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# Synthesis of 3,6-Disubstituted-2-nitrotoruenes by Methylation of Aromatic Nitrocompounds with Dimethylsulfonium Methylide

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# SYNTHESIS OF 3,6-DISUBSTITUTED-2-NITROTORUENES BY METHYLATION OF AROMATIC NITROCOMPOUNDS WITH DIMETHYLSULFONIUM METHYLIDE

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**ABSTRACT:** 3,6-disubstituted-2-nitrotoluenes were obtained in moderate yield by methylation of 2,5-disubstituted nitrobenzenes with dimethylsulfonium methylide in DMSO-THF mixture.



2-Nitrotoluene derivatives are important compounds as one of the key intermediates for the preparation of indole-2-carboxylic acid derivatives[1]. Indole-2-carboxylic acid derivatives are also valuable intermediates for the preparation of biologically active agents such as $Na^+/H^+$ exchanger inhibitor[2].

In connection with our synthetic approach to ethyl 7-benzyloxy-4-trifluoromethyl-1*H*-indole-2- carboxylate (**1c**), we sought to prepare the key intermediate, 4-benzyloxy-2-methyl-3-nitrobenzotrifloride (**1b**). To this end, we variously examined the methylation of 4-benzyloxy-3-nitrobenzene (**1a**). Consequently,

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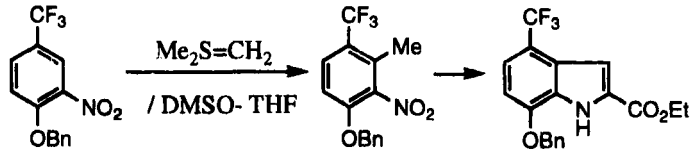
we have found that the selective methylation of nitrobenzene **1a** with dimethylsulfonium methylide ($Me_2S=CH_2$) in DMSO-THF mixture at room temperature to give the desired 2-nitrotoluene **1b** (**Scheme 1**) [3].




**1a** **1b** **1c**

**Scheme 1**

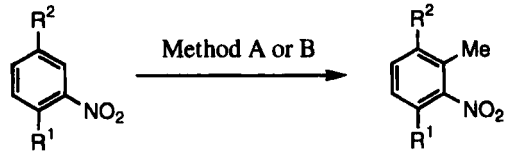
Several methods have beeen reported for the preparation of 2-nitrotoluene derivatives using the methylation of nitrobenzen derivatives. Methyl introducing reagents such as Grignard reagents (MeMgBr) [4], methylsulfinylcarbanion ($CH_3S(O)CH_2^-$) [5] and dimethyloxosulfonium methylide ($Me_2S(O)=CH_2$) [6] have been used for this purpose. However, these methods were not effective for preparation of the 2-nitrotoluene **1b**. Here, we wish to report the facile preparation of 3,6-disubstituted-2-nitrotoluene derivatives by methylation of 2,5-disubstituted nitrobenzene derivatives with dimethylsulfonium methylide. First, we examined the effect of the reaction temperature on the methylation of nitrobenzene **1a** to find that the preferable reaction temperature was at 10~20℃. The reaction did not procced below 5℃. Next, we investigated the effects of varying the base, the solvent and the amount of base and $Me_3SI$ on the methylation of nitrobenzene **1a** (**Table1**).

**Table 1.** Effect of base, solvent and amount of base and $Me_3SI$ on the methylation of nitrobenzene **1a**

| Entry | base(eq.) | Me3SI(eq.) | DMSO/ THF (v/ v) | Yield(%)* | Recoverd starting material(%)* |
|---|---|---|---|---|---|
| 1 | NaH(1.5) | 1.5 | 3/ 1 | 45.8 | 18.3 |
| 2 | NaH(2.0) | 2.0 | 3/ 1 | 60.5 | 0 |
| 3 | NaH(2.0) | 2.0 | 1/ 1 | 51.6 | 15.4 |
| 4 | NaH(2.0) | 2.0 | 2/ 3 | 29.1 | 26.9 |
| 5 | NaH(3.0) | 3.0 | 1/ 1 | 50.9 | 0 |
| 6 | $^t$BuOK(2.0) | 2.0 | 3/ 1 | 56.7 | 0 |
| 7 | n-BuLi(2.0) | 2.0 | 0/ 1 | 0 | 0 |

* The values given are for isolated yields obtained by purification with chromatography.

