

SHORT  
COMMUNICATIONS

# O-Alkylation of Amide Carbonyl Group with Diazo Compounds: A New Way for Functionalizing Saccharin and Its Analogs

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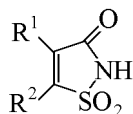
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Received January 9, 2001

Reactions of carbenoids insertion into X-H bonds of various compounds are now extensively used in the organic synthesis [1]. Among well-developed kinds of such reactions should be mentioned the insertion of metal-carbenoids into N-H bonds of amines and amides that is profitably used in the synthesis of  $\beta$ -lactam structures and the other nitrogen-containing heterocycles [1, 2]. Yet the reactions of carbenoids with substrates containing imide N-H bond apparently were not investigated [3].

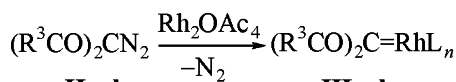
Within the framework of studies on reactions of saccharin and its analogs with aliphatic diazo compounds and various intermediates based thereon we attempted to perform an insertion of diacylcarbenoids into the free N-H bond of the mentioned imide-containing substrates. Here we report on the results of experiments with a number of 3(2H)-oxoisothiazoles [4].

As objects of the study were selected 3-oxo-2,3-dihydrobenzo[d]isothiazole-1,1-dioxide (**Ia**) (saccharin) and its hydrogenated analog, 3-oxo-2,3,4,5,6,7-hexahydrobenzo[d]-isothiazole-1,1-dioxide (**Ib**), and also a monocyclic representative of the series of isothiazoles under consideration, 5-methyl-3-oxo-4-phenyl-2,3-dihydroisothiazole-1,1-dioxide (**Ic**).



**Ia-c**

**I**, R<sup>1</sup>, R<sup>2</sup> = benzo (**a**), (CH<sub>2</sub>)<sub>4</sub> (**b**); R<sup>1</sup> = Ph, R<sup>2</sup> = Me (**c**).



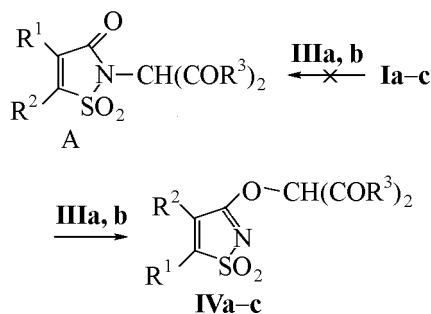
**IIa, b**

**IIIa, b**

**II, III**, R<sup>3</sup> = Me (**a**), OEt (**b**).

The diacylcarbenoids **IIIa, b** were generated from diazoacetylacetone (**IIa**) and diazomalonate (**IIb**). The catalytic decomposition of the diazo compounds **IIa, b** was effected by dirhodium tetraacetate (1-2 mol%) in anhydrous dichloromethane or dichloroethane at 15-20°C or at elevated temperature (80-83°C). The reaction mixture was separated by chromatography on silica gel.

In all experiments were separated as reaction products the 1:1 adducts of oxoisothiazole substrate **I** and diacylcarbenoid **III**. However the spectral data revealed that the compounds obtained instead of expected structure of *N*-alkylamides (**A**) possessed the structure of enol esters **IVa-c**. Thus the diacylcarbenes formally inserted into an O-H bond of the enol form of 3(2H)-oxoisothiazoles **Ia-c**.



**IV**, R<sup>1</sup>, R<sup>2</sup> = benzo, R<sup>3</sup> = Me (**a**); R<sup>1</sup>, R<sup>2</sup> = (CH<sub>2</sub>)<sub>4</sub>, R<sup>3</sup> = OEt (**b**); R<sup>1</sup> = Ph, R<sup>2</sup> = R<sup>3</sup> = Me (**c**).

The reaction provided the products in very good preparative yields (73-95%), and the <sup>1</sup>H NMR spectroscopy did not detect in the reaction mixture any notable amounts of side products.

The structure of enol esters **IVa-c** was established from the data of <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and the X-ray diffraction study of adduct **IVa** formed

from saccharin and diacetylcarbene. The latter data will be published in the next communication.

The formation of the insertion products **IV** along a common scheme [1, 5] via oxonium ylide (with participation of the enol form of the saccharins) seems hardly probable for 3(2H)-oxoisothiazoles **Ia-c** do not undergo enolization [6]. A primary formation of a carbonyl ylide is apparently more probable: The latter can be stabilized by migration of the proton from the N-H group to the anionic center of the ylide intermediate.

