A Novel Method for the Nitration of Simple Aromatic Compounds

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Simple aromatic compounds such as benzene, alkylbenzenes, halogenobenzenes, and some disubstituted benzenes are nitrated in excellent yields with high regioselectivity under mild conditions using zeolite β as a catalyst and a stoichiometric quantity of nitric acid and acetic anhydride. The zeolite can be recycled, and the only byproduct is acetic acid, which can be separated easily from the nitration product by distillation; the process is inexpensive and represents an attractive method for the clean synthesis of a range of nitroaromatic compounds. For example, nitration of toluene gives a quantitative yield of mononitrotoluenes, of which 79% is 4-nitrotoluene; fluorobenzene gives a quantitative yield of mononitro compounds, of which 94% is 4-nitrofluorobenzene; and 2-fluorotoluene gives a 96% yield of mononitro products, of which 90% is the 5-nitro isomer and 10% is the 4-nitro isomer.

Introduction

Nitration of aromatic substrates is one of the most important and widely studied chemical reactions.[1] Despite this, industry still largely relies upon early technology involving mixtures of nitric and sulfuric acids. Mixed-acid nitration systems, however, have many disadvantages. They are not very selective, particularly if the para isomer is the commercially more desirable isomer; they are corrosive and used in excess; they often lead to overnitration or to oxidized byproducts; and they require an aqueous washing stage that results in a waste inorganic acid stream which is environmentally unfriendly or costly to treat.[2] Thus, there is a great need for new nitration methods that can overcome such problems.

The use of lanthanide triflates as catalysts offers reduced acidity but requires the use of chlorinated solvents and does not improve the regioselection.[3] The use of solid acid catalysts is potentially more attractive because of the ease of removal and recycling of the catalyst and the possibility that the solid might influence the selectivity. Consequently, in recent years there has been a spate of activity aimed at the development of new nitration methods using solid acid catalysts, and partial success has been achieved.

For example, the use of Nafion-H and other polysulfonic acid resins reduces the corrosive nature of the reaction mixtures, though it does not substantially improve regioselection for the para isomer.[4] Toluene has been nitrated more para selectively with benzoyl nitrate over zeolite catalysts, but the reagent is inconvenient,

and other disadvantages remain. For example, when large-port mordenite is used as a catalyst, mononitrotoluenes are formed in almost quantitative yield, giving 67% of the para isomer in 10 min, but tetrachloromethane is needed as solvent.[5] When ZSM-11 in hexane is used, with the external acid sites of the zeolite selectively poisoned by treatment with tributylamine, excellent para selectivity (98%) is achieved, but in low yield.[6] Toluene has also been successfully nitrated with alkyl nitrates using a commercially unavailable form of ZSM-5 zeolite (Si/Al = 1000), with toluene as its own solvent.[7] This produced mononitrotoluenes in 54% yield, based on the alkyl nitrate, with a product distribution of o/m/p = 5/0/95, but commercially available ZSM-5 (Si/Al < 300) was less selective (o/m/p = 32/1/67), and very large quantities of the zeolite were required. Copper(II) nitrate supported on montmorillonite clay quantitatively nitrates toluene in the presence of acetic anhydride in tetrachloromethane, but affords high para selectivity (o/m/p = 20/1/79) only under conditions of high dilution, extremely slow addition of toluene, and a long reaction time (120 h).[8] When the amount of tetrachloromethane was reduced from 2000 to 50 mL for each 1 mL of toluene, the product distribution changed to o/m/p = 35/2/65. Unfortunately, therefore, none of the methods which exhibit para regioselectivity are attractive for large-scale use.

We continue to research into the development of useful synthetic methods that make use of solids as catalysts or controlling agents.[9] Therefore, we have undertaken further investigations of nitration in an attempt to develop a method which would allow high yield and selectivity with inexpensive reagents and without the

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(1) (a) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; VCH: New York, 1989. (b) Schofield, K. *Aromatic Nitration*; Cambridge University Press: Cambridge, 1980. (c) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley & Sons: Chichester, 1990.

(2) Clark, J. H., Ed. *Chemistry of Waste Minimisation*; Chapman & Hall: London, 1995.

(3) Waller, F. J.; Barrett, A. G. M.; Braddock, D. C.; Ramprasad, D. *Chem. Commun.* **1997**, 613.

