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1,3-Dipolar cycloadditions of fluorinated nitrones with thioketones

Grzegorz Mlostoń [a],*, Emilia Obijalska [a], Małgorzata Celeda [a], Verena Mittermeier [a],[1], Anthony Linden [b], Heinz Heimgartner [b],*

[a] Department of Organic and Applied Chemistry, University of Łódź, Tamka 12, PL-91-403 Łódź, Poland
[b] Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

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ABSTRACT

Fluorinated nitrones derived from fluoral and difluoroacetaldehyde react with thioketones via [3 + 2] cycloaddition yielding 1,4,2-oxathiazolidines in a regioselective manner. Unexpectedly, cycloaliphatic thioketones react faster than aromatic thioketones. Due to the presence of a fluorinated alkyl group, the cycloadducts display a remarkable stability and do not decompose at room temperature in the crystalline form nor in solution.

1. Introduction

A general and widely applied method for the preparation of five-membered heterocycles is the 1,3-dipolar cycloaddition [1]. Among the N-containing 1,3-dipoles, nitrones form an important class, and they are well known to undergo reactions with diverse dipolarophiles such as activated and non-activated C═C and C≡C bonds [2]. According to Sustmann's classification of 1,3-dipoles, nitrones belong to the so-called type II, i.e., the concerted cycloaddition step occurs via $\text{LUMO}_{\text{Dipole}}$–$\text{HOMO}_{\text{Dipolarphile}}$ as well as via $\text{HOMO}_{\text{Dipole}}$–$\text{LUMO}_{\text{Dipolarophile}}$ interactions [3].

In the last two decades, thioketones have attracted attention as extremely reactive dipolarophiles, and based on a reactivity scale toward 1,3-dipoles such as nitrones, diazoalkanes and thiocarbonyl ylides, they were named as 'superdipolarophiles' [4].

Fluorinated nitrones are a lesser-known group of nitrones. From the point of view of potential applications for the synthesis of fluorinated heterocycles, nitrones of type **1**, derived from fluorinated acetaldehydes, are of special interest. However, reports on their preparation and reactivity are scarce. The first syntheses of *N*-phenyl- and *N*-(tert-butyl)nitrones of type **1** were performed by treatment of the corresponding nitroso compound with 2,2,2-trifluorodiazoethane [5]. Practically useful protocols are based on the reactions of fluoral hydrate or fluoral hemiacetals with *N*-alkyl hydroxylamines [6]. The latter method corresponds to the general approach to nitrones.

An extended study on the 1,3-dipolar cycloadditions of the *N*-methyl-substituted nitrone of type **1**, derived from fluoral, was carried out using alkynes and alkenes as dipolarophiles [6a,b]. It is worth mentioning that, typically for 1,3-dipoles of type II, this nitrone reacted with both electron-deficient and non-activated alkynes and alkenes yielding 3-trifluoromethyl isoxazole derivatives. To the best of our knowledge, there are no reports of 1,3-dipolar reactions of nitrones, derived from fluorinated acetaldehydes, with hetero-dipolarophiles.

In a recent paper, we described a new application of fluoral carbohydrazones for the synthesis of diverse five-membered heterocycles via addition/cyclization procedures [7]. Due to our ongoing interest in the exploration of thioketones for the synthesis of *S*-containing heterocycles [4d,8], we decided to apply them for 1,3-dipolar cycloadditions with fluorinated nitrones.

2. Results and discussion

The fluorinated nitrones **1a** and **1b** used in the present study were prepared by reacting the corresponding aldehyde hydrate (in the case of **1a**) or ethylhemiacetal (for **1b**) with *N*-benzyl hydroxylamine, followed by dehydration of the initially formed

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* Corresponding authors. Tel.: +48 42 635 57 61.
E-mail addresses: gmloston@uni.lodz.pl (G. Mlostoń), heinz.heimgartner@chem.uzh.ch (H. Heimgartner).

[1] IAESTE research practica participant from the TU Munich, June–July 2013.

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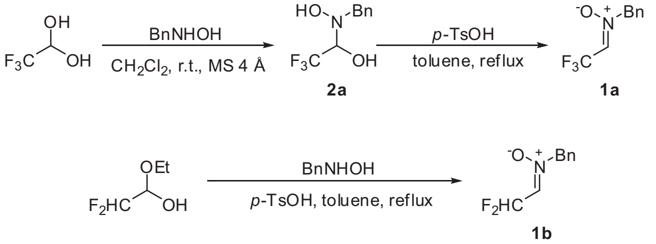


Scheme 1. Preparation of fluorinated *N*-benzylnitrones **1a** and **1b**.

aminals [6] (Scheme 1). In the case of **1a**, a significant enhancement of the yield was achieved via the two-step procedure. The first step was carried out in dichloromethane at room temperature to give the nitrone hydrate **2a**. The subsequent dehydration was performed in boiling toluene in the presence of catalytic amounts of *para*-toluenesulfonic acid (*p*-TsOH) by using a Dean-Stark trap.

Several nitrone hydrates (hemiaminals) have been mentioned in the literature as intermediates [9], detected as metabolites by mass spectrometry [10] or by ^{1}H NMR spectroscopy as compounds with low stability existing in an equilibrium with the nitrone [11]. But to the best of our knowledge, only one example, the *N*-methyl analog of **2a**, has been isolated and characterized by spectroscopic methods [6a].

