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# Synthesis of 4-methoxy-3,5-dinitrobenzaldehyde: a correction to supposed *tele* nucleophilic aromatic substitution

Keith A. Monk, Rogelio Siles, Kevin G. Pinney and Charles M. Garner*

*Department of Chemistry and Biochemistry, Baylor University, PO Box 97348, Waco, TX 76798, USA*

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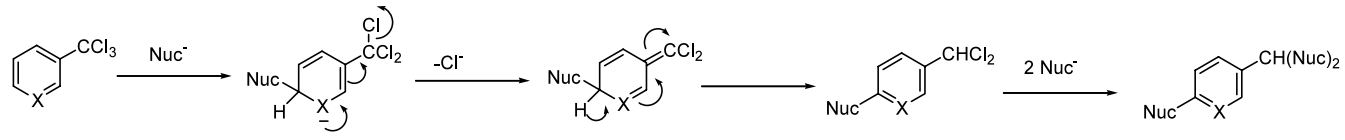
**Abstract**—1,3-Dinitro-5-trichloromethylbenzene (**2**) was reacted with sodium methoxide in an attempt to prepare 4-methoxy-3,5-dinitrobenzaldehyde (**7**) via a reported *tele* nucleophilic aromatic substitution. The product from this reaction was methyl 3,5-dinitrobenzoate (**5**) and not the methoxy aldehyde as had been reported. The desired product was prepared by conventional nitration methodology from 4-methoxy-3-nitrobenzaldehyde. 

The efficient synthesis of benzaldehydes containing both the nitro and amine functionalities has become very important to researchers in the area of drug discovery. These compounds have presented promise in the current therapy for Parkinson's disease[1] and as precursors in the synthesis of *cis*-stilbenoid compounds that have demonstrated to be valuable in the treatment of certain cancers.[2–5] Traditional nitrating procedures often give low yields of a desired regioisomer and are perhaps dangerous because of the potential for explosive di- and tri-nitration products.

Nucleophilic aromatic substitution has been reported in both heterocyclic systems and carbocyclic systems through the formation of a Meisenheimer complex when at least two strongly electron-withdrawing groups are positioned on the aromatic system.[6,8,9] Cartwright and co-workers reported an atypical reaction of 3-trichloromethylpyridines (Scheme 1) termed *tele* nucleophilic substitution.[9] Nucleophilic attack occurs at the 6-position followed by displacement of chlorine and 1,5-hydrogen migration. When the nucleophile is methoxide, subsequent nucleophilic attack will displace the remaining chlorines giving the acetal. The trichloromethyl group *beta* to the nitrogen is vital in the formation of the 2-substituted-5-dichloromethyl pyridines. These concepts[6] were applied by Giannopoulos, et al., in the synthesis of 4-methoxy-3,5-dinitrobenzaldehyde (**7**) and seemed to have potential as an alternative to harsh nitrating procedures.

We wish to report a correction to the supposed[6] preparation of 4-methoxy-3,5-dinitrobenzaldehyde via a *tele* nucleophilic aromatic substitution reaction of 1,3-dinitro-5-trichloromethyl benzene (**2**). Compound **2** was prepared in 87% yield by reaction with phosphorous pentachloride in phenylphosphonic dichloride under conditions described by Giannopoulos (Scheme 2).[6] It was reported there that reaction of **2** with sodium methoxide in methanol yielded intermediate acetal **3**, which hydrolyzed to 4-methoxy-3,5-dinitrobenzaldehyde during purification by column chromatography. However, the authors neither isolated nor characterized the acetal **3**. Under identical conditions,[7] we isolated compound **4**, which was unambiguously identified by $^1$H NMR. The methoxy singlet at $\delta$ 3.21 integrated to nine protons and the aromatic region of the spectra gave a doublet and triplet with $J=2.1$, suggesting *meta* coupling. Hydrolysis of compound **4** using dilute HCl afforded the methyl ester **5** in 60% yield. Once again the $^1$H NMR showed the aromatic protons as a doublet




**Scheme 1.**

* Corresponding author.

