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Synthesis of 5,7-dinitroquinolines from 2,4,6-trinitrotoluene

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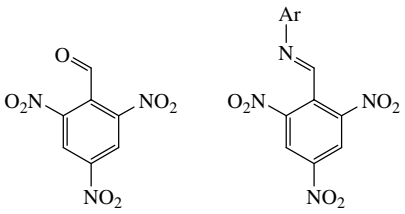
A method for synthesising hitherto unknown 5,7-dinitroquinolines has been developed.

This study aimed at the utilisation of an explosive, 1,3,5-trinitrobenzene (TNB), as a key starting compound for the synthesis of polyfunctional benzannelated heterocycles.[1,2]

Previously, benzannelated heteroaromatic systems were obtained by modification of the methyl group in trinitrotoluene (TNT) followed by cyclisation.[2–10]

It is well known that quinolines can be obtained by cyclocondensation of *ortho*-aminobenzaldehydes or *ortho*-aminoanils with carbonyl compounds containing a reactive methylene fragment.[11]

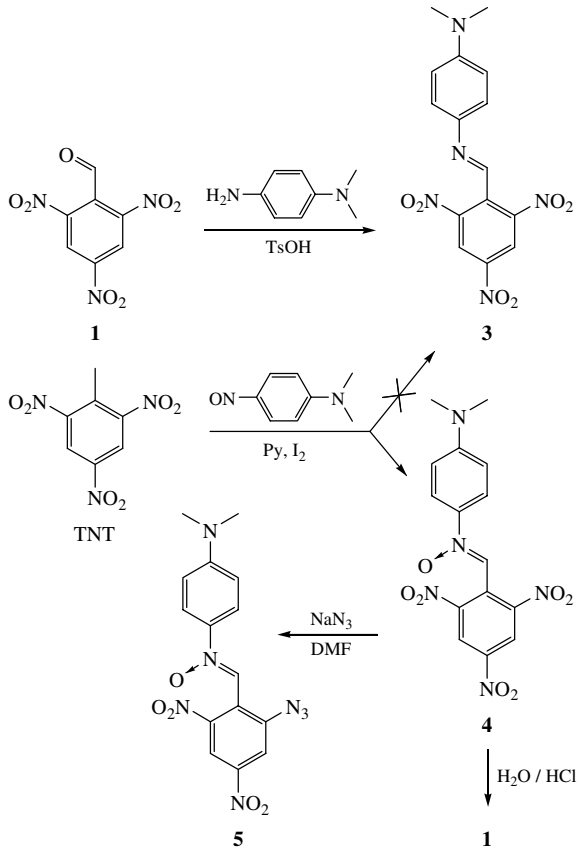
TNT can be readily converted to 2,4,6-trinitrobenzaldehyde **1**[12] and *N*-(2,4,6-trinitrobenzylidene)anilines **2**.[6] To obtain starting compounds for the synthesis of quinolines, we selectively reduced an *ortho*-nitro group in aldehyde **1** or anil **2** to the amino group.



1 **2**

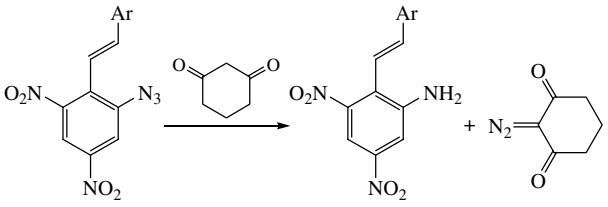
However, the direct selective reduction of *o*-NO_2 in aldehyde **1** or anils **2** was found impossible: no matter what reducing agent was used, complex product mixtures were always formed. Another method could involve replacement of *o*-NO_2 with an azido group followed by reduction of the latter. However, azidation is non-selective in the case of aldehyde **1**: both *o*- and *p*-NO_2 are replaced on treatment with NaN_3. It is known[6] that only *o*-NO_2 is replaced in the azidation of anils **2**, but they concurrently undergo cyclisation to give 2-aryl-4,6-dinitroindazoles. Anil **3** (its *N*-oxide **4**) is the only exception: treatment of this compound with NaN_3 results in a quite stable 2-azidoanil (Scheme 1). Note that anils **2** have been obtained by condensation of aldehyde **1** with anilines,[6] whereas anil **3**, as it was previously reported, was supposedly obtained by condensation of TNT with 4-nitroso-*N*,*N*-dimethylaniline (Scheme 1) in pyridine in the presence of a catalytic amount of iodine.[12]

