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Kenneth W. Stagliano [a], Helena C. Malinakova [a] & Akiko Takayama [a]
[a] Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois, 60616
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SYNTHESIS OF CONTIGUOUSLY SUBSTITUTED NITRO AROMATICS VIA DIRECTED *ORTHO*-METALATION NITRATION

Kenneth W. Stagliano*, Helena C. Malinakova and Akiko Takayama

Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616

ABSTRACT: A new protocol for the synthesis of contiguously substituted aromatic nitro compounds based on directed *ortho*-metalation followed by reaction with methyl nitrate is described.

Traditional electrophilic aromatic substitution is of limited value for the synthesis of contiguously substituted aromatic nitro compounds. Preparation of 6-nitrosalicylic acid from 2-chloro-6-nitrobenzoic acid required three steps and proceeded in 10% overall yield.[1] 2-Methoxy-6-nitrobenzonitrile has been obtained in one step from m-dinitrobenzene in 20% yield.[2] Direct nitration of m-methoxybenzoic acid yields the 1,2,3-trisubstituted isomer but only in 10% yield.[3] Thus, the development of new synthetic strategies which would extend the range of available substitution patterns and increase yields are highly desirable.

Directed *ortho*-metalation has provided excellent solutions to difficult regiochemical and stereochemical problems in synthetic aromatic chemistry.[4] Although a variety of electrophiles have been introduced onto the aromatic ring using directed metalation strategies,[4] to the best of our knowledge no reports on the application to the synthesis of aromatic nitro compounds have appeared.

*To whom correspondence should be addressed.

Herein we report the first example of a regiospecific aromatic nitration reaction *via* the directed *ortho*-metalation nitration protocol. We envisioned that the nitro group could be introduced onto the aromatic ring by the reaction of a lithioaryl anion with the nitrogen atom of methyl nitrate (CH_3ONO_2)[5] forming a tetrahedral intermediate. Collapse of the intermediate with loss of a methoxyl group would lead to the nitroarene. Lithiation of N,N-diisopropylbenzamide (**1**) and 2-methoxy-N,N-diisopropylbenzamide (**2**) utilizing TMEDA/sec-BuLi followed by addition of excess methyl nitrate resulted in complete conversion of the starting benzamides to single nitration products (**4**) and (**5**) respectively (**Table**). The reaction mixtures developed a dark red color and isolation of the product was complicated by the presence of red colored oily residues.

In the case of m-methoxybenzamides, careful optimization of metalation conditions was necessary. Metalation of 3-methoxy-N,N-diethylbenzamide, by the standard procedure[6] and subsequent addition of methyl nitrate resulted in the isolation of the ketone (3-methoxyisobutylphenone) as the sole product. Under the reaction conditions developed for the nitration of (**1**) and (**2**) 3-methoxy-N,N-diisopropylbenzamide (**3**) gave only a 15% yield of the nitrated product (**6**). Successful nitration of (**3**) was accomplished by lithiation with sec-BuLi (without TMEDA!) as reported by Beak.[7] A notable difference is the increased yield (based on recovered starting material) and a significant reduction in side products formed in the absence of TMEDA.

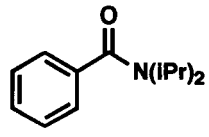
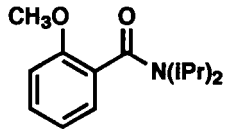
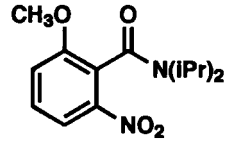
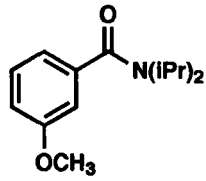
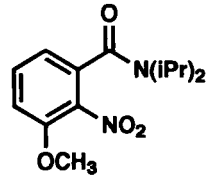
In conclusion, we have demonstrated the first example of directed *ortho*-metalation nitration by application to the synthesis of 1,2,3-contiguously substituted aromatic nitro compounds in 44-55% yield.

EXPERIMENTAL

Infrared Spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a 300-MHz Nicolet NT-300 FT-

Table

Directed *ortho*-Metalation Nitration

Entry	Substrate	Nitration Product	Method[a]	Yield
1	 (1)	 (4)	A	55%
2	 (2)	 (5)	A	48%
3	 (3)	 (6)	B	44% (88%)[b]

[a] Method A: lithiation with TMEDA/*sec*-BuLi/-78°C
Method B: lithiation with *sec*-BuLi/-78°C
[b]Yield based on recovered starting material.

NMR Spectrometer using $CDCl_3$ as the solvent. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. High resolution mass spectra were obtained under electron impact (EI) measurements. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Thin layer chromatography (TLC was carried out on Analtech precoated silica gel 60F 254

plates. Flash chromatography was performed with Acros silica (0.034-0.07 mm). N,N-diisopropylbenzamides **(1)**, **(2)** and **(3)** were prepared using standard methods.[7] Methyl nitrate was prepared fresh for each reaction and used without purification by distillation.[8,9] **CAUTION: EXPLOSIONS HAVE BEEN REPORTED WHEN METHYL NITRATE WAS OVER HEATED DURING DISTILLATION.** Tetrahydrofuran was distilled from sodium benzophenone ketyl in a recirculating still. All reactions were performed under a dry nitrogen atmosphere.

