Unexpected Regioselectivity in Cycloisomerization of 2-Alkynyl-3-nitrothiophenes

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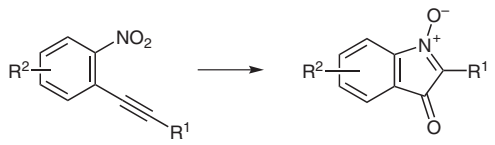
Received 7 October 2010

Abstract: The intramolecular cycloizomerization of 2-alkynyl-3-nitrothiophenes was catalyzed by $AuCl_3$ or CF_3CO_2Ag to produce the corresponding thieno[3,2-*c*]isoxazoles bearing carbonyl functionality in position 3 instead of expected 5-substituted 6*H*-thieno[3,2-*b*]pyrrol-6-one 4-oxides.

Key words: 2-alkynyl-3-nitrothiophenes, thieno[3,2-*c*]isoxazoles, cycloizomerization, catalysis

The cyclization of alkynes containing proximate nucleophilic centers is currently of great interest and developing into a most effective strategy for heterocyclic ring construction. This chemistry provides a straightforward approach to the synthesis of functionalized carbo- and heterocycles through the regio- and stereoselective addition of a nucleophile and an unsaturated carbon unit across the carbon–carbon triple bond.[1] Thus a variety of transition-metal or electrophile-induced 5-*exo*-dig or 6-*endo*-dig cyclization reactions have been reported.[2] The *ortho*-alkynyl nitrobenzenes are well known as precursors for the preparation of isatogens (Scheme 1). The classical cycloisomerizations of starting compounds can be initiated by pyridine,[3a–e] nitrosobenzene,[3e,f] concentrated sulfuric acid,[3g,h] tetrabutylammonium fluoride (TBAF),[3c] and UV light.[3i–k] Usually these reactions take long times and require high temperatures. However, few years ago, it was shown that the presence of transition-metal salts such as gold(III) bromide[4a] or silver (I) nitrate[4b] initiates smooth cyclization reaction.



Scheme 1 Literature results

On the other hand, recently, we have developed a novel, concise, and high-yielding formation of pyrrolo[3,2-*d*]-pyrimidin-7-one 5-oxides via smooth cycloisomerization of 2,4-disubstituted 6-arylethynyl-5-nitropyrimidines in the presence of pyridine. We have shown that the triple bond of the starting compounds is electron poor, so the cycloisomerization reaction takes only a few minutes and does not require transition-metal catalysts.[5]

Encouraged by knowledge from literature and our previous results, we envisioned that cycloizomerization of all aromatic and heteroaromatic compounds, bearing triple bond and nitro group in close proximity to each other, would always lead to the formation of pyrolone *N*-oxide ring containing compounds. However, to our great surprise, we observed different regioselectivity in cycloisomerization of 2-alkynyl-3-nitrothiophenes, so herein we would like to report on these unexpected results.

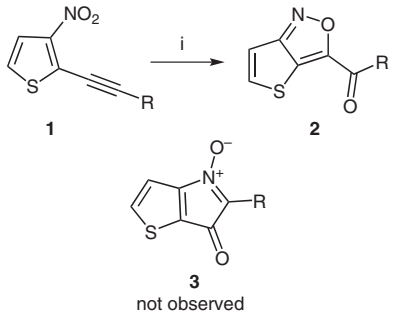
The starting compounds **1** were synthesized by well-known Sonagashira reaction[6] from 2-bromo-3-nitrothiophene (Scheme 2).[7] First of all, it should be noted that classical pyridine initiated cycloisomerization of the title compounds was not successful. During the long heating of 3-nitro-2-phenylethynylthiophene **1a** in dry pyridine, no changes of the starting material were observed by TLC. This result can be easily explained by the fact that triple bonds in starting compounds are electron-rich due to neighboring electron-donating thiophene ring, so nucleophilic activation becomes impossible. So we decided to take advantages of transition-metal salts catalytic potency. When we added 5 mol% of gold(III) chloride to the solution of 3-nitro-2-phenylethynylthiophene (**1a**) in dry dichloromethane, the quick and selective conversion of the starting material was observed by TLC. The NMR, IR, and microanalysis data of isolated product were not at variance with the expected structure – 5-phenyl-6*H*-thieno[3,2-*b*]pyrrol-6-one 4-oxide (**3a**), but we had doubt because of the substance's slightly yellowish color, which is not common for structural analogues of isatogens (the latter compounds are usually from deep red to deep violet). And we were really intrigued to see the results from X-ray analysis, which enabled the outcome of the reaction to be elucidated unambiguously (Figure 1).[8] We were surprised when crystallographic data showed that during cycloisomerization of the starting compound phenylthieno[3,2-*c*]isoxazol-3-yl methanone (**2a**) was formed.