(4) Olah, G. A.; Malhotra, R.; Narang, S. C. *J. Org Chem.* **1978**, *43*, 4628.

(5) Smith, K. *Bull. Soc. Chim. Fr.* **1989**, 272. Smith, K.; Fry, K.; Butters, M.; Nay, B. *Tetrahedron Lett.* **1989**, *30*, 5333. Butters, M. In *Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood: Chichester, 1992; p 130.

(6) Nagy, S. M.; Yarovoy, K. A.; Shakirov, M. M.; Shubin, V. G.; Vostrikova, L. A.; Ione, K. G. *J. Mol. Catal.* **1991**, *64*, L31.

(7) Kwok, T. J.; Jayasuriya, K.; Damavaparu, R.; Brodman, B. W. *J. Org. Chem.* **1994**, *59*, 4939.

(8) Laszlo, P. *Acc. Chem. Res.* **1986**, *19*, 121. Laszlo, P.; Vandormael, J. *Chem. Lett.* **1988**, 1843. Laszlo, P.; Cornelis, A.; Gerstmans, A. *Chem. Lett.* **1988**, 1839. Cornelis, A.; Delaude, L.; Gerstmans, A.; Laszlo, P. *Tetrahedron Lett.* **1988**, *29*, 5657.

need for large quantities of solvent. We now report substantial progress in this endeavor.[10]

Results and Discussion

We chose the mononitration of toluene (eq 1) as the test reaction during development of the method. Following the success of our previous work with benzoyl nitrate as the reagent,[5] we decided to try in situ generation of acetyl nitrate from nitric acid and acetic anhydride according to eq 2.[1] This would provide a cheaper reagent and avoid the need for its isolation or extraction.

$$Ac_2O + HNO_3 \longrightarrow AcONO_2 + AcOH \quad (2)$$
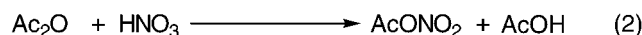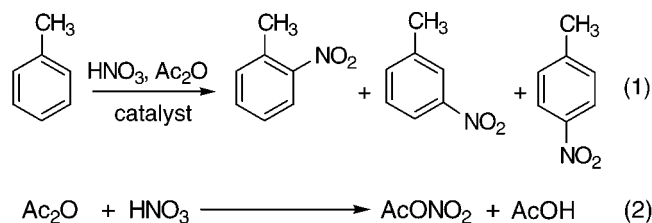
In the initial experiments, we used a large excess of acetic anhydride to ensure complete conversion of all of the nitric acid into acetyl nitrate and 3A molecular sieves to remove some water. Zeolite Hβ was used as catalyst because preliminary screening suggested that it was quite active. To discover whether the order of addition of the materials had a significant effect on the para selectivity of the process, the addition sequence was systematically varied. The initial arbitrary sequence was rotated until all five components had held the last place in the order of addition and the final component was fixed as that in the order giving the best para selectivity. The remaining four components were then rotated to find the best penultimate component, and this was fixed, and so on. Finally, the two possible sequences of the first two components were compared. The entire set of results is given in Table 1.

As can be seen from Table 1, the order of addition of the materials had a significant effect on the para selectivity of the process. The best order involved pre-mixing the zeolite with nitric acid, followed by addition of the anhydride and lastly the molecular sieves and toluene. This is consistent with the formation of acetyl nitrate predominantly within the pores of the zeolite, where reaction subsequently takes place with the toluene. However, the selectivity was only slightly less (7%) when the anhydride was mixed with the zeolite followed by the addition of the nitric acid and then the toluene. This could still provide a very useful procedure if necessary (see section on safety for a case in point). Also, when a preprepared mixture of nitric acid and the zeolite was added, as a sticky solid, to acetic anhydride, and toluene was added last, the selectivity was the same as in the optimum procedure. However, the yield was lower

(9) Smith, K.; Butters, M.; Paget, W. E.; Nay, B. *Synthesis* **1985**, 1155. Smith, K.; Butters, M.; Nay, B. *Synthesis*, **1985**, 1157. Smith, K. *Stud. Surf. Sci. Catal.* **1991**, *59*, 55. Smith, K.; Fry, K. B. *J. Chem. Soc., Chem. Commun.* **1992**, 187. Smith, K.; James, D. M.; Mistry, A. G.; Bye, M. R.; Faulkner, D. J. *Tetrahedron* **1992**, *48*, 7479. Smith, K.; James, D. M.; Matthews, I.; Bye, M. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1877. Delaude, L.; Laszlo, P.; Smith, K. *Acc. Chem. Res.* **1993**, *26*, 607. Smith, K.; Pollaud, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3519. Smith, K.; Bahzad, D. *Chem. Commun.* **1996**, 467.

