Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2020, **30**, 427–429

Mendeleev Communications

Synthesis of novel 8-nitro-substituted 1,3-benzothiazin-4-ones

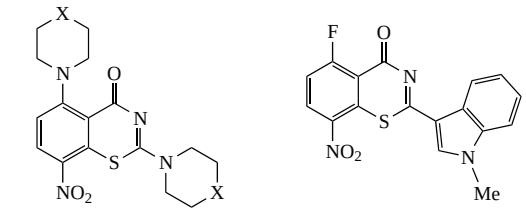
Emiliya V. Nosova,*[a,b] Olga A. Batanova,[a] Galina N. Lipunova[a,b] and Valery N. Charushin[a,b]

[a] *Institute of Chemical Engineering, Ural Federal University, 620002 Ekaterinburg, Russian Federation. E-mail: emily74@rambler.ru*

[b] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620990 Ekaterinburg, Russian Federation*

DOI: 10.1016/j.mencom.2020.07.007

New 2,5-bis(azacyclohex-1-yl)-8-nitro-1,3-benzothiazin-4-ones were synthesized from 2,6-difluorobenzoic acid in two preparative stages. The ethoxycarbonylpiperazino derivative surpasses in tuberculostatic activity (MIC 4 μg ml^{-1}) its 5-fluoro-8-H-counterpart. The first representative of 5-fluoro-8-nitro-1,3-benzothiazin-4-ones was obtained through the condensation of 2,6-difluoro-3-nitrobenzoyl isothiocyanate and *N*-methylindole.

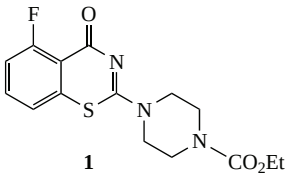


X = S, O, NCO_2Alk, NAc, NMe

Keywords: 1,3-benzothiazin-4-ones, nitro compounds, benzoyl isothiocyanates, heterocyclization, amino defluorination, organofluorine compounds, tuberculostatic activity.

2-Amino-1,3-benzothiazin-4-ones represent a modern class of antitubercular agents.[1–5] Benzothiazinone PBTZ169 bearing the trifluoromethyl group at C-6 and the nitro group at C-8 is the most promising in this respect,[6,7] and its introduction into medical practice is expected next year. The mechanism of action of new antitubercular agent involves the reduction of the nitro group into nitroso one, which then interacts with Cys387 of micobacretial decaprenylphosphoryl-β-D-ribose 2′-epimerase (DprE1) to form a stable semimercaptal.[8]

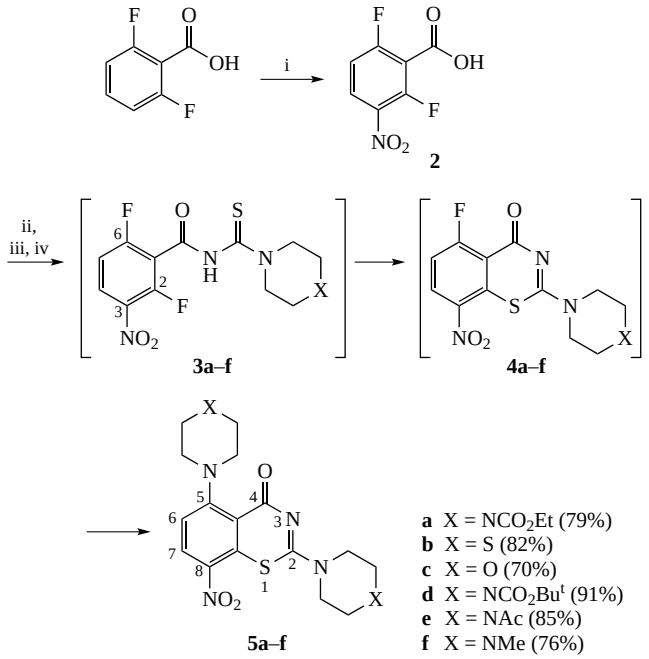
Recently, we reported the synthesis of novel fluorinated 2-amino-1,3-benzothiazin-4-ones through the addition of N-nucleophiles to *o*-fluorobenzoyl isothiocyanates and subsequent cyclization of fluorobenzoyl-thioureas.[9] 5-Fluoro-2-(4-ethoxycarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one **1** was chosen as leading compound. 2-Hetaryl-substituted 5-fluoro-1,3-benzothiazin-4-ones and 6,7,8-trifluoro-1,3-benzothiazin-4-ones have been prepared by reacting *o*-fluorobenzoyl isothiocyanates with *N*-methylindole or *N*-methylpyrrole as C-nucleophiles, followed by cyclization of the intermediates under heating in the presence of a base.[10]