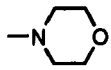
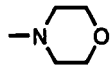
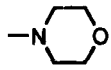
As a base, either NaH or t-BuOK was effective on this methylation reaction but the use of n-BuLi failed to give any nitrobenzene **1b**. As for the amount of base and $Me_3SI$, the reaction proceeded to completion by treating with a 2: 2: 1 base/ $Me_3SI$/ substrate molar ratio, whereas the reaction was not completed with a 1.5: 1.5: 1 base/ $Me_3SI$/ substrate molar ratio. As a solvent effect, the use of DMSO and THF mixture in a 3: 1 ratio gave the best result.




**1a-8a** **1b-8b**

**Scheme 2**

**Table 2.** Results of methylation of some functionalized nitrobenzenes with dimethylsulfonium methylide

| Entry | Substrate | $R_1$ | $R_2$ | Method[a)] | Product | Yield(%)[b)] |
|---|---|---|---|---|---|---|
| 1 | **1a** | OBn | $CF_3$ | B | **1b** | 60.5 |
| 2 | **2a** |  | $CF_3$ | A<br>B | **2b** | 42.8<br>0 |
| 3 | **3a** | OBn | Cl | B | **3b** | 3 |
| 4 | **4a** |  | Cl | A<br>B | **4b** | 19.9<br>32.3 |
| 5 | **5a** | $NMe_2$ | Cl | A<br>B | **5b** | 18.7<br>48.0 |
| 6 | **6a** | OMe | Me | A | **6b** | 55.0 |
| 7 | **7a** | OBn | Me | A | **7b** | 55.0 |
| 8 | **8a** |  | Me | A<br>B | **8b** | 65.6<br>19.3 |

a) Method A: $^t$BuOK(2.0eq), $Me_3SI$(2.0eq)/ DMSO: THF(2: 1=v: v)
Method B: NaH(2.0eq), $Me_3SI$(2.0eq)/ DMSO: THF(3: 1=v: v)
b) The values given are for isolated yields obtained by purification with chromatography.

Next, we examined the methylation of various 2,5-disubstituted nitrobenzenes (**1a-8a**) with dimethylsulfonium methylide (**Scheme 2**). As shown in Table 2, replacement of the benzyloxy moiety by 4-morpholino at the nitrobenzene **1a** led to the desired 2-nitrotoluene **2b** in 42.8% yield using t-BuOK as a base (method A), whereas it failed to give any desired compound using NaH as a base (method B). Replacement of the trifluoromethyl moiety by chloro atom at nitrobenzene **1a** gave the desired 2-nitrotoluene **3b** in only a 3% yield. Methylation of the chloro compounds (**4a**, **5a**) under the condition of method B gave the desired 2-nitrotoluenes (**4b**, **5b**) in 32.3%, 48.0% yield respectively, however, the use of method A condition led to the decline of yields of both 2-nitrotoluenes (**4b**, **5b**).

Replacement of the trifluoromethyl moiety by methyl moiety at the nitrobenzene **1a** led to the desired 2-nitrotoluene **7b** in 55.0% yield under the condition of method A. Methylation of the methoxy compound **6a** and the morpholino compound **8a** under the condition of method A also gave the desired 2-nitrotoluenes (**6b**, **8b**) in 55.0% and 65.6% yields, respectively. However, methylation of morpholino compound **8a** under the condition of method B gave the 2-nitrotoluene **8b** in only 19.3% yield.