(10) For a preliminary communication on some aspects of the work, see: Smith, K.; Musson, A.; DeBoos, G. A. *Chem. Commun.* **1996**, 469. See also: Smith, K.; Musson, A.; DeBoos, G. A. UK Patent Appl. 9510166.3, May 19, 1995; 9521705.5, Oct 24, 1995.

Table 1. Effect of Order of Introduction of Reactants in Eq 1[a]

order of addn	time (min)	yield (%)[c]	o[d]	m[d]	p[d]
1-2-3-4-5	5	>99	46	3	51
5-1-2-3-4	5	24	47	0	53
	30	41	47	0	53
4-5-1-2-3[b]	5	>99	33	3	64
3-4-5-1-2	5	>99	46	3	51
2-3-4-5-1	5	>99	48	3	49
2-4-5-1-3[b]	5	>99	32	3	65
1-2-4-5-3	5	80	36	3	61
	30	>99	37	3	60
5-1-2-4-3	5	8	31	0	69
5-2-4-1-3[b]	5	40	25	3	72
	30	>99	25	3	72
4-5-2-1-3	5	88	36	0	64
	30	>99	36	0	64
2-5-4-1-3	5	49	27	3	70
	30	64	27	4	69
5-2-4-1-3[e]	5	>99	17	4	79
5-2-4-3[f]	5	85	26	2	72
	30	>99	26	3	71

[a] 1 = 3A molecular sieves (0.2 g), 2 = H$^+\beta$ (0.1 g), 3 = toluene + hexadecane (0.23 g + 0.3 g), 4 = acetic anhydride (20 mL), 5 = nitric acid (0.25 g, 70%). [b] Selected as the best order in subset. [c] Yields are GC yields. [d] Proportions of isomers (%) determined by GC. [e] H$^+\beta$ (1.0 g instead of 0.1 g) used. [f] 3A molecular sieves omitted, H$^+\beta$ (0.1 g).

Table 2. Effect of Zeolite Type in Eq 1[a]

zeolite	Si/Al[b]	time (min)	yield (%)[c]	o[d]	m[d]	p[d]
H$^+$Mord	35	5	8	54	0	46
		30	17	53	3	44
H$^+$ZSM-5	80	5	13	62	0	38
		30	26	64	0	36
H$^+$ZSM-5	300	5	4	62	0	38
		30	19	57	0	43
H$^+$Y	5	5	trace	67	0	33
		30	4	61	0	39
H$^+$Y	40	5	>99	52	3	45
H$^+$Y	80	5	>99	53	3	43
Na$^+\beta$	13	5	2	46	0	54
		30	3	50	0	50
Fe$^{3+}\beta$	13	5	>99	25	3	72
Al$^{3+}\beta$	13	5	>99	25	3	72
H$^+\beta$	13	5	>99	25	3	72

[a] Nitric acid (70%, 2.5 mmol), zeolite (0.1 g), acetic anhydride (20 mL), toluene (0.23 g, 2.5 mmol), 20 °C. [b] Ratio of Si/Al in the zeolite. [c] Determined by GC against an internal standard. [d] Proportions of products as determined by GC.

because of incomplete transfer of the nitric acid–zeolite mixture. The last three entries in Table 1 show that the selectivity was even greater when a larger quantity of zeolite β was used, and that the 3A molecular sieves had no beneficial effect. The latter component was therefore omitted from all future reaction mixtures.

Using the optimum order of addition, a range of different zeolites was tested for efficacy at catalyzing the reaction. In view of our earlier findings with benzoyl nitrate, we looked mainly at large-pore zeolites, but ZSM-5, a medium-pore zeolite, was included for comparison. The results are shown in Table 2.

