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Regiospecific substitution of the 4-nitro group in 3-amino-4,6-dinitrobenzo[*b*]thiophene-2-carboxylates: unexpected activating effect of the amino group

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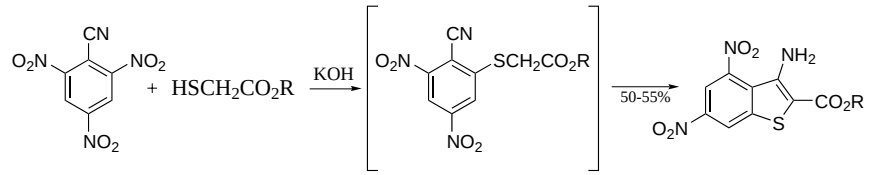
Abstract—The cyclocondensation of 2,4,6-trinitrobenzonitrile with the esters of thioglycolic acid results in the formation of 3-amino-4,6-dinitrobenzo[*b*]thiophene-2-carboxylates **3**. The interaction of **3** with anionic nucleophiles RO^- ($R=CF_3CH_2$, $CH{\equiv}CCH_2$), RS^- ($R=Ph$, $PhCH_2$, $(CH_3)_2CHCH_2$), N_3^- in NMP or DMF leads to the substitution of only the 4-NO_2 group. The replacement of the electron-donating NH_2 group in **3** with hydrogen unexpectedly and significantly hampers nucleophilic substitution of the nitro group. It is assumed that increased reactivity of the 4-NO_2 in **3** is connected with the twist of this group with respect to the plane of the aromatic ring under the influence of the NH_2 group as indicated by semi-empirical quantum chemical calculations.

The interaction of 2,4,6-trinitrobenzonitrile (TNBN)[1] with the esters of thioglycolic acid **1** in the presence of KOH in CH_3CN/H_2O (4:1) at 25°C leads to the formation of *ortho*-nitro group substitution products—sulphides **2**—which undergo cyclisation in situ with the formation of the corresponding 3-amino-4,6-dinitrobenzo[*b*]thiophene-2-carboxylic acid **3**[2] (Scheme 1).[3]

We have found, that dinitrobenzothiophenes **3** possess an interesting feature in that they react with anionic O-, S- and N-nucleophiles (Nu^-): RO^- ($R=CF_3CH_2$, $CH{\equiv}CCH_2$), RS^- ($R=Ph$, $PhCH_2$, $(CH_3)_2CHCH_2$), N_3^- in 1-methyl-2-pyrrolidone (NMP) or DMF in such a way that selective substitution of the 4-NO_2 group takes place, giving previously unknown 4-substituted esters of 3-amino-6-nitrobenzo[*b*]thiophenecarboxylic acid **4**–**9**[4] (Scheme 2).

Nucleophiles RO^- and RS^- were generated in situ, using the mixture of ROH or RSH with powdered K_2CO_3 (molar ratio of dinitrobenzothiophene **3**/ROH (RSH)/K_2CO_3 = 1:1:2). For azidation, an equimolar amount of NaN_3 has been used. Reactions were maintained at 25°C in the case of RSH and NaN_3, and at 80–90°C for ROH until full conversion of the starting material was achieved. The yields of isolated nitrobenzothiophenes **4** were 80–90%. According to ^1H NMR data, the 6-NO_2 group does not undergo substitution, making this reaction regiospecific.



TNBN **1** **2** **3**

R = Me (**3a**), Et (**3b**)

Scheme 1.

Keywords: benzo[*b*]thiophenes; nitro group; aromatic nucleophilic substitution; regiospecificity; deamination.

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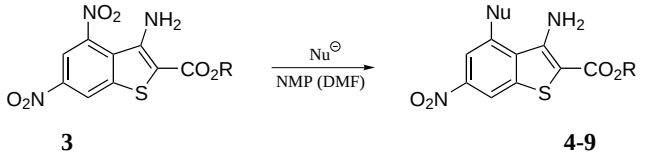


3 **4-9**

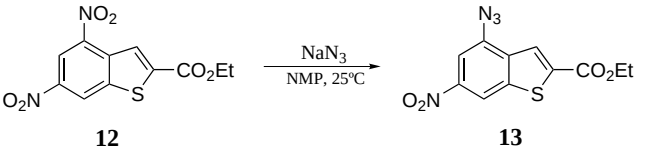
Scheme 2. R = Me (**a**), Nu = PhS (**4a**), $PhCH_2S$ (**5a**), $(CH_3)_2CHCH_2$ (**6a**); R = Et (**b**), Nu = PhS (**4b**), $PhCH_2S$ (**5b**), $(CH_3)_2CHCH_2S$ (**6b**), CF_3CH_2O (**7b**), $CH{\equiv}CCH_2O$ (**8b**), N_3 (**9b**).

