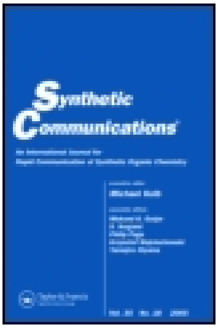


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Nitration of Electron-Rich Aromatic Compounds by Cerium Ammonium Nitrate Coated on Silica

Jean-Luc Grenier [a] , Jean-Pierre Catteau [a] & Philippe Cotelle [a]
[a] Laboratoire de Chimie Organique Physique associé au CNRS, ENSCL Université de Lille 1, F-59655, Villeneuve d'Ascq, France

Version of record first published: 17 Sep 2007.

To cite this article: Jean-Luc Grenier, Jean-Pierre Catteau & Philippe Cotelle (1999): Nitration of Electron-Rich Aromatic Compounds by Cerium Ammonium Nitrate Coated on Silica, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:7, 1201-1208

To link to this article: http://dx.doi.org/10.1080/00397919908086091

SYNTHETIC COMMUNICATIONS, 29(7), 1201–1208 (1999)

NITRATION OF ELECTRON-RICH AROMATIC COMPOUNDS BY CERIUM AMMONIUM NITRATE COATED ON SILICA

Jean-Luc Grenier, Jean-Pierre Catteau and Philippe Cotelle*

Laboratoire de Chimie Organique Physique associé au CNRS, ENSCL
Université de Lille 1, F-59655 Villeneuve d'Ascq, France

Abstract: Treatment of electron-rich aromatic derivatives with cerium (IV) ammonium nitrate coated on silica (CAN/SiO_2) affords nitro aromatic compounds. The scope and the limitation of this reaction are discussed.

During the past few years, we have studied the chemical and biological properties of nitrodihydroxybenzenes and nitrocaffeic acids[1,2]. Most of these compounds were prepared by demethylation of the nitrodimethoxyphenyl derivatives. In connection with this project, we needed a mild method for the regioselective mononitration of the starting phenolic ethers.

To whom correspondence should be addressed

Standard procedures for NO_2^+ generation have employed nitric acid directly or have produced nitric acid *in situ* by means of nitrate salts in protic media. However, polynitration, low regioselectivity, total oxidation of the reactant or ipso nitration may occur leading to poor yields in pure compounds. Seeking milder conditions, we focused on the use of cerium (IV) ammonium nitrate coated on silica (CAN/SiO_2) which has been employed on polynuclear aromatics[3] or heterocycles[4,5]. Despite the apparent utility of this reagent, it has not been widely used for nuclear nitration, which may be due to side reactions. CAN in protic solvent (water/acetonitrile or methanol) has been widely employed for the oxidative demethylation of 1,4-dimethoxyphenyl derivatives[6], oxidation of benzylamines or benzylalcohols into benzaldehydes[7] and we have reported the use of CAN/SiO_2 for the deprotection of benzaldehyde diacetates[8].

In this paper, we describe the high regioselectivity achieved in the ring nitration of several methoxyphenyl derivatives with CAN/SiO_2. An important purpose of this paper is to clearly define the reaction conditions and to refocus attention on the excellent ability of CAN/SiO_2 to ring nitrate activated aromatic compounds. We reacted several polymethoxyphenyl derivatives with CAN/SiO_2[9] in dichloromethane during 15 min or 48h (in the cases of no reaction or low yield after 15 min) at room temperature. Results are reported in table 1 (scheme 1). Under these conditions, anisole **1a** did not react whereas dimethoxybenzenes gave nitrodimethoxybenzenes in high yields. 1,2-Dimethoxybenzene **1b** and 1,4-

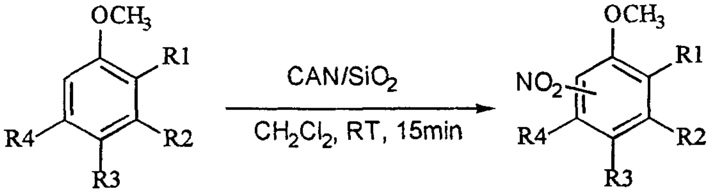
Table 1: Reaction of **1** with CAN/SiO_2