The rate of reaction and para selectivity with the medium-pore zeolite, ZSM-5, were both low, suggesting that little of the reaction was occurring inside the pores. The situation with the three larger-pore zeolites, however, was very interesting. Mordenite, with its one-dimensional pore network that imposes greater diffusion

Table 3. Effect of Temperature in Eq 1[a]

temp (°C)	time (min)	yield (%)[b]	o[c]	m[c]	p[c]
30	5	85	26	2	72
	30	>99	26	3	71
0	5	91	25	3	72
	30	98	25	2	73
−50	5	58	25	0	75
	30	>99	25	1	74

[a] Zeolite H^{+}β (0.1 g), nitric acid (70%, 2.5 mmol), acetic anhydride (20 mL), toluene (2.5 mmol). [b] By quantitative GC of aliquots that were filtered as rapidly as possible to remove catalyst before warming. [c] Proportion of the isomer (%) in the product, as determined by GC.

restrictions than the three-dimensional networks of Y and β type zeolites, gave a low yield but with somewhat better para selectivity than the homogeneous reaction, suggesting that a proportion of the reaction was occurring selectively within the pores but that the limited rate of diffusion was allowing competition from reactions at the external sites. Zeolite Y, which has the largest cavities within its structure, allowed a rapid reaction with limited improvement in para selectivity, suggesting that diffusion was not a problem, but that the geometrical constraints on the transition state were not very severe. It was also clear that the strength of the acid sites was important as the sample of zeolite Y with a low Si/Al ratio (and consequently with a large number of low-strength sites) resulted in a much lower level of reaction. It was not considered worthwhile to test zeolite X, which has the same pore structure as Y but with an even lower Si/Al ratio.

The result with the proton form of zeolite β (H^{+}β), as already observed in Table 1, was remarkable: a rapid reaction and an outstanding degree of para selectivity. Apparently, the geometrical constraints are such as to allow relatively easy diffusion but to impose some order on the transition state. Several cation-exchanged forms of zeolite β were tested in an attempt to find an even more selective catalyst. However, Al and Fe forms gave results that were almost identical to those of the proton form, while Na^{+}β gave a poor yield. (The last zeolite possesses very few Brønsted acid sites, which is consistent with the reaction's being catalyzed by such sites.) Therefore, H^{+}β was selected for more detailed study.

The effect of lowering the reaction temperature was next investigated. The results are presented in Table 3.

As can be seen from Table 3, lowering the reaction temperature retards the rate of reaction, as expected, but only slightly increases the para selectivity. Also, at lower temperatures there appears to be a reduction in the amount of *m*-nitrotoluene formed. Although there is no major advantage to be gained from carrying out the reaction at low temperature on the scale used here, the use of lower temperatures would not prevent reaction if such temperatures were desirable for large-scale work.

Thus far, all experiments had utilized a large excess of acetic anhydride, which had fulfilled the role of solvent as well as reagent. It was of interest to know if such a large excess were actually necessary. A series of reactions was therefore conducted in which the ratio of the anhydride to the nitric acid was varied. In view of the impracticality of working with very small amounts of material for operations involving sampling and filtration, especially with the heterogeneous nature of the reaction mixture, some of the reaction mixtures were concocted by increasing the amount of substrate, catalyst, and nitric

Table 4. Effect of Concentrating the Mixture in Eq 1[a]

Ac$_2$O/HNO$_3$ molar ratio[b]	nitric acid concn (%)	yield (%)[c]	o[d]	m[d]	p[d]
67.3	70	>99	26	4	70
33.9	70	>99	26	3	71
8.4	70	>99	24	4	72
2.7	90	>99	25	3	72
1.0	90	>99	18	4	78
0.2	90	8	38	5	57

[a] Ratio toluene/nitric acid/H^{+}β = 35 mmol/35 mmol/1.0 g; relative amount of acetic anhydride varied. [b] Ratio calculated by assuming that the water in the nitric acid destroys an equivalent amount of anhydride, leaving only the residual amount to interact with nitric acid. [c] By quantitative GC. [d] Proportion of products by GC.

Table 5. Effect of Catalyst Quantity in Eq 1[a]

H$^+$β (g)	time (h)	yield (%)[b]	o[c]	m[c]	p[c]
0.106	24	89	42	3	55
0.644	0.5	43	21	3	76
1.06	0.5	>99	18	3	79
2.03	0.5	>99	15	4	81

[a] All reactions carried out using toluene (35 mmol), nitric acid (35 mmol of 90%), and acetic anhydride (5 mL, 53 mmol) at ambient temperature for the time stated. [b] By quantitative GC. [c] Proportion of the isomer (%) in the product, as determined by GC.

acid, while others involved reducing the amount of anhydride. Furthermore, since the nitric acid used in these experiments was an aqueous solution, it would be expected that some of the anhydride would be hydrolyzed and could not take part in the reaction depicted in eq 2. Consequently, the ratio of anhydride to nitric acid recorded takes this into account. The results are shown in Table 4.