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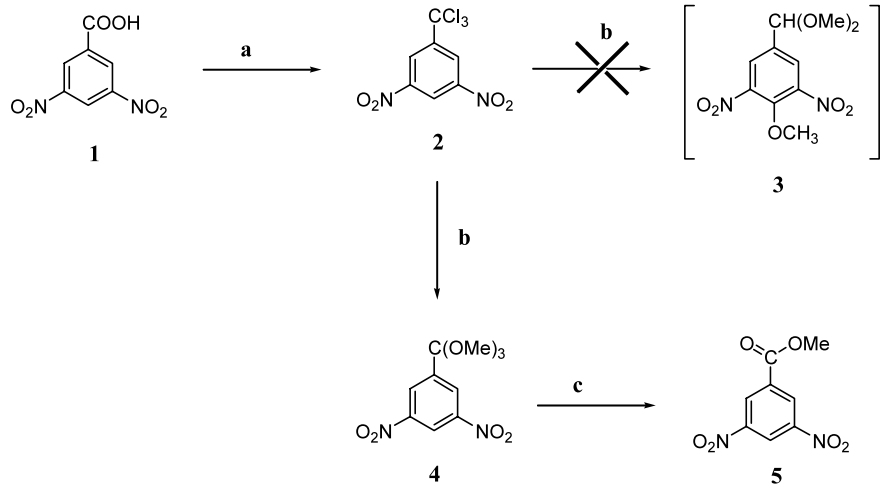
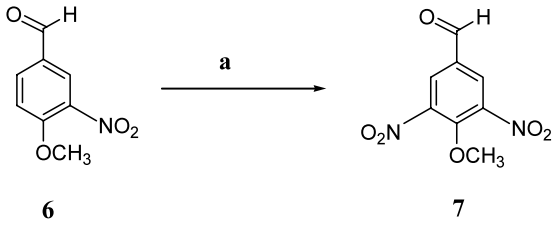



**Scheme 2.** *Reagents and conditions*: (a) $PhP(O)Cl_2$, $PCl_5$, reflux 15 h; (b) $NaOCH_3$, $CH_3OH$, rt; (c) dil. HCl, acetone.




**Scheme 3.** *Reagents and conditions*: (a) fuming $HNO_3$, conc. $H_2SO_4$, 0°C.

and triplet with $J=2.1$ Hz, indicative of *meta* coupling rather than a long-range coupling between the aldehyde and aromatic protons as reported.[6] This result can be attributed to a classical $S_N2$ substitution reaction mechanism rather than a *tele* nucleophilic aromatic substitution mechanism.

Synthesis of 4-methoxy-3,5-dinitro benzaldehyde (**7**) by conventional synthetic methodology (Scheme 3) was successful in providing the desired compound. Commercially available 3-nitro-4-methoxybenzaldehyde was nitrated using fuming nitric acid in 48% yield.[10] NMR results were now entirely suggestive of compound **7**, with sharp singlets at $\delta$ 4.1, 8.5, and 10.0, and integrations of 3:2:1 for methoxy, aromatic, and aldehydic protons, respectively, consistent with a literature report[9] by which the desired compound was prepared in a three-step procedure from 4-bromobenzaldehyde.

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6. Giannopoulos, T.; Ferguson, J. R.; Wakefield, B. J.; Varvounis, G. *Tetrahedron* **2000**, *56*, 447–453. Experimental for 1,3-dinitro-5-trichloromethylbenzene (**2**). To a 100 ml round-bottom flask was added 3,5-dinitrobenzoic acid (5.0368 g, 23.7 mmol), and the flask was purged with argon. Phenylphosphonic dichloride (3.70 ml, 26.1 mmol) was added to the flask via syringe and the solution was heated to 50°C. A $CaCl_2$ drying tube was attached and $PCl_5$ was added to the flask portionwise over 1 h. After addition was complete, the solution was refluxed for 16 h. Phosphorous oxychloride was distilled off to give a brown oil. The oil was transferred to a separatory funnel containing 180 ml of 20% $Na_2CO_3$ solution. The product was extracted with methylene chloride. The organic phases were combined, dried with magnesium sulfate, filtered, and solvent removed to give a pale yellow solid (5.83 g, 87%, 98% pure by GC–MS). $R_f$ (5% ethyl acetate/hexanes) = 0.50. $^1H$ NMR ($CDCl_3$, 300 MHz): 9.13–9.15 (m, 3H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): 93.6, 120.4, 126.0, 147.7, 148.4. MS: 284 ($M^+$), 249 (base peak). $\nu_{max}$ (Nujol): 1552, 1342 $cm^{-1}$. Melting point: 73–75°C (lit.[11] mp 76.5–77.5°C). Experimental for methyl-3,5-dinitrobenzoate (**5**). To a 250 ml oven-dried round bottom flask with stir bar was added 3,5-dinitro trichloromethylbenzene (5.75 g, 20.2 mmol). The flask was evacuated and placed under an argon atmosphere. Spec. grade methanol (150 ml) was transferred to the flask via cannula, and the solution was stirred to dissolve all solid. The flask was cooled in an ice bath to 0°C, and sodium methoxide (12.03 g, 222 mmol) was added portionwise. The clear solution turned to a cloudy orange and was stirred

