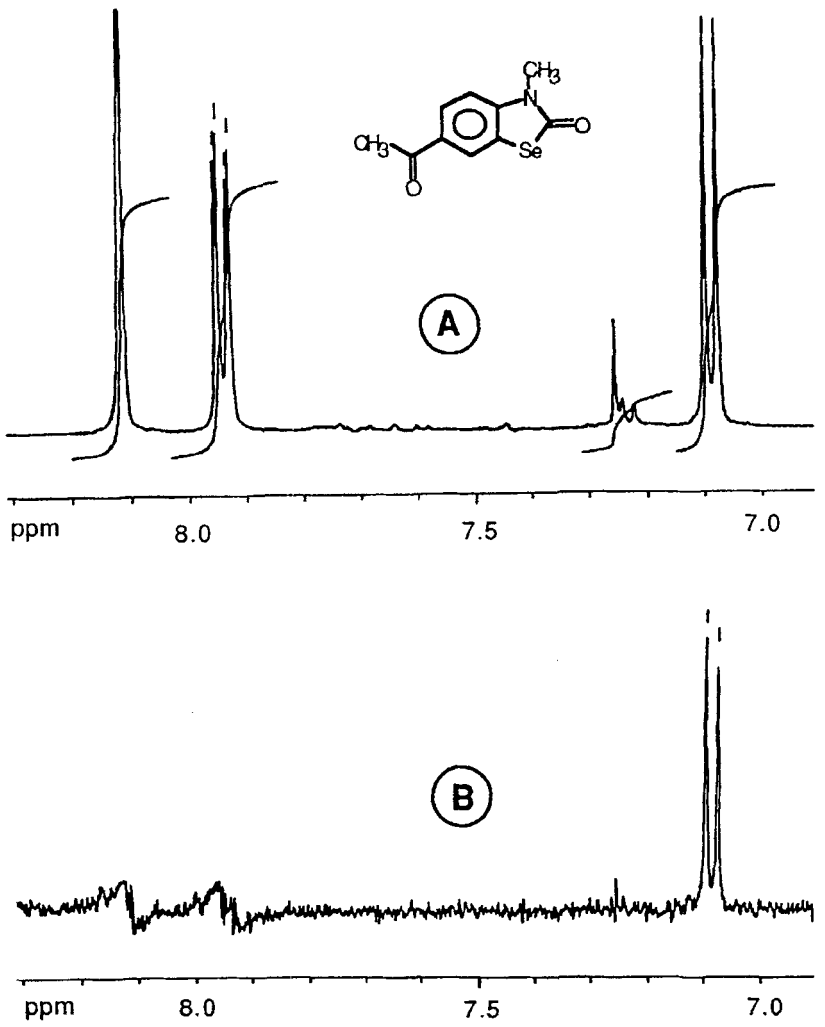

FIG 1:

A 400 MHz ^{1}H NMR spectrum of 4b in the aromatic region

B Difference spectrum after irradiation at 3.50 ppm

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regions of other ^1H NMR spectra were all in accordance with a similar attribution, substanciating the above assertion and leading to the conclusion that the acylation took place exclusively at C_6 position for all compounds **3a-e** and **4b-f**.

In conclusion, we found that the introduction of a selenium moiety in the isosteric series of benzoxazolinone did not modify electrophilic properties of the nucleus since a regioselective acylation at the C_6 position occured when the 1,3-benzoselenazolinones were treated either by acids or acid chlorides. Thus, these compounds may be functionnalized at 6-position, and N-methylated, leading to series of 1,3-benzoselenazolinones of potential therapeutic interest. The ring opening, under alkaline conditions, was more easily performed in the series of benzoselenazolinones than benzothiazolinones or benzoxazolinones which can give a hint for a different biological behavior and metabolism.

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EXPERIMENTAL

Melting points were taken in a capillary tube using a Büchi SMP 20 melting point apparatus and are uncorrected. IR spectra were obtained in potassium bromide pellets using a Perkin-Elmer spectrophotometer model 297. NMR spectra were determined with Bruker model WP 20 SY and a Bruker AM 400 WB spectrophotometer using TMS as the internal standard. The mass spectra were performed by the analytical center of the Lille II university. Elemental analyses were carried out by the analysis departement of CNRS, at Solaise Vernaison, France. TLC was performed on alumina 60 F 254 precoated plate (MERCK) using a mixture of acetone (2), toluene (3), cyclohexane (5) as the eluent.