Substrate	R1	R2	R3	R4	Yield (in %)^a	Product
1a	H	H	H	H	0	b
1b	OCH_3	H	H	H	93	1,2-dimethoxy-4-nitrobenzene
1c	H	OCH_3	H	H	93	1,3-dimethoxy-2-nitrobenzene (33%) 1,3-dimethoxy-4-nitrobenzene (33%) 1,3-dimethoxy-5-nitrobenzene (33%)
1d	H	H	OCH_3	H	84	1,4-dimethoxy-2-nitrobenzene
1e	Br	H	OCH_3	H	87	5-bromo-1,4-dimethoxy-2-nitrobenzene
1f	OCH_3	H	OCH_3	H	88	1,4,5-trimethoxy-2-nitrobenzene
1g	$NHCOCH_3$	H	OCH_3	H	81	2,5-dimethoxy-4-nitroacetanilide
1h	SeCN	H	OCH_3	H	60	2,5-dimethoxy-4-nitro-1-selenocyanatobenzene
1i	CH_2OH	H	OCH_3	H	58	2,5-dimethoxy-4-nitro-1-hydroxymethylbenzene
1j	CH_2Br	H	OCH_3	H	64	2,5-dimethoxy-4-nitro-1-bromomethylbenzene
1k	NO_2	H	OCH_3	H	0	b
1l	CHO	H	OCH_3	H	45^c	2,5-dimethoxy-4-nitrobenzaldehyde (67%) 2,5-dimethoxy-6-nitrobenzaldehyde (33%)
1m	COOH	H	OCH_3	H	0	b
1n	$Se\text{-})_2$	H	OCH_3	H	0	b
1o	$CH(OCOCH_3)_2$	H	OCH_3	H	0	b
1p	OH	H	H	H	90	2-methoxy-4-nitrophenol (48%) 2-methoxy-6-nitrophenol (44%) 2-methoxy-4,6-dinitrophenol (8%)
1q	H	H	OH	H	95	benzoquinone
1r	H	CHO	OH	H	41^c	2-hydroxy-5-methoxy-3-nitrobenzaldehyde
1s	H	COOH	OH	H	50^c	2-hydroxy-5-methoxy-3-nitrobenzoic acid
1t	COOH	H	OCH_3	OCH_3	46^c	1,4,5-trimethoxy-2-nitrobenzene
1u	CHO	H	OCH_3	OCH_3	39^c	1,4,5-trimethoxy-2-nitrobenzene

a. Yields are given in pure isolated compounds except for compounds **1c** and **1p**. In this cases, the percentages of the different compounds were calculated from the ^1H nmr spectrum of the crude mixture.

b. Starting material was recovered quantitatively.

c. Yields obtained with a reaction time of 48 hours.



Scheme 1

dimethoxybenzene **1c** gave the expected 1,2-dimethoxy-4-nitrobenzene and 1,4-dimethoxy-2-nitrobenzene respectively. 1,3-Dimethoxybenzene **1d** gave an equimolar mixture of 1,3-dimethoxy-2-nitrobenzene, 1,3-dimethoxy-4-nitrobenzene and 1,3-dimethoxy-5-nitrobenzene.

1,4-Dimethoxybenzenes **1e-j** which possess an additional electron-donor group gave a nitration in position para to the additional group leading in good to excellent yields to 1,4-dimethoxy-2-nitro-5-substituted benzenes. The hydroxymethyl group (**1i**) was not oxidized under this conditions whereas we have reported that CAN can easily oxidized hydroxymethyl, methoxymethyl and dimethylaminomethyl groups when it is dissolved in a mixture of water and acetonitrile.

1,4-Dimethoxybenzenes **1k-o** are not nitrated even when the reaction time was increased to 48 hours except for **1l** which gave 2,5-dimethoxy-4-nitrobenzaldehyde and 2,5-dimethoxy-6-nitrobenzaldehyde in a ratio 2:1. This ratio is quite different than that obtain by nitration with nitric acid (1 :2)[10]. This difference may be explain by the occurrence of another nitration mechanism : Ce(IV) reacts with the aromatic compoundto give a radical cation leading to a different regioselectivity of the nitration[11]. More curiously, 2,5-dimethoxyphenyldiselenide **1n** was totally unreactive versus CAN (even under protic conditions whereas **1h** was oxidized to the selenocyanatobenzoquinone[12] under protic conditions).

In a second series of reaction, we reacted some methoxyphenols under the same conditions. 2-Methoxyphenol **1p** gave in high yield a mixture of 2-methoxy-4-nitrophenol (48%), 2-methoxy-6-nitrophenol (44%) and 4,6-dinitro-2-methoxyphenol (8%) whereas 4-methoxyphenol **1q** was readily oxidized to benzoquinone almost quantitatively. This unexpected result and the low or absence of reactivity of **1l** and **1m** led us to react 2-hydroxy-5-methoxybenzaldehyde and benzoic acid (**1r** and **1s** respectively) with CAN/SiO_2. In these two cases, the nitration occurred leading to 2-hydroxy-5-methoxy-3-nitrobenzaldehyde and benzoic acid in acceptable yields (41 and 50% respectively) after a long reaction time. Since we have reported[13] the nitrodecarboxylation and the nitrodeformylation of electron-rich benzoic acids and benzaldehydes we finally tested 2,4,5-trimethoxybenzoic acid and benzaldehyde **1s** and **1t** respectively. As expected, the nitrodecarboxylation or the nitrodeformylation occur but in moderate yields.

In conclusion, we have shown that CAN/SiO_2 in dichloromethane is an efficient and mild nitrating agent of electron-rich aromatic compounds. The nitration occurs under the reaction conditions described when the aromatic ring is substituted by at least two electron donating groups. In the cases of 1,2,4-substitution the nitration occurs selectively at the position 5. The limitations are due to (i) low reactivity of the substrate, (ii) competition with the oxidative demethylation leading to benzoquinones in the cases of highly oxidizing substrates and (iii) ipso nitration.