**General procedure of catalytic decomposition of diazoacetylacetone (IIa).** To a solution of 0.3 g (2.5 mmol) of diazoacetylacetone (**IIa**) in 3–4 ml of anhydrous dichloromethane or dichloroethane was added 2 mmol of oxoisothiazole **Ia** or **Ic** (0.37 g or 0.45 g respectively), to the mixture obtained at 15–20°C while stirring was added 11 mg (24 μmol) of the rhodium catalyst. After total decomposition of the diazo compound (TLC monitoring) the reaction mixture was diluted with 1–2 ml of dry ethyl ether and charged into a small column packed with neutral silica gel, elution with a mixture pentane-ether, 1:1. The residue after elimination of volatile components in a vacuum of 10–15 mm Hg at 15–20°C was purified by recrystallization from a mixture dichloromethane-ethyl ether, 1:5 (for compounds **IVa, b**) or from ethyl ether (compound **IVc**).

**Catalytic decomposition of diazomalonate (IIb).** To a solution of 0.24 g (1.3 mmol) of tetrahydro-saccharin (**IIb**) in 2 ml of anhydrous dichloroethane was added 5 mg (11 μmol) of dirhodium tetraacetate and then to the stirred mixture at 15–20°C was added dropwise within 1 h a solution of 0.28 g (1.5 mmol) of diazomalonate **IIb** in 0.5 ml of dichloroethane. At the completion of reaction (TLC monitoring) the mixture was treated as above, eluent ether-hexane, 1:2.

**3-(Diacetyl)methoxybenzo[9]isothiazole-1,1-dioxide (IVa).** Yield 86%, mp 166–168°C. <sup>1</sup>H NMR spectrum, δ, ppm: 2.43 s (6H, 2CH<sub>3</sub>), 5.92 s (1H, CH), 7.75–7.97 m (4H arom). <sup>13</sup>C NMR spectrum, δ<sub>C</sub>, ppm: 89.8 (OCH), 197.0 (C=O), 168.3 (C<sup>3</sup>), 144.1 (C<sup>5</sup>), 126.0 (C<sup>4</sup>); 135.2; 134.2, 123.9, 122.7 (all C arom); 27.8 (CH<sub>3</sub>). MS EI, *m/z*: 281.0.

**4,5-Tetramethylene-3-bis(ethoxycarbonyl)-methoxyisothiazole-1,1-dioxide (IVb).** Yield 95%,

mp 59–60°C. <sup>1</sup>H NMR spectrum, δ, ppm: 1.26 t (6H, 2CH<sub>3</sub>, *J* 7.0 Hz), 1.74 m (4H), 2.40 m (2H), 2.52 m (2H), 4.26 q (4H, 2CH<sub>2</sub>O, *J* 7.0 Hz), 5.68 s (1H, CH). <sup>13</sup>C NMR spectrum, δ<sub>C</sub>, ppm: 76.3 (OCH), 162.9 (C=O), 170.6 (C<sup>3</sup>), 155.2 (C<sup>5</sup>), 131.9 (C<sup>4</sup>), 63.3 (OCH<sub>2</sub>); 21.0, 20.84, 20.79, 20.4 (4CH<sub>2</sub>); 14.1 (CH<sub>3</sub>). MS EI, *m/z*: 345.0.

**3-Di(acetyl)methoxy-5-methyl-4-phenyl-1,2-isothiazole-1,1-dioxide (IVc).** Yield 73%, mp 154–155°C. <sup>1</sup>H NMR spectrum, δ, ppm: 2.27 s (6H, 2CH<sub>3</sub>), 2.34 s (3H, CH<sub>3</sub>), 5.82 s (1H), 7.52 s (5H). <sup>13</sup>C NMR spectrum, δ<sub>C</sub>, ppm: 90.4 (OCH), 196.9 (C=O), 170.4 (C<sup>3</sup>), 153.1 (C<sup>5</sup>), 129.5 (C<sup>4</sup>); 130.7, 129.8, 129.3, 126.7 (all C arom); 27.6 (CH<sub>3</sub>CO), 10.4 (CH<sub>3</sub>C=). MS EI, *m/z*: 321.1.

<sup>1</sup>H and <sup>13</sup>C NMR spectra were registered on spectrometer Bruker AM 500 (500 MHz for <sup>1</sup>H, 126 MHz for <sup>13</sup>C) in CDCl<sub>3</sub>, internal reference TMS. Mass spectra of compounds **IVa-c** were obtained at electron impact (MS EI) with direct input of the sample into the ionizing chamber, ionizing electrons energy 70 eV.

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