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Regioselective nitration of *N*,*N*-dialkylanilines using cerium(IV) ammonium nitrate in acetonitrile

Xianghua Yang, Chanjuan Xi* and Yanfeng Jiang

Key Laboratory for Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China

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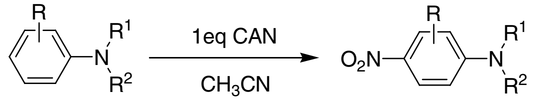
Abstract—A highly regioselective and inexpensive nitration of *N*,*N*-dialkylanilines by cerium(IV) ammonium nitrate (CAN) in acetonitrile under room temperature to yield *p*-nitryl-*N*,*N*-dialkylanilines in good yields was reported.

The nitroaromatic compounds are widely utilized in the industry and act as chemical feedstock for a great range of useful materials such as dyes, pharmaceuticals, perfumes, and plastics. Consequently, there is significant interest in the development of new synthetic methodologies to access nitroaromatic derivatives in optically pure form. Conventional procedures for nitration of aromatic compounds, mainly based on mixed nitric acid and sulfuric acid,[1] are found to be low selective and not environmental-friendly. Scientists have long been searching for alternative nitration procedures, especially for aromatic compounds, and a number of methods have been reported. Mellor and Mittoo et al.[2,3] developed a nitration system by suspending sulfuric acid on silica gel following nitration with metal nitrate, in which the procedure seemed to be complicated and the selectivity was not very high. Another strategy has been the use of lanthanide triflates as catalysts in nitric acid, but it required a strong acid, chlorinated solvents and did not improve the regioselectivity significantly.[4] Other nitration systems for aromatic compounds, such as nitration using nitrocyclohexadienones,[5] cerium(IV) ammonium nitrate (CAN) on silica gel,[6,7] nitric acid–acetic anhydride–zeolite β system,[8] and similar systems,[9–11] more or less have their limitations for utilization. The use of metal nitrates has received much attention. Recently a vanadium nitrate $VO(NO_3)_3$ has proved to be useful[12] in nitration of simple aromatics. However this nitrate must be prepared from dinitrogen pentoxide. Earlier, iron,[13,14] copper,[14] chromium,[15] and cerium[16] nitrates have been studied but have failed to be generally useful. Great demand still exists for a high regioselectivity, inexpensive, and mild nitration system. Herein, we would like to report a nitration system for aromatic substrates, *N*,*N*-dialkylanilines, using cerium(IV) ammonium nitrate (CAN) in acetonitrile as the solvent (Scheme 1).



Scheme 1.

CAN has been used earlier for many oxidative purposes including deprotections[17] and ultrasound-aided oxidations.[18] Recently, we have reported that reaction of *N*,*N*-dialkylanilines with CAN in water afforded N,N,N',N'-tetraethylbenzidines in high yields.[19] During the course of our studies, we found that treatment of *N*,*N*-dialkylanilines with CAN in acetonitrile gave *N*,*N*-dialkyl-4-nitroanilines in good yields with high regioselectivity.

To start with, experiments were carried out to choose the proper reaction conditions. First of all, a number of solvents were tried and the results are listed in Table 1. It was interesting to see that nitration tend to happen only in non-protic and CAN-dissolvable solvents, such as acetonitrile. Then, the amount of CAN was varied from 0.5 to 2 equiv. We found 1 equiv of CAN gave the best results in this reaction.[24] Moreover, when

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* Corresponding author. E-mail: cjxi@tsinghua.edu.cn

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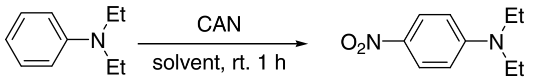
Table 1. Effect of solvent and amount of CAN on the nitration of anilines



Entry	Solvent	CAN (equiv)	Yield (%)[a]
1	CH_2Cl_2	1	0
2	$CHCl_3$	1	0
3	CCl_4	1	0
4	THF	1	0
5	CH_3CN	1	65
6	CH_3CN	2	Complex[b]
7	CH_3CN	0.5	0
8	CH_3CN	1.2	41[c]
9	CH_3CN	1.5	10[d]
10	CH_3OH	1	Coupling[e]
11	CH_3OH+CH_3CN (1:1)	1	Coupling[e]

[a] Isolated yield.

[b] Starting material disappeared but no major product.

[c] Another product (*N*,*N*,*N*′,*N*′-tetraethylbenzidine) was isolated in 31% yield.

[d] Other two products were isolated: *N*,*N*-diethyl-2,4-dinitrobenzenamine in 34% yield; *N*,*N*,*N*′,*N*′-tetraethylbenzidine in 45% yield.

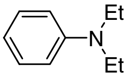
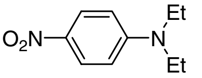
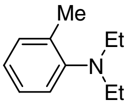
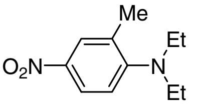
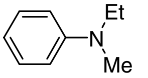
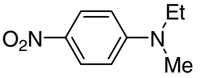
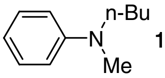
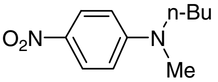
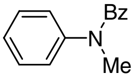
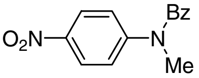
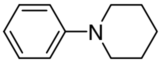
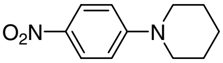
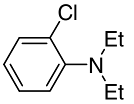
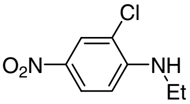
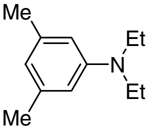
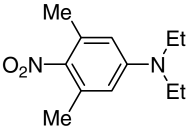
[e] Major product is *N*,*N*,*N*′,*N*′-tetraethylbenzidine.

