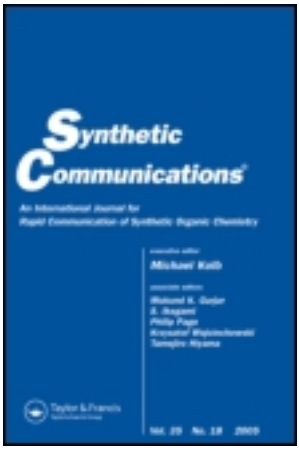

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A Convenient One Pot Procedure for N-Methylation of Aromatic Amines Using Trimethyl Orthoformate

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A CONVENIENT ONE POT PROCEDURE FOR N-METHYLATION OF AROMATIC AMINES USING TRIMETHYL ORTHOFORMATE

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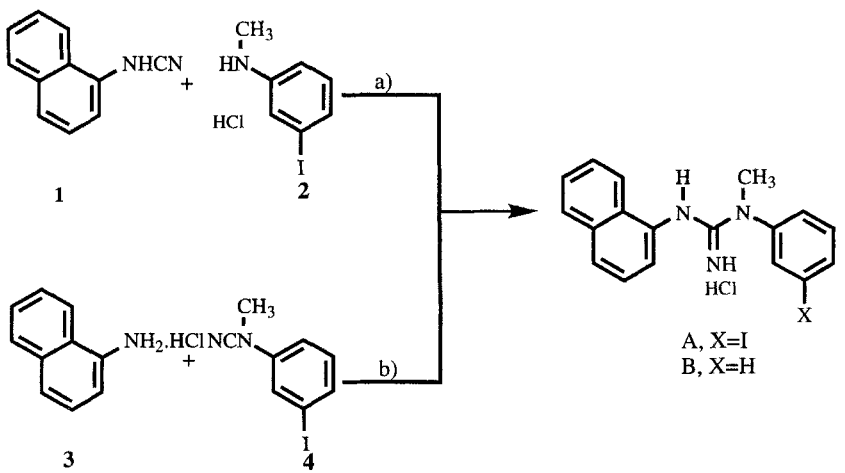
Abstract: Aromatic amines react with trimethyl orthoformate in the presence of concentrated sulfuric acid followed by acid hydrolysis to afford mono methylated amines in moderate to good yields.

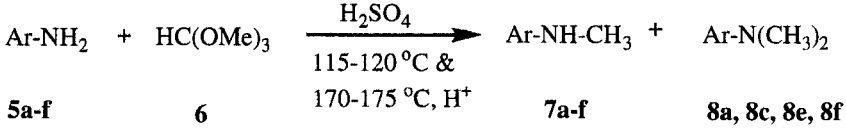
Synthesis and structure-activity studies of N,N-diarylguanidine derivatives, in search of new and selective NMDA (N-methyl-D-aspartate) receptor antagonists, have been pursued in our laboratory. During the course of our work, we became interested in the diaryl guanidine derivative [^{125}I] **CNS-1261A** as a potential radioligand for NMDA receptors[1] and the unlabelled compound, **A** (**CNS-1261A**) was required in grams quantity. Initially, we approached the synthesis of target molecule **A** through route **a** (Scheme). This

method involves the preparation of 3-iodo-N-methylaniline hydrochloride (**2**). Attempts were made to prepare 3-iodo-N-methylaniline (**7a**) through reduction[2] of the formanilide[3] derivative of 3-iodoaniline (**5a**). Subsequent conversion of the resulting N-methylaniline derivative to the corresponding hydrochloride salt and condensation of **2** with the cyanamide derivative **1**, gave the desired product, **A**. However, HPLC analysis and ^{1}H-NMR of the isolated product indicated the presence of another component. This component may result from concomittant dehalogenation during the reduction stage or in the formation of formanilide itself. This speculation was confirmed by synthesis of an authentic sample of the impurity, through the condensation of **1** and N-methylaniline hydrochloride, followed by analysis of HPLC retention time data. The guanidine derivative **A**, contaminated with the dehalogenated guanidine derivative **B**, could not be separated effectively. In an attempt to overcome this problem, route **b** was followed, involving the thermal condensation of the cyanamide derivative **4** with 1-naphthylamine hydrochloride (**3**) at elevated temperature (195 ^{o}C). This resulted in the isolation of **A** in <30% yield.