1

Herein, we describe the synthesis of new 8-nitro-substituted 1,3-benzothiazin-4-ones bearing azacycloalkyl residues at positions 2 and 5 as well as provide the example of 2-substituted 5-fluoro-8-nitro-1,3-benzothiazin-4-one. We tried to incorporate nitro group into position 8 of 5-fluorobenzothiazinone **1**. However, the reaction of compound **1** with a nitration mixture at reduced or room temperature did not proceed, while the application of nitronium tetrafluoroborate led to a complex mixture.

In another approach to 2-(azacycloalkyl)-5-fluoro-8-nitro-1,3-benzothiazin-4-ones **4** (Scheme 1), *in situ* generated 2,6-difluoro-3-nitrobenzoyl isothiocyanate was reacted with secondary cyclic amines. The desired isothiocyanate was obtained from commercially accessible 2,6-difluorobenzoic acid whose nitration according to the described procedure[11] afforded 3-nitro-2,6-difluorobenzoic acid **2**. Its chloride was converted into 3-nitro-2,6-difluorobenzoyl isothiocyanate on quenching with ammonium thiocyanate. The crude isothiocyanate without isolation from the solution was treated with cyclic secondary amines (2 equiv.). Neither anticipated benzoylthioureas **3a–f** nor



Scheme 1 *Reagents and conditions*: i, HNO_3, H_2SO_4; ii, $SOCl_2$, PhMe, 90 °C; iii, NH_4NCS, MeCN, PhMe, room temperature; iv, cyclic amine, MeCN, room temperature.

5-fluoro-8-nitro-1,3-benzothiazin-4-ones **4a–f** were detected, while ultimate 2,5-bis(azacycloalk-1-yl)-1,3-benzothiazin-4-ones **5a–f** were formed in 70–91% yields (see Scheme 1).

Importantly, 2,6-difluoro-3-nitrobenzoyl intermediates **3** undergo intramolecular cyclization into **4** under milder conditions than their 2,6-difluoro- and 2,3,4,5-tetrafluoro counterparts. The presence of 8-positioned nitro group in benzothiazinone intermediate **4** facilitates the amino-defluorination process at C-5, so, at room temperature all stages up to the formation of 2,5-bis(cycloalkylamino) derivative **5** proceed readily. Using less than 2 equiv. of amine or reducing the duration of the process did provide pure 5-fluoro derivative **4**; unfortunately, those reaction mixtures were impossible to be resolved. When less amine was applied (1–1.5 equiv.), the fluorine signal for the minor product **4** at –98.4 to –102.8 ppm could be observed in the ^{19}F NMR spectra.

The structural evidence for benzothiazinones **5a–f** has been obtained from the ^{1}H and ^{13}C NMR and mass spectra. The ^{1}H NMR spectra of all compounds are characterized by two doublet signals of H-6 and H-7 at 7.16−7.21 and 8.27−8.32 ppm (*J* 8.1−9.8 Hz) as well as signals for two azacycloalkyl residues; no signals were observed in ^{19}F NMR spectra. In the ^{13}C NMR spectra, signals for C-8 at 167.9–168.8 ppm and singlets for C-4 at 159.6–160.5 ppm were detected. Notably that in the case of 6,7,8-trifluoro- and 5-fluorobenzothiazinones the signals for C(4) were located at 164–165 ppm.[9] In the mass spectra of compounds **5a–f**, the peaks of molecular ions with 1−23% intensity were observed.