Moreover, it was interesting to note that optically inactive phenylthieno[3,2-*c*]isoxazol-3-yl methanone (**2a**) in its solid state forms chiral crystals with symmetry space group *P*212121.[8]

Thus, we decided to look for the best conditions to trigger the cycloisomerization of the title compounds and to study

SYNLETT 2010, No. 20, pp 3027–3030
Advanced online publication: 17.11.2010
DOI: 10.1055/s-0030-1259053; Art ID: G30510ST

the influence of the catalyst for reaction rate and regioselectivity. It should be noted that in all successful cases phenylthieno[3,2-*c*]isoxazol-3-yl methanone (**2a**) was formed and no formation of 5-phenyl-*6H*-thieno[3,2-*b*]pyrrol-6-one 4-oxide (**3a**) was observed.



Scheme 2 Cycloisomerization reaction of 2-alkynyl-3-nitrothiophenes. *Reagents and conditions*: i) $AuCl_3$ (5 mol%), CH_2Cl_2, r.t., 15–45 min or CF_3CO_2Ag (10 mol%), DCE, reflux, 2 h.

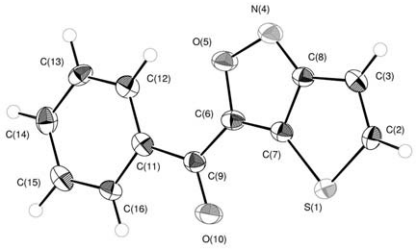


Figure 1 ORTEP view of phenylthieno[3,2-*c*]isoxazol-3-yl methanone (**2a**)

Firstly, we noted, that the use of gold(III) chloride (5 mol%) in dichloromethane at room temperature gave the best result (Table 1, entry 3). While CF_3CO_2Ag in boiling dichloroethane provided a slightly lower yield of the desired product **2a** (Table 1, entry 5), CF_3CO_2Ag, CuI, and $PdCl_2(PPh_3)_2$ in dichloromethane at room temperature as well as $AgNO_3$ in boiling dichloroethane proved to be far less effective (entries 4, 6–8). Cycloisomerization of **1a** on silica gel in microwave oven was unsuccessful (entry 9) and the use of pyridine did not initiate the reaction at all (entries 1, 2). So, we have found that the preliminarily optimal reaction conditions are: 5 mol% of gold(III) chloride in dichloromethane at room temperature, or 10 mol% of silver trifluoroacetate in dichloroethane at reflux.

Encouraged by these results we decided to perform the cycloisomerization reactions of the other 2-alkynyl-3-nitrothiophenes **1**. The results are summarized in Table 2. It is noteworthy that the nature of the substituent on alkynyl group does not have influence on the cycloisomerization regioselectivity – in all cases the corresponding substituted thieno[3,2-*c*]isoxazol-3-yl methanones have been formed. In the case of 3-nitro-2-trimethylsilylethynylthiophene (**1e**), slow decomposition of the starting material was observed (Table 2, entry 5). We solved this problem by performing the deprotection of alkynyl moiety, followed by cycloisomerization of obtained 2-ethynyl-3-nitrothiophene (**1f**). The latter reaction was smooth enough and the thieno[3,2-*c*]isoxazol-3-ylcarbaldehyde (**2f**) was isolated in high yield (Table 2, entry 6).

Moreover, we decided to study the cycloisomerization of 3-alkynyl-2-nitrothiophenes (**4a**,**b**). The latter two compounds were prepared from the corresponding 3-bromo-2-nitrothiophene,[9] using Sonogashira coupling reaction. It should be noted, that compounds **4a**,**b** underwent the same regioselective cycloisomerization reaction to form arylthieno[2,3-*c*]isoxazol-3-yl methanones **5a**,**b**. But on the other hand, the conversions of starting materials were incomplete after long reactions times, and the yields of the final products were not high (Table 2, entries 9 and 10).

