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Anna G. Lyapunova, Dmitry A. Androsov, Mikhail L. Petrov

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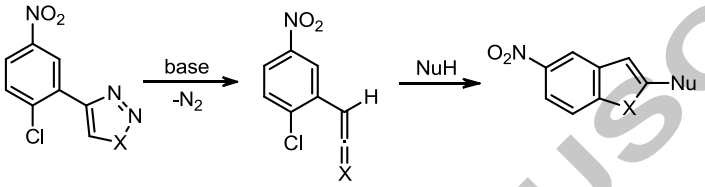

X = S: benzo[*b*]thiophenes; X = Se: benzo[*b*]selenophenes; NuH = ROH, R^1R^2NH

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Anna G. Lyapunova, Dmitry A. Androsov*, Mikhail L. Petrov

Department of Organic Chemistry, Saint-Petersburg State Institute of Technology, Moskovskii prospekt 26, Saint-Petersburg 190013, Russia

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ABSTRACT

An unusual base-promoted transformation of readily available 4-(2-chloro-5-nitrophenyl)-1,2,3-thia- and selenadiazoles affords a convenient approach toward benzo[*b*]thiophenes and benzo[*b*]selenophenes.

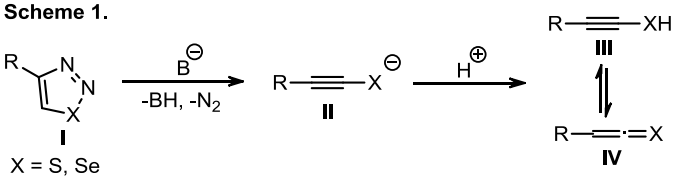
Benzo[*b*]thiophene and related derivatives represent an important class of fused thiophene compounds in the field of bioactive and optoelectronic materials. In particular, polythiophene fused aromatic compounds are attracting current interest as promising electronic materials for organic conductors, organic light-emitting diodes, photovoltaic cells, and field-effect transistors.[1]

The synthesis and characterization of benzo[*b*]selenophenes are of current interest owing to their potential applications as organic semiconductors for various optoelectronic devices.[2] Benzo[*b*]selenophenes have received little attention as potential drugs, although their potent biological activity and synthetic utility have been discussed in the literature.[3]

One of the most versatile and efficient routes to benzo[*b*]thiophenes and benzo[*b*]selenophenes involves metal-catalyzed cyclization reactions of *ortho*-ethynylthiophenols[4] and *ortho*-ethynylselenophenols.[2b,5] These precursors are typically obtained by nucleophilic displacement of halogen atom at the *ortho* position relative to the ethynyl group by the corresponding chalcogenide.[2b]

5-Unsubstituted 1,2,3-thiadiazoles and 1,2,3-selenadiazoles (**I**) are usually easily cleaved with liberation of nitrogen to form alkynethiolates and alkyneselenolates[6] (**II**) under the action of strong bases, such as organolithium reagents or potassium ethoxide. The acetylenic thiolates and selenolates have been widely used in organic chemistry for the synthesis of acetylenic sulfides and selenides, in cycloaddition reactions leading to new heterocycles or, after protonation, as a source of highly reactive ethynylchalcogenols (**III**) and tautomeric chalcogenoketenes[7] (**IV**) (Scheme 1).

Scheme 1.

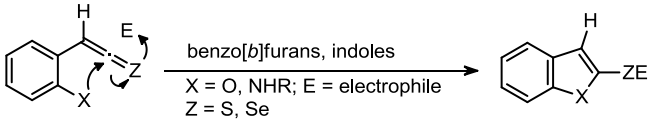


Our previous research and that of W. Dehaen[8] has shown the 5-*exo-dig* cyclization reaction of the *in situ* generated *ortho*-hydroxy- and -aminochalcogenoketenes to be a facile and efficient approach toward benzo[*b*]furans and indoles. These results prompted us to examine the possible synthesis of benzo[*b*]chalcogenophenes by 5-*exo-trig* cyclization reaction of the *in situ* generated *ortho*-halo chalcogenoketenes with nucleophiles (Nu = RO^-, R_2NH, Scheme 2).

