PHASE TRANSFER CATALYSED N-SUBSTITUTION OF 2*H*-1,2-BENZISOTHIAZOLIN-3-ONE 1,1-DIOXIDE

Jiří SVOBODA, Jaroslav PALEČEK and Václav DĚDEK

Department of Organic Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6

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The title compound on reaction with alkylating reagents and under the conditions of phase catalysis affords 2-substituted 2*H*-1,2-benzisothiazolin-3-one 1,1-dioxides (*III*). The conditions of the reaction and the mass spectra of the products are discussed.

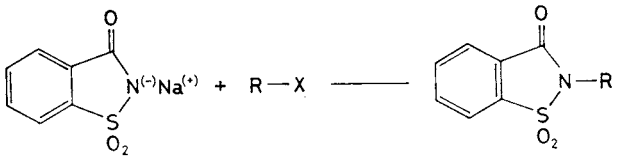
N-Substituted derivatives of 2*H*-1,2-benzisothiazolin-3-one 1,1-dioxide possess interesting biological properties[1-5] and they are often used as intermediates in the synthesis of antiinflammatory drugs on the basis of the so-called oxicams[6-8]. A number of examples of the preparation of compounds of this type are described in literature, based on the alkylation of alkali salts of 2*H*-1,2-benzisothiazolin-3-one 1,1-dioxide, either without using solvents[9-14] or in various solvents such as acetone[3,5], 2-methoxyethanol[15], and dimethylformamide[4,7,8,16-21]. All these methods afford the required products in average or good yields in dependence on the procedure applied, but often under relatively drastic reaction conditions. Recently a successful N-substitution in the presence of 18-crown-6-ether and under the conditions of phase catalysis has been described[22].

In this paper we describe a new method of preparation of N-substituted 2*H*-1,2-benzisothiazolin-3-one 1,1-dioxides (*IIIa*–*IIIj*), by reaction of the sodium salt of 2*H*-1,2-benzisothiazolin-3-one 1,1-dioxide (*I*, saccharin) with alkylating reagents *IIa*–*IIj*, using quaternary ammonium salts as phase transfer catalysts (Scheme 1).

When using the classical procedure for the reaction of compound *I* with 2-methoxyethyl chloroacetate (*IIf*) under the conditions of liquid/liquid phase catalysis in dichloromethane–water or toluene–water system and catalysis with trioctylmethylammonium chloride (Adogen^{R}) we could not detect the required product *IIIf* in the reaction mixture. When using the solid/liquid phase transfer catalysis we obtained the product *IIIf* in a very low yield (see Table I). This fact inspired us to check the effect of various quaternary ammonium salts and solvents on the reaction course and the yields of the product. The results of these experiments are given in Table I.

From this table it is evident that an optimum catalytic activity in the reaction was displayed by hexadecyltrimethylammonium bromide in a 10% mol. concentration. When decreasing the amount of this catalyst to 5% mol. the yield of product *IIIf*

dropped to 15%, while in its absence it was only about 2%. Technical dodecylbenzyldimethylammonium chloride (Orthosan MB, Society for Chemical and Metallurgical Production, Ústí nad Labem) also displayed very good catalytic activity under the conditions mentioned. We further demonstrated that the polarity of the solvent has no substantial effect on the reaction course.



I *IIa – IIj* *IIIa – IIIj*

In formulae *II* and *III* :

a, R = CH_3
b, R = $C_6H_5CH_2$
c, R = CH_3COCH_2
d, R = $C_6H_5COCH_2$
e, R = CH_3OCOCH_2
f, R = $CH_3OCH_2CH_2OCOCH_2$
g, R = $CH_3CH_2OCH_2CH_2OCOCH_2$
h, R = $C_6H_5OCH_2CH_2OCOCH_2$
i, R = $CH_3OCOCH(CH_3)$
j, R = $CH_3CH_2OCOCH_2CH_2CH_2$

SCHEME 1

TABLE I

Results of alkylation reaction of 2*H*-1,2-benzisothiazolin-3-one 1,1-dioxide (*I*) with 2-methoxyethyl chloroacetate (*IIf*)