After a thorough literature search, we had found find only one literature source where the formation of isoxazole ring from the neighboring nitro and ethynyl groups was described.[4a] In 2003, Asao and co-workers, during investigations of gold-catalyzed intramolecular cyclizations of *o*-(alkynyl)nitrobenzenes, found that, besides the production of the desired isatogens, anthranyls were also formed

Table 1 Reaction Conditions for the Cycloisomerization of 3-Nitro-2-phenylethynylthiophene (**1a**)

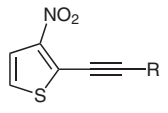
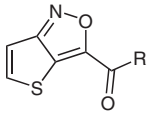
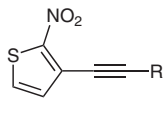
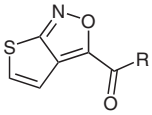
Entry	Reaction conditions	Time	Conversion	Yield of **2a** (%)
1	pyridine, reflux	10 h	0[a]	0
2	pyridine, DMAP, reflux	12 h	0[a]	0
3	$AuCl_3$ (5 mol%), CH_2Cl_2, r.t.	20 min	100	97
4	CF_3CO_2Ag (5 mol%), CH_2Cl_2, r.t.	50 h	43	33
5	CF_3CO_2Ag (10 mol%), DCE, reflux	2 h	100	93
6	CuI (5 mol%), CH_2Cl_2, r.t.	50 h	30	11
7	$PdCl_2(PPh_3)_2$ (5 mol%), CH_2Cl_2, r.t.	50 h	44	40
8	$AgNO_3$ (10 mol%), DCE, reflux	8 h	80	77
9	SiO_2, MW	20 min	0[a]	0

[a] Starting material **1a** was isolated.

as side products in low yields.[4a] The authors proposed a mechanism for these reactions and postulated therein that water present in the solvents played a key role in the cycloisomerization step.

However, we speculate that the cycloisomerization of aromatic or heteroaromatic compounds bearing nitro group and triple bond moiety in close proximity to each other takes place via intramolecular oxidation–reduction processes via subsequent ring cleavage and recyclization reactions. Moreover, we performed the cycloisomerization reactions in absolute solvent and precisely avoided the presence of water; so therefore, we think that oxygen in carbonyl function came from the nitro group, not from the water.

Table 2 Cycloisomerization of 2-Alkynyl-3-nitrothiophenes **1** and 3-Alkynyl-2-nitrothiophenes **4** by the Presented Method

Entry	Starting material	Product	Yield (%)
			
1	**1a**, R = Ph	**2a**, R = Ph	97
2	**1b**, R = 4-MeC_6H_4	**2b**, R = 4-MeC_6H_4	92
3	**1c**, R = 4-EtC_6H_4	**2c**, R = 4-EtC_6H_4	98
4	**1d**, R = 2-pyridyl	**21d**, R = 2-pyridyl	89
5	**1e**, R = $SiMe_3$	slow decomposition of starting material	-
6	**1f**, R = H	**2f**, R = H	87
7	**1g**, R = Bu	**2g**, R = Bu	90
8	**1h**, R = *t*-Bu	**2h**, R = *t*-Bu	88
			
9	**4a**, R = Ph	**5a**, R = Ph	45[a]
10	**4b**, R = 4-FC_6H_4	**5b**, R = 4-FC_6H_4	41

[a] incomplete conversion of starting material.

In conclusion, we have presented unexpected regioselective cycloisomerization reactions of 2-alkynyl-3-nitrothiophenes. The novel, simple, and high-yielding synthetic method of thieno[3,2-*c*]isoxazole framework was proposed. Extension of regioselective cycloizomerizations of aromatic and heteroaromatic compounds, bearing triple bond and nitro group in close proximity to each other, is currently under way in our laboratory. More detailed study of the mechanism of the cycloisomerizations together with their scope and limitations are in progress, and the results will be published in due course.

Acknowledgment

We thank the Lithuanian Research Council for the financial support from the Global Grant Programme (Grant No. VP1-3.1-ŠMM-07-K-01-002). Rokas Sazinas acknowledges Student Research Fellowship Award from the Lithuanian Research Council.