EXPERIMENTAL

TLC analyses were performed on a 3×10 cm plastic sheet precoated with silica gel 60F254 (Merck) (Solvent system: ethyl acetate/cyclohexane 1:1). melting points were obtained on a Reichert Thermopan microscope and are uncorrected. NMR spectra were obtained on a AC 200 Bruker spectrometer in the appropriate solvent with TMS as internal reference. Mass spectra were recorded on a Ribermag R 10-10 (Electron Impact, 60eV). Elemental analysis were performed by CNRS laboratories (Vernaison) and were within 0.4% of he theorical value.

Starting compounds were purchased from Aldrich-Chimie (St Quentin-Fallavier) except for compounds **1h**[10], **1n** and **1o**[8].

2,5-Dimethoxyphenyldiselenide **1n** was obtained by reduction of **1h** with $NaBH_4$ followed by air oxidation in 90% yield. m.p.= 69-71°C; ^{1}H nmr (DMSO-6d): 3.63 (s, 3H), 3.81 (s, 3H), 6.82 (d, 1H, ^{4}J=3.0Hz), 6.95 (dd, 1H, ^{4}J=3.0Hz, ^{3}J=8.8Hz), 6.98 (d, 1H, ^{3}J=8.8Hz); ^{77}Se nmr (DMSO-6d): 341ppm; EIMS: 434 ($M^{+\circ}$(^{80}Se), 2%), 218 (M+°(^{80}Se),-216, 8%); Elemental analyses for $C_{16}H_{18}O_4Se_2$: Calcd C: 44.46; H: 4.20; Found C: 44.75; H: 4.57.

Typical procedure: The Substrate (1, 1 mmol.) in dichloromethane (15ml) is added with stirring to the CAN/SiO_2 (6.94g, 2.1 mmol. of Ce(IV)). The mixture is stirred for 15 min. or more and filtered. The residue is washed with dichloromethane (2×15ml). Evaporation of the solvent from the combined filtrates gives a crude product which was purified by column chromatography if necessary. Purity of product was controlled by tlc, melting point and ^{1}H nmr.

2,5-Dimethoxy-4-nitro-1-selenocyanatobenzene gave the following analytical data: m.p.= 184-5°C; ^{1}H nmr (DMSO-6d): 3.92 (s, 3H), 3.93 (s, 3H), 7.50 (s, 1H), 7.69 (s, 1H); ^{77}Se nmr (DMSO-6d): 314ppm; EIMS: 288 ($M^{+°}$(^{80}Se), 98%), 273 (M+°(^{80}Se),-15, 10%); Elemental analyses for $C_9H_8N_2O_4Se$: Calcd C: 37.65; H: 2.81; Found C: 37.26; H: 2.47.

REFERENCES

1. Grenier, J.L.; Cotelle, P.; Cotelle, N.; Catteau, J.P. *J. Chim. Phys.* **1995**, *92*, 97.
2. Grenier, J.L.; Cotelle, N.; Cotelle, P.; Catteau, J.P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 431.
3. Chawla, H.M.; Mittal, R.S. *Synthesis* **1985**, 70.
4. Del Mar Blanco, M.; Avendano, C.; Cabezas, N.; Menendez, J.C. *Heterocycles* **1993**, *36*, 1387.
5. Chakrabarty, N.; Batabyal, A. *Synth. Commun.* **1994**, *24*, 1.
6. Peyton, J.; Callery, P.S.; Shulgin, A.T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 627.
7. Badea, I., Cotelle, P.; Catteau, J.P. *Synth. Commun.* **1994**, *24*, 2011.
8. Cotelle, P.; Catteau, J.P. *Tetrahedron Lett.* **1992**, *33*, 3855.
9. Fischer, A.; Henderson, G.N. *Synthesis* **1985**, 641.
10. Mahmoud, C.; Cotelle, P.; Catteau, J.P. *Heterocycles* **1992**, *34*, 1749.
11. Perrin, C.L. *J. Amer. Chem. Soc.* **1997**, *99*, 5516 .

12. The oxidation of **1h** with CAN in water/acetonitrile 9/1 gave selenocyanatobenzoquinone in 54% yield. m.p.= 205-7°C; ^{1}H nmr (DMSO-6d): 6.98 (dd, 1H, $^{4}J=2.4Hz$, $^{3}J=10.0Hz$), 7.06 (d, 1H, $^{3}J=10.0Hz$), 7.11 (d, 1H, $^{4}J=2.4Hz$); ^{77}Se nmr (DMSO-6d): 317ppm; EIMS: 213 ($M^{+\circ}$(^{80}Se), 73%), 218 (M+°(^{80}Se)-CN, 11%); Elemental analyses for $C_7H_3NO_2Se$: Calcd C: 39.65; H: 1.43; Found C: 39.58; H: 1.07.

13. Cotelle, P.; Catteau, J.P. *Synth. Commun.* **1996**, *26*, 4105.

Accepted 8-8-98