Solvent	Catalyst[a] % mol.	Temperature °C	Yield *IIIf*[b] %
Dichloromethane/water	A (10)	20	0
Toluene/water	A (10)	100	0
Toluene	A (10)	100	8
Toluene	B (10)	100	91
Toluene	B (5)	100	15
Toluene	—	100	2
Toluene	C (10)	100	74
1,2-Dichloroethane	B (10)	80	78
Benzene	B (10)	80	86
Chlorobenzene	B (10)	110	82

[a] A trioctylmethylammonium chloride (Adogen[R]), B cetyltrimethylammonium bromide, C dodecylbenzyldimethylammonium chloride (Orthosan MB, Society for Chemical and Metallurgical Production); [b] reaction time was 6 h in all instances.

In connection with these optimalization experiments we carried out the alkylation of saccharin *I* with a number of various alkylating reagents, *IIa–IIj*, under standard conditions. The results of these alkylation reactions are given in Table II. In all instances, with the exception of *IIIj*, we obtained products *IIIa–IIIi* in excellent yields.

The infrared, mass, and ^{1}H NMR spectra of the synthetized compounds *IIIa–IIIj* are in agreement with the structural formulae. In the infrared spectra of compounds *IIIa–IIId* the dominant bands at 1 700–1 740 cm^{-1} or 1 340–1 380 and 1 170 to 1 185 cm^{-1} correspond to the stretching vibrations of the CO or SO_2 group, respectively, in benzisothiazoline grouping. In other compounds, *IIIe–IIIj*, intensive bands at 1 740–1 755 cm^{-1} are further present, belonging to the CO stretching vibration in the ester moiety.

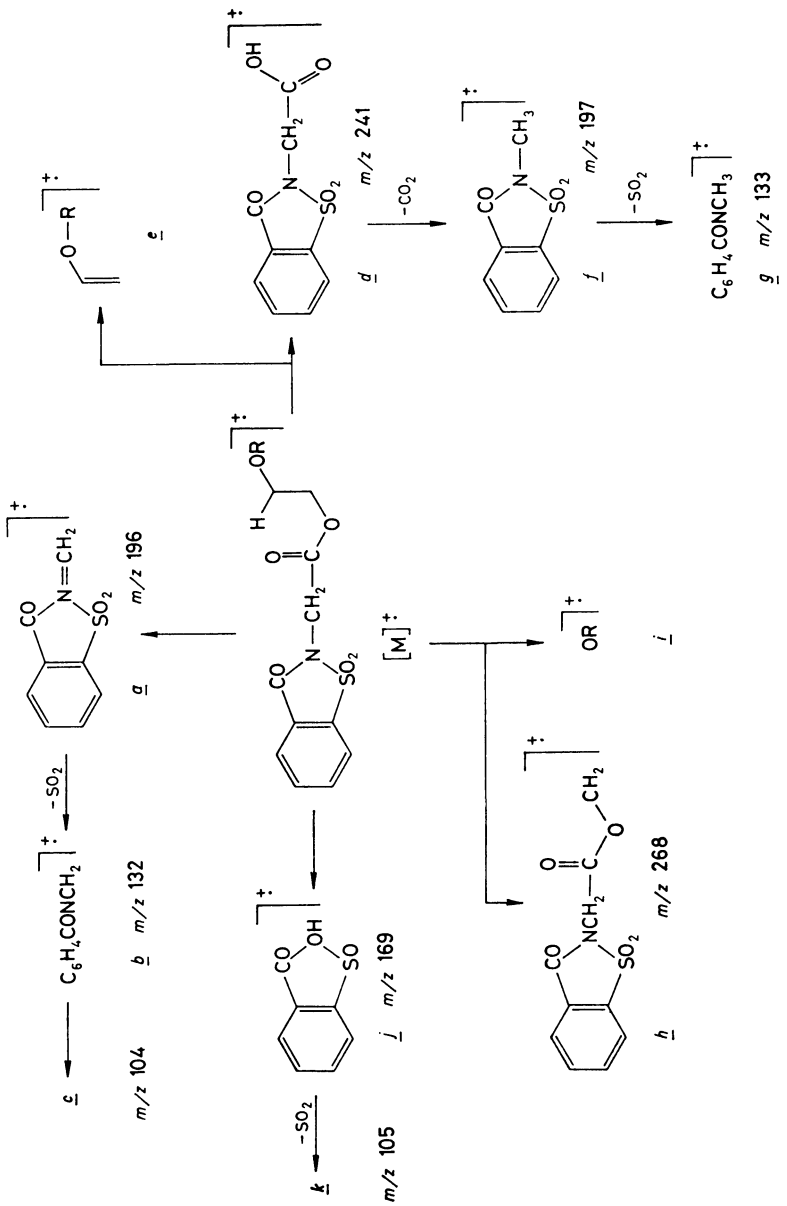
The course of fragmentation of compounds *IIIa–IIIh* under the electron impact conditions is affected substantially by the character of the substituent bound to the nitrogen atom. The probable fragmentation mechanism of compounds *IIIa–IIIh* is represented in Scheme 2. In all instances the molecular ion M^+ displays a low relative abundance (1–12%). The ionic species *a* (*m/z* 196) easily splits off sulfur dioxide by elimination of the alkoxycarbonyl group from the molecular ion, under