overnight, warming from 0°C to room temperature under argon. Solvent was removed and the flask was placed under vacuum for 2 h. The compound was purified by column chromatography using 5% ethyl acetate/hexanes, giving 1,3-dinitro-5-trimethoxymethylbenzene (**4**, 5.18 g, 94%) as an orange oil. $^1$H NMR ($CDCl_3$, 300 MHz): 3.21 (s, 9H), 8.76 (d, 2H, $J=2.1$), 9.07 (t, 1H, $J=2.1$). $^{13}$C NMR ($CDCl_3$, 75 MHz): 50.2, 113.1, 119.4, 127.9, 142.1, 148.6. This product was stirred in 50 ml of 1 M HCl and 25 ml of acetone overnight. The solution was extracted with ethyl acetate, dried with magnesium sulfate, filtered, and solvent was removed to give an orange solid. The product was purified by column chromatography using 15% ethyl acetate/hexanes, collecting 2.520 g of pure white solid (60%). $R_f$ (15% ethyl acetate/hexanes) = 0.39. $^1$H NMR ($CDCl_3$, 300 MHz): 4.08 (s, 3H), 9.18 (d, 2H, $J=2.1$ Hz), 9.24 (t, 1H, $J=2.1$ Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): 53.6, 122.4, 129.5, 133.8, 148.7, 163.0. MS: 226 ($M^+$), 195 (base peak). $\nu_{max}$ (Nujol): 1728, 1543, 1302 $cm^{-1}$. Melting point: 104–106°C (lit.[12] mp 106.5–106.8°C).

7. We have employed conditions identical to those reported, but those described here give identical results in somewhat higher yields and/or purities.
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10. Procedure adapted from Vogel's *Textbook of Practical Organic Chemistry*, 5th ed. 1989; pp. 854–856. Experimental for 4-methoxy-3,5-dinitrobenzaldehyde (**7**). To a 100 ml round bottom flask containing a mixture of 4-methoxy-3-nitrobenzaldehyde (3.89 g, 21.5 mmol) and 25 ml concentrated sulfuric acid previously cooled to 0°C in an ice bath, was added slowly a 0°C mixture of fuming nitric acid (13.6 g, 217 mmol) and concentrated sulfuric acid (15.9 g, 162 mmol). The reaction was stirred for 3.5 h and cautiously added to 100 ml of ice-water. After 1 h at 0°C, the resultant mixture was filtered and the solid was rinsed with ice-water (10 ml). Purification by flash column chromatography (10% ethyl acetate/hexanes) afforded the aldehyde as a pale yellow solid (2.31, 48%, >99% pure by GC–MS). $^1$H NMR ($CDCl_3$, 300 MHz): 4.14 (s, 3H), 8.51 (s, 2H), 10.02 (s, 1H). $^{13}$C NMR ($CDCl_3$, 75 MHz): 65.1, 129.1, 131.2, 145.6, 151.6, 186.6. MS: 226 ($M^+$), 196 (base peak). $\nu_{max}$ (Nujol): 1531, 1462, 1377 $cm^{-1}$. Melting point: 87–89°C (lit.[9] mp 87°C).
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