JOC Article

Electrophilic Tetraalkylammonium Nitrate Nitration. II. Improved Anhydrous Aromatic and Heteroaromatic Mononitration with Tetramethylammonium Nitrate and Triflic Anhydride, Including Selected Microwave Examples†

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A new one-pot nitration employing tetramethylammonium nitrate and trifluoromethanesulfonic anhydride in dichloromethane to provide a ready source of the nitronium triflate nitrating agent is presented. Rapid and selective nitration with a variety of aromatic and heteroaromatic substrates is achieved resulting in the synthesis of several novel organic compounds. A distinct advantage is the removal of undesired byproducts by aqueous workup. This very mild nitration permits large-scale syntheses and gives high isolated product yields that often require no further purification. This tetramethylammonium nitrate-based nitration also has been applied to microwave-assisted conditions, and the results with several compounds are outlined.

Introduction

A convenient one-pot nitration reaction using tetramethylammonium nitrate **1a** and trifluoromethanesulfonic (triflic) anhydride **2** in dichloromethane readily generates the nitronium triflate (NO_2OTf) **3** nitrating agent. The addition of an aromatic substrate **5** to the in situ-generated nitronium triflate **3** effects an anhydrous electrophilic nitration that is both selective and amenable to large-scale synthesis efforts. Reactions are conducted from −78 °C to room temperature and at reflux with less activated reactants (Scheme 1). A simple aqueous workup removes the ionic tetramethylammonium triflate salt **4a** and triflic acid byproducts. Subsequent in vacuo solvent removal gives the mononitrated product **6** in high isolated yield and purity. Further purification often is unnecessary, and some products are analytically pure.

Hygroscopic nitronium triflate **3** initially was synthesized by reacting anhydrous HNO_3,[1] N_2O_5,[2] or NO_2Cl[3] with triflic acid. Because of its hygroscopicity, **3** is formed in situ as a nitrating agent in an appropriate organic solvent. An initial report on aromatic mononitration described the formation of **3** in situ by reacting anhydrous HNO_3 with two moles of triflic acid in CH_2Cl_2, CCl_4, $CFCl_3$, or pentane solvent.[1] A later aromatic nitration used 94% HNO_3 with triflic anhydride **2** to produce **3**.[4] Subsequently reported was a convenient in situ generation of **3** by reacting commercially available organic tetraalkylammonium nitrate salts, tetrabutyl- **1b** and tetraethylammonium nitrate **1c**, with **2** in CH_2Cl_2 to effect saturated heterocycle ring N-atom nitration and bromobenzene mononitration.[5,6]

Using commercially available reagent **1a** offers a distinct advantage over the previously reported higher **1b** and **1c** homologues because pure nitrated product **6** is isolated more easily.[5,6] When **1a** with **2** generate nitrating agent **3**, hydrophilic byproduct **4a** also results, which is removed during aqueous workup. Reagents **1b** and **1c** produce less hydrophilic byproducts **4b** and **4c**; however, these remain during aqueous workup, and column chromatographic separation of **4b** or **4c** from the desired product **6** is necessary.[5,6] Reactions of NH_4NO_3 with **2** in CH_2Cl_2 or CH_3NO_2 required no column chromatographic separation but gave inconsistent results and lower product yields.[5]

Five novel nitroaromatic compounds, including two heterocycles, are reported using using reactant **1a** to generate nitrating reagent **3**. Also discussed are the directional effects, substituent compatibility, product selectivity, and purity, as well as direct scale-up results available from this nitration. Some parametric studies

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(2) Schmeisser, M.; Sartori, P.; Lippsmeir, B. *Z. Naturforsch*. **1973**, *28b* 573−574.

(3) Yarbro, S. K.; Noftle, R. E. *J. Fluorine Chem*. **1975**, *6*, 187−189 and references therein.

(4) Umemoto, T.; Ishihara, S. *Tetrahedron Lett*. **1990**, *31*, 3579−3582.

(5) Shackelford, S. A.; Sharts, C. M.; Adams, C. M. *11th Rocky Mountain Regional Am. Chem. Soc. Mtg.*, Albuquerque, NM, July 10−12, 1992.

(6) Adams, C. M.; Sharts, C. M.; Shackelford, S. A. *Tetrahedron Lett*. **1993**, *34*, 6669−6671.

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SCHEME 1. Aromatic and heteroaromatic compounds 5 (A = C, N, O, S), ring size = 5 and 6, plus R groups as seen in 5−45

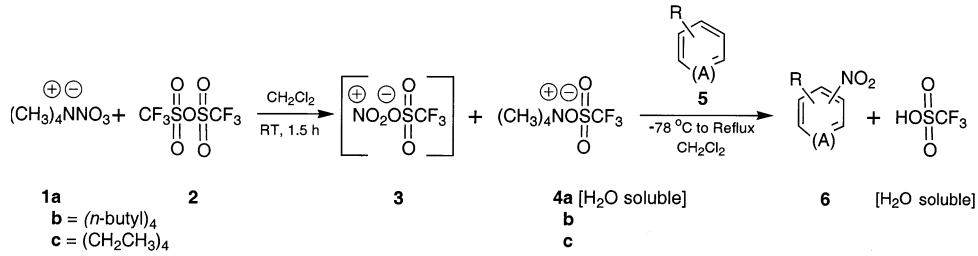


TABLE 1. $(CH_3)_4NNO_3$-Based Nitration of Monosubstituted Benzenes (7.5 mmol Scale)

reactant R group	no.	conversion (%)[a]	product	isolated yield (%)	o/m/p isomers (%)	time (h)
−OCH_3	**5a**	100	**6a**	97	63/5/32	24
−OH	**5b**	100	**6b**	74	90/0/10	23
−CH_3	**5c**	100	**6c**	99	62/0/38	24
−Br	**5d**	95	**6d**	90	33/0/67	26
−CHO	**5e**	ND	**6e**	70	31/63/6	97
−CF_3	**5f**	ND	**6f**	68	8/88/4	24
−CF_3	**5f**	ND	**6f**	68	7/89/4	48
−COOH	**5g**	71	**6g**	52	16/78/6	26
−SO_2CH_3	**5h**	57	**6h**	89[b]	13/84/3	102

[a] ND = not determined because of reactant volatility and its loss during solvent removal. [b] Actual yield in a pure isolated mixture contained only reactant (43%) and product isomers (57%).

presented suggest optimum reaction times for complete reactant conversion in both the conventional benchtop and microwave-assisted nitrations.