As the results in Table 4 show, no deleterious effect was observed until the amount of acetic anhydride was reduced to below the stoichiometric amount required to convert all the nitric acid into acetyl nitrate and all the water into acetic acid. At the stoichiometric point, the nitration of toluene (35 mmol) was effected by nitric acid (2.5 g, 90%, 35 mmol) and acetic anhydride (5.0 mL, 53 mmol) over H^{+}β (1.0 g), and the yield and para selectivity were excellent. Below that amount, the mechanism presumably switches to that of a nitric acid nitration, consequently leading to a slower reaction and a lower degree of para selectivity. Interestingly, in contrast to the nitration of toluene with acetyl nitrate catalyzed by Claycop in tetrachloromethane,[8] the more concentrated reaction mixture provides increased para selectivity, presumably because a greater proportion of the reaction takes place inside the pores.

It was next of interest to optimize the amount of catalyst. A series of experiments was conducted in which the amount of catalyst employed was the only variable (Table 5).

It is clear from the results in Table 5 that the reaction can be conducted successfully with a smaller quantity of catalyst than we had used heretofore. Even with as little as 0.1 g of catalyst (ratio H^{+}β/toluene = 0.033), the reaction exhibited significant para selectivity. However, increasing the amount of catalyst resulted in both a faster reaction and a higher degree of para selectivity. Increasing the amount of catalyst provides an increased pore volume and a greater number of catalytic sites. Consequently, a greater proportion of the acetyl nitrate can be located inside the pores, leading to the increased para

Table 6. Effect of Method of Recycling Catalyst in Eq 1

meth of recycling	yield (%)[b]	o[c]	m[c]	p[c]
filtration	18	34	3	63
AcOH wash	23	26	3	71
CH$_2$Cl$_2$ wash−calcination[a]	22	18	4	78
vacuum distillation	>99	19	2	79

[a] Zeolite calcined at 600 °C. [b] Yields are of isolated, pure products. [c] Proportions of isomers (%) determined by GC.

Table 7. Efficacy of Recycled Catalyst in Eq 1[a]

cycle no.	toluene used (g)	nitric acid used (g)	nitro-toluenes produced (g)[b]	time (min)[c]	yield (%)[d]	o[e]	m[e]	p[e]
1	3.096	2.454	4.605	30	>99	19	3	78
2	3.098	2.452	4.600	30	>99	19	2	79
3	3.032	2.419	4.337	30	96	22	3	75
4	3.065	2.422	4.293	30	94	25	3	72
5	2.978	2.425	3.596	30	81	32	3	65
6	3.068	2.538	4.226	60	93	33	3	64
7	2.972	2.460	3.651	60	82	37	3	60
8	3.048	2.479	4.060	120	89	36	3	61
9	3.078	2.449	3.784	120	82	42	3	55
total	27.435	22.098	37.152		817	244[f]	24[f]	558[f]
			av		91	30[f]	3[f]	68[f]

[a] Each reaction was carried out on toluene (ca. 3.0 g, 35 mmol) with nitric acid (ca. 2.5 g of 90%, 35 mmol) and acetic anhydride (ca. 5.0 mL, 53 mmol) over the same batch of H$^+\beta$ (1.0 g initially), which remained in the reaction flask following reduced-pressure distillation of the acetic acid byproduct and then the nitrotoluenes. [b] Actual weight of the distilled product. [c] When the isolated yield from a particular run had dropped to almost 80%, the reaction time was increased in subsequent runs. [d] By isolation. [e] Proportion of the isomer (%) in the product, as determined by GC. [f] These totals and averages are weighted according to the amounts obtained in each run.

regioselectivity. From the point of view of the optimal way of conducting the reaction, there is a balance to be struck between factors such as the cost of the catalyst, the ability to manipulate the reaction mixture, the selectivity required, and so on. However, since H$^+\beta$ (1.0 g) was sufficient to absorb enough nitric acid (2.5 g, 35 mmol) to give the appearance of a dry powder, and since only a little benefit was obtained by increasing the quantity of catalyst further, 1.0 g was used in subsequent experiments.