This considerable difference in the behaviour of the azide based on anil **3** and azides based on other anils **2**, as well as the fact that the condensation product of 2,4-dinitrotoluene with 4-nitroso-*N*,*N*-dimethylaniline obtained under the same conditions as anil **3** is not an anil but its *N*-oxide (nitrone), which has been proved chemically,[13] has suggested that anil **3** is in fact nitrone **4** and its azidation product is nitrone **5** (Scheme 1). In fact, condensation of aldehyde **1** with 4-(*N*,*N*-dimethylamino)-aniline (refluxing in benzene in the presence of *p*-toluenesulfonic acid) gave anil **3**, which was completely different from the condensation product of TNT with 4-nitroso-*N*,*N*-dimethylaniline (^{1}H NMR data and mp). Mass spectra provide little information for establishing the structure of compound **4**, since the spectrum of **3** contains a molecular ion whereas that of **4** contains [M – 16]. Confirmation that compound **4** has a nitrone structure was obtained by elemental analysis of the purified individual product, which differed considerably from the elemental analysis of anil **3** and was totally consistent with its *N*-oxide, *i.e.*, nitrone **4**. It should be noted that the structure of the condensation product of TNT with 4-nitroso-*N*,*N*-dimethylaniline was assigned previously without reliable proof.[14,15] The acidic hydrolysis of anil **3** to 2,4,6-trinitrobenzaldehyde **1**, which is used[12] to synthesise **1**, is in fact the hydrolysis of nitrone **4** (Scheme 1).



Scheme 1

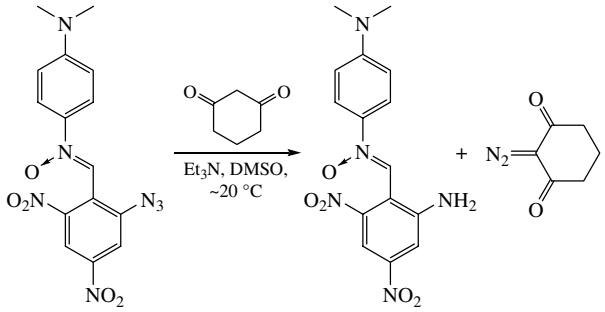
Thus, of the above TNT derivatives, only 2-azidonitrone **5** could be a starting compound for the synthesis of quinolines, provided that the N_3 group could be reduced to NH_2 without affecting the nitro groups. It was found that selective reduction of the N_3 group in 2-azidonitrone **5** with standard reducing agents failed, even if agents that reportedly reduce the N_3 group in the presence of an aromatic nitro group were used.[16,17] The selective N_3 reduction in the presence of nitro groups was performed previously[18] in 2-azido-4,6-dinitrostilbenes **6**: treatment of stilbene **6** with cyclohexane-1,3-dione results in diazo transfer (instead of aryl azide cycloaddition 1,3-diketone observed usually) to give 2-amino-4,6-dinitrostilbenes **7** and 2-diazocyclohexane-1,3-dione (Scheme 2).



6 **7**

Scheme 2

2-Azidonitrone **5** was smoothly converted into 4-(*N*,*N*-dimethylamino)phenylimine *N*-oxide **8** (yield of above 80%) on treatment with cyclohexane-1,3-dione (Scheme 3).†

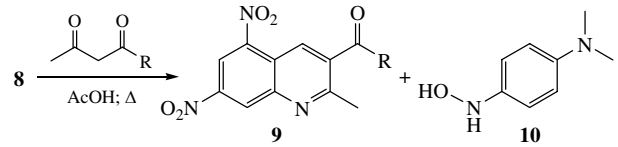


5 **8**

Scheme 3

The condensation of 2-aminonitrone **8** with 1,3-dicarbonyl compounds in boiling acetic acid results in 5,7-dinitroquinoline derivatives **9** in 25–35% yields (Scheme 4).‡

The condensation direction in the case of non-symmetrical 1,3-dicarbonyl compounds was assigned by analogy with the known syntheses of quinolines by condensation of *ortho*-aminoaldehydes and *ortho*-aminoanils with 1,3-dicarbonyl compounds: the more reactive carbonyl group undergoes condensation with the amino group[11] (in the examples we studied, the aliphatic MeC=O group is much more reactive than the aromatic PhC=O group and even more reactive than the carbonyl in the ester group EtOC=O).



9 **10**

a R = Me
b R = Ph
c R = OEt

Scheme 4

† The ^{1}H NMR spectra were recorded with a Bruker AC-200 instrument. Two-dimensional spectra were recorded in the gradient mode using a Bruker DRX-500 instrument at frequencies of 500.13 and 125.26 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported relative to TMS. Mass spectra were obtained using a Kratos MS-30 instrument; the ionization energy was 70 eV. The melting points of the resulting compounds were determined on a Boetius hot stage using Koffler's technique (the heating rate was 4 K min^{-1}).