Results and Discussion

Aromatic Nitration. A wide scope of monosubstituted benzenes can be nitrated under the mild conditions this **1a**-based anhydrous nitration reaction allows (Table 1). Nitrations were conducted with 1.05 equiv of **3** as described by the General Procedure (Experimental Section). These nitration conditions are compatible with many pendant electron-donating and withdrawing substituents found on the benzene ring, including unsaturated cyano, aldehyde, and ester functional groups.

Table 1 reflects the regiospecificity found with monosubstituted benzenes. Isomeric percentages were determined by proton NMR on the isolated products. Aniline gave no nitrated product, and nitrobenzene showed a trace of *m*-dinitrobenzene. These exploratory reactions were not optimized because our goal was to assess comparative substituent compatibility, directing effects, and compound reactivity.

The pronounced ortho-nitration (o/p = 90/10) with phenol **5b** may result from the electrophilic nitronium cation interacting with the lone pair electrons on the oxygen atom of the directing hydroxyl group.[7a,8] IPSO addition followed by a 1,2-migration also would predict the same result.[7b] The two nitrations of α,α,α-trifluorotoluene **5f** confirm the reproducibility of this reaction. The earlier anhydrous HNO_3 and triflic acid nitration procedure gives a similar isomeric product distribution with toluene **5c** (o/m/p) = 62/1/37) and **5f** (o/m/p = 14.3/85.6/0.1).[1] A 1:2 HNO_3/H_2SO_4 mixed acid nitration of **5c** also provides a similar o/m/p isomeric distribution (62/5/33).[9] Proton NMR analyses of the isolated products from reactants **5a**−**d** and **5f**−**h** show very clean compounds with little or no byproduct formation. Some unidentified byproduct was seen in the isolated isomeric product mixture of benzaldehyde **5e**.

These same reaction conditions were also applied to multiple-substituted benzenes (Table 2). Isolated product purities seen in Table 2, and all subsequent tables, were determined by HPLC at a 220 nm UV wavelength detection. Purities determined by ^{1}H NMR are specifically noted.

The only previous synthesis of **12** by direct nitration used fuming nitric acid at 5 °C for 1 h and gave a 70% isolated product yield before further purification.[10] The ratio of products **10a** and **10b** from **9** reveals that the sterically crowded position between 1,3-disubstituted methoxy groups is hardly attacked when less hindered sites are available. With no alternative, nitration readily occurs between two 1,3-positioned methoxy groups with reactant **13** giving product **14**. Product **14** represents an unreported compound. As seen in the nitration of **13**, increasing the number of equivalents of **3** can drive reactions to completion. A slower reaction warming profile was used in the latter two nitrations of **13**.[11]

The General Procedure for this nitration scales directly from 7.5 to 100 mmol by a proportional increase of reagents and solvent while keeping reaction times the same (Table 3). The addition time of **2** into the CH_2Cl_2 suspension of **1** to generate **3** may be increased to dissipate a mild exotherm. Isolated product purities and yields compare favorably with those obtained using standard nitration methods. Our nitration of 4-*tert*-butyltoluene **15** on an 86 mmol scale exclusively produced

(7) (a) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 1st ed.; McGraw-Hill: New York, 1968; p 388. (b) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; Wiley & Sons: New York, 1992; pp 512−513.

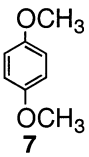
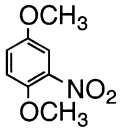
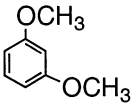
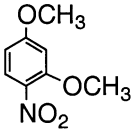
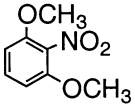
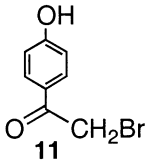
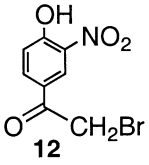
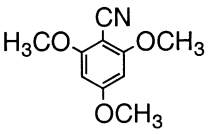
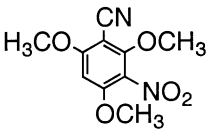
(8) Strazzolini, P.; Giumanini, A. G.; Scuccato, M. *J. Org. Chem.* **1998**, *63*, 952−958.

(9) Roberts, J. D.; Caserio M. C. *Modern Organic Chemistry*; W. A. Benjamin, Inc.: New York, 1967; p 545.

(10) Garg, H. G.; Singh, P. P. *J. Chem. Soc. C* **1969**, 607.

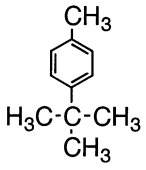
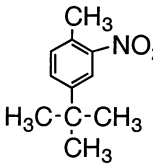
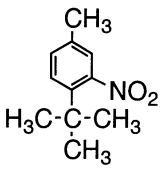
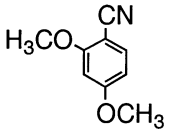
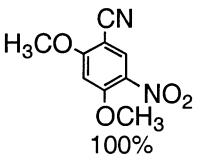
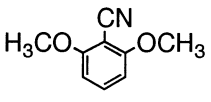
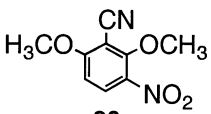
(11) Reactant **13** (Table 2). The first two runs are described in the General Procedure. Replacing the CO_2/acetone bath with a CO_2/acetonitrile cold bath for 2.5 h (from −49.6 to −35.0 °C) produced the best result (run 3). This bath then was allowed to warm to 9.0 °C over the next 2.5 h before removal; the reaction then was stirred another 48 h at room temperature. In the large-scale nitrations with **13**, **17**, and **19**, the CO_2/acetone bath remained for 1 h, was replaced with a CO_2/acetonitrile bath (ca. −45 °C) for 3 h, and then was permitted to warm unattended to room temperature over the next 48 h. For compound **15**, the CO_2/acetone bath was removed immediately, and the reaction was stirred for 24 h. For compound **11** (large scale), the CO_2/acetone bath was left in place to warm unattended to room temperature over the next 23 h.

