Tetrahedron Letters 51 (2010) 1038–1040

Contents lists available at ScienceDirect

Tetrahedron Letters

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

# Synthesis and reactions of 3-halomethyl-substituted oxazine *N*-oxides

Andrey A. Mikhaylov[a,b], Alexander D. Dilman[a,*], Roman A. Kunetsky[a], Yulia A. Khomutova[a], Marina I. Struchkova[a], Alexander A. Korlyukov[c], Sema L. Ioffe[a,*], Vladimir A. Tartakovsky[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Leninsky prosp. 47, 119991 Moscow, Russian Federation*
[b] *Higher Chemical College of the Russian Academy of Sciences, Miusskaya sq. 9, 125047 Moscow, Russian Federation*
[c] *A. N. Nesmeyanov Institute of Organoelement Compounds, 119991 Vavilova str. 28, Moscow, Russian Federation*

ARTICLE INFO

*Article history:*
Received 10 November 2009
Revised 3 December 2009
Accepted 11 December 2009
Available online 21 December 2009

*Keywords:*
Nitronates
5,6-dihydro-1,2-Oxazine-*N*-oxides
Halogenation

ABSTRACT

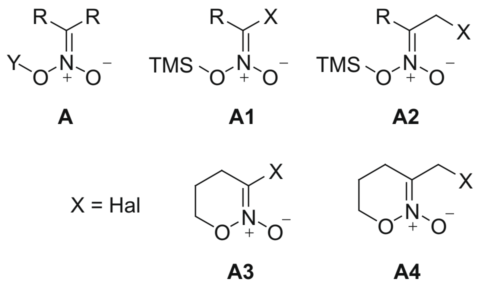
A series of 3-halomethyl-5,6-dihydro-1,2-oxazine *N*-oxides (halogen = Cl, Br, I) is prepared from 4-phenyl-3,6,6-trimethyl-5,6-dihydro-4*H*-oxazine *N*-oxide by means of a silylation/halogenation sequence. The obtained halogenated *N*-oxides undergo reactions typical of cyclic six-membered nitronates including 1,3-dipolar cycloaddition, addition of nucleophiles, and substitution of the halogen by C-, S-, and N-nucleophiles.

Nitronates **A** constitute an interesting class of nitro derivatives, and in recent years there has been a significant development of the chemistry of these compounds[1] (Scheme 1). Alkyl nitronates (**A**, Y = Alk) undergo various transformations such as dipolar cycloaddition,[1,2] nucleophilic addition,[3] reduction,[4] and silylation reactions,[5] while silyl nitronates (**A**, Y = $SiR_3$) have been employed in a number of catalytic asymmetric processes.[6] It was demonstrated that cyclic alkyl nitronates can serve as key intermediates in the synthesis of natural products,[1c,2] medicinal substances,[7] and various functionalized molecules.[8]

Despite significant advances in the field of nitro group derivatives, nitronates bearing a halogen atom have remained virtually unexplored. Recently, we demonstrated that halo-substituted silyl nitronates **A1** exhibit specific properties, allowing for their application in the synthesis of cyclic five-membered nitronates.[9] Nitronates **A2** were proposed as short-lived intermediates in the oxidative transformation of nitro alkanes into conjugated nitro alkenes, and their instability is associated with facile elimination of halosilane (TMS-X).[10] As for cyclic nitronates, compounds **A3** are known,[11] while nitronates **A4** have not been described.

Herein we report the synthesis of 3-halomethyl-substituted cyclic six-membered nitronates (5,6-dihydro-1,2-oxazine *N*-oxides, **A4**) by means of functionalization of the 3-methyl group of nitronate **2**, and provide preliminary results on the investigation of their chemistry.

Nitronate **2** was readily obtained from isobutylene, benzaldehyde, and nitroethane[5a] (Scheme 2). Silylation of **2** with trimethylsilyl triflate afforded *N*-(silyloxy)enamine **3** in high yield, according to a modified literature procedure.[5]



**Scheme 1.**

Given that enamines **3** exhibit nucleophilic reactivity towards carbocationic electrophiles,[5] we decided to study their behavior with different halogenating reagents.[12,13] The results are presented in Table 1.

The reaction of enamine **3** with *N*-chloro- and *N*-bromosuccinimide proceeded cleanly to afford chloro- and bromonitronates **4a** and **b** in almost quantitative yield after column chromatography.[14] Alternatively, we used elemental halogens in combination with a source of acetate, which can trap the reactive halosilane arising after halogenation of **3**. Though tetrabutylammonium acetate was successfully employed, the use of triethylamine together with acetic acid was more convenient, since in this case, ammonium by-products were removed upon work-up to furnish bromo- and iodonitronates **4b** and **c** in good purity. Fluorination using sev-

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[*] Corresponding authors. Fax: +7 499 1355328.
*E-mail addresses:* adil25@mail.ru (A.D. Dilman), iof@ioc.ac.ru (S.L. Ioffe).