N-*(2,4,6-Trinitrobenzylidene)-4-(*N′,N′*-dimethylamino)aniline* **3**. A solution of 2,4,6-trinitrobenzaldehyde (3 mmol) and *N*,*N*-dimethyl-*p*-phenylenediamine (3 mmol) in benzene (50 ml) was refluxed with a water separator (Dean-Stark trap) in the presence of several TsOH crystals until the starting compounds disappeared completely (5–6 h, TLC). The azomethine precipitate was filtered off and washed with benzene, then recrystallised from DMF. Yield 68%; mp 218–219 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 9.07 [s, 2H, $C_6H_2(NO_2)_3$], 8.85 (s, 1H, CH), 7.25 (d, 2H, C_6H_4), 6.80 (d, 2H, C_6H_4), 2.99 (s, 6H, NMe_2). Found (%): C, 50.39; H, 3.70; N, 19.60. Calc. for $C_{15}H_{13}N_5O_6$ (%): C, 50.14; H, 3.65; N, 19.49.

N-*(2,4,6-Trinitrobenzylidene)-4-(*N′,N′*-dimethylamino)aniline* N-*oxide* **4**.[12] Recrystallised from EtOH; mp > 250 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 9.05 [s, 2H, $C_6H_2(NO_2)_3$], 8.91 (s, 1H, CH), 7.71 (d, 2H, C_6H_4), 6.80 (d, 2H, C_6H_4), 3.02 (s, 6H, NMe_2). Found (%): C, 48.09; H, 3.47; N, 18.71. Calc. for $C_{15}H_{13}N_5O_7$ (%): C, 48.01; H, 3.49; N, 18.66.

*(2-Azido-4,6-dinitrobenzylidene)-4-(*N′,N′*-dimethylamino)aniline* N-*oxide* **5**. NaN_3 (10 mmol) was added with stirring to a solution of **4** (10 mmol) in DMF (20 ml). The stirring of the solution was continued for another 6 h (TLC) at room temperature. The reaction mixture was poured onto ice. The precipitate was filtered off and recrystallised from acetonitrile. Yield 85%; mp 175 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.52 [s, 1H, $C_6H_2(NO_2)_2$], 8.44 [d, 2H, $C_6H_2(NO_2)_2$ + CHN], 7.72 (d, 2H, C_6H_4), 6.75 (d, 2H, C_6H_4), 3.02 (s, 6H, NMe_2). Found (%): C, 48.50; H, 3.55; N, 26.38. Calc. for $C_{15}H_{13}N_7O_5$ (%): C, 48.52; H, 3.53; N, 26.41.

*(2-Amino-4,6-dinitrobenzylidene)-4-(*N′,N′*-dimethylamino)aniline* N-*oxide* **8**. Triethylamine (1.5 mmol) was added to a solution of azide **5** (3 mmol) and cyclohexane-1,3-dione (3 mmol) in DMSO (8 ml) with stirring. The stirring of the solution was continued for another 5 to 6 h (TLC) at room temperature. The reaction mixture was poured onto ice. The precipitate was filtered off and washed with chloroform (2×5 ml). Yield 81%; mp > 350 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.57 [s, 1H, $C_6H_2(NO_2)_2$], 7.94 [s, 1H, $C_6H_2(NO_2)_2$], 7.84 (s, 1H, CH), 7.78 (d, 2H, C_6H_4), 6.79 (d, 2H, C_6H_4), 6.71 (s, 2H, NH_2), 3.02 (s, 6H, NMe_2). Found (%): C, 51.79; H, 4.63; N, 20.57. Calc. for $C_{15}H_{15}N_5O_5$ (%): C, 52.17; H, 4.38; N, 20.28.

‡ *General procedure for the synthesis of 5,7-dinitroquinolines.* A solution of compound **8** (3 mmol) and a corresponding 1,3-dicarbonyl compound (6 mmol) was refluxed for 8 h in acetic acid (30 ml) (TLC). The solution was concentrated to dryness. HCl (5% solution) was added, and the mixture was extracted with chloroform. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The residue was passed through a column filter packed with silica gel. The resulting compound was recrystallised from ethanol.

1-(2-Methyl-5,7-dinitroquinolin-3-yl)ethanone **9a**. Yield 33%; mp 114–115 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 9.19 [s, 1H, $C_6H_2(NO_2)_2$], 9.04 [s, 1H, $C_6H_2(NO_2)_2$], 8.98 (s, 1H, C_5NH), 2.83 (s, 3H, Me), 2.75 (s, 3H, Me). Found (%): C, 52.38; H, 3.33; N, 15.30. Calc. for $C_{12}H_9N_3O_5$ (%): C, 52.37; H, 3.30; N, 15.27.