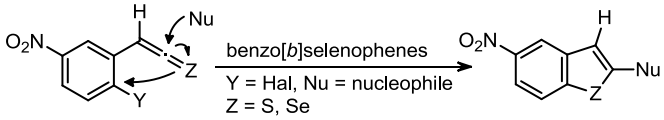
* Corresponding authors. Tel.: +7-812-494-9354; fax: +7-812-494-9354; e-mail: da_androsov@hotmail.com

Scheme 2. Possible cyclization pathways for *ortho*-substituted arylchalcogenoketenes

5-*exo*-*dig* ring closure (previous work)

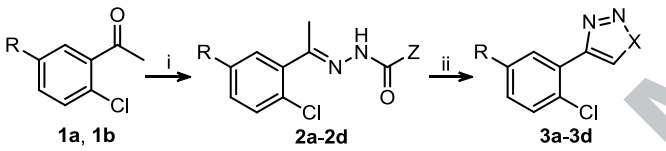


5-*exo*-*trig* ring closure (this work)



The Hurd-Mori reaction gives 4-substituted 1,2,3-thiadiazoles from methyl ketones under the action of thionyl chloride on their ethylcarbazones or tosylhydrazones.[6a,9] This procedure was used for the synthesis of 4-(2-chloroaryl)-1,2,3-thiadiazoles **3a** and **3b** from 2-chloroacetophenones **1a** and **1b** by treatment of their ethoxycarbonylhydrazones **2a** and **2b** with thionyl chloride. The reaction of 2-chloroacetophenones **1a** and **1b** with semicarbazide hydrochloride gave semicarbazones **2c** and **2d**, which were converted into 4-(2-chloroaryl)-1,2,3-selenadiazoles **3c** and **3d** under the action of selenium dioxide in acetic acid (Scheme 3).

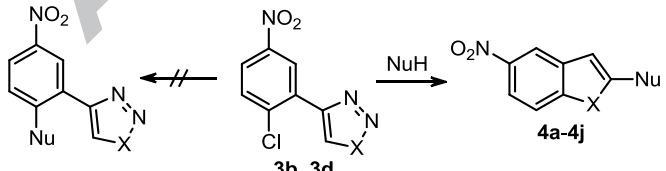
Scheme 3.



2a, **2b**: Z = OEt; **2c**, **2d**: Z = NH_2
3a: X = S, R = H (83%); **3b**: X = S, R = NO_2 (95%)
3c: X = Se, R = H (65%); **3d**: X = Se, R = NO_2 (63%)
Conditions:
X = S: (i) $NH_2NHC(O)OEt$, *i*-PrOH, 3 h, 80 °C; (ii) $SOCl_2$, 2 h, 80 °C
X = Se: (i) $NH_2NHC(O)NH_2$·HCl, *i*-PrOH, 3 h, 80 °C; (ii) SeO_2, AcOH, 3 h, 65 °C

We next attempted the base-promoted (K_2CO_3, KOH) alkylamination of chalcogenadiazoles **3** with a variety of primary and secondary amines at room temperature in DMF or aliphatic amine. The products of the reaction were unexpected 2-aminobenzo[*b*]chalcogenophenes **4a**-**4i** (Scheme 4, Table 1). It was found, that the reaction was tolerant to the nature of the solvent and MeCN, Me_2CO or MeOH could be used as the reaction medium. The use of DMF allowed the reaction to proceed at room temperature (20-25 °C).

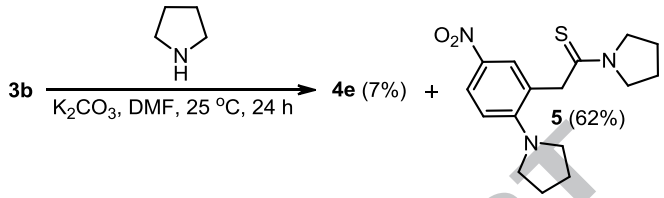
Scheme 4.



conditions:
4a-4e: K_2CO_3, DMF, 25 °C, 24 h; **4f-4i**: KOH, excess Nu, 25 °C, 24 h
4j: MeONa, MeOH, reflux, 24 h

Compound **4e** was obtained in a low yield (7%) due to the relatively high nucleophilicity of pyrrolidine which displaces the chlorine atom on the benzene ring faster than cyclization into **4e** occurs, affording thioamide **5** (62%) as major product (Scheme 5). Similar decomposition of the more labile selenadiazole ring of compound **3d** under the action of pyrrolidine occurs faster compared to that of the thiadiazole ring of **3b**, providing a higher yield (79%) of the cyclization product **4g**.

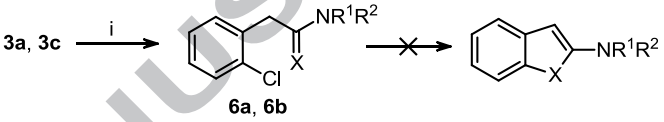
Scheme 5.



A similar reaction of thiadiazole **3b** with MeONa in MeOH under an inert atmosphere led to 2-methoxy-5-nitrobenzo[*b*]thiophene (**4j**) (23%, Scheme 4, Table 1).

Treatment of compounds **3a** and **3c**, having no nitro group on the phenyl ring, with amines in the presence of a base afforded amides **6a** and **6b**. Formation of cyclic products was not observed even at a temperature of 130 °C (Scheme 6).

Scheme 6.