## Experimental

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10 IR spectrophotometer, $^1$H-NMR spectra were recorded on JEOL GX-270 and JEOL-JNM-LA300 instruments with TMS as an internal standard. The coupling constants (*J*) are reported in Hz. Mass-spectra were recorded with a Finnigan ITS40 mass spectrometer. CHN-analyses were done with a Heraeus elemental analyzer.

**General Procedure** Method A: To a solution of a nitrobenzene derivative (8.22 mmol) and trimethylsulfonium iodide (16.4 mmol) in DMSO (30 ml), a solution of t-BuOK (16.4 mmol) in THF (15 ml) was added dropwise and the mixture was stirred at 10~20℃ for 5h. The reaction mixture was then cooled to 5℃. Acetic acid (2 ml) was added dropwise to the mixture and the resulting

mixture was stirred at 5~10℃ for 1h. The reaction mixture was poured into ice water. The resulting mixture was then extracted three times with AcOEt. The combined extracts were washed with brine. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/ n-hexane= 2/ 98) to give the desired 2-nitrotoluene as described in Table 2.

Method B: To a suspension of 60% sodium hydride (202 mmol) and trimethylsulfonium iodide (202 mmol) in DMSO (390 ml) and THF (150 ml), a solution of the nitrobenzene (101 mmol) in DMSO (60 ml) was added dropwise and the mixture was stirred at 10~20℃ for 5h. The reaction mixture was poured into ice water. The resulting mixture was then extracted three times with toluene. The combined extracts were washed with brine. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/ n-hexane= 2/ 98) to give the desired 2-nitrotoluene as described in Table 2.

**1b**. mp 92-93℃; IR (KBr) 1536, 1372, 828 $cm^{-1}$; $^1$HNMR ($CDCl_3$) $\delta$ 7.63 (1H, d, $J$=8.7Hz, H-5), 7.42-7.31(5H, m, $C_6H_5$), 6.94(1H, d, $J$=8.9Hz, H-4), 5.22(2H, s, $CH_2$), 2.38(3H, d, $J$=1.3Hz, $CH_3$); MS (*m/z*) 205, 177, 145, 127, 107, 91(100); Anal. Calced. For $C_{15}H_{12}F_3NO_3$: C, 57.88; H, 3.89; N, 4.50. Found: C, 57.59; H, 3.83; N, 4.56.

**2b**. oil; IR (neat) 1539, 1374, 831 $cm^{-1}$; $^1$HNMR ($CDCl_3$) $\delta$ 7.70(1H, d, $J$=8.6Hz, H-5), 7.15(1H, d, $J$=8.6Hz, H-4), 3.80-3.77(4H, m, 2× $CH_2$), 3.03-

2.99(4H, m, 2× $CH_2$), 2.36(3H, d, *J*=1.3Hz, $CH_3$); MS (*m/z*) 290($M^+$), 273, 227, 214, 201(100), 159.

**3b**. mp 115-116℃; IR (KBr) 1528, 1372, 847 $cm^{-1}$; $^1$HNMR ($CDCl_3$) $\delta$ 7.40-7.29(6H, m, 5-H, $C_6H_5$), 6.83(1H, d, *J*=9.2Hz, 4-H), 5.14(2H, s, $CH_2$), 2.31(3H, s, $CH_3$); MS (*m/z*) 171, 152, 143, 128, 107, 91(100); Anal. Calced. for $C_{14}H_{12}ClNO_3$: C, 60.55; H, 4.36; N, 5.04. Found: C, 60.43; H, 4.61; N, 5.09.