TABLE 2. $(CH_3)_4NNO_3$-Based Nitration of Multiple-Substituted Benzenes (7.5 Mmol Scale)

Compound	% Converted	Product(s)	Reaction Time (h)	% Isolated Yield (Purity)
 **7**	100	 **8**	17	71 (92)
 **9**	100	 95% **10a**  5% **10b**	15	82 (-----)
 **11**	100	 **12**	27	94 (91)
 **13**	58 [a] 96 [a] 100 [b]	 **14**	15 46 53	43 (-----) 80 (81) 86 (95)

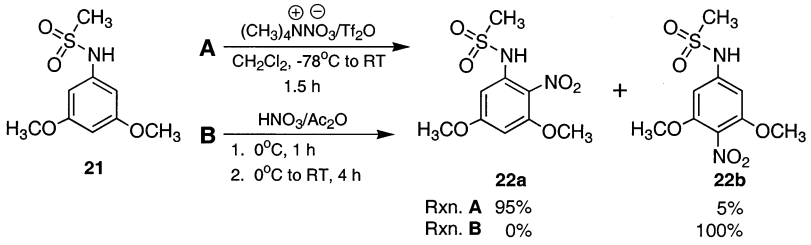
[a] NO_2OTf equivalents = 1.05 relative to reactant **13**. [b] NO_2OTf equivalents = 1.50 relative to **13**.

TABLE 3. $(CH_3)_4NNO_3$-Based Nitration at Large-Scale (86 to 100 Mmol Scale)

Reactant	Scale (mmol)	Equiv. of **3**	Product(s)	Reaction Time (h)	% Isolated Yield (Purity)
11	93	1.1	**12**	23	91 (88)[a]
13	90-100	1.5 -1.7	**14**	48-52	82-84 (90-95)
 **15**	86	1.05	 100% **16a**  0% **16b**	24	94 (93)[a]
 **17**	100	1.5	 100% **18**	52	91-96 (78-82)
 **19**	100	1.5	 **20**	48-52	100 (97)

[a] Determined by NMR analysis.

SCHEME 2



the 4-*tert*-butyl-2-nitrotoluene isomer **16a**. Electrophilic nitration of **15** with NO_2BF_4 in tetramethylenesulfone gave 5% of the other *tert*-butyl-3-nitrotoluene isomer **16b**.[12]

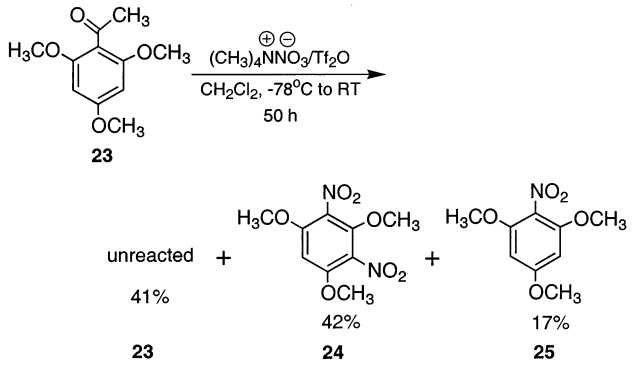
An excellent selectivity also was obtained in the nitration of 2,4-dimethoxybenzonitrile **17**. Only the novel, unreported 2,4-dimethoxy-5-nitrobenzonitrile **18** isomer was obtained. Efficient stirring was necessary for optimum yields and purity, so a mechanical stirrer rather than magnetic stirring was used in most large-scale reactions. Nitration of **15** using a magnetic stirring bar selectively provided product **16a**. Isolated product **16a** was reduced to its aniline analogue without purification. Reactant **19** gave an exceptional yield and purity of **20**.

Reactant **21** gave a second example of preferred ortho-nitration relative to its pendant methylsufonamide substituent by forming an isomeric mixture containing 95% **22a** and 5% **22b** (Scheme 2). The familiar fuming HNO_3/acetic anhydride nitration gave only the para-isomer **22b**.

This nitration reaction normally affords monosubstituted nitroaromatic products. Two specific electron-rich aromatic substrates under the General Procedure conditions unexpectedly gave isomeric mixtures that contained some dinitro-substituted products.

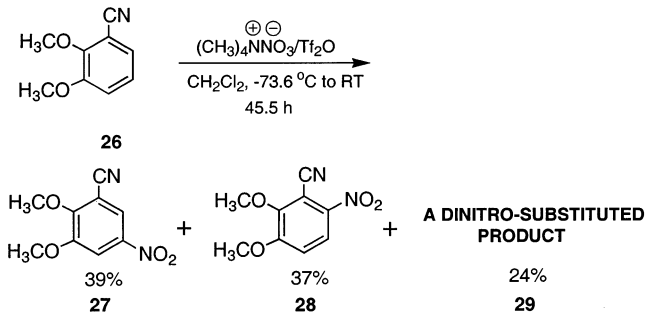
The nitration 2,4,6-trimethoxyacetophenone **23** reproducibly gave products devoid of the acetyl group (eq 1). While N-atom nitration via nitrative deacetylation occurs with saturated N-acetylated heterocycles with **3**,[6] formation of **25** by an aromatic C-atom nitrative deacetylation was not expected, because the two mechanisms would differ substantially.

Equation 1



Dinitration also occurred with 2,3-dimethoxybenzonitrile **26** using 1.5 equiv of **3** (eq 2). Unlike its two isomers **17** and **19**, a 100% conversion of **26** gave an isolated mixture consisting of 24% dinitro-substituted product **29**. The nearly equal presence of isomers **27** and **28** also was unexpected. If the cyano group meta-directing influence were significant, isomer **27** would predominate.