6a: X = S, R^1 = H, R^2 = *n*-Bu (97%); **6b**: X = Se, R^1 = R^2 = Me (79%)
Conditions:
6a: *n*-$BuNH_2$, K_2CO_3, DMF, 24 h, 130 °C; **6b**: Et_2NH, KOH, 1 h, 55 °C

Table 1. Synthesis of benzo[*b*]chalcogenophenes

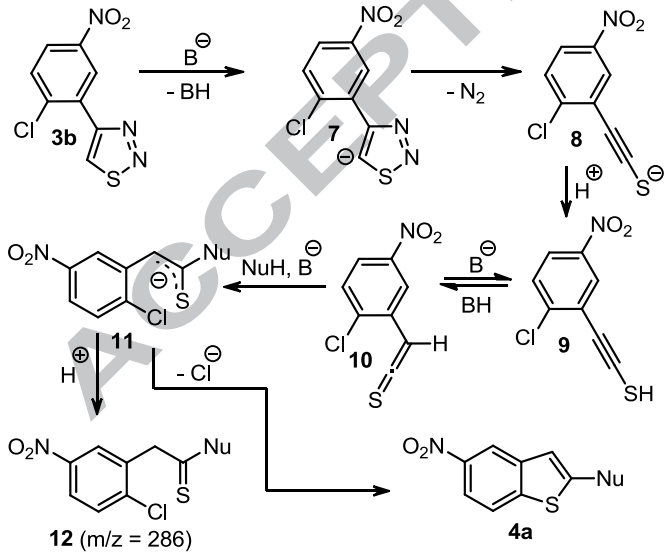
Entry	RH	Product	Yield (%)
1	H_2N	**4a**	92
2		**4b**	23
3	Me_2NH[a]	**4c**	75
4	HN N—	**4d**	74
5	HN	**4e**	7
6	HN	**4f**	54
7	HN	**4g**	79
8	HN	**4h**	47
9	HN O	**4i**	71
10	—OH	**4j**	23

[a] Me_2NH was obtained from K_2CO_3, NH_4OAc and DMF.

The progress of the reaction was followed by ^{1}H NMR monitoring of a reaction mixture containing compound **3b**, *n*-butylamine, and K_2CO_3 in DMF at 25 °C (Scheme 7, Figures 1 and 2).

Initially, the thiadiazole ring-opening was indicated by the disappearance of the thiadiazole hydrogen atom H5Het at δ_H 9.19 ppm (the formation of an 1,2,3-thiadiazol-5-yl intermediate anion **7** was not observed in our experiment, but is supported by data reported in literature. For example, the 4-phenyl-1,2,3-thiadiazol-5-yl anion was generated on treatment of 4-phenyl-1,2,3-thiadiazole with methyllithium in THF at –78 °C. Subsequent quenching of the reaction mixture with 38% deuterium chloride in deuterium oxide resulted in 5-deutero-4-phenyl-1,2,3-thiadiazole.[6h] Similarly, the 4-phenyl-1,2,3-thiadiazol-5-yl anion was generated on treatment with lithium diisopropylamide in THF at –78 °C. This anion was successfully trapped as 5-trimethylsilyl-4-phenyl-1,2,3-thiadiazole (55%) on addition of chlorotrimethylsilane.[6h] In addition, it was shown that the H5Het atom of 4-(2-hydroxyphenyl)-1,2,3-thiadiazole was partially deuterated when treated with tetrabutylammonium hydroxide in CD_3CN at room temperature, proving the intermediacy of the 1,2,3-thiadiazol-5-yl anion[8a]). Decomposition of the thiadiazole ring was accompanied by nitrogen evolution and formation of enthiolate **11**, which can be trapped as thioamide **12** on addition of acid [signals at δ_H (ppm) 7.44 (NH) 7.57 (H3Ph), 8.11 (H4Ph) and 8.32 (H6Ph), Figure 1 (b)]. The progress of the reaction was also followed by GC-MS. The observation of an intermediate with *m/z* = 286 (compound **12**) supported the formation of **11**. After 22 hours the transformation was complete and the NMR spectrum showed a clean absorption pattern for *N*-butyl-5-nitrobenzo[*b*]thiophen-2-amine (**4a**) [δ_H (ppm): 0.97 ($CH_3CH_2CH_2CH_2$-NH), 1.46 ($CH_3CH_2CH_2CH_2$-NH), 1.67 ($CH_3CH_2CH_2CH_2$-NH), 3.24 ($CH_3CH_2CH_2CH_2$-NH), 4.28 ($CH_3CH_2CH_2CH_2$-NH), 6.12 (H3Het), 7.59 (H7Ph), 7.87 (H6Ph), 8.21 (H4Ph)]. There were no detectable impurities present.

