Tetrahedron xxx (2015) 1–4

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Unexpected synthesis of pyrazolone derivatives

Olena O. Shyshkina [a,*], Volodymyr V. Medviediev [a], Oleg V. Shishkin [b,c,†], Andrii I. Kysil [a], Yulian M. Volovenko [a]

[a] Department of Chemistry, Taras Shevchenko National University of Kyiv, 12 L. Tolstoho Str., Kyiv 01033, Ukraine
[b] Division of Functional Materials Chemistry, SSI "Institute for Single Crystals" of National Academy of Science of Ukraine, 60 Lenina Ave., Kharkiv 61001, Ukraine
[c] Department of Chemistry, V. N. Karazin Kharkiv National University, 4 Svobody Sq, Kharkiv 61122, Ukraine

ARTICLE INFO

Article history:
Received 19 November 2014
Received in revised form 17 December 2014
Accepted 23 December 2014
Available online xxx

Keywords:
Isothiochroman-4-one 2,2-dioxide
Nitration
Pyrazolone
X-ray diffraction
Cyclization

ABSTRACT

Unexpected, but simple synthesis of 2,2′-[(3-oxo-3*H*-pyrazole-4,5-diyl)bis(sulfonyl-methylene)]dibenzoic acid was carried out via nitration of isothiochroman-4-one 2,2-dioxide in the environment of nitric acid.

1. Introduction

In many families from different countries, the pyrazolone derivatives, which include dipyrone, antipyrine, aminopyrine and propyphenazone, are widely used analgesics.[1] However, the synthesis of pyrazolone ring always requires the participation of the N–N fragment (hydrazine, hydrazide, etc).[2] At the same time, sulfones are an important class of compounds that have attracted considerable attention.[3] Recognizing the value of this heterocyclic system, chemists continue to develop novel routes for their synthesis.

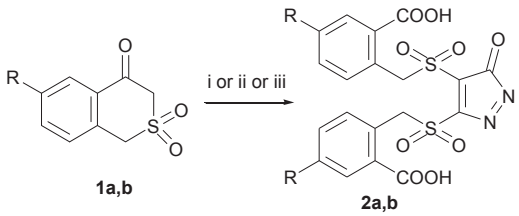
In this paper we introduce the interesting behavior of isothiochromanones in the environment of nitric acid.

2. Results and discussion

The synthesis of isothiochromen-4-one 2,2-dioxides **1a**,**b** has been previously described.[4] Transformation of 1*H*-isothiochromen-4(3*H*)-one 2,2-dioxide are scarcely reported in the literature[5] and we resolved to amend this situation.

When trying to perform nitration of sulfone **1a** under conditions of HNO_3/AcOH we synthesized pyrazolone **2a** in 78% yield (Scheme 1).

Finally, the structure of 2,2′-[(3-oxo-3*H*-pyrazole-4,5-diyl)bis(sulfonylmethylene)]dibenzoic acid (**2a**) was proved by X-ray diffraction (Fig. 1), because NMR and IR spectroscopy proved uninformative for interpretation of the structure of this compound. ^{1}H NMR spectra showed the presence of the CH_2 group and aromatic protons at 5.58 and 7.53–7.98 ppm, respectively. In the IR spectra there are characteristic intensive band groups of C=O at 1689 and 1630 cm^{-1}, but it became clear after the X-ray diffraction study. The molecules of compound **2a** in the crystal occupy the special position at the 2 fold symmetry axis crossing via the N_2 atom (Fig. 1). Pyrazolone ring is disordered over two positions with equal population.



i: 65% HNO_3, RCOOH (R: Me, Et, CF_3, $CH_3CH(Br)$)
ii: 50% HNO_3, AcOH or fuming HNO_3, AcOH
iii: 65% HNO_3, heating; R: (**a**) H; (**b**) F

Scheme 1. Synthesis of 2,2′-[(3-oxo-3*H*-pyrazole-4,5-diyl)bis(sulfonylmethylene)]dibenzoic acids.

* Corresponding author. Tel.: +38 067 984 1970; e-mail address: olena.o.shyshkina@gmail.com (O.O. Shyshkina).
† Deceased.

http://dx.doi.org/10.1016/j.tet.2014.12.082
0040-4020/

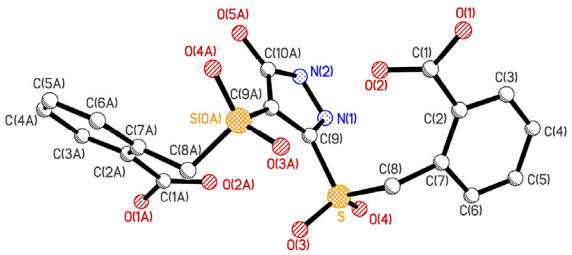


Fig. 1. Molecular structure of compound **2a** according to X-ray diffraction data with the atom numbering used in the crystallographic analysis. Only one orientation of disordered pyrazolone ring is shown.