Equation 2



Heteroaromatic Nitration. Although the heterocyclic aromatic ring is less susceptible to electrophilic substitution, this nitration reaction was extended to heteroaromatic compounds. Initially, the General Procedure reaction conditions were applied and then modified as necessary.

Reactant 2-chloro-4,6-dimethoxypyrimidine **30** formed 2-chloro-4,6-dimethoxy-5-nitropyrimidine **31** in an exceptionally high isolated yield and purity (Table 4). An increase from 1.05 to 1.50 equiv of **3** effected a complete conversion to product **31**. The nitration of **30** also scales easily from 7.5 mmol of **30** (1.31 g) to 2864 mmol (500 g) with little reduction in isolated product yield and purity. Product **31** was analytically pure as isolated and represents an unreported compound.

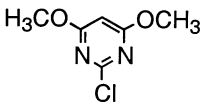
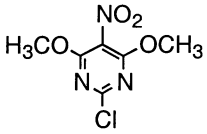
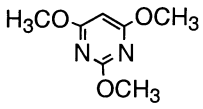
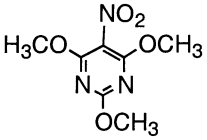
Nitrating agent **3** usually is generated in situ over a 1.5 h in CH_2Cl_2 solvent followed by addition of reactant **5** (Scheme 1). If **5** contains no substituent groups susceptible to attack by the triflic anhydride **2**, a mixture of **1** and **5** can be treated with **2** (Alternative Method). The alternate method also used heptane to effect precipitation of product **31** from CH_2Cl_2 solvent to produce the slightly lower 83% yield. A second crop then gave a comparable overall product yield. The thermal stability and impact initiation properties of **31** suggest that one should exercise care in the heating, handling, and storage of this and other nitrated heterocyclic compounds.[13]

Reactant 2,4,6-trimethoxypyrimidine **32** can be nitrated to 2,4,6-trimethoxy-5-nitropyrimidine **33** in a high isolated yield and purity (Table 4). Previously, product **33** was synthesized by the methanolysis of 2,4,6-trichloro-

(12) Olah, G. A.; Kuhn, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 1067−1070.

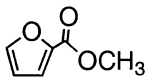
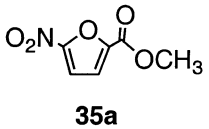
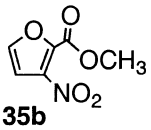
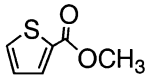
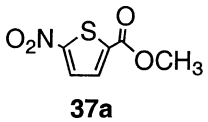
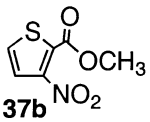
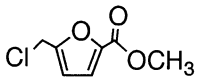
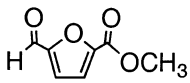
(13) High-pressure DSC thermal screening of **31** at a 10 °C/min temperature rise gave decomposition between 200 and 250 °C. Impact sensitivity initiation resulted in a 20−30 J impact energy. When reacting, handling, or isolating **31**, temperatures probably should not exceed 100 °C.

TABLE 4. $(CH_3)_4NNO_3$-Based Nitration of Trisubstituted Pyrimidines 30 and 32

Reactant	Scale (mmol)	Equiv. of **3**	% Converted	Product	Time (h)	% Isolated Yield (Purity)
	7.5	1.05	68		48	----- (-----)
	7.5	1.25	88		48	----- (-----)
	7.5	1.50	100		48	98 (99)
30	57.9	1.50	100	**31**	48	98 (>95)[c]
	100[a]	1.50	-----		18	83 (98)
	2864	1.50	100		38	94 (>95)[c]
	27.3	1.25	100		48	73 (85)
	371	1.05	100		20	82 (98)
32	452	1.49	100	**33**	Overnight	52[b] (>95)[c]

[a] Alternative Method. [b] Recrystallized product. [c] Determined by NMR analysis.

TABLE 5. $(CH_3)_4NNO_3$-Based Nitration of Furan and Thiophene Derivatives 34, 36, and 38

Reactant	Equiv. of **3**	% Converted	Product(s)	% **a/b**	Time (h)	% Yield (Purity)
	1.05	76		-----[a]	72	----- (-----)
	1.5	100		92/8	48	83 (99)
34	1.5	100	**35a** **35b**	91/9	27	84 (100)
	1.5	100	 	62/38	42	91 (95)[b]
36			**37a** **37b**			
	1.10	71		-----	76	----- (71)[b]
38			**39**			

[a] Only isomer **35a** appeared in a proton NMR using $CDCl_3$ solvent. [b] Determined by NMR analysis.

5-nitrobenzene.[14] Our results represent the first synthesis of **33** by direct nitration.

Nitration of methyl 2-furoate **34** produced a good yield of isomers **35a** and **35b** with a 99% combined HPLC purity (Table 5). Recrystallization from methanol/water gave an overall 61−66% product yield of pure isomer **35a**. Previously, compound **34** has been nitrated with acetyl nitrate at temperatures from −10 to −5 °C to give seven different products with isomer **35a** comprising 26% of the product mixture.[15] More recently, a two-pot nitration using fuming nitric acid in acetic anhydride at −5 °C was described that gave a 91% yield of **35a** following an extractive workup, filtration through a silica gel pad, and a methanol recrystallization.[16]

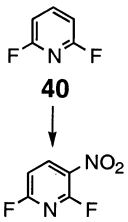
The analogous methyl thiophene-2-carboxylate **36** afforded two 5-nitro- **37a** and 4-nitro-substituted **37b** isomeric products in a 91% combined, isolated yield (Table 5). A reported nitration of **36** conducted with fuming HNO_3 in concentrated H_2SO_4 from −20 to 0 °C gave a 50/50 mixture of **37a** and **37b**.[17] A 50 year old reference describes the nitration of **36** with HNO_3 in acetic acid from 3 to 30 °C giving a 53% yield of **37a** after methanol recrystallization.[18] A 66−67 °C melting point was reported with no spectral data.