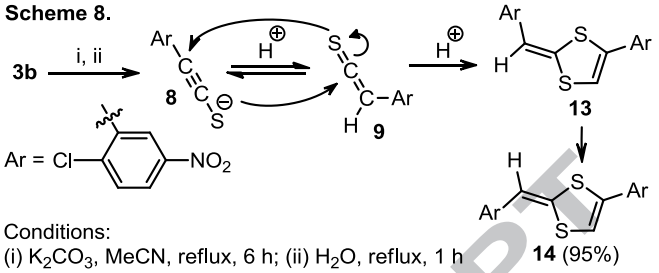
Scheme 7.



NuH = *n*-$BuNH_2$, base = K_2CO_3, solvent DMF, 25 °C

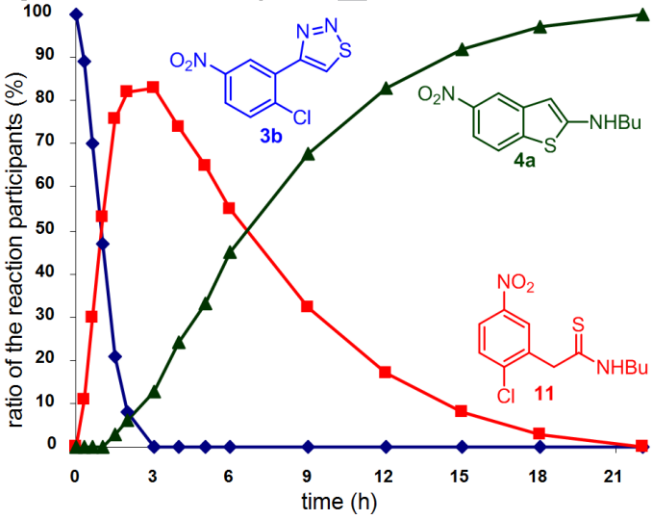
An experiment with addition of weakly nucleophilic proton donors, such as water, supported the formation of presumed intermediates **8**-**10**.[6b,c,h] Thus, the potassium carbonate promoted decomposition of thiadiazole **3b** in boiling acetonitrile gave alkynylthiolate **8**. Addition of water resulted in immediate protonation and dimerization of intermediates **8** and **10** into *cis*-dithiafulvene **13**, which further rearranged into the more stable *trans*-dithiafulvene **14**, after heating in boiling water (Scheme 8).

Scheme 8.

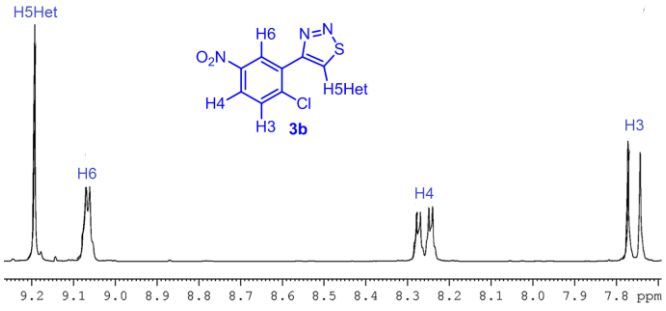


Conditions:
(i) K_2CO_3, MeCN, reflux, 6 h; (ii) H_2O, reflux, 1 h

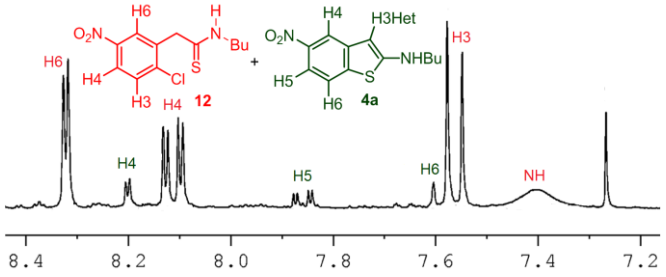
Figure 1. Transformation of thiadiazole **3b** into benzothiophene **4a** (DMF, 25 °C) as monitored by ^{1}H-NMR spectroscopy. ^{1}H NMR spectra of the aromatic region after selected reaction intervals.



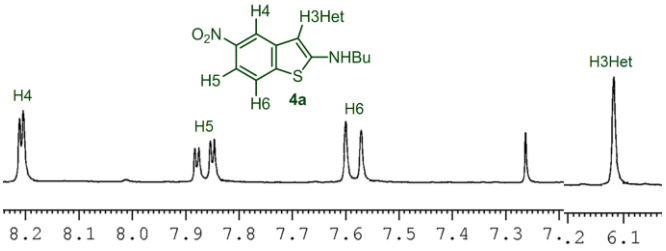
(a) beginning of the reaction (0 hours elapsed)



(b) progress of the reaction (3 hours elapsed)



(c) end of the reaction (22 hours elapsed)



In conclusion, we have reported a simple and convenient synthetic approach toward benzo[*b*]chalcogenophenes from readily accessible 4-(2-chloroaryl)-1,2,3-chalcogenadiazoles.

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