Acylation of benzoselenazolinone: method A

A stirred mixture of benzoselenazolinone (2g ; 0.01 mole), polyphosphoric acid (50g), and the corresponding acid (0.01 mole) was

TABLE 1: Acylation products of benzoselenazolinone

Nr	3a	3b	3c	3d	3e
R	CH_3	propyl	C_6H_5	Cl-C_6H_4	pyridine
Method	B	A	A	A	B
Time (h)	4	2,5	3	4	8
Temp.	80-90	90-95	130	130	100-110
Rec. solvt	toluene	ethanol 70	ethanol 95	ethanol 95	ethanol 95
m.p.	185	166	204	>260	70
Yield (%)	70-80	48	70-80	70	50

TABLE 2: Methylation products of 6-acyl benzoselenazolinones

N°	R	method	Recryst. solvt	m.p (°C)	Yield(%)
4a	No substitution	E or F	cyclohexane	57-58	80
4b	CH_3-CO	E	cyclohexane	132-133	85
4c	C_3H_7-CO	E	ethanol 20%	126-127	66
4d	C_6H_5-CO	E	ethanol 95%	156	73
4e	Cl-C_6H_4-CO	E	ethanol 95%	180	65
4f	Nicotinoyl	E*	ethanol 95%	210	50

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heated in an oil bath under reflux for the indicated time, at the appropriate temperature (table 1), and then poured into cold water. The precipitate was collected, washed with water, dried, and recrystallized from appropriate solvent.

Acylation of benzoselenazolinone: method B

In a round bottomed flask containing aluminium chloride (12g ; 0.09 mole), was added dropwise dimethylformamide (3.1 cm^3 ; 0.04 mole). Then, benzoselenazolinone (2g ; 0.04 mole) was added. The mixture was heated to 70-80°C and homogeneized. Acid chloride (0.011 mole) was

added slowly, and a condenser was fitted. The temperature was raised as indicated (in table 1) and maintained for the appropriate time. The mixture was poured onto crushed ice. The precipitate was collected, washed with water, dried, and recrystallized from appropriate solvent.

^{1}H NNMR ; δ (ppm) : **3a** (DMSO D_6) : 2.50 (s, 3H, CH_3) ; 7.20 (d, 1H, H_4 Aromatic) ; 7.90 (dd, 1H, H_5 Aromatic) ; 8.40 (d, 1H, H_7) ; 12.00 (broad peak exchangeable with D_2O, 1H, NH). **3b** ($CDCl_3$) : 1.00 (t, 2H, CH_3) ; 1.80 (m, 2H, CH_2-$\underline{CH_2}$-CH_3) ; 3.00 (t, 2H, $\underline{CH_2}$-CH_2-CH_3) ; 7.20 (d, 1H, H_4) ; 7.90 (d, 1H, H_5) ; 8.15 (s, 1H, H_7) ; 9.50 (broad peak exchangeable with D_2O, 1H, NH). **3c** ($CDCl_3$) : 7.20 (d, 1H, H_4) ; 7.60 (m, 6H, H_5 + H Aromatic benzoyl) ; 8.20 (d, 1H, H_7) ; 12.00 (broad peak exchangeable with D_2O, 1H, NH). **3d** ($CDCl_3$) : 7.20 (d, 1H, H_4) ; 7.75 (m, 5H, H_5 + H Aromatic parachlorobenzoyl) ; 8.20 (d, 1H, H_7) ; 12.00 (broad peak exchangeable with D_2O, 1H, NH). **3e** (DMSO D_6) : 7.25 (d, 1H, H_4 Aromatic) ; 7.60 (dd, 1H, Hc) ; 7.75 (d, 1H, H_5 Aromatic) ; 8.20 (s, 1H, H_7) ; 8.80 (s, 1H, Ha) ; 8.80 (d, 1H, Hb) ; 12.10 (broad peak exchangeable with D_2O, 1H, NH).