TABLE II

Conditions and results of the alkylation reactions with the reagents *IIa–IIh*

Alkylation reagent *II*	Product *III*	Reaction time, h	Yield %	M.p., °C (solvent)	Ref.
IIa $(CH_3O)_2SO_2$	*IIIa*	2	92	130–131 (CH_3OH)	16
IIb $C_6H_5CH_2Cl$	*IIIb*	8	89	109–110 (C_2H_5OH)	16
IIc CH_3COCH_2Cl	*IIIc*	8	84	141–143 (C_2H_2OH)	21
IId $C_6H_5COCH_2Br$	*IIId*	8	82	191–193 (C_2H_5OH)	9
IIe $ClCH_2COOCH_3$	*IIIe*	4	88	117–119 (C_2H_5OH)	10
IIf $ClCH_2COOCH_2CH_2OCH_3$	*IIIf*	6	81	91– 92 (C_2H_5OH)	7
IIg $ClCH_2COOCH_2CH_2OCH_2CH_3$	*IIIg*	6	86	58– 59 (CH_3OH, H_2O)	[a]
IIh $ClCH_2COOCH_2CH_2OC_6H_5$	*IIIh*	6	87	109–110 (C_2H_5OH)	[a]
IIi $BrCH(CH_3)COOCH_3$	*IIIi*	12	76	106–108 (C_2H_5OH)	[a]
IIj $BrCH_2CH_2CH_2COOCH_2CH_3$	*IIIj*	20	66	Oil	[a]

[a] For *IIIg* $C_{13}H_{15}NO_6S$ (313·3) calculated: 49·83% C, 4·82% H, 4·47% N, 10·23% S; found: 49·76% C, 4·96% H, 4·21% N, 10·08% S; for *IIIh* $C_{17}H_{15}NO_6S$ (361·4) calculated: 56·50% C, 4·18% H, 3·88% N, 8·87% S; found: 56·26% C, 4·11% H, 3·61% N, 8·70% S; for *IIIi* $C_{11}H_{11}NO_5S$ (269·3) calculated: 49·07% C, 4·12% H, 5·20% N, 11·91% S; found: 48·68% C, 4·24% H, 5·07% N, 11·74% S; for *IIIj* $C_{13}H_{15}NO_5S$ (297·3) calculated: 52·52% C, 5·09% H, 4·71% N, 10·78% S; found: 52·38% C, 5·29% H, 4·53% N, 10·68% S.


[M]+·
a m/z 196
b m/z 132
c m/z 104
d m/z 241
e
f m/z 197
g m/z 133
h m/z 268
i
j m/z 169
k m/z 105
-SO2
-CO2
-SO2
C6H4CONCH2
C6H4CONCH3

SCHEME 2

formation of ion *b* (*m/z* 132), which probably affords ions *c* (*m/z* 104) after the loss of the CH_2N fragment. The formation of the ionic species *k* (*m/z* 105) can be explained by elimination of sulfur dioxide from fragment *j* (*m/z* 169), which is formed by rearrangement from the molecular ion. An analogous rearrangement is also described in the case of phthalic acid ester[23].

