# Three-Step Synthesis of Highly Substituted Phenols from 1,3-Dinitropropanes

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**Abstract:** Reaction of 1,3-dinitropropanes with acrolein under heterogeneous conditions (neat $Al_2O_3$) gives dinitrocyclohexanols, which, by treatment with potassium carbonate followed by acidic work-up, allow access to nitrocyclohexenone derivatives. The latter, by reaction with phenyltrimethylammonium tribromide, concludes a three-step synthesis of nitro-dibromophenols in satisfactory yields.

**Key words:** bromophenols, aromatization, 1,3-dinitroalkanes, Nef reaction, nitrocyclohexanols

The regiospecific preparation of polyfunctionalized aromatic compounds represents a major challenge in organic synthesis.[1] Classical approaches are based on the modification of arenes, and rely heavily on conventional electrophilic or nucleophilic substitutions, catalyzed coupling reactions, and metallation–functionalization reactions. However, these synthetic routes suffer from long multistep reaction sequences, low yields of target products, and, in particular, serious regiochemical ambiguities due to the activating/deactivating and orienting effects of the substituents. Alternatively, aromatization of acyclic precursors is undoubtedly a useful reaction in the synthesis of highly substituted aromatic rings, and several methods are known for this purpose. In this context, nitroalkane derivatives have emerged, over recent years, as versatile precursors for the one-pot synthesis of a variety of aromatic structures, such as polyalkylated acetophenones[2,3] and benzoates.[3]

Phenols are of great interest in organic synthesis since they are found in a large number of biologically active compounds and/or are employed as key building blocks for the preparation of important targets.[4] Of particular interest are the polyfunctionalized derivatives such as nitrophenol derivatives that possess a range of versatile applications as functional materials such as dyes,[5] pharmaceutical agents or their synthetic intermediates,[6] and bromophenols which are present in algae, such as *Polysiphonia lanosa*, where they are thought to be responsible for the cytotoxic activity against human colon adenocarcinoma.[7]

However, the synthesis of both of these classes of compounds suffers, in general, from low regioselectivity and/or rearrangements that make the introduction of alkyl groups, longer than an ethyl group, difficult.[8]

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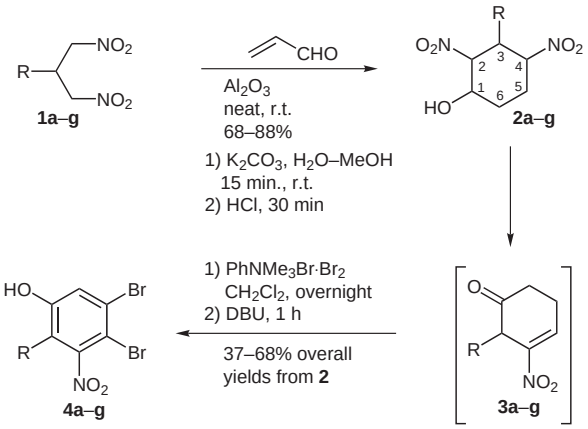
During the course of our studies on the chemistry of nitroalkanes,[9] we reported the one-pot synthesis of a new class of nitrocyclohexanols **2** obtained by treatment of 1,3-dinitroalkanes **1** with acrolein, under basic conditions (basic $Al_2O_3$, neat), through tandem Michael/nitroaldol (Henry) reactions.[10] These results prompted us to explore the feasibility of the construction of a substituted phenolic ring relying upon the utilization of 1,3-dinitropropanes as key precursors. Thus, we wish to report herein a new, three-step synthesis of polyfunctionalized phenols by aromatization of **1** (Scheme 1).




**Scheme 1** Three-step synthesis of **4**.

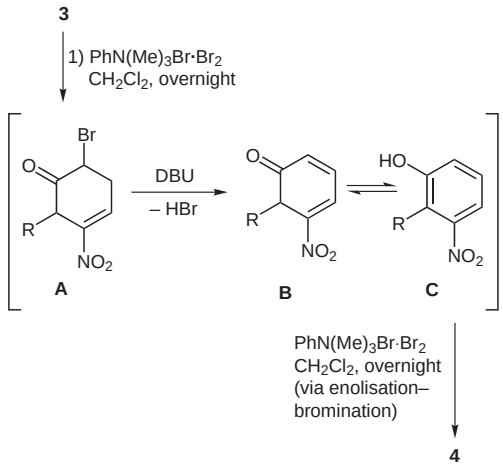
Reaction of 1,3-dinitroalkanes **1** with acrolein, under $Al_2O_3$ catalysis, affords nitrocyclohexanols **2** in one pot. Treatment of compounds **2** with potassium carbonate, followed by acidic work up, transforms them via water elimination from C1–C2 and nitro to carbonyl conversion (Nef reaction)[11] at C4 to nitrocyclohexenones. Reaction of the crude nitrocyclohexenones **3** with phenyltrimethylammonium tribromide (a well-known α-keto brominating agent[12]) allows the direct synthesis of nitro dibromophenols **4**. All the reactions proceeded smoothly to afford the corresponding substituted phenols **4** in satisfactory yields (Tables 1, 37–68% overall yield from **2**).[13]

Although we have no clear evidence of the mechanism for the conversion of **3** to **4**, a possible hypothesis could be that reported in Scheme 2. Nitrocyclohexenone **3**, after both bromination and HBr elimination, is converted into the structure **B** in equilibrium with its enol form **C**. Subsequent bromination of **C** allows the one-pot synthesis (from **3**) of the target phenol derivatives **4**.