We have also found that the reduction of a nitro group in **3** is regioselective as well: under the action of hydrazine hydrate in the presence of $FeCl_3$, only the 4-NO_2 group in **3b** can be reduced thus giving 3,4-diamino-6-nitrobenzo[*b*]thiophene-2-ethylcarboxylate **10**[5] and the 6-NO_2 group is left intact even when a reducing agent is used in excess (Scheme 3). The ease of nucleophilic substitution of the 4-NO_2 group in dinitrobenzothiophenes **3**, despite the π-excessive character of thiophene and *meta* positioned nitro groups is notable. In this respect, dinitrobenzothiophenes **3** considerably surpass, for example, 1,3-dinitrobenzene, which does not react with NaN_3 or CF_3CH_2OH+K_2CO_3 under the same conditions.

The reactivity of the nitro group in nucleophilic substitution reactions would be expected to increase on replacement of the electron-donating amino group in **3** with hydrogen.

With this in mind, we performed diazotization on **3b** using $NO^+BF_4^-$. Diazonium salt **11** was then treated with EtOH in the presence of Cu_2O to form 4,6-dinitrobenzo[*b*]thiophene-2-ethylcarboxylate **12**,[6] Scheme 3.

We have found that despite our expectations, replacement of the amino group in **3b** by hydrogen significantly hampers nucleophilic substitution of the nitro group. Thus, **12** does not react with CF_3CH_2OH+K_2CO_3 under the same conditions as **3b**. It was observed that the reaction of **12** with NaN_3 is much slower compared to **3b**. Full conversion of **3b** upon interaction of NaN_3 in NMP (25°C) takes 3 h whereas, under the same conditions, azidation of **12** requires 17 h giving ethyl 4-azido-6-nitrobenzo[*b*]thiophene carboxylate **13** (60%),[7] Scheme 4.



12 **13**

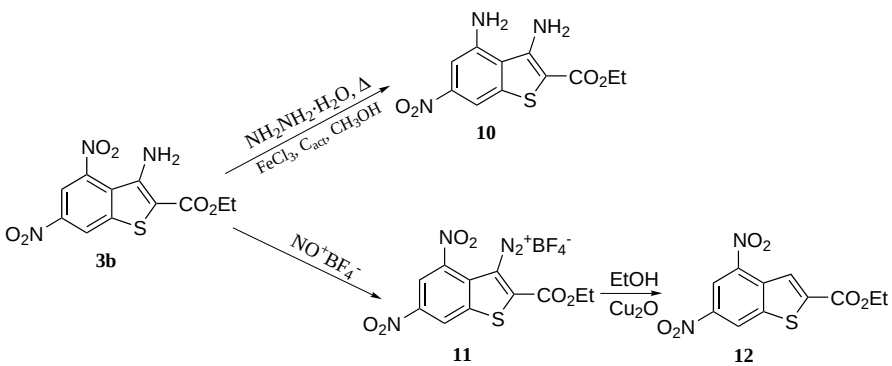
Scheme 4.

As is seen, in going from **3b** to **12** the selectivity for the nucleophilic substitution of 4-NO_2 is the same, but the reactivity considerably decreases.

Here, we observed an unexpected activating effect of the amino group during nucleophilic substitution, despite its +M and +I effects.[8]

It is safe to assume that in this case steric hindrance is the controlling factor. Recent reports have shown that[9] the twist in the plane of the nitro group, with respect to the aromatic ring under the influence of a neighbouring substituent speeds up the formation of a Meisenheimer *ipso*-complex and therefore facilitates the process of nucleophilic substitution of this nitro group. Most probably, the significant disruption of the coplanarity between the nitro group and the aromatic ring promotes alteration of the hybridisation of the *ipso*-carbon atom from sp^2 to sp^3 upon formation of the Meisenheimer *ipso*-complex, because the twist of the nitro group decreases its conjugation with the aromatic ring in the starting material. According to quantum-chemical calculations (AM1), owing to the steric influence of the NH_2, the 4-NO_2 group is turned by an angle of ~56° and the 6-NO_2 group lies within the plane of the aromatic ring. At the same time, in dinitrobenzothiophene **12**, the angle of rotation of the 4-NO_2 group is just 9°.