Scheme

We were therefore obliged to explore other methods for preparing 3-iodo-N-methylaniline (**7a**) that would lead to the target molecule **A** in good yields and totally avoid the use of reducing agents. This led to a convenient one pot procedure for N-methylation of amines using trimethyl orthoformate in the presence of sulfuric acid. Heating a mixture of 3-iodoaniline (**5a**) and trimethyl orthoformate (**6**) in the presence of sulfuric acid at 115-120 °C, followed by heating at 170-175 °C to effect the rearrangement,[4,5] led to the corresponding N-methylformanilide derivative. Hydrolysis of the formanilide derivative in refluxing aqueous hydrochloric acid (10%) gave 3-iodo-N-methylaniline. Initially, attempts were made to remove any unreacted starting material or dimethyl derivative formed, by washing the ethyl acetate extract of the reaction mixture with dilute hydrochloric acid. This resulted in loss of material leading to 3-iodo-N-methylformanilide in lower yields (42%). Switching to a one pot reaction, involving direct hydrolysis without the isolation of N-methylformanilide intermediate, gave the desired product, **7a** in good yield (85%). Various N-methylated aromatic amines (**7b-e**) were prepared following this procedure in moderate to good yields (45-85%). In some cases dimethylated derivatives were isolated in minor amounts (3-9%) as by products. However during the methylation of 4-nitroaniline (**5f**) under the reaction conditions considerable amounts of decomposed product were formed leading to the isolation of mono methylated and dimethylated products in low yields.



Ar= a) 3-Iodophenyl, b) 3-Methylmercaptophenyl, c) 4-Methoxyphenyl ,d) 2,4-Dichlorophenyl, e) 3,4,5-Trimethoxyphenyl, f) 4-Nitrophenyl

Methylation of amines has been achieved by numerous methods. Some of the reagents previously studied include dimethyl sulfate in the presence of alkali (with and without phase transfer catalysts[6]), methyl iodide,[7] aqueous formaldehyde[8] in the presence of sulfuric acid,[9] and formic-acetic anhydride in the presence of n-butyl methyl sulfide,[10] formaldehyde and formic acid,[11] etc. Direct conversion of aldehydes and ketones to amines has been accomplished through reductive amination using sodium cyanoborohydride.[12,13,14] However, it has not been possible to mono-methylate primary amines under reductive amination conditions.[15] Other methods include high pressure hydrogenolysis of N-(arylaminomethyl)phthalimides[8] over Raney Nickel, reduction of N-(arylaminomethyl)succinimides,[16,17] lithium aluminum hydride reduction of formanilide derivatives,[18] urethanes,[19] N-benzyloxycarbonyl derivatives.[20] Mono alkylation of primary aromatic and heteroaromatic amines with trialkyl orthoesters has been reported and this involves the reduction of the intermediate, alkyl imidate with sodium borohydride.[21] Primary and secondary amines can be N-ethylated by treatment with acetic acid and sodium borohydride.[22,23] Recently, alkylation of amines using trivalent bismuth derivatives in the presence of cupric acetate has also been reported.[24]

There have been a few reports on N-alkylation of nitrogen heterocycles using orthoformic acid derivatives.[25] Surprisingly, the synthetic use of trimethyl orthoformate for N-methylation of aromatic amines has not been reported to the best of our knowledge. In conclusion, trimethyl orthoformate can be safely and advantageously employed for mono methylation of anilines containing reductively labile groups including iodo. Using 3-iodo-N-methylaniline hydrochloride, synthesized following this procedure, target molecule **A**, **CNS-1261A** was prepared in 74% yield (HPLC purity >98%)

EXPERIMENTAL

All starting aromatic amines and trimethyl orthoformate (anhydrous) were obtained from Aldrich and were used as such without any further purification. Melting points were determined in open capillary tubes on a Mel-Temp II apparatus and are uncorrected. Yields are of pure homogenous products and are not optimized. Thin-layer chromatography was performed on Merck silica gel Baker-Flex 1B2-F silica gel plates and spots were visualized with 254 nm UV light. Column chromatography purifications were carried out using EM silica gel 60. ^{1}H-NMR were run on a Varian Gemini 300 MHz spectrophotometer using $CDCl_3$ as solvent with tetramethylsilane as internal standard. HPLC purity determinations were carried out using a Beckman 126 gradient system with UV detection at 220 nm. Linear 30 min. gradient:2to 98% CH_3CN in H_2O (0.1% TFA) Column: Ultrasphere ODS (AC-2) 5mm 4.6X 250 mm with C-18 guard column, flow rate 1ml/min.