Crystallization of **2a** from hexane/diethyl ether yielded colorless crystals suitable for an X-ray crystal-structure determination, which unambiguously confirmed the structure of the nitrone hydrate (Fig. 1).

The space group is centrosymmetric and, therefore, the compound in the selected crystal is racemic. The hydroxy group bonded to the N-atom forms an intermolecular hydrogen bond with the other hydroxy group of an adjacent molecule and thus links the molecules into extended chains which run parallel to the [1 0 0] direction and can be described by a graph set motif [13] of C(5). The second hydroxy group forms an intermolecular hydrogen bond with the N–OH O-atom of a centrosymmetrically related molecule and thus links pairs of molecules into centrosymmetric dimers in which the $R_2^2(10)$ hydrogen bond motif is discernable. The combination of both interactions links the molecules into ladders, which run in the [1 0 0] direction. Within the rungs of the ladders, the aforementioned $R_2^2(10)$ motif alternates with a $R_4^4(8)$ motif.

In a first experiment, a mixture of equimolar amounts of nitrone **1a** and adamantanethione (**3a**) in THF solution was heated at reflux for 3 h until the orange-red color of the thioketone disappeared. The ^{1}H NMR analysis of the crude mixture indicated the presence of the expected 1,4,2-oxathiazolidine **4a** (Scheme 2). The characteristic AB-system of the benzylic CH_2 group of **4a** appeared at 4.22 and 4.29 ppm with J_{AB} = 12.6 Hz. The isolation of the product was achieved by chromatographic workup to give **4a** in 83% yield (Table 1). The spectroscopic data proved the structure of **4a**. For example, in the ^{13}C NMR spectrum, the characteristic quartet of the CF_3 group absorbed at 123.5 ppm with $^1J_{C,F}$ = 277.9 Hz. A second quartet attributed to C(3) appeared at 72.3 ppm with $^2J_{C,F}$ = 33.4 Hz. The C(5) atom gave a singlet located at 109.2 ppm, corresponding to the chemical shift of the C(2) atom of 1,3-oxathiols [8a–c] and 1,3-oxathiolanes [8d,e]. Finally, the molecular structure of **4a** was established by X-ray crystallography (Fig. 2). Since the space group is centrosymmetric, the compound in the crystal is racemic.

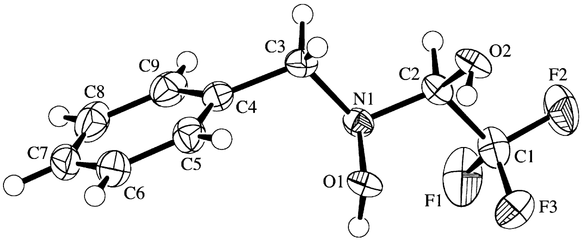
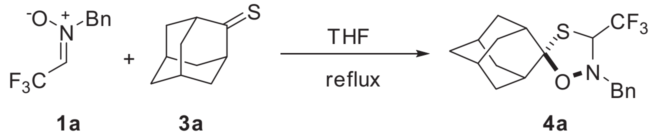
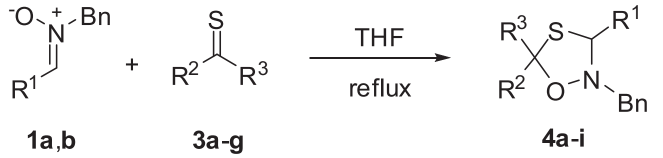


Fig. 1. ORTEP plot [9] of the molecular structure of **2a** (50% probability ellipsoids; arbitrary numbering of the atoms).

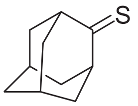
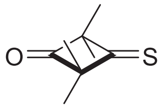
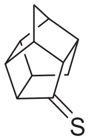
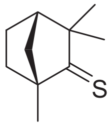
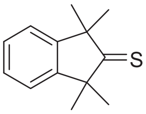
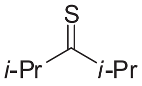
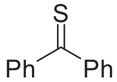
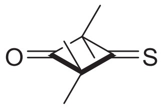
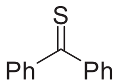


Scheme 2. 1,3-Dipolar cycloaddition of nitrone **1a** with adamantanethione (**3a**).



Scheme 3. Reactions of nitrones **1a**,**b** with thiones **3**.

Table 1
Reaction of fluorinated nitrones **1a**,**b** with thioketones **3** in THF at reflux.

Entry	R^1	Thioketone **3**	Reaction time [h]	Product	Yield [%]
1	CF_3	 **a**	3	**4a**	83
2	CF_3	 **b**	3	**4b**	72
3	CF_3	 **c**	0.5	**4c**	85
4	CF_3	 **d**	3	**4d**	75
5	CF_3	 **e**	3	**4e**	75
6	CF_3	**f** 	3	**4f**	55
7	CF_3	**g** 	3	**4g**	71
8	CHF_2	 **b**	4	**4h**	89
9	CHF_2	**g** 	4[a]	**4i**	72

[a] Reaction carried out in 1,2-dichloroethane.