1-(2-Methyl-5,7-dinitroquinolin-3-yl)(phenyl)methanone **9b**. Yield 27%; mp 138–140 °C. ^{1}H NMR ([$^2H_6$]acetone) δ: 9.19 [s, 1H, $C_6H_2(NO_2)_2$], 9.10 [s, 1H, $C_6H_2(NO_2)_2$], 9.02 (s, 1H, C_5NH), 7.95 (d, 2H, Ph), 7.77 (t, 1H, Ph), 7.62 (t, 2H, Ph), 2.75 (s, 3H, Me). Found (%): C, 60.55; H, 3.31; N, 12.49. Calc. for $C_{17}H_{11}N_3O_5$ (%): C, 60.54; H, 3.29; N, 12.46.

Ethyl 2-methyl-5,7-dinitroquinoline-3-carboxylate **9c**. Yield 25%; mp 168–170 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 9.31 [s, 1H, $C_6H_2(NO_2)_2$], 9.08 [s, 1H, $C_6H_2(NO_2)_2$], 9.00 (s, 1H, C_5NH), 4.48 (q, 2H, CH_2), 2.95 (s, 3H, Me), 1.41 (t, 3H, Me). Found (%): C, 51.18; H, 3.62; N, 13.75. Calc. for $C_{13}H_{11}N_3O_6$ (%): C, 51.15; H, 3.63; N, 13.77.

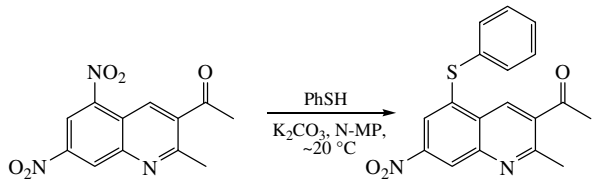
1-[2-Methyl-7-nitro-5-(thiophenyl)quinolin-3-yl]ethanone **11**. Thiophenol (3 mmol) and K_2CO_3 (3 mmol) were added to a solution of 5,7-dinitroquinoline **9a** (3 mmol) in N-MP (8 ml) with stirring. The stirring of the solution was continued for another 6 h (TLC) at room temperature. The reaction mixture was poured onto ice. The precipitate was filtered off and recrystallised from ethanol. Yield 63%; mp 163–165 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.96 [s, 1H, $C_6H_2NO_2$], 8.62 [s, 1H, $C_6H_2(NO_2)$], 8.00 (s, 1H, C_5NH), 7.60–7.46 (m, 5H, Ph), 2.81 (s, 3H, Me), 2.69 (s, 3H, Me). Found (%): C, 63.86; H, 4.16; N, 8.30. Calc. for $C_{18}H_{14}N_2O_3S$ (%): C, 63.89; H, 4.17; N, 8.28.

Furthermore, the structure of compound **9b** was established based on HSQC and HMBC spectral data: the HMBC spectrum contained cross-peaks between the methyl group protons and the C-2 and C-3 atoms of the quinoline ring (but there were no cross-peaks between the methyl group protons and C-4), as well as between H-4 and the carbonyl carbon atom. These data show unambiguously that the methyl group is located at C-2, whereas the benzoyl group is located at C-3.

All carbons and protons were discovered in 1D spectra by HSCQ and HMBC: HSQC showed one-bond H-C correlations thus all non-quarternary carbon atoms were discovered. Benzoyl group at C-3 was revealed using 3-bond correlations between H-4 and the carbonyl carbon atom, as well as between *ortho* protons of a phenyl ring and this carbonyl atom. Because there is no other position of substitution of a quinoline ring leading to these results, it is clear that benzoyl is placed at C-3.

The low yields of 5,7-dinitroquinolines **9** may be due to the ability of the second reaction product, N-substituted hydroxylamine **10** (Scheme 4), to react with both the starting reagents and the products (reduction, condensation *etc.*). As far as we are aware, there are no reported examples of the formation of quinolines in condensation of *ortho*-aminoanil *N*-oxides with carbonyl compounds.

It is known that for 4,6-dinitro-substituted five-membered aromatic benzannelated heterocycles obtained from TNT, treatment of them with anionic O-, S- and N-nucleophiles results in regioselective replacement of 4-NO_2, *i.e.*, the nitro group adjacent to the heterocyclic frame.[9,10,12,19–22] We have shown for the reaction of 5,7-dinitroquinoline **9a** with thiophenol in the presence of K_2CO_3 (in N-MP) that, in the case of the six-membered dinitro-substituted benzannelated aromatic heterocycle, again only the nitro group, which is most proximate to the heterocyclic frame, *i.e.*, 5-NO_2, is replaced selectively (Scheme 5).‡



9a **11**

Scheme 5

The structure of compound **11** was determined using two-dimensional NOESY NMR spectra. The NOESY spectrum contained intense cross-peaks between the H^6 and H^4 protons of the quinoline ring and the *ortho* protons of the phenyl substituent (H-2′), whereas signals between the H-8 and H-2′ were absent, which is only possible if the nitro group at the 5-position is replaced.

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