**4b**. mp 71-72℃; IR (KBr) 1534, 1373, 875 $cm^{-1}$; $^1$HNMR ($CDCl_3$) $\delta$ 7.45(1H, d, *J*=8.6Hz, 5-H), 7.10(1H, d, *J*=9.0Hz, 4-H), 3.78-3.75(4H, m, 2×$CH_2$), 2.94-2.91(4H, m, 2×$CH_2$), 2.29(3H, s, $CH_3$); MS (*m/z*) 256($M^+$), 239, 222, 193, 181, 167(100); Anal. Calced. for $C_{11}H_{13}ClN_2O_3$: C, 51.47; H, 5.10; N, 10.91. Found: C, 51.37; H, 5.21; N, 10.74.

**5b**. oil ; IR (neat) 1532, 1373, 883 $cm^{-1}$; $^1$HNMR ($CDCl_3$) $\delta$ 7.36(1H, d, *J*=8.9Hz, 5-H), 6.97(1H, d, *J*=8.9Hz, 4-H), 2.74(6H, s, $N(CH_3)_2$), 2.28(3H, s, $CH_3$); MS (*m/z*) 214($M^+$)(100), 197, 180, 167, 152, 139.

**6b**. mp 60-61℃; IR (KBr) 1526, 1376, 881 $cm^{-1}$; $^1$HNMR ($CDCl_3$) $\delta$ 7.17(1H, d, *J*=8.4Hz, 5-H), 6.77(1H, d, *J*=8.4Hz, 4-H), 3.84(3H, s, $OCH_3$), 2.24(3H, s, $CH_3$), 2.16(3H, s, $CH_3$), MS (*m/z*) 181($M^+$), 164(100), 149, 136, 129, 104; Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.56; H, 6.03; N, 7.59.

**7b**. mp 70-71℃; IR (KBr) 1525, 1377, 846 $cm^{-1}$; $^1$HNMR ($CDCl_3$) $\delta$ 7.39-7.26(5H, m, $C_6H_5$), 7.11(1H, d, *J*=8.4Hz, 5-H), 6.78(1H, d, *J*=8.4Hz, 4-H),

5.12(2H, s, $CH_2$), 2.23(3H, s, $CH_3$), 2.17(3H, s, $CH_3$); MS (*m/z*) 257($M^+$), 181, 151, 123, 107, 91(100); Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.87; H, 5.87; N, 5.38.

**8b**. mp 76-77℃; IR (KBr) 1527, 1374, 866 $cm^{-1}$; $^1$HNMR ($CDCl_3$) $\delta$ 7.22(1H, d, *J*=8.2Hz, 5-H), 7.06(1H, d, *J*=8.2Hz, 4-H), 3.78-3.74(4H, m, $2\times CH_2$), 2.93-2.90(4H, m, $2\times CH_2$), 2.29(3H, s, $CH_3$), 2.15(3H, s, $CH_3$); MS (*m/z*) 236($M^+$; 100), 219, 202, 173, 160, 147; Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.88; H, 6.64; N, 11.79.

**References:**

1. Sundberg, R. J. " The Chemistry of Indoles, " Academic Press, New York and London, **1970**, pp. 176-178.
2. Kitano, M., Ohashi, N., Kojima, A. and Noguchi, T. *Japan Kokai Tokkyo Koho*, JP08208602, **1996** and *Chem Abstr.*, 125: 58312, **1996**; *idem*, *Eur. Pat.*, 708,091, **1996**, and *Chem Abstr.*, 125: 58312, **1996**.
3. Kitano, M., Takamura, M. and Ohashi, N. *Japan Kokai Tokkyo Koho*, JP09143127, **1997** and *Chem Abstr.*, 127: 50382, **1997**.
4. (a) Bartoli, G., Bosco, M. and Baccolini, G. *J. Org. Chem.* **1980**, 45, 522. (b) Bartoli, G., Bosco, M. and Dalpozzo, R. *Tetrahedron Lett.* **1985**, 115.
5. Russell, C. A. and Weiner, S. A. *J. Org. Chem.* **1966**, 31, 248.
6. Traynelis, V. J. and McSweeney, $S_R$. J. V. *J. Org. Chem.* **1966**, 31, 243.

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