Unexpectedly, an attempted nitration of methyl 5-(chloromethyl)-2-furoate **38** resulted in a 71% conversion to a single oxidized product, methyl 5-formyl-2-furanoate, **39** without ring nitration (Table 5). Only unreacted **38** and product **39** were found in the isolated product mixture from oxidation of the chlorinated "benzylic-like"

(14) Cherkasov, V. M.; Remennikov, G. Ya.; Kisilenko, A. A. *Chem. Heterocycl. Compd*. (Engl. Transl.) **1982**, 526−529.
(15) Kolb, V. M.; Darling, S. D.; Koster, D. F.; Meyers, C. Y. *J. Org. Chem*. **1984**, *49*, 1636−1639.
(16) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Tianhua, W. *J. Org. Chem*. **1997**, *62*, 4088−4096.
(17) Elliott, R. L.; O'Hanlon, P. J.; Rogers, N. H. *Tetrahedron* **1987**, *43*, 3295−3302.
(18) Guathier, B.; Maillard, J. *Ann. Pharm. Fr*. **1953**, *XI*, 509−522.

TABLE 6. Parametric $(CH_3)_4NNO_3$-Based Nitration Investigation of 2,6-Difluoropyridine 40[a]

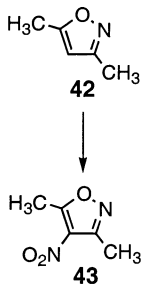
Conditions	Equiv. of 3	mmol of 40	Conc. 40	% Converted	Product 41 Amt.	% Isolated Yield (Purity)
RT, 42 h	1.6	7.57	0.25M	69	0.69 g	57 (<69)
RT, 24 h	1.5	16.41	1.09M	78	2.58 g	98 (78)
Reflux, 8 h	1.5	16.41	1.09M	100	2.58 g	98 (99)
Reflux, 16 h	1.5	16.41	1.09M	99	2.33 g	89 (99)
Reflux, 24 h	1.5	16.41	1.09M	100	2.46 g	94 (99)



[a] RT = room temperature.

TABLE 7. Parametric $(CH_3)_4NNO_3$-Based Nitration of 3,5-Dimethylisoxazole 42

Conditions	Equiv. of 3	mmol of 42	Conc. 42	% Converted	% Isolated Yield (Purity)
RT, 48 h	1.5	11.30	0.19M	100	94 (100)
RT, 48 h	1.5	16.92	1.13M	100	96 (99)
RT 24 h	1.5	16.92	1.13M	90	87 (87)
Reflux, 3.5 h	1.5	16.92	1.13M	95	92 (95)
Reflux, 6 h	1.5	16.92	1.13M	95	90 (95)
Reflux, 16 h	1.5	16.92	1.13M	95	90 (95)



position. Product **39** was authenticated by comparison with a known sample. The potential scope and synthetic usefulness of this result is being evaluated.

The complete conversion of 2,6-difluoropyridine **40** to 2,6-difluoro-3-nitropyridine **41** presented a challenge. Previously, compound **41** has been synthesized from the analogous chlorinated reactant, 2,6-dichloro-3-nitropyridine, to produce **41** in an 81% yield.[19] A stringent direct nitration of **40** using concentrated H_2SO_4 and 100% HNO_3 gave **41** in a 78% yield.[20] Direct nitration of **40** for 24 h with another nitronium salt, NO_2BF_4 in refluxing CH_2Cl_2, gave a 20% yield of product **41**.[21]

Our initial attempts to nitrate reactant **40** with the General Procedure (0.25 M **40**) converted only 50−67% to product **41** (Table 6). Other unidentified byproduct(s) also were observed.

Two General Procedure modifications effected a complete conversion (Table 6). First, this reaction was conducted at a 4.4-fold increase in reactant **40** concentration (1.09 M). Second, the reaction was stirred at reflux instead of room temperature. A 100% reactant **40** conversion was achieved in 8 h. Following aqueous workup, the directly isolated 98% yield of product **41** proved to be analytically pure by C, H, F, and N analysis.[22] Extended reaction times of 16 and 24 h had no deleterious effect on the product **41** yield and purity. The clean 78% conversion of concentrated (1.09 M) **40** to **41** at room temperature over 24 h suggests that a longer reaction time would provide a complete reaction.

With a more activated aromatic ring, 3,5-dimethylisoxazole **42** formed 3,5-dimethyl-4-nitroisoxazole **43** in 100% conversion using the more dilute (0.19 M **42**), room temperature General Procedure conditions (Table 7). A 6-fold concentration increase in reactant **42** (1.13 M) produced a comparable product **43** yield and purity. Both conditions gave analytically pure isolated product **43**. Curiously, employing this concentrated reactant condition at reflux repeatedly gave a 95% conversion of **42** regardless of reaction time. Extended reflux reaction times had no deleterious effect on product yield or isolated purity. Product **43** obtained by reflux conditions was analytically pure when treated for several hours in a 45 °C vacuum oven.

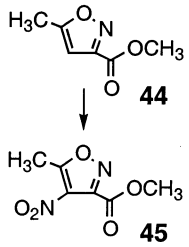
Nitration of the less activated methyl 5-methylisoxazole-3-carboxylate **44** under comparable General Procedure conditions with 0.23 M reactant gave an 86% conversion to product **45** (Table 8). Again, only desired product **45** and 14% unconverted reactant **44** were in the isolated mixture. A 5-fold increase in reactant **44** concentration and refluxing the stirred reaction for 24 h gave a 100 % isolated yield of analytically pure product **45**. Product **45** is an unreported compound.

(19) Radl, S.; Hradil, P. *Collect. Czech. Chem. Commun.* **1991**, *56*, 2420−2429.
(20) Mutterer, F.; Weiss, C. D. *Helv. Chem. Acta* **1976**, *59*, 229−235.
(21) Duffy, J. L.; Laali, K. K. *J. Org. Chem.* **1991**, *56*, 3006−3009.