N-methylation: method 1

To a stirred slurry containing sodium (0.35g ; 0.015 at./g) and ethanol, was added benzoselenazolinone or 6-acyl benzoselenazolinone (0.01 mole). After 1/4 hour was added dropwise methyl iodide (3.1 cm^3 ; 0.05 mole). The mixture was stirred overnight, and the solvent was eliminated under reduced pressure. The resulting solid was washed with water, dried, and recrystallized from appropriate solvent.

N-methylation: method 2

To a stirred slurry of benzoselenazolinone or 6-acyl benzoselenazolinone (0.01 mole), sodium hydroxide 10% in water (4 cm^3 ; 0.01 mole), and 150 cm^3 of water, cooled in an ice bath, was added dropwise dimethyl

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sulfate (0.95 cm^3 ; 0.01 mole). The mixture was stirred overnight, and the precipitate was collected, rapidly washed with a solution of sodium hydroxide 5% in water, washed another time with water, dried, and recrystallized from appropriate solvent.

^1H NNMR ; δ (ppm) : **4a** (DMSO D_6) : 3.50 (s, 3H, CH_3) ; 7.40 (m, 4H, H Aromatic). **4b** ($CDCl_3$) : 2.50 (s, 3H, $COCH_3$) ; 3.50 (s, 3H, NCH_3) ; 7.08 (d, 1H, H_4) ; 7.93 (dd, 1H, H_5) ; 8.12 (d, 1H, H_7). **4c** (DMSO D_6) : 1.00 (t, 3H, CH_2-CH_2-$\underline{CH_3}$) ; 1.80 (m, 2H, CH_2-$\underline{CH_2}$-CH_3) ; 3.0 (t, 2H, $\underline{CH_2}$-CH_2-CH_3) ; 3.50 (s, 3H, NCH_3) ; 7.10 (d, 1H, H_4 Aromatic) ; 8.00 (dd, 1H, H_5 Aromatic) ; 8.20 (d, 1H, H_7). **4d** ($CDCl_3$) : 3.50 (s, 3H, CH_3) ; 7.20 (d, 1H, H_4) ; 7.60 (m, 6H, H_5 + H Aromatic benzoyl) ; 8.20 (d, 1H, H_7). **6e** ($CDCl_3$) : 7.15 (d, 1H, H_4) ; 7.45 (d, 2H, Hb and Hb') ; 7.60 (d, 2H, Ha and Ha') ; 7.80 (d, 1H, H_5) ; 8.00 (d, 1H, H_7). **6f** ($CDCl_3$) : 3.50 (s, 3H, CH_3) ; 7.10 (d, 1H, H_4) ; 7.50 (dd, 1H, Hc) ; 7.75 (d, 1H, H_5) ; 8.10 (d, 1H, H_7) ; 8.10 (d, 1H, Hd) ; 8.80 (d, 1H, Hb) ; 9.00 (s, 1H, Ha).

REFERENCES

1 **PARNHAM M.J , GRAF E.,** Biochem. Pharmacol., 1987, 36, 3095.

2 **EPP O. , LADENSTEIN R. , WENDEL A.,** Eur. J. Biochem., 1984, 133, 51.

3 **REICH H.J. , JASPERSE C.P.,** J. Am. Chem. Soc., 1987 109, 5549.

4 **CHAN P. , COTELLE P. , BERNIER J.L. , HENICHART J.P.,** Bioorg. Med. Chem. Lett., 1991, 1, 277.

5 **WENDEL A. , FAUSEL M. , SAFAYHI H. , TIEGS G. , OTTER R.,** Biochem. Pharmacol., 1984, 33, 3241.

6 **MULLER A. , CADENAS E. , GRAF P. , SIES H.,** Biochem. Pharmacol., 1984, 33, 3235.

Synthetic Communications 1993.23:621-629.

7 PARNHAM M.J , KINDT S., Biochem. Pharmacol., 1984, 33, 3247.

8 Unpublished data

9 BAUER H., 1912, Ber. Chem., 92.

(Received in UK 11 September, 1992)

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