In the case of participation of C^{6}F of benzamides **3** in intramolecular cyclisation instead of C^{2}F, isomeric 6-nitro analogues of products **5** could form (see Scheme 1). To provide the evidence for structure **5**, multibond heteronuclear ^{1}H-^{15}N correlation HMBC spectrum for representative **5a** was recorded [Figure 1(*a*)]. The observed two cross-peaks justify that both aromatic protons H-6 and H-7 correlate with nitrogen atoms, namely, one of them with nitro group and another with amine

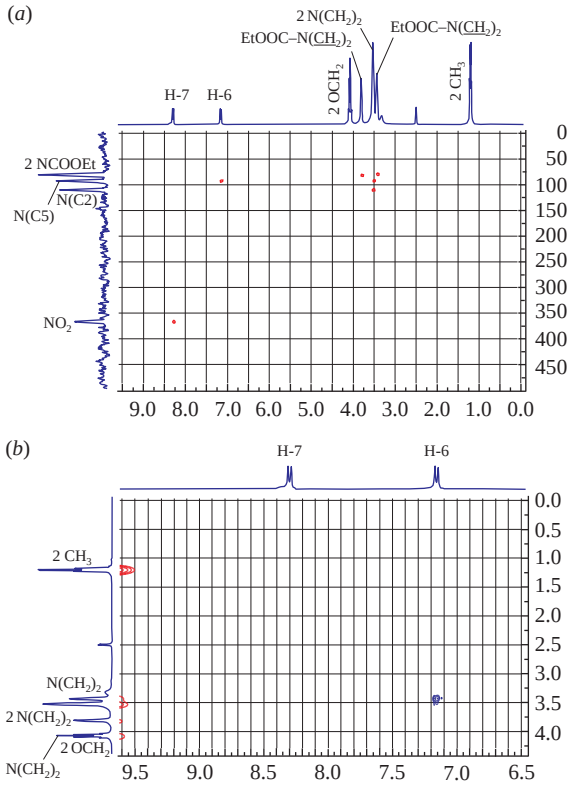
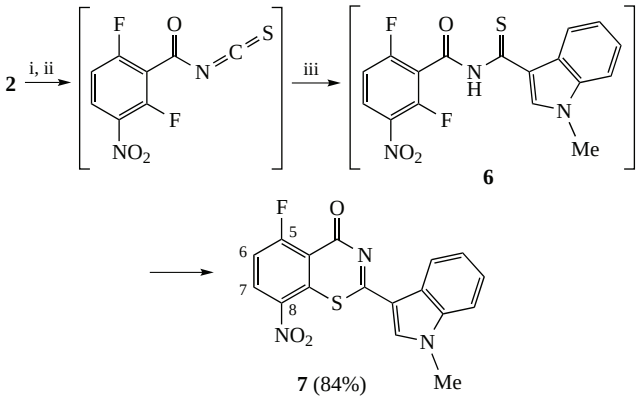


Figure 1 (*a*) HMBC ^{1}H-^{15}N and (*b*) NOESY spectra for 2,5-bis(4-ethoxycarbonylpiperazin-1-yl)-8-nitro-1,3-benzothiazin-4-one **5a**.



Scheme 2 *Reagents and conditions*: i, $SOCl_2$, PhMe, 90 °C; ii, NH_4NCS, MeCN, PhMe, room temperature; iii, 1-methylindole, MeCN, room temperature.

one. In case of the 6-nitro isomer, only one cross-peak would appear between C^{7}H and nitro group. Additional evidence was obtained from NOESY spectrum [Figure 1(*b*)] showing the cross peak between C^{6}H and piperazine CH_2 group, which indicates the formation of **5**; in the case of the isomer such a peak would be absent.

The addition of 1-methylindole (1.5 equiv.) as C-nucleophile at the N=C bond of 2,6-difluoro-3-nitrobenzoyl isothiocyanate occurred smoothly in acetonitrile at room temperature (Scheme 2). According to the ^{1}H and ^{19}F NMR spectra, the reaction affords 1,3-benzothiazin-4-one **7**, the primary product **6** was not isolated, and the 5-positioned fluorine atom was not replaced by the nucleophile. Worthy of note, the intramolecular cyclization of **6** into **7** proceeded under milder conditions than in the case of 2,6-difluoro and 2,3,4,5-tetrafluoro counterparts (the refluxing in MeCN or DMF in the presence of trimethylamine was reported as suitable cyclization conditions for those intermediates[10]).