(22) While compound **41** shows a propensity to retain trace amounts of CH_2Cl_2 solvent and still give analytically pure analyses, this residual solvent retention was not seen with the other nitrated products investigated.

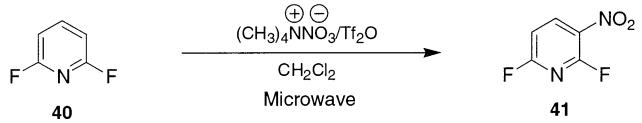
TABLE 8. $(CH_3)_4NNO_3$-Based Nitration of Methyl-5-methylisoxazole-3-carboxylate 44

Conditions	Equiv. of **3**	mmol of **44**	Conc. **44**	Converted %	% Isolated Yield (Purity)
RT 189 h	1.5	11.27	0.23 M	86	95 (86)[a]
Reflux 24 h	1.5	17.19	1.15 M	100	100 (99)



[a] Determined by NMR analysis.

TABLE 9. Microwave-Assisted $(CH_3)_4NNO_3$-Based Nitration of a 2,6-Difluoropyridine 40



run no.	equiv of **3**	temp	irradiation time (min)	conversion (%)	% isolated yield (purity)
1	1.3	60 °C	10/5	91	
2	1.3	60 °C	15/5	96[a]	75
3	1.3	60 °C	30	91	
4	1.3	100 °C	15/15	97	92
5	1.5	110 °C	10/5	100	91 (98)
6	1.5	100 °C	10/5	100[b]	91 (98)
7	1.5	100 °C	10/5	100	91 (98)
8	1.5	60 °C	10/5	96	85
9	1.5	80 °C	10/5	100	94 (100)

[a] Momentary temperature spike to ca. 125 °C. [b] Initial pressure spike greater than 20 bar.

Microwave-Accelerated Nitration. Microwave-assisted reaction conditions were applied to this tetramethylammonium nitrate-based nitration. Reactions were conducted under an N_2 gas in sealed reaction vessels at high reactant concentrations (1.09−1.15 M) with 1.5 equiv of **3** and reaction temperatures above the CH_2Cl_2 solvent boiling point. A Personal Microwave "Smith Creator" apparatus was used in all small-scale reactions. Two large-scale nitrations were conducted in a Milestone "Ethos" oven. Reagent **3** was generated first by reacting **1** and **2** at room temperature for at least 1.5 h before adding reactant **5** and initiating microwave irradiation. To ensure adequate mixing of the reactant suspension, small-scale microwave nitrations were conducted in two irradiation steps. Time entries in Tables 9 and 11, separated by a forward slash, denote the two-step microwave irradiations that sandwich reaction vessel hand agitation or magnetic stirring to ensure adequate reaction suspension mixing.

The optimum microwave nitration conditions needed for a 100% conversion of 2,6-difluoropyridine **40** to analytically pure isolated product **41** appear in run 9 of Table 9.

When a rapid temperature rise to ca. 125 °C occurred in run 2, microwave irradiation was manually stopped, and the sample was cooled below 60 °C. The microwave was restarted, and no further exotherm resulted. Microwave irradiation in run 6 initially produced a very rapid pressure increase. An equipment safety feature automatically stopped the reaction at a pressure of 20 bar. The reaction vessel was vented and resealed, and run 6 was reinitiated with no further pressure anomaly.

Several conclusions are drawn from Table 9. The nitration is complete after no more than 15 min of irradiation (runs 1 and 3). The temperature and number of equivalents of nitrating agent **3** have a distinct effect in driving the reaction to completion (runs 2−4 and 7−9). Higher temperature reactions for longer periods of time appear to have no significant deleterious effect on product yield or purity (runs 5−7).

This microwave-assisted nitration successfully was scaled 15.8 times larger with **40** using a 250 mL reaction vessel (Table 10). After aqueous workup, a quantitative 8.89 g yield of 98% analytically pure product **41** was obtained. Table 10 compares the smaller and larger scale 15 min microwave-assisted reactions with the 8 h large-scale conventional benchtop nitration conducted at reflux (Table 6).

Four other compounds were nitrated under small-scale microwave conditions with excellent results (Table 11). The distribution of nitrated *ortho*-, *meta*-, and *para*-nitromethylphenyl sulfone isomers **6h**, obtained at a high reactant **5h** concentration, is similar to that obtained with the General Procedure conditions (Table 1). An elemental analysis of the isomeric product mixture **6h** obtained at 80 °C was consistent with the $C_7H_7NO_4S$ formulation of the three mononitrated isomers. The isomeric o/m/p percentages for mixture **6h** were assigned by proton NMR using data reported for pure isomers.[23a,b]

A total conversion with very high yields of analytically pure nitrated heteroaromatic products **31**, **43**, and **45** occurred with pyrimidine **30**, as well as isoxazoles **42** and **44**, respectively, with isolated yields and purities comparable to those of our conventional benchtop nitrations (Tables 4, 7, and 8). Small-scale microwave nitration of **44** gave 0.64 g of product **45** (Table 11). A large-scale nitration of **44** using the Ethos microwave instrument afforded a quantitative 5.03 g isolated yield of analytically pure **45**.

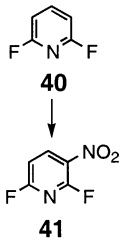
Summary

Our use of inexpensive tetramethylammonium nitrate **1** with trifluoromethanesulfonic anhydride **2** to generate the nitronium triflate **3** in situ with CH_2Cl_2 solvent introduces a convenient, new one-pot nitration for aromatic and heteroaromatic compounds **5**. Advanta-

(23) (a) Caccamese, S.; Finocchiaro, P.; Maravigna, P.; Montaudo, G.; Recca A. *Gazz. Chim. Ital.* **1977**, *107*, 163−169. (b) Montaudo, G.; Finocchiaro, P.; Trivellone, E.; Bottino, F.; Maravigna, P. *J. Mol. Struct.* **1973**, *16*, 299−306.