N,*N*-diethylaniline was treated with 2 equiv of CAN in acetonitrile at 0 °C, the reaction did not proceed. It is different from known CAN-mediated reaction of *N*,*N*-dialkylanilines in water to form *N*,*N*,*N*′,*N*′-tetraethylbenzidines, in which 2 equiv of CAN was required.[19]

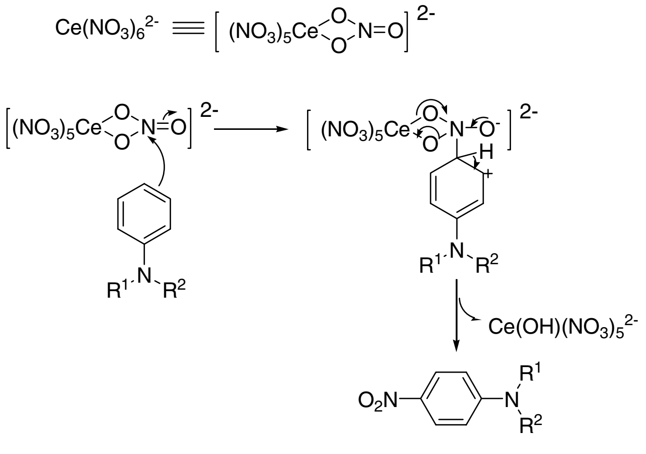
The results of a series of *N*,*N*-dialkylanilines (**1a**–**h**) under the chosen condition were collected and are reported in Table 2. In most cases, the reaction afforded satisfactory results. The reaction of aniline derivative **1g** (entry 7), containing an electron-withdrawing substituted group such as chloride on the phenyl ring, with 1 equiv of CAN in acetonitrile gave compound **2g** in low yield accompanied by the dealkylation.[20] This result was probably due to low electron density of phenyl ring. In other ways, treatment of compound **1h** (entry 8) with CAN in acetonitrile did not give the desired product, even prolonged the reaction time and increased the reaction temperature. It may be **1h** with two methyl groups on the *m*-position, which made NO_2 group harder to attack the *para*-position. For other *N*,*N*-dialkylanilines, moderate to good yields of *p*-nitryl-products were collected.

For the nitration reaction it can be noted that the nitro-groups are introduced in the aromatic nucleus as by electrophilic nitration. In this work, the CAN acts as a carrier of nitronium species and the CAN nitration is similar to that noted with other metal nitrates such as the nitratocomplexes of Ti^{IV},[21] Zr^{IV}, and Fe^{III}.[22] The

Table 2. Nitration of *N*,*N*-dialkylanilines with CAN in acetonitrile

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	 **1a**	2	 **2a**	65
2	 **1b**	Over night	 **2b**	60
3	 **1c**	2	 **2c**	53
4	 **1d**	2	 **2d**	54
5	 **1e**	Over night	 **2e**	46
6	 **1f**	4	 **2f**	40
7	 **1g**	Over night	 **2g**	26
8	 **1h**	Over night	 **2h**	Trace

[a] Isolated yield.



Scheme 2.

behavior of the nitrato-group as a bidentate ligand has been indicated to be a condition for the nitration reaction.[23] We therefore proposed the mechanism shown in Scheme 2. The nitration reaction occurred through a molecular rearrangement within a co-ordination complex of the substrate with a metal-containing species.

In summary, a nitration system using CAN as a nitration reagent in acetonitrile for *N*,*N*-dialkylanilines was developed. This reaction has several advantages, including high regioselectivity, easy handling, and low cost.

Acknowledgments

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24. Representative procedure for the nitration of *N*,*N*-dialkylanilines. Nitration of *N*,*N*-diethylaniline. *N*,*N*-Diethylaniline (1 mmol) was added dropwise after CAN (1 mmol) completely dissolved in CH_3CN (20 mL), then the reaction mixture was stirred constantly until *N*,*N*-diethylaniline totally disappeared. The reaction mixture was quenched with aqueous solution of K_2CO_3, followed by extraction of the organic phase with ethyl acetate. The solvent was evaporated under reduced pressure and product was isolated by chromatography on neutral Al_2O_3. The product, *p*-nitryl-*N*,*N*-diethylaniline, was isolated (126 mg, 65%) as yellow solid using 1:10 EtOAc/petroleum ether mixture as eluent. ^{1}H NMR ($CDCl_3$, $SiMe_4$) δ 1.23 (t, $J = 7.0$ Hz, 6H), 3.44 (q, $J = 7.2$ Hz, 4H), 6.58 (d, $J = 9.6$ Hz, 2H), 8.10 (d, $J = 9.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ 12.5, 45.0, 109.9, 126.6, 136.5, 152.3. ESI-MS: $M+H^+$ (m/z) 195.