Directed *ortho*-Metalation Nitration

Method A. To a stirred solution of 1.1 mmol of TMEDA in 20 mL of THF, which was cooled to -78°C, was added 1.1 mmol of *sec*-BuLi (Aldrich 1.3 M in cyclohexane). After stirring for 15 min., a solution of the benzamide (1.0 equiv.) in 5 mL of THF was added dropwise *via* canula. After stirring for 15-20 minutes at -78°C the solution was treated with freshly prepared methyl nitrate (10.0 mmol). After the addition was complete, the mixture was stirred at -78°C for 1 hr and then allowed to warm gradually to ambient temperature prior to the addition of ca. 4 mL of HOAc. The organic portion was extracted with methylene chloride, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product.

Method B. To a stirred solution of the benzamide (1.0 mmol) in 15.8 mL of THF cooled to -78°C was added 1.2 mmol of *sec*-BuLi (Aldrich 1.3 M in cyclohexane) dropwise. The resulting solution was kept at -78°C for 1 hr. Method A was subsequently followed.

2-Nitro-N,N-diisopropylbenzamide (4) Method A: 0.249 g (1.21 mmol) of benzamide **(1)**, 1.0 mL (1.30 mmol) of *sec*-BuLi, 0.20 mL (1.32 mmol) of TMEDA. A 0.80 mL (12.47 mmol) sample of methyl nitrate was added. The compound was purified by flash chromatography over silica (EtOAc/hexane,

1:4) providing 0.166 g (55%) of a white solid after trituration with hexane: mp = 107-109°C, ^{1}H-NMR ($CDCl_3$) δ 1.12 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H), 1.57 (d, J = 6.6 Hz, 3H), 1.63 (d, J = 6.6 Hz, 3H), 3.50-3.65 (m, 2H), 7.34 (d, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 8.18 (d, J = 7.57, 1H); IR (KBr) 1635, 1575, 1528, 1480, 1441, 1348, 1339 cm^{-1}; MS (EI) m/z (%) 250 (3.8, M$^+$), 235 (6.0), 150 (100), 134 (5.3), 121 (4.6), 100 (46.7), 84 (14.9), 51 (10.7), 43 (11.6); HRMS (EI) calcd. for $C_{13}H_{18}N_2O_3$: (M$^+$), 250.1317, found (M$^+$), 250.1325; Anal. calcd. for $C_{13}H_{18}N_2O_3$: C, 62.37; H, 7.25; N, 11.2. Found: C, 62.55; H, 7.43; N 10.94.

2-Methoxy-6-Nitro-N,N-diisopropylbenzamide (5) Method A: 0.551 g (2.34 mmol) of benzamide (**2**), 2.0 mL (2.60 mmol) of *sec*-BuLi, 0.40 mL (2.65 mmol) of TMEDA. A 1.50 mL (23.37 mmol) sample of methyl nitrate was added. The compound was purified by flash chromatography over silica (EtOAc/hexane, 3:2) providing 0.314 g (48%) of a yellow solid after trituration with hexane: mp = 159-161°C, ^{1}H-NMR ($CDCl_3$) δ 1.14 (s, 3H), 1.16 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H), 1.62 (d, J = 6.6 Hz, 3H), 3.50-3.63 (m, 2H), 3.89 (s, 3H), 7.18 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H); IR (KBr) 1636, 1609, 1534, 1475, 1435, 1371, 1342, 1307, 1270 cm^{-1}; MS (EI) m/z (%) 280 (1.3, M$^+$), 180 (100), 151 (10.1), 134 (4.6), 100 (65.1), 84 (11.8), 76 (24.9), 58 (5.9); HRMS (EI) calcd. for $C_{14}H_{20}N_2O_4$: (M$^+$) 280.1423, found (M$^+$) 280.1411; Anal. calcd. for $C_{14}H_{20}N_2O_4$: C, 59.97; H, 7.20; N, 10.00. Found: C, 59.96; H, 7.16; N, 9.82.

3-Methoxy-2-Nitro-N,N-diisopropylbenzamide (6) Method B: 0.523 g (2.22 mmol) of benzamide (**3**), and 2.0 mL (2.60 mmol) of *sec*-BuLi. A 1.5 mL (23.37 mmol) sample of methyl nitrate was added. The compound was purified by flash chromatography over silica (EtOAc/hexane, 1:3) providing 0.273

g (44%) of a white solid: mp = 174-175°C, ^{1}H-NMR ($CDCl_3$) δ 1.11-1.22 (m, 6H); 1.51 (d, J = 6.9 Hz, 6H); 3.40-3.53 (m, 1H), 3.70-3.77 (m, 1H), 3.95 (s, 3H), 6.85 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H); IR (KBr) 3089, 2970, 1629, 1577, 1530, 1461, 1367, 1343, 1281 cm^{-1}; MS (EI) m/z (%) 280 (3.4, M^+), 180 (100), 164 (11.9), 100 (64.7), 84 (20.8), 76 (35.6), 53 (15.0), 43 (19.6); HRMS (EI) calcd. for $C_{14}H_{20}N_2O_4$: (M^+) 280.1423, found (M^+) 280.1419; Anal. calcd. for $C_{14}H_{20}N_2O_4$: C, 59.97; H, 7.20; N, 10.00. Found: C, 58.22; H, 7.16; N, 9.42.

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