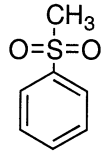
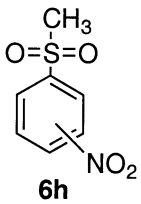
TABLE 10. Conventional Benchtop and Microwave-Assisted Nitration of 2,6-Difluoropyridine 40[a]

Conditions	Equiv. of **3**	mmol of **40**	Conc. **40**	% Converted	Product **41** Amt.	% Isolated Yield (Purity)
Small Microwave 80 °C, 15 min	1.5	3.44	1.15M	100	0.52 g	94 (100)
Large Microwave 80 °C, 15 min	1.5	54.47	1.09M	98	8.89 g	100 (98)
Conventional Reaction Reflux, 8 h	1.5	16.41	1.09M	100	2.58 g	98 (99)



[a] Note: all samples of isolated product **41** were analytically pure by C, H, F, and N analysis.

TABLE 11. Microwave-Assisted $(CH_3)_4NNO_3$-Based Nitration of Other Aromatics

Reactant	Equiv. of **3**	Temperature	Time (min)	Product	% Conversion	% Isolated Yield (Purity)
	1.5	60 °C	10/10		96	-----[a] (-----)
	1.5	80 °C	10/5		100	94[b] (100)[c]
5h				**6h**		
30	1.5	60 °C	10/5	**31**	100	91 (100)
42	1.5	60 °C	10/5	**43**	100	92 (99)
44	1.5	60 °C	10/5	**45**	100	100 (99)

[a] Percentage of o/m/p isomers: 16/80/4. [b] Percentage of o/m/p isomers: 17/79/4. [c] Total of all three o/m/p isomers.

geously, simple aqueous workup removes primary byproducts from the desired isolated product **6**. Compared with traditional literature nitrations, improved isolated product yield, isomer selectivity, and purity often result using this nitration reaction. Directly isolated products frequently require no further purification, and many were found to be analytically pure.

Complete reactant conversion to mononitrated products can be effected with a wide scope of electron-rich to electron-deficient compounds by optimizing reactant concentration, temperature, and time. Both conventional benchtop and microwave-assisted reaction procedures are suitable for this nitration. Particularly noteworthy is the demonstrated ease and safety of our nitration reaction on a 1 to 500 g scale. Two known compounds were obtained for the first time by direct nitration, and five novel, unreported nitrated aromatic and heteroaromatic compounds were synthesized and characterized.

Experimental Section

General Considerations. All NMR spectra were obtained at 300 MHz. Use of FI/MS, GC/MS, or ES/MS analyses was compound dependent. FTIR data were obtained as KBr pellets or as thin film deposits using the attenuated total reflectance method. Unless stated otherwise, product purities were determined by HPLC/UV at 220 nm. Anhydrous, low-water, or reagent-grade dichloromethane (DCM) solvent was used as received. Both the tetramethylammonium nitrate (96%) and trifluoromethanesulfonic anhydride were used as received. Millimole calculations reflect the stated purity of each reactant. Elemental analyses were conducted by Atlantic Microlab, Inc., Norcross, GA, or Quantitative Technologies, Inc., Whitehouse, NJ. The term "isolated product" refers to the product obtained directly from reaction workup without any additional purification. Where more or less than 7.50 mmol of reactant **5** was nitrated using the General Procedure, all amounts were scaled directly by the same factor, including workup quantities. Reactant **2** addition times were adjusted as necessary.

General Procedure. Under a N_2 gas blanket at room temperature, between 2.26 and 2.39 g (8.01−8.47 mmol) of **2** were added dropwise to a stirred suspension of 1.12 g (7.89 mmol) 96% tetramethylammonium nitrate **1** in 20 mL of DCM with a slight temperature rise.[24] The addition funnel was rinsed with 8 mL of anhydrous DCM that was added to the reaction suspension. After stirring for at least 1.5 h at room temperature, the stirred suspension was cooled in a CO_2/acetone bath. To the stirred nitronium triflate suspension was added dropwise 7.50 mmol of aromatic substrate **5** dissolved in 10 mL of DCM while keeping the reaction temperature at −65.0 °C or lower. The addition funnel was then rinsed with 2 mL of anhydrous DCM that was added to the stirred reaction suspension giving a 0.19 M reactant concentration. The reaction suspension was kept under N_2. The cooling bath could then be removed; some reactions proceeded more cleanly if the bath remained and gradually warmed unattended to room temperature.[25] The stirred reaction was quenched with 15 mL of 5% aqueous $NaHCO_3$ to give an aqueous layer of pH 8 (with

(24) The small-scale (7.50 mmol) reactions used a 6−12 min addition time with a resultant 2−3 °C temperature rise. The larger scale (86−100 mmol) reactions used a 12−20 min addition time with a corresponding 3−5 °C temperature rise. The maximum temperature occurred 25−40 min after addition was begun. Exothermicity during this addition presented no serious issue.

acidic compounds **5b**, **5g**, and **11**, water was substituted to keep an acidic pH). The lower DCM layer was separated and washed with 5 × 25 mL of H_2O. The combined H_2O washes were back-extracted with 25 mL of DCM. The two combined DCM portions were dried over $MgSO_4$. DCM removal by rotary evaporation gave the isolated product **6**.

1,4-Dimethoxy-2-nitrobenzene (8). *Small Scale.* Reacted 1.04 g (7.50 mmol) **7** with 1.05 equiv of **3** in 40 mL of DCM (0.19 M **15**) for 17 h to obtain an isolated yield of 0.97 g (71%): FW = 183.1; ^{1}H NMR (DMSO-d_6) δ 7.46 (s, 1H), 7.28 (m, 2H), 3.93 (s, 3H), 3.86 (s, 3H); GC/MS (CI, *m*/*z*) 183 (M^+ and base peak); FTIR (KBr) 3071, 3024, 2982, 2946, 2844, 1528, 1355 cm^{-1}; mp uncorrected, (crude = 68.6−70.0 °C), (HPLC purified = 70.8−71.2 0 °C), lit. mp = 71−73 °C,[26a] 68−70 °C,[26b] 71 °C.[26c] Anal. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.55; H, 4.94; N, 7.63.