McLafferty rearrangement of the molecular ion brings about both the formation of the fragment ion *e*, the relative intensity of which changes in dependence on the residue R, and the not very numerous ionic species *d* (*m/z* 241). Decarboxylation of ion *d* gives rise to fragment *f* (*m/z* 197) which is in fact the molecular ion of compound *IIIa*. A similar course of the fragmentation, with subsequent decarboxylation, was already described earlier for 1-alkoxycarbonylmethyl-1,4-dihydropyridine derivatives[24]. On elimination of sulfur dioxide, fragment *g* (*m/z* 133) is formed from this ion, then giving rise to ionic species *a*, *b*, *c* by a mechanism already mentioned. Earlier, an analogous fragmentation course was demonstrated[25], *i.e.* the elimination of sulfur dioxide and the formation of the ionic species *m/z* 104 and 105 in derivatives of 1,2-benzothiazine 1,1-dioxides. As stated, the relative abundance of the ionic species *h* or *i* is dependent on the properties of substituent R. While in compound *IIIg* (R = C_2H_5) the ionic species *h* is practically not formed, it forms the base peak in the case of compound *IIIh* (R = C_6H_5). In the ionic species *i* their abundances with respect to ion *h* are reversed.

The fragmentation of ester *IIIe* proceeds substantially by the M → *a* → *b* → *c* mechanism, shown in Scheme 2. A similar course of the fragmentation of the molecular ion is also observed in the case of compounds *IIIc* and *IIIb*, with the difference that the base peak is formed by CH_3CO (*m/z* 43) particles or C_6H_5CO (*m/z* 105) particles, respectively. The formation of a relatively intensive ionic species *f* (*m/z* 197) in the spectrum of compound *IIIc* may be explained by the splitting off of the neutral CH_2CO particle.

EXPERIMENTAL

The temperature data are not corrected. The melting points were determined on a Boetius block (Carl Zeiss, Jena). The infrared spectra were measured on a Perkin–Elmer 325 (Bodenseewerk) instrument in KBr pellets (*IIIa*–*IIIi*) or in chloroform (*IIIj*). The ^1H NMR spectra were recorded on a Varian XL-100-15 (Palo Alto) instrument, using tetramethylsilane as internal reference. The mass spectra were measured on a Jeol DX 300 instrument, electron energy 70 eV.

Esters *IIf*–*IIh* were prepared by acylation of corresponding 2-alkoxyethanols with chloroacetyl chloride in dichloromethane–pyridine system; ester *IIf* b.p. 95–98°C/2·66 kPa, yield 85%; *IIg* b.p. 103–104°C/2·66 kPa, yield 84%, and *IIh* b.p. 125–130°C/266 Pa, yield 79%.

N-Substitution of the Sodium Salt of 2*H*-1,2-Benzisothiazolin-3-one 1,1-Dioxide (*I*)

A mixture of finely ground saccharin (*I*) (10 mmol), the alkylating reagent (10·5 mmol), and hexadecyltrimethylammonium bromide (1 mmol) in toluene (15 ml) was heated at 100°C under thorough