GENERAL PROCEDURE FOR N-METHYLATION: 3-IODO-N-METHYLANILINE (7a)

To a mixture of 3-iodoaniline (**5a**, 10g, 0.0457 mole) and trimethyl orthoformate (7.5 ml, 0.0685 mole), sulfuric acid (3 drops) was added and slowly heated to 115-120 ^{o}C in a distillation setup suitable for collecting the methanol liberated. The initially thick reaction mixture went into solution at 110 ^{o}C and was maintained in the oil bath at around 120 ^{o}C for 2 h and later at 170 ^{o}C for 30 mins. The cooled reaction mixture was refluxed with 40 ml of HCl (10%) for 3 h and cooled in an icebath and slowly neutralized with 20% NaOH to alkaline pH (~12). Extraction with EtOAc (2X30 ml), followed by extraction of the aqueous layer with EtOAc (15 ml), with subsequent concentration of the organic layer gave the crude product. Purification by column chromatography using Hexanes:EtOAc 9:1 gave the desired product, 3-iodo-N-

methylaniline[26,27] (**7a**) as second fraction 7.56 g. Further elution with hexanes:EtOAc 1:1 gave the unreacted starting material, **5a** (1.66 g). Yield 85%; oil (HPLC purity 99.17%, RT=17.05 min); ^{1}H-NMR δ 2.78 (s, 3H), 3.75 (br. s, 1H), 6.53 (m, 1H), 6.89 (m, 2H), 7.02 (m, 1H).

N,N-Dimethyl-3-iodoaniline (8a): Yield <3%; oil (b. p.[28] 142-143 °C/12 mm, HPLC purity 98.5%, RT=19.80 min); ^{1}H-NMR δ 2.90 (s, 6H), 6.64 (dd,1H), 6.92 (m, 1H), 7.01 (m, 2H).

N-Methyl-3-methylthioaniline (7b): Yield 74% (based on the recovery of starting aniline, 16%); oil[27,29,30] (HPLC purity 99.78%, RT=12.44 min); ^{1}H-NMR δ 2.43 (s, 3H), 2.85 (s, 3H), 3.75 (br. s, 1H), 6.40 (m, 1H), 6.52 (m, 1H), 6.62 (m, 1H), 7.11 (m, 1H).

4-Methoxy-N-Methylaniline (7c): Yield 45%; oil (b. p.[31] 123-125 °C/13 mm, HPLC purity 97.9%, RT=10.03 min); ^{1}H-NMR δ 2.78 (s, 3H), 3.73 (s, 3H), 6.58 (dd, 2H), 6.78 (dd, 2H).

N,N-Dimethyl-4-methoxyaniline (8c): Yield 9%; m. p. 44-46 °C (m. p.[32] 45-47° C, HPLC purity 99.6%, RT=10.48 min); ^{1}H-NMR δ 2.85 (s, 6H), 3.75 (s, 3H), 6.75 (m, 2H), 6.83 (m, 2H).

2,4-Dichloro-N-methylaniline (7d): Yield 60%; oil (m. p.[33] 25 °C, HPLC purity 96.5%, RT=26.1 min); ^{1}H-NMR δ 2.88 (s, 3H), 6.56 (dd, 1H), 7.12 (m, 1H), 7.26 (m, 1H).

N-Methyl-3,4,5-trimethoxyaniline (7e): Yield 45%; oil (m. p.[34] 44.5-45.5 °C, HPLC purity 97.2%, RT=10.9 min); ^{1}H-NMR δ 2.82 (s, 3H), 3.75 (s, 3H), 3.82 (2s, 6H), 5.85 (s, 2H).

N,N-Dimethyl-3,4,5-trimethoxyaniline (8e): Yield 7%; oil[35]; ^{1}H-NMR δ 2.90 (s, 6H), 3.77 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 5.80 (s, 2H).

N-Methyl-4-nitroaniline (7f): Yield 20%; m. p. 148-150° C(m. p.[36] 152 °C); ^{1}H-NMR δ 2.95 (s, 3H), 4.63 (s, 1H), 6.53 (d, 2H), 8.09 (d, 2H).

N,N-Dimethyl-4-nitroaniline (8f): Yield 13%; m. p. 156-158° C(m. p.[37] 162 °C); ^{1}H-NMR δ 3.11 (s, 6H), 6.61 (d, 2H), 8.13 (d, 2H).

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