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(8) **Crystal Structure Analysis for 2a**
$C_{12}H_7NO_2S$, M_r = 229.25 g mol^{-1}, orthorombic, space group *P*212121, *a* = 3.86590 (10), *b* = 9.5511 (4), *c* = 26.7855 (12) Å, $\alpha = \beta = \gamma = 90.00$, *V* = 989.02 (7) Å^3, ρ = 1.540 g/cm^3, *F*(000) = 472. X-ray diffraction data were collected on a Nonius Kappa CCD diffractometer at the temperature 293 K using graphite-monochromated MoK_α radiation (λ = 0.71073 Å). Structure **2a** was solved by direct methods with SIR97 program[10] and refined by full-matrix least squares techniques with anisotropic nonhydrogen atoms. Hydrogen atoms were refined in the riding model. The refinement calculations were carried out with the help of SHELX97 program.[11] ORTEP[12] view of the molecule is shown in Figure 1. Crystallographic data for structure **2a** have been deposited at the Cambridge Crystallographic Data Centre (CCDC number 795865. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif).
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(13) **Typical Procedures for the Cycloisomerization of 2-Alkynyl-3-nitrothiophenes 1**
Method A
To a solution of the corresponding 2-arylethynyl-3-nitrothiophene **1** (0.3 mmol) in dry CH_2Cl_2 (5 mL) $AuCl_3$ (5 mol%) was added. The resulting reaction mixture was stirred for 15–60 min at r.t. After the evaporation of solvent, the crude was purified by column chromatography, eluting with benzene and hexane mixtures.
Method B
To a solution of the corresponding 2-arylethynyl-3-nitrothiophene **1** (0.3 mmol) in dry DCE (5 mL) silver trifluoroacetate (10 mol.%) was added. The resulting reaction mixture was refluxed for 1.5–2 h. After the evaporation of solvent, the crude was purified by column chromatography, eluting with benzene and hexane mixtures.
Phenylthieno[3,2-*c*]isoxazol-3-yl Methanone (2a)
Yield 97%; mp 114–115 °C. IR (KBr): ν_{max} = 1635 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 [1 H, d, *J* = 5.4 Hz, C(6)H], 7.57–7.63 (2 H, m, ArH), 7.68–7.73 (1 H, m, ArH), 7.70 [1 H, d, *J* = 5.4 Hz, C(5)H], 8.35–8.38 (2 H, m, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ = 112.0 [C(6)], 127.0 [C(3a)], 128.8 (ArC), 130.1 (ArC), 134.0 (ArC), 135.0 (ArC), 143.1 [C(5)], 158.2 [C(6a)], 170.5 [C(3)], 179.3 (C=O) ppm. Anal. Calcd for $C_{12}H_7NO_2S$: C, 62.87; H, 3.08; N, 6.11. Found: C, 62.90; H, 3.10; N, 6.08.
Thieno[3,2-*c*]isoxazole-3-carbaldehyde (2f)
Yield 87%; mp 66–67 °C. IR (KBr): ν_{max} = 1683 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 [1 H, d, *J* = 5.4 Hz, C(6)H], 7.68 [1 H, d, *J* = 5.4 Hz, C(5)H], 10.14 (1 H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ = 111.7 [C(6)], 123.4 [C(3a)], 142.4 [C(5)], 156.8 [C(6a)], 171.0 [C(3)], 177.3 (C=O) ppm. Anal. Calcd for $C_6H_3NO_2S$: C, 47.05; H, 1.97; N, 9.15. Found: C, 47.00; H, 2.01; N, 9.18.
1-Thieno[3,2-*c*]isoxazol-3-yl-1-pentanone (2g)
Yield 90%; mp 62–63 °C. IR (KBr): ν_{max} = 1681 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (3 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.44 (2 H, sext, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.76 (2 H, sext, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 3.04 (2 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 7.09 [1 H, d, *J* = 5.4 Hz, C(6)H], 7.63 [1 H, d, *J* = 5.4 Hz, C(5)H] ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ = 13.8 ($CH_2CH_2CH_2CH_3$), 22.3 ($CH_2CH_2CH_2CH_3$), 25.5 ($CH_2CH_2CH_2CH_3$), 39.3 ($CH_2CH_2CH_2CH_3$), 111.9 [C(6)], 123.4 [C(3a)], 142.7 [C(5)], 157.4 [C(6a)], 170.9 [C(3)], 188.6 (C=O) ppm. Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.45; H, 5.31; N, 6.88.
(14) Compounds **1a–h**, **2b–d**,**h**, **4a**,**b**, and **5a**,**b** were also fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopic and microanalytical data.