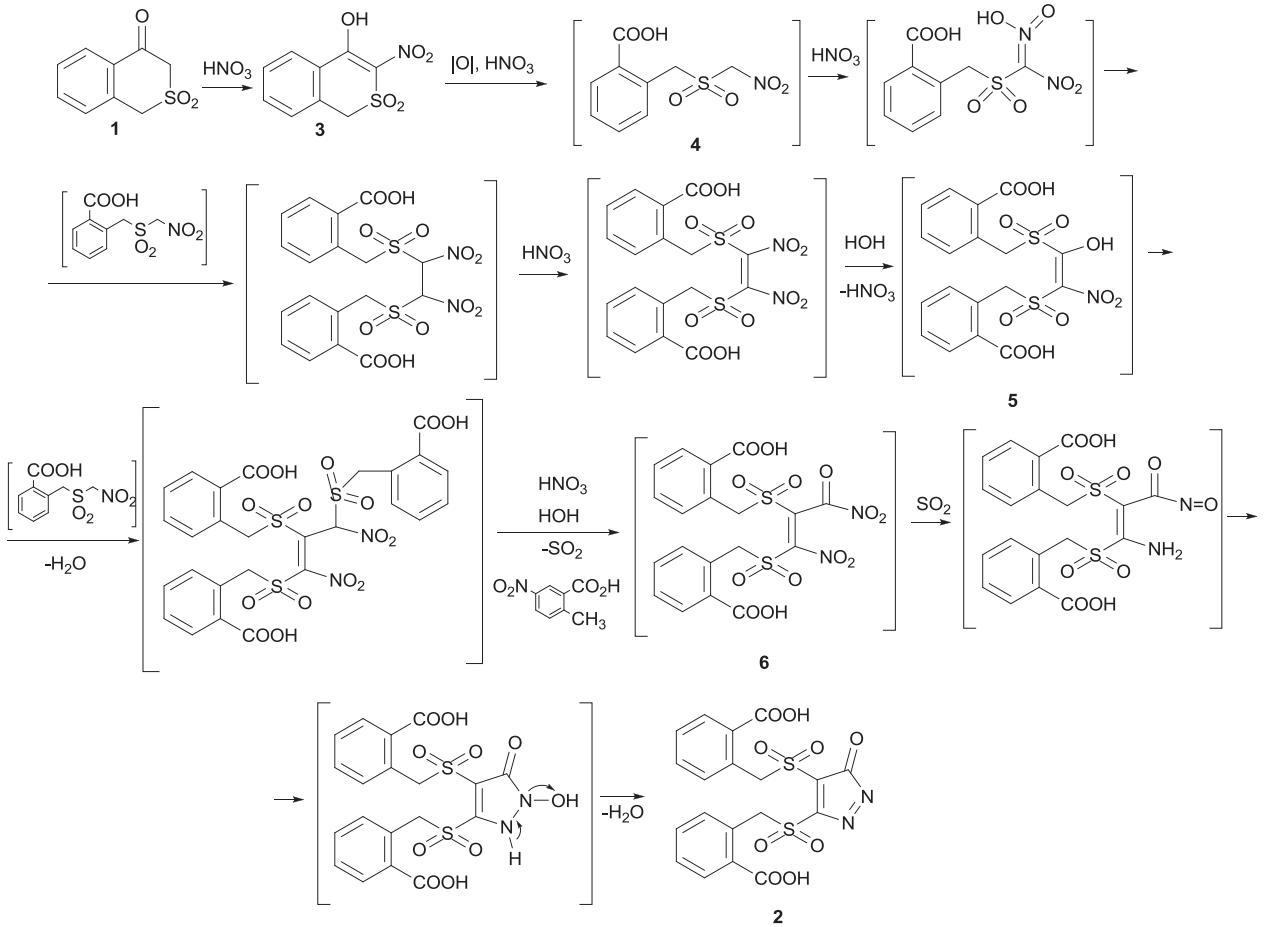
If the presence of nitrogen atoms in structure **2**, can be to some extent understood, the presence of the additional carbon atom caused surprise. It has been suggested that the additional carbon originates from acetic acid by its oxidation. But the question arises. Which one carbon atom among two of available in acetic acid participates in the transformation? Therefore, acetic acid has been replaced by several other carboxylic acids (propionic acid, trifluoroacetic acid and 2-bromopropionic acid), but the product of the reaction was the same (Scheme 1). Therefore it is possible to suggest that the additional carbon originates from a third molecule of sulfone **1**. To confirm this hypothesis we conducted the reaction using a nitric acid as reagent and solvent. Heating the solution of isothiochromanone **1a** in 65% nitric acid for 5 min resulted in compound **2a** in a yield of 92%. The reaction was accompanied by emission of gas.

The next task, which was successfully solved, was to investigate the influence of nitric acid concentration on the reaction rate. It turned out that replacement of 65% nitric acid with red fuming nitric acid significantly slows down the speed of the reaction, when using the acetic acid as solvent (from 7 days to 2 months). At the same time, when using 50% nitric acid, the reaction occurs more rapidly (4 days). Thus, we can assume that water participates in the formation of pyrazolone **2**.

Given the above, we proposed a mechanism for this reaction (Scheme 2). In the first step, the nitroenole **3** was formed by nitration of isothiochomanone **1**. The crystals of compound **3** are unstable and decompose in air after a few minutes. The structure of compound **3** was proven by X-ray diffraction data only (Fig. 2) due to its high instability.

The next steps are opening of the thiopyran ring, nitration of activated methylene group and addition of the second molecule of intermediate **4**. We assume that next step is addition of a third molecule of intermediate **4** to the double bond of intermediate **5** with simultaneous elimination of nitric acid. The intermediate **6** is the result of elimination of 2-methyl-5-nitrobenzoic acid under stabilization of the molecule. The formation of 2-methyl-5-nitrobenzoic acid results from coordinated orientation of substituents in the 2-methylbenzoic acid, which was eliminated during the reaction.

Under the influence of SO_2, as a reductant, there are full and partial reductions of the nitro groups, which can be regarded as aromatic and aliphatic nitro groups, respectively. At the same time we must remember that the nitrozo group is an analog of the carbonyl group. Consequently, we can assume that the next step is



Scheme 2. Possible mechanism of the reaction synthesis on the example of 2,2′-[(3-oxo-3*H*-pyrazole-4,5-diyl)bis(sulfonylmethylene)] dibenzoic acid (**2a**).

Please cite this article in press as: Shyshkina, O. O.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2014.12.082