2,6-Dimethoxy-3-nitrobenzonitrile (20). *Large Scale.* Reacted 16.82 g (100.0 mmol) **19** (97%) with 1.50 equiv of **3** in 400 mL of DCM (0.25 M **19**) for 1 h in a dry ice/acetone bath, 3 h in a dry ice/acetonitrile bath, and 48 h at room temperature[11] to obtain an isolated yield of 20.85 g (100%): FW = 208.2; ^{1}H NMR (DMSO-d_6) δ 8.34 (d, 1H), 7.18 (d, 1H), 4.04 (s, 6H); FI/MS (APCI, *m*/*z*) 209 ($M^+ + 1$), 208 (M^+), 179 (base peak); GC/MS (CI, *m*/*z*) 208 (M^+), 178 (base peak); FTIR (ATR film) 3096, 2995, 2955, 2884, 2852, 2236, 1584, 1520, 1353 cm^{-1}; HPLC purity analysis = 96.7%. A second nitration of **19** on the same scale using a 44 h reaction time at room temperature[11] gave isolated product **20**: HPLC purity analysis = 97.2%. Recrystallized from methanol. Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.11; H, 3.90; N, 13.46.

Modified Concentrated Procedure: 2,6-Difluoro-3-nitropyridine (41). Under N_2 in a 100 mL three-necked reaction flask fitted with a H_2O-cooled reflux condenser and containing 3.49 g (24.60 mmol) of 96% **1** in a 10 mL DCM suspension, 7.04 g (24.96 mmol) of neat **2** was added via capillary pipet followed by 2 mL of DCM. The suspension was stirred at room temperature for 1.5 h. Reactant **5** (1.89 g, 16.4 mmol) was added directly to a magnetically stirred suspension via capillary pipet at room temperature followed by 3 mL of DCM. The reaction was stirred under reflux for 8 h. The cooled reaction was quenched by adding 42 mL of 5% $NaHCO_3$ to bring the aqueous layer to pH 8. The DCM layer was separated and washed with 5 × 50 mL of H_2O. The combined H_2O portions were back-extracted with 15 mL of DCM. The two DCM portions were combined and dried over $MgSO_4$. Solvent removal by rotary evaporation and drying for 46 min in a room temperature vacuum oven gave 2.58 g (99%) of **41** as a golden-colored oil: FW = 160.1; ^{1}H NMR (DMSO-d_6) δ 8.94 (overlapped dd, 3H), 7.45 (d, 3H); FTIR (ATR film) 3018, 1534, 1348 cm^{-1}; HPLC purity analysis = 99.4%; GC/MS (CI, *m*/*z*) 161 ($M^+ + 1$). Anal. Calcd for $C_5H_2F_2N_2O_2$: C, 37.52; H, 1.26; F, 23.74; N, 17.50. Found: C, 37.69; H, 1.26; F, 23.92; N, 17.34.

Microwave-Assisted Small-Scale Procedure: 2-Chloro-4,6-dimethoxy-5-nitropyrimidine (31). A 5 mL Personal Microwave reaction vessel with a stir bar was charged with 0.72 g (5.07 mmol) of 96% **1** and 1 mL of DCM. Under N_2, 1.50−1.58 g (5.32−5.60 mmol) of **2** was added to the suspension with a capillary pipet followed by 1 mL of DCM. The reaction vessel was stoppered, and the suspension was stirred at room temperature for 1.5 h. To this stirred suspension of **3** under N_2 were added 0.60 g (3.44 mmol) of **30** and 1 mL of DCM (1.15 M **30**). The crimp-sealed vessel contents briefly were stirred and then irradiated at 60 °C for 10 min. The vessel was removed and stirred and then irradiated for another 5 min. The cooled reaction contents were quenched by being added to 25 mL of 5% aqueous $NaHCO_3$ to give an aqueous layer with a pH = 8. The vessel was rinsed with 10 mL of DCM and then 25 mL of H_2O, and both were added to the stirred $NaHCO_3$ solution. The DCM layer was separated and washed with 5 × 10 mL of H_2O. The combined H_2O portions were back-extracted with 10 mL of DCM. The two DCM portions were combined and dried over $MgSO_4$. DCM removal by rotary evaporation followed by room temperature vacuum oven drying gave 0.69 g (91%) of white solid isolated product **31**: FW = 219.6; ^{1}H NMR (DMSO-d_6) δ 4.06 (s, 6H); GC/MS (CI, *m*/*z*) 220 ($M^+ + 1$ and base peak); HPLC purity = 100%; FTIR (ATR) 3045, 3017, 2958, 2942, 2885, 1529, 1376 cm^{-1}. Anal. Calcd for $C_6H_6ClN_3O_4$: C, 32.82; H, 2.75; Cl, 16.15; N, 19.14. Found: C, 33.00; H, 2.70; Cl, 16.36; N, 19.20.

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Supporting Information Available: Small and large-scale conventional benchtop plus microwave irradiation procedures, reaction conditions, and spectral characterization of products **10a**, **10b**, **12**, **14**, **16a**, **18**, **22a**, **22b**, **31**, **33**, **35a**, **35b**, **37a**, **37b**, **39**, **41**, **43**, **45**, and **46o/m/p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Compounds **7** and **9** reacted immediately at CO_2/acetone bath temperature. Compounds **11**, **13**, **17**, and **19** appeared to react slightly above −50 °C. More deactivated compounds **5d**−**h** reacted only slowly at room temperature. For these, reactants could be added at room temperature.

(26) The three most recently reported melting points for **16** are found in the following references: (a) Sankararaman, S.; Kochi, J. K. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 278−285. (b) Errazuriz, B.; Tapia, R.; Valderrama, J. A. *Tetrahedron Lett.* **1985**, *26*, 819−822. (c) Rajamohan, K.; Rao, N. V. S. *Indian J. Chem.* **1973**, *11*, 1076−1077.