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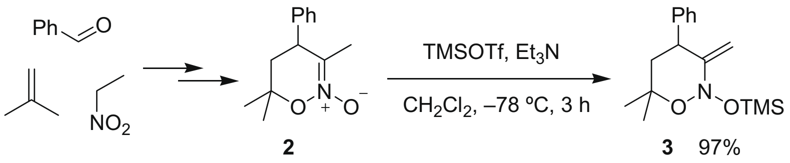
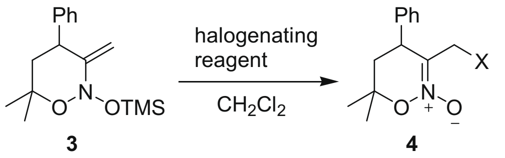
doi:10.1016/j.tetlet.2009.12.066



**Scheme 2.**

**Table 1**
Halogenation of enamine **3**



| Entry | X | Conditions[a] | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Cl | NCS, −78 °C→rt | **4a** | 96 |
| 2 | Br | NBS, −78 °C→rt | **4b** | 93 |
| 3 | Br | $Br_2$, $Bu_4NOAc$, −78 °C | **4b** | 83 |
| 4 | Br | $Br_2$, $Et_3N$/AcOH, −94 °C→−30 °C | **4b** | 90 |
| 5 | I | $I_2$, $Bu_4NOAc$, −78 °C→rt | **4c** | 76 |
| 6 | I | $I_2$, $Et_3N$/AcOH, −94 °C→−30 °C | **4c** | 81 |
| 7 | I | ICl, −78 °C→rt | **4c** | 60 |

[a] After raising the temperature, the mixture was stirred for 10–30 min; see Supplementary data for details.

[b] Isolated yield.

eral reagents (Selectfluor, $PhIF_2$, and $XeF_2$) was unsuccessful, and in all cases, either decomposition or rearrangement of enamine **3** into 3-oxymethyl-1,2-oxazine was observed.[15]

The crystal structure of iodo-nitronate **4c** was studied by X-ray diffraction analysis (Fig. 1).[16] The relative positions of the iodine atom and C=N bond can be considered as *syn*-clinal with the torsion angle I(1)C(5)C(1)N(1) equal to 77.5(2)°. Other parameters, such as the C=N and N–O bond lengths and the distorted half-chair conformation with a displaced C(4) atom were similar to those characteristics for previously reported cyclic nitronates.[1a,5a]

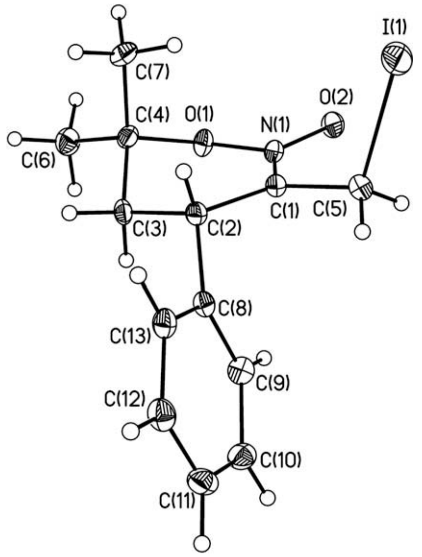


**Figure 1.** The molecular structure of **4c**. Non-hydrogen atoms are presented by thermal ellipsoids at 50% probability. Selected bond lengths and angles (Å and °): I(1)–C(5) 2.182(2), O(1)–N(1) 1.411(3), O(2)–N(1) 1.259(2), N(1)–C(1) 1.307(3), C(1)N(1)O(1) 122.35(19), N(1)C(1)C(5) 115.6(2), C(1)C(5)I(1) 111.13(16), C(4)O(1)N(1)C(1) 26.9(3), C(1)C(2)C(3)C(4)–41.6(3).

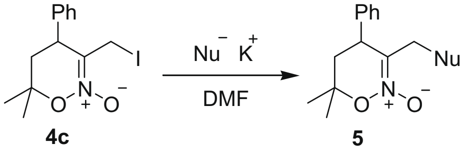
Nitronates **4** undergo typical reactions of a halomethyl group, as well as those of a nitronate fragment. Thus, we demonstrated that the halogen can be displaced by different heteroatom- and carbon-centered nucleophiles, thereby providing the opportunity for a facile access to functionalized cyclic nitronates. Reactions of iodo-nitronate **4c** with the potassium salts of phthalimide, *p*-tolylthiol, and dimethyl malonate proceeded cleanly in DMF leading to the products of nucleophilic substitution **5** in high yields (Table 2).

For nitronates **4**, dipolar cycloaddition[1,2] and Lewis acid-mediated nucleophilic addition to the C=N bond[3] were also studied. Nitronate **4c** reacted with excess methyl acrylate under reflux conditions affording bicyclic product **6** as a mixture of two diastereoisomers in a ratio of 7.3:1 (Scheme 3).

