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Regioselectivity of nucleophilic substitution of the nitro group in 2,4,6-trinitrobenzamide

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Abstract

Under the action of anionic nucleophiles RO^- (R = Ph, $HCF_2CF_2CH_2$), $R'S^-$ (R′ = Ph, $PhCH_2$, $C_2H_5OC(O)CH_2$), N_3^- on 2,4,6-trinitrobenzamide in MeCN or DMF, the *ortho*-nitro group is substituted with high selectivity. Intramolecular cyclisation involving *ortho*-positioned fragments SX and $-CONH_2$ (X=$C_2H_5OC(O)CH_2$, Cl) has been achieved with the formation of 2-ethoxycarbonyl-3-hydroxy-4,6-dinitrobenzo[*b*]thiophene and 4,6-dinitro-2*H*-benzo[*b*]isothiazol-3-one correspondingly. © 2000 Elsevier Science Ltd. All rights reserved.

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The details of nucleophilic substitution of the nitro group in aromatic di- and polynitro-compounds, though being of great importance, are little known, especially for compounds with *meta* arranged nitro groups.[1]

Upon investigation of the chemistry of 2,4,6-trinitrobenzoic acid derivatives we have found some interesting properties in the behaviour of 2,4,6-trinitrobenzamide (TNBA) in the reactions of nucleophilic substitution. Upon reaction of TNBA with a range of anionic *O*-, *S*- and *N*-nucleophiles (Nu^-): RO^- (R = Ph, $HCF_2CF_2CH_2$), $R'S^-$ (R′ = Ph, $PhCH_2$, $C_2H_5OC(O)CH_2$) in MeCN (at 80–82°C) or DMF (in the case of $HCF_2CF_2CH_2O^-$ at 75°C and N_3^- at 20°C) selective *ortho*-nitro group substitution, with the formation of the corresponding 2-Nu-4,6-dinitro-benzamides (**1**), takes place in high yields (Scheme 1).

Nucleophiles RO^- and RS^- were generated in situ using a mixture of ROH or RSH with solid K_2CO_3 (molar ratio TNB/ROH(RSH)/K_2CO_3 was 1:1:1). For azidation NaN_3 (equimolar amount) was employed and the reaction was continued until the full conversion of TNBA was observed (6–10 h). According to the ^1H NMR data, under such conditions, *para*-isomers are either not formed at all (in the case of PhOH, PhSH, $C_2H_5OC(O)CH_2SH$) or appeared in trace

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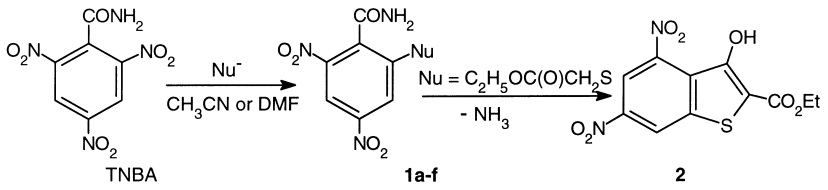


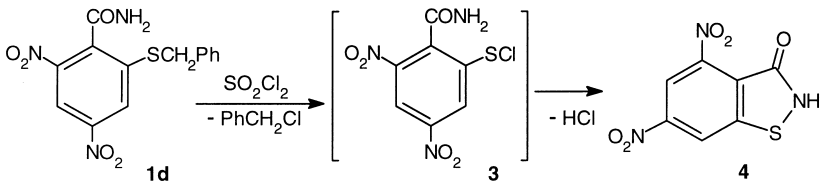
Scheme 1. **a**: $Nu^- = PhO^-$; **b**: $HCF_2CF_2CH_2O^-$; **c**: PhS^-; **d**: $PhCH_2S^-$; **e**: $C_2H_5OC(O)CH_2S^-$; **f**: N_3^-

quantities; no more than 2% (in the case of $HCF_2CF_2CH_2OH$, $PhCH_2SH$). Only in the case of NaN_3 is the *para*-isomer formed in amounts of 5–7%.[2]

In the case of $C_2H_5OC(O)CH_2SH$, when the process is carried out in refluxing MeCN, the product of *ortho*-substitution **1e** cyclises to form 2-ethoxycarbonyl-3-hydroxy-4,6-dinitrobenzo[*b*]thiophene 2[2a] (Scheme 1). At the same time, **1e** can be obtained if the reaction is conducted in 1-methyl-2-pyrrolidinone (NMP) at 20°C.

We have found that the polarity increase of an aprotic solvent leads to an increase in an amount of the *para*-isomer: in NMP, *ortho*/*para* ratio for PhOH was 4:1, for PhSH and $PhCH_2SH$ = 5:1 and for $C_2H_5OC(O)CH_2SH$ = 6:1. However, even in these cases, the *ortho*-isomers can be easily separated from *para*-isomers by means of crystallisation from an appropriate solvent. After this, the yield of isolated *ortho*-isomers is 55–80%.