The positions of fluoro and nitro substituents in product **7** were proved by ^{19}F NMR spectrum without the suppression of spin–spin F–H interaction which contained a double doublet signal with $^{3}J_{F–H}$ = 10.1 Hz and $^{4}J_{F–H}$ = 3.9 Hz, that justified the formation of 5-fluoro-8-nitro isomer. The molecular ion peak in the mass spectra of benzothiazinone **7** has a relative intensity of 16%. The ion IndCN^{+} (*m*/*z* 156) has 100% intensity, notably that the elimination of RCN represent the typical fragmentation way for 2-R-substituted 1,3-benzothiazin-4-ones.[9]

Benzothiazinone **5a** exhibited higher tuberculostatic activity towards *M. tuberculosis* $H_{37}R_v$ (MIC 4 μg ml^{-1}) than previously described[9] 5-fluoro derivative **7** (MIC 64 μg ml^{-1}). For this reason the provided way of fluorobenzothiazinone modification is useful for the development of new antitubercular agents.

To sum up, we have found short and convenient synthetic approach to 2,5-bis(azacycloalk-1-yl)-8-nitro-1,3-benzothiazin-4-ones **5a–f** and 5-fluoro-8-nitro-2-(1-methylindol-3-yl)-1,3-benzothiazin-4-one **7**. The proposed modification of fluorobenzothiazinones can be of great value for design of new antitubercular agents.

The work was carried out with financial support from the Ministry of Education and Science of the Russian Federation (State Contract no. 0836-2020-0058). The authors are thankful to V. Makarov (Federal Research Center ‘Fundamental Bases of Biotechnology’ of Russian Academy of Sciences, Moscow) for assistance with biological tests.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.07.007.

References

1 V. Kumar, S. Patel and R. Jain, *Med. Res. Rev*., 2018, **38**, 684.
2 E. V. Nosova, G. N. Lipunova, V. N. Charushin and O. N. Chupakhin, *Mini-Rev. Med. Chem*., 2019, **19**, 999.
3 S. Chetty, M. Ramesh, A. Singh-Pillay and M. E. S. Soliman, *Bioorg. Med. Chem. Lett*., 2017, **27**, 370.
4 S. D. Joshi, D. Kumar, S. R. Dixit, A. S. Joshi and T. M. Aminabhavi, *Mini-Rev. Org. Chem*., 2016, **13**, 262.
5 F. S. C. Branco, A. C. Pinto and N. Boechat, *Curr. Top. Med. Chem*., 2013, **13**, 2808.
6 V. Makarov, B. Lechartier, M. Zhang, J. Neres, A. M. van der Sar, S. A. Raadsen, R. C. Hartkoorn, O. B. Ryabova, A. Vocat, L. A. Decosterd, N. Widmer, T. Buclin, W. Bitter, K. Andries, F. Pojer, P. J. Dyson and S. T. Cole, *EMBO Mol. Med*., 2014, **6**, 372.
7 S. M. Batt, M. C. Izquierdo, J. C. Pichel, C. J. Stubbs, L. V.-G. Del Peral, E. Pérez-Herrán, N. Dhar, B. Mouzon, M. Rees, J. P. Hutchinson, R. J. Young, J. D. McKinney, D. B. Aguirre, L. Ballell, G. S. Besra and A. Argyrou, *ACS Infect. Dis*., 2015, **1**, 615.
8 C. Trefzer, M. Rengifo-Gonzalez, M. J. Hinner, P. Schneider, V. Makarov, S. T. Cole and K. Johnsson, *J. Am. Chem. Soc*., 2010, **132**, 13663.
9 E. V. Nosova, O. A. Batanova, G. N. Lipunova, S. K. Kotovskaya, P. A. Slepukhin, M. A. Kravchenko and V. N. Charushin, *J. Fluorine Chem*., 2019, **220**, 69.
10 E. V. Nosova, A. D. Poteeva, G. N. Lipunova, P. A. Slepukhin and V. N. Charushin, *Russ. J. Org. Chem*., 2019, **55**, 384 (*Zh. Org. Khim*., 2019, **55**, 446).
11 Y. Yoshida, D. Barrett, H. Azami, C. Morinaga, S. Matsumoto, Y. Matsumoto and H. Takasugi, *Bioorg. Med. Chem*., 1999, **7**, 2647.

Received: 2nd March 2020; Com. 20/6149