A significant difference in the reactivity of bromo and iodo derivatives was observed in the reactions of nitronates with silyl ketene acetal **7**. Thus, the reaction of bromo-nitronate **4b** with **7** in the presence of TBS-triflate gave the expected product **9a** in high yield (Scheme 4). On the other hand, under similar conditions, iodo-nitronate **4c** smoothly furnished, after chromatography, a mixture of enamine **10** and oxime **11** (the product of rearrangement of enamine **10**).[15] Both these reactions proceed through the initial generation of iminium species **8**, observed by low temperature NMR measurements, by mixing nitronates **4b** and **c** with *tert*-butyldimethylsilyl triflate (TBSOTf). While bromo-substituted cation **8b** undergoes conventional nucleophilic addition, iodinated species **8c** can serve as a source of positive iodine on reaction with the silyl ketene acetal.

In summary, a series of halogenated cyclic six-membered nitronates has been prepared starting from 3-methyl-substituted nitronate **2** by means of a silylation/halogenation sequence. These compounds were found to undergo nucleophilic substitution of the halogen leading to new functionalized oxazine-*N*-oxides. The

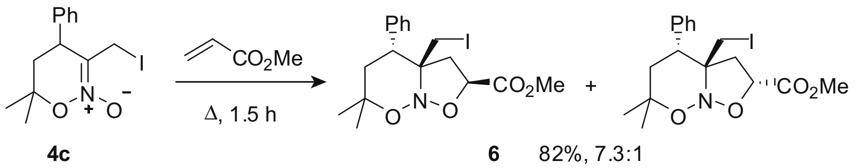
**Table 2**
Nucleophilic substitution reactions of **4c**



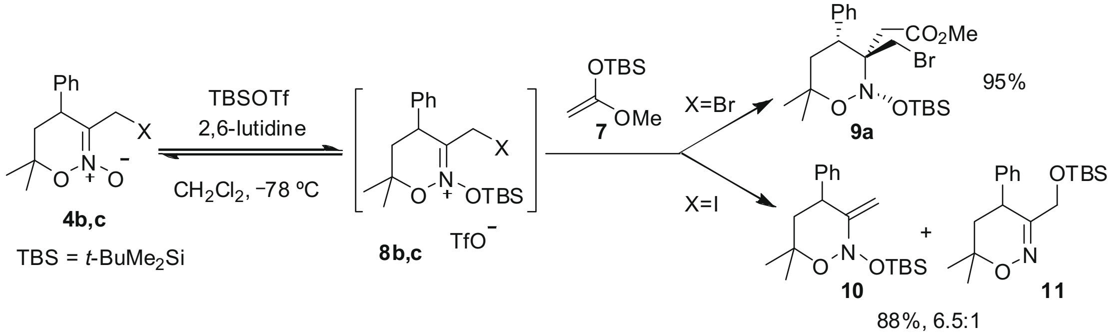
| $Nu^-$ | Conditions | Product | Yield[a] (%) |
|---|---|---|---|
| $PhthalN^-$ | 0 °C→rt, 1 h | **5a** | 82 |
| $p$-$MeC_6H_4S^{-b}$ | −40→0 °C, 1 h | **5b** | 87 |
| $(MeO_2C)_2CH^{-b}$ | −40→0 °C, 30 min | **5c** | 88 |

[a] Isolated yield.

[b] Generated from Nu–H using *t*-BuOK.



**Scheme 3.**



**Scheme 4.**

nitronate fragment of the halo-nitronates took part in nucleophilic addition and 1,3-dipolar cycloaddition reactions.

## Acknowledgements

This work was supported by the Russian Academy of Sciences (Programs 1 and 18), the Russian Foundation for Basic Research (Project 05-03-32733), the Russian Science Support Foundation, and the Federal program 'Scientific and educational personnel of innovative Russia' (Project 02.740.11.0258). We are grateful to Mr. A. Levykin and Mr. I. Krylov for experimental contributions.

## Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.066.

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14. Before work-up, methanol should be added to the reaction mixture to convert silylsuccinimide into succinimide, since the latter can be easily separated by chromatography.
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16. The crystal of **4c** ($C_{13}H_{16}INO_2$) was monoclinic at 100 K, space group $P2_1/n$, $a = 8.2376(9)$, $b = 22.788(3)$, $c = 7.2234(7)$ Å, $\beta = 91.046(2)°$, $V = 1355.7(3)$ Å$^3$, $Z = 4$, $M = 345.17$, $d_{calcd} = 1.691$ g cm$^{-3}$, $\mu$ (Mo K$\alpha$) = 2.353 cm$^{-1}$, $F(000) = 680$. 18,025 reflections were collected using a Smart APEX II diffractometer, 4140 reflections were unique. $R_1 = 0.0346$ was calculated against $F^2$ for 3409 reflections with $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 753679) and are available free of charge at CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].