Thus obtained, are previously unknown, *ortho*-substituted benzamides **1** which are of interest in the synthesis of benzannelated heterocycles with a novel combination of functional substituents. The formation of benzothiophene **2** can serve as an example of this. Besides, we have found, that upon treatment of sulfide **1d** with SO_2Cl_2, the product **3** spontaneously cyclises to form 4,6-dinitro-2*H*-benzo[*d*]isothiazol-3-one (**4**)[3] (Scheme 2).



Scheme 2.

The structure of the compounds obtained was proven by ^1H and ^{13}C NMR spectroscopy, mass-spectrometry, IR spectroscopy and elemental analysis.

Some preliminary considerations concerning the reasons for high selectivity of *ortho*-substitution in TNBA. In some earlier works[4,5] it was reported, that the turn of the nitro group's plane with respect to the plane of aromatic ring under the influence of a neighbouring group, favours the substitution of this nitro group. This aids the transition from sp^2 to sp^3 hybridization of the carbon atom at the formation of the *ipso*-σ-complex of the nitro compound with a nucleophile (cf. see Ref. 4). In accordance with quantum-chemical calculations (AM1, Chem3D Pro, version 5.0), the 2-NO_2 group in TNBA is turned relative to the plane of aromatic ring by 68°, the 6-NO_2- by 30° and the 4-NO_2 is in the plane of the aromatic ring, which probably governs the high regioselectivity of *ortho*-substitution. The plane of the $CONH_2$ fragment is turned by 62° which decreases the steric hindrance of a nucleophile approach.

It must be noted that quantum-chemical calculations using this method quite adequately reflects the known experimental data on the geometry of aromatic di- and polynitrocompounds (to be published later).

Acknowledgements

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2. General procedure for nucleophilic substitution. (a) Synthesis of **1a**, **1c**, **1d** and **2**. A mixture of K_2CO_3 (0.28 g, 2 mmol), 2 mmol of corresponding NuH and TNBA (0.51 g, 2 mmol) was refluxed in 20 mL of MeCN. After the completion of the reaction the solvent was evaporated in vacuo and 20 mL of water was added to the residue. The precipitate was filtered off, washed with 5% HCl, water and recrystallised. (b) Synthesis of **1b**, **1e** and **1f**. The reaction was carried out under the same conditions in 5 mL of DMF (NMP for **1e**). After the completion of the reaction, the mixture was poured into water (70 mL), acidified with HCl (pH = 5–6), precipitate filtered off and recrystallised. Compound **1a**: Mp 173°C (EtOH:H_2O); ^{1}H NMR (d_6-DMSO) δ 7.19–7.22 (m, 2H), 7.29–7.35 (m, 1H), 7.46–7.54 (m, 2H), 7.81 (s, 1H), 7.79 (s, 1H), 8.26 (s, 1H), 8.55 (s, 1H). Compound **1b**: Mp 148°C (MeCN); ^{1}H NMR (d_6-DMSO) δ 4.97 (t, 2H, J = 13.65 Hz), 6.50 (t.t, 1H, J = 3.37, 51.86 Hz), 7.96 (s, 1H), 8.14 (s, 1H), 8.43 (d, 1H, J = 1.44 Hz), 8.51 (d, 1H, J = 1.55 Hz). Compound **1c**: Mp 248°C ($CHCl_3$); ^{1}H NMR (d_6-DMSO) δ 7.51–7.65 (m, 5H), 7.68 (s, 1H), 8.09 (s, 1H), 8.32 (s, 1H), 8.58 (s, 1H). Compound **1d**: Mp 170°C (EtOH:H_2O); ^{1}H NMR (d_6-DMSO) δ 4.99 (s, 2H), 7.27–7.96 (m, 5H), 7.97 (s, 1H), 8.15 (s, 1H), 8.41 (s, 1H), 8.55 (s, 1H). Compound **1e**: Mp 162°C (H_2O); ^{1}H NMR (d_6-DMSO) δ 1.41 (t, 3H, J = 5.85 Hz), 4.21–4.40 (m, 4H), 8.04 (s, 1H), 8.41 (s, 1H), 8.59 (s, 1H), 8.69 (s, 1H). Compound **1f**: Mp 200°C (H_2O); ^{1}H NMR (d_6-DMSO) δ 7.97 (s, 1H), 8.11 (s, 1H), 8.48 (d, 1H, J = 1.45 Hz), 8.55 (d, 1H, J = 1.56 Hz). Compound **2**: Mp 164°C (EtOH:H_2O); ^{1}H NMR (d_6-DMSO) δ 1.35 (t, 3H, J = 4.40 Hz), 4.36 (q, 2H, J = 4.40 Hz), 8.70 (s, 1H); 9.31 (s, 1H).
3. Compound **4**: Mp 311°C (EtOH:H_2O); ^{1}H NMR (d_6-DMSO) δ 8.66 (s, 1H), 9.34 (s, 1H).
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