It is felt that the present calculations adequately reflect the tendency of dihedral angle alteration between NO_2 and the aromatic ring in **3b** and **12**. In support of this conjecture, it is important to note the comparison of calculated and X-ray[10] data for the twist of the NO_2 group caused by *peri*-interaction in 1,5-dinitronaphthalene (calculated angle 31°, found 48.7°) and 9-nitroanthracene (calculated angle 51°, found 85°). The structures of all the new products were established from microanalysis, mass-spectrometry and ^1H NMR spectra, which showed all the expected signals.



Scheme 3.

Acknowledgements

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3. Dinitrobenzothiophene **3b** described in Ref. 2. **3a**: mp 196–198°C (Pr^iOH); ^1H NMR (d_6-DMSO): δ 3.9 (s, 3H, CH_3), 6.6 (br s, 2H, NH_2), 8.7 (s, 1H, H-7) 9.4 (s, 1H, H-5).
4. **Substitution in 3. General procedure**
   Synthesis of 4a, 5a, 6a and 4b, 5b, 6b. A mixture of K_2CO_3 (0.56 g, 4 mmol), 2 mmol of NuH and **3a** (0.62 g, 2 mmol) or **3b** (0.59 g, 2 mmol) was stirred at 25°C in 15 mL of NMP (DMF). The resultant solution was poured into 30 mL of water, acidified with 25% HCl (pH 1), washed with water. The precipitated solid was collected by filtration and recrystallised.
   Synthesis of **7b** and **8b** was performed at 80–90°C
   Synthesis of 9b: A mixture of NaN_3 (0.13 g, 2 mmol), **3b** (0.62 g, 2 mmol) was stirred in 15 mL of NMP at 25°C. The resultant solution was poured into 30 mL of water and acidified with 25% HCl (pH 1). The precipitated solid was collected by filtration and washed with water and acetone.
   Compound **4a**: 95%, mp 235°C (Pr^iOH), ^1H NMR (d_6-DMSO): δ 3.82 (s, 3H, OMe), 7.22 (br s, 2H, NH_2), 7.42 (m, 5H, Ph), 7.89 (s, 1H, H-5), 8.92 (s, 1H, H-7).
   Compound **4b**: 84%, mp 157°C (Pr^iOH); ^1H NMR (d_6-DMSO): δ 1.28 (t, 3H, $J=3.0$ Hz, CH_3), 4.28 (q, 2H, $J=3.0$, OCH_2), 7.15 (br s, 2H, NH_2), 7.39 (m, 5H, Ph), 7.84 (s, 1H, H-5), 8.86 (s, 1H, H-7).
   Compound **5a**: 88%, mp 186°C (Pr^iOH); ^1H NMR (d_6-DMSO): δ 3.83 (s, 3H, OMe), 4.38 (s, 2H, CH_2), 7.21 (br s, 2H, NH_2), 7.27 (m, 5H, Ph), 7.94 (s, 1H, H-5), 8.75 (s, 1H, H-7).
   Compound **5b**: 98%, mp 156°C (Pr^iOH); ^1H NMR (d_6-DMSO): δ 1.32 (t, 3H, $J=2.5$ Hz, CH_3), 4.29 (q, 2H, $J=2.5$ Hz, OCH_2), 4.38 (s, 2H, CH_2), 7.18 (br s, 2H, NH_2), 7.23 (m, 5H, Ph), 7.91 (s, 1H, H-5), 8.70 (s, 1H, H-7).
   Compound **6a**: 90%, mp 127°C (Pr^iOH); ^1H NMR (d_6-DMSO): δ 1.02 (d, 6H, $J=2.0$ Hz, Me_2), 1.86 (m, 1H, CH), 3.05 (d, 2H, J = 2.0 Hz, CH_2), 3.82 (s, 3H, OMe), 7.26 (br s, 2H, NH_2), 8.00 (s, 1H, H-5), 8.75 (s, 1H, H-7).