**Table 1** Preparation of Nitrodibromophenols **4**

| | R | Yields (%)[a] of **2** (reaction time, h) | Yields (%)[a] of **4** |
|---|---|---|---|
| **a** | $Me(CH_2)_4$ | 88 (8) | 44 |
| **b** | $Ph(CH_2)_2$ | 74 (6) | 46 |
| **c** | Ph | 71 (4) | 51 |
| **d** | *p*-$MeOC_6H_4$ | 76 (18) | 37 |
| **e** | *p*-$CNC_6H_4$ | 70 (20) | 68 |
| **f** | *m*-$NO_2C_6H_4$ | 68 (48) | 54 |
| **g** | *o*-Py | 71 (6) | 47 |

[a] Yield of pure, isolated product.




**Scheme 2** Hypothesis of the mechanism for the conversion of **3** to **4**.

Whatever the details of the mechanism, the reaction represents an unprecedented, reproducible, and useful method for the preparation of a variety of polyfunctionalized phenol derivatives from acyclic precursors. Additionally, in our procedure, by choosing the appropriate starting 1,3-dinitroalkane **1**, a multiplicity of groups in the *ortho*-position can be easily introduced, comprising aryls and heteroaryls. The specific features of our approach, include, the preparation of tetrasubstituted phenols with the avoidance of *ortho-meta-para* mixtures common in conventional aromatic synthesis. In fact, our method appears as a regiodefined synthesis of 2-alkyl-4,5-dibromo-3-nitrophenols, which are very difficult to obtain by other means. It should be noted that the synthesis of substituted biphenyls (compounds **4c**–**f**) can also be accomplished, and the reaction conditions allow the survival of other functionalities such as methoxy and nitrile.

In summary, the letter reports a novel synthetic strategy for the preparation of highly functionalized phenols from acyclic precursors. The simplicity of execution, ready availability of substrates, and the variety of potential products make this procedure very attractive and practical.

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(13) **Preparation of Nitrodibromophenols 4; General Procedure**
To a stirred mixture of dinitroalkane **1** (2 mmol) and acrolein (2.6 mmol, 0.174 mL) was added, at 0 °C, basic $Al_2O_3$ (2 g, activity I). The resulting mixture was stirred at the same temperature for 15 min, then at r.t. for the appropriate reaction time (Table 1). The heterogeneous mixture was directly charged onto a chromatography column (EtOAc–hexane) giving the pure compound **2**.[13] To a solution of **2** (1 mmol) in $H_2O$–MeOH (1:1, 10 mL), $K_2CO_3$ (0.2 g, 2 mmol) was added at r.t. After stirring for 15 min, the solution was acidified with 4 N HCl (pH 2–3) and left at r.t. for 30 min. The organic solution was washed with $NaHCO_3$ (3 × 5 mL), brine (1 × 10 mL), and then evaporated. The residue was dissolved in $CH_2Cl_2$ (20 mL), followed by the addition

of $PhN(CH_3)_3Br{\cdot}Br_2$ (0.38 g, 1 mmol). The solution obtained after stirring overnight at r.t. was treated with DBU until the color changed, and the reaction was left to proceed for 1 h. The mixture was washed with $H_2O$ (2 × 5 mL), brine (10 mL), and the organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography ($SiO_2$, hexane–EtOAc) giving pure compounds **4**.

Compound **4a**: $^1$H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (m, 3 H), 1.32 (m, 4 H), 1.58 (m, 2 H), 2.59 (m, 2 H), 5.90 (br s, 1 H), 7.63 (s, 1 H). $^{13}$C NMR ($CDCl_3$, 50 MHz) δ = 14.1, 22.4, 27.8, 28.9, 31.9, 103.0, 112.3, 124.8, 132.97, 132.98, 105.8. GC-MS (70 eV): *m*/*z* = 367 [$M^+$]. Anal. Calcd for $C_{11}H_{13}Br_2NO_3$: C, 36.0; H, 3.57; N, 3.82. Found: C, 36.31; H, 3.66; N, 3.69. Compound **4e**: $^1$H NMR ($CDCl_3$, 200 MHz): δ = 7.22 (d, 2 H, *J* = 8.2 Hz), 7.51 (d, 2 H, *J* = 8.2 Hz), 7.64 (s, 1 H), 9.38 (br s, 1 H). $^{13}$C NMR ($CDCl_3$, 50 MHz) δ = 101.9, 112.6, 114.5, 118.2, 123.0, 130.4, 132.1, 136.0, 136.1, 150.7. GC-MS (70 eV): *m*/*z* = 398 [$M^+$]. Anal. Calcd for $C_{13}H_6Br_2N_2O_3$: C, 39.23; H, 1.52; N, 7.04. Found: C, 39.45; H, 1.61; N, 6.89. Compound **4g**: $^1$H NMR ($CDCl_3$, 200 MHz): δ = 7.37 (m, 2 H), 7.80 (td, 1 H, *J* = 7.8, 2.0 Hz), 8.27 (s, 1 H), 8.65 (d, 1 H, *J* = 4.3 Hz). $^{13}$C NMR ($CDCl_3$, 50 MHz): δ = 110.2, 123.1, 123.7, 124.3, 129.0, 131.0 (2 C), 137.2, 150.0, 150.5, 150.7. GC-MS (70 eV): *m*/*z* = 294 [$M^+$ – Br]. Anal. Calcd for $C_{11}H_6Br_2N_2O_3$: C, 35.33; H, 1.62; N, 7.49. Found: C, 35.54; H, 1.73; N, 7.28.