stirring for 2 to 20 h (see Table II). After cooling the mixture was filtered, the solvent evaporated and the crude product *IIIa*—*IIIi* recrystallized. Compound *IIIj* was purified by column chromatography (silica gel, chloroform). ^{1}H NMR spectra of compounds *IIIa*—*IIIj* (the spectra labelled *A* were measured in $(C^2H_3)_2CO$, those labelled *B* in C^2HCl_3, chemical shifts in δ units, coupling constants *J* in Hz): compound *IIIa* (*A*): 3·25 s (3 H, CH_3), 7·76—8·07 m (4 H, nucleus); compound *IIIb* (*B*): 4·87 s (2 H, CH_2), 7·21—7·50 m (5 H, nucleus), 7·73—8·01 m (4 H, nucleus); compound *IIIc* (*B*) 2·28 s (3 H, CH_3), 4·47 s (2 H, CH_2), 7·88—8·01 m (4 H, nucleus); compound *IIId* (*A*): 5·40 s (2 H, CH_2), 7·51 m (5 H, nucleus), 8·01—8·26 m (4 H, nucleus); compound *IIIe* (*A*): 3·64 s (3 H, OCH_3), 4·56 s (2 H, CH_2), 8·00 m and 8·27 m (4 H, nucleus); compound *IIIf* (*A*): 3·17 s (3 H, OCH_3), 3·46 t (2 H, CH_2), 4·17 t (2 H, CH_2) *J* 6, 4·56 s (2 H, CH_2), 8·01 m and 8·23 m (4 H, nucleus); compound *IIIg* (*A*): 0·99 t (3 H, CH_3) *J* 7, 3·33 m (2 H, CH_2), 3·48 m (2 H, CH_2), 4·13 t (2 H, CH_2), 4·55 s (2 H, CH_2), 8·01 m and 8·21 m (4 H, nucleus); compound *IIIh* (*A*): 4·09 m (2 H, CH_2), 4·36 m (2 H, CH_2), 4·57 s (2 H, CH_2), 6·58 t and 7·16 t (5 H, nucleus), 7·98 m and 8·20 m (4 H, nucleus); compound *IIIi* (*B*): 1·74 d (3 H, CH_3) *J* 7, 3·89 s (3 H, OCH_3), 5·54 q (1 H, CH), 7·68—7·90 m (4 H, nucleus); compound *IIIj* (*B*): 1·15 t (3 H, CH_3), 2·24 m (2 H, CH_2), 3·82 t (2 H, CH_2) *J* 6, 4·13 t (2 H, OCH_2), 4·64 t (2 H, CH_2), 7·66—8·06 m (4 H, nucleus). Mass spectra *IIIa*—*IIIh* (the letters at *m/z* values indicate the ions in the fragmentation Scheme 2, rel. int.% in brackets). Compound *IIIa*: 197 (12), 169 (0·3), 133 (36), 132 (27), 106 (9), 105 (43), 104 (64), 92 (10), 78 (17), 77 (41), 76 (100), 75 (23), 74 (22), 63 (12), 51 (19), 50 (77); compound *IIIb*: 273 (1), 210^i (14), 209 (100), 208 (23), 180 (12), 169 (3), 132 (3), 105 (22), 104 (72), 91 (27), 78 (18), 77 (34), 76 (26), 75 (5), 65 (14), 51 (17), 50 (17); compound *IIIc*: 240 (2), 239 (10), 209 (10), 198 (10), 197 (58), 196 (74), 175 (4), 169 (13), 147 (8), 133 (52), 132 (22), 121 (5), 105 (25), 104 (36), 91 (16), 78 (8), 77 (32), 76 (33), 58 (12), 52 (13), 51 (20), 43 (100); compound *IIId*: 301 (1), 196 (2), 106^i (7), 105 (100), 104 (5), 77 (36), 76 (5), 51 (10); compound *IIIe*: 255 (5), 197^i (10), 196 (100), 169 (7), 105 (7), 104 (19), 77 (20), 76 (12), 51 (5), 50 (12); compound *IIIf*: 299 (1), 197 (13), 196 (57), 169 (5), 133 (15), 132 (5), 105 (11), 104 (7), 77 (19), 76 (20), 59 (42), 58 (100), 51 (7), 50 (9), 45 (43), 31 (10); compound *IIIg*: 313 (1), 268 (5), 197 (13), 196 (69), 133 (22), 132 (12), 105 (27), 104 (28), 77 (29), 76 (30), 72 (100), 59 (44), 51 (7), 50 (15), 45 (53), 44 (25), 43 (17); compound *IIIh*: 361 (6), 269 (13), 268 (100), 197 (2), 196 (34), 169 (3), 132 (3), 120 (6), 105 (3), 104 (8), 100 (26), 93 (3), 77 (27), 76 (7), 65 (5), 51 (5), 50 (2).

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