   Compound **6b**: 81%, mp 117°C (Pr^iOH); ^1H NMR (d_6-DMSO): δ 1.02 (d, 6H, $J=2.5$ Hz Me_2), 1.31 (t, 3H, $J=2.5$ Hz, CH_3), 1.87 (m, 1H, CH), 3.05 (d, 2H, $J=3.0$ Hz, CH_2), 4.29 (q, 2H, $J=2.0$ Hz, OCH_2), 7.24 (s, 2H, NH_2), 7.99 (s, 1H, H-5), 9.60 (s, 1H, H-7).
   Compound **7b**: 86%, mp 195°C (Pr^iOH); ^1H NMR (d_6-DMSO): δ 1.32 (t, 3H, $J=3.0$ Hz, CH_3), 4.35 (q, 2H, $J=2.0$ Hz, OCH_2), 5.21 (q, 2H, $J=2.0$ OCH_2), 6.78 (s, 2H, NH_2), 7.83 (s, 1H, H-5), 8.53 (s, 1H, H-7).
   Compound **8b**: 78%, mp 150°C (Pr^iOH); ^1H NMR (d_6-DMSO): δ 1.29 (t, 3H, $J=3.0$ Hz, CH_3), 3.78 (s, 1H, CH), 4.28 (q, 2H, $J=2.0$ Hz, OCH_2), 5.19 (s, 2H, OCH_2), 6.98 (br s, 2H, NH_2), 7.69 (s, 1H, H-5), 8.50 (s, 1H, H-7).
   Compound **9b**: 90%, mp 180°C, ^1H NMR (d_6-DMSO): δ 1.30 (t, 3H, $J=2.5$ Hz, CH_3), 4.28 (q, 2H, $J=3.0$ Hz OCH_2), 7.02 (s, 2H, NH_2), 7.84 (s, 1H, H-5), 8.63 (s, 1H, H-7).
5. **Synthesis of 10**: A mixture of **3b** (0.95 g, 3 mmol), 10 mmol of $N_2H_4 \cdot H_2O$, $FeCl_3 \cdot 6H_2O$ and C_{act} was refluxed for 4 h in 18 mL of MeOH. Precipitated solid was collected by filtration washed with acetone and the combined filtrates were evaporated. 62%, mp 228°C, ^1H NMR (d_6-DMSO): δ 1.30 (t, 3H, $J=3.0$ Hz CH_3), 4.27 (q, 2H, $J=3.0$, OCH_2), 6.18 (s, 2H, NH_2), 6.82 (s, 2H, NH_2), 7.37 (s, 1H, H-5), 7.84 (s, 1H, H-7).
6. **Synthesis of 12**: A mixture of **3b** (0.3 g, 1 mmol) and 1.5 mmol of $NOBF_4$ was stirred for 2 h at 25°C in 10 mL of $CHCl_3$. The precipitated salt was collected by filtration and washed with $CHCl_3$. The solid obtained was dissolved in 3 mL of EtOH, Cu_2O was added in one portion (0.15 g, 1 mmol) and the mixture was left to stand at 20°C for 20 h. Precipitated solid was collected by filtration and recrystallised. 55%, mp 145°C (EtOH), ^1H NMR (d_6-DMSO): δ 1.38 (t, 3H, $J=2.5$ Hz, CH_3), 4.41 (q, 2H, $J=2.5$ Hz, OCH_2), 8.47 (s, 1H, H-3), 8.87 (s, 1H, H-7), 9.54 (s, 1H, H-5).
7. **Synthesis of 13**: A mixture of **12** (0.5 g, 1.7 mmol) and NaN_3 (0.11 g, 1.7 mmol) was stirred at 25°C in 15 mL of NMP until full conversion of the starting material. The solution was poured into 30 mL of water, acidified with 25% HCl (pH 1) and the precipitated solid washed with water and recrystallised. 60%, mp 115° (EtOH), ^1H NMR (d_6-DMSO): δ 1.35 (t, 3H, $J=3.0$ Hz, CH_3), 4.39 (q, 2H, $J=2.0$ Hz, OCH_2), 7.93 (s, 1H, H-3), 7.97 (s, 1H, H-5), 8.91 (s, 1H, H-7).
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