For large-scale application of the reaction, it would be desirable to be able to recycle the catalyst. Several methods were investigated for this purpose. Table 6 records the results of reactions carried out under the same conditions as those recorded in Table 5 for the case of 1 g of catalyst.

Vacuum distillation to remove the organic materials proved to be a particularly effective method for recovery of the catalyst. When the catalyst thus obtained was reused in an identical reaction, the yield and selectivity were unchanged. It appears that this method allows materials that may be capable of restricting entry to the pores to be removed without unduly damaging the zeolite structure. To ascertain how long the efficacy of the catalyst would last, the reaction was repeated several times using the same batch of catalyst. The results are recorded in Table 7.

The results given in Table 7 show that a single batch of H$^+\beta$ (1 g) was capable of catalyzing the nitration of toluene (total 27 g) to yield mononitrotoluenes in an average of 91% yield and 68% para regioselectivity over a sequence of nine reactions, by which time the rate of

Table 8. Nitration of PhR According to Eq 3[a]

R	time (min)	yield (%)[b]	2[c]	3[c]	4[c]
F	30	>99	6	0	94
Cl	30	>99	7	0	93
Br	5	>99	13	0	87
H	30	>99			
Me	30	>99	18	3	79
Et	10	>99	15	3	82
iPr	30	>99	9	3	88
tBu	30	92	8	tr[d]	92
Ph[e]	30	70	tr	0	>99

[a] H$^+\beta$ (1 g), HNO$_3$ (2.5 g of 90%, 35 mmol), Ac$_2$O (5.0 mL, 53 mmol), PhR (35 mmol), ambient temperature for the indicated time followed by distillation under reduced pressure. [b] All yields are of isolated products following distillation. The identity of the products was established by GC, ^{1}H NMR, ^{13}C NMR, and GC−MS. [c] Proportion of the isomer (%) in the product, as determined by GC. [d] Trace. [e] Only 0.38 g of H$^+\beta$ used.

reaction and para selectivity in the individual runs had fallen significantly. After the nine recycles, the catalyst was dissolved in hydrofluoric acid, the solution was extracted with dichloromethane (3 × 30 mL), and the extract was evaporated to dryness. The mass of the extract was 90 mg, which corresponds to a 0.22% yield, and was shown by GC−MS to consist of dinitrotoluenes (83%) and undistilled mononitrotoluenes (17%). The only other compound identified in any of the product mixtures was unreacted toluene. This was sufficient to account for the lost material and was present in the distilled acetic acid fractions of runs that had resulted in relatively low yields.

The result of using a 1 g batch of catalyst nine times compares favorably with the single use of a 0.1 g batch of catalyst (Table 5). It is clear that it is preferable to use larger quantities of catalyst and recycle rather than to use smaller quantities of fresh catalyst each time. For practical purposes, a protocol whereby 10% of used catalyst was replaced with fresh catalyst after each run would eventually lead to a constant catalyst composition that would effect both a high yield and high para selectivity. Another approach could be to use each batch of catalyst about four times before disposal, which would again lead to both high yield and high para selectivity. Whichever detailed procedure should be chosen to suit the needs of a particular user, it is clear that for the first time it is possible to nitrate toluene in essentially quantitative yield with high para selectivity and without recourse to expensive or relatively inaccessible reagents or to conditions (temperature, solvent, etc.) that would preclude application on a large scale. It was therefore of interest to determine whether the reaction was more generally applicable. A standard procedure was therefore applied to a range of monosubstituted benzenes (eq 3). The results are shown in Table 8.
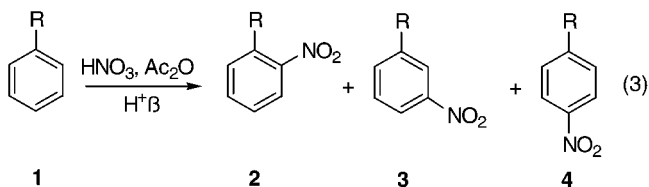
As the results in Table 8 show, the new method is applicable to a range of substrates of moderate activity, which are the ones that often give selectivity problems in traditional nitrations. Indeed, the present results

**Table 9. Nitration of 1,2-Disubstituted Benzenes According to Eq 4[a]**

series	X	Y	meth[b]	yield (%)[c]	6[d]	7[d]	8[d]	9[d]
a	F	F	A	87(98)[e]		100		
			B	72		100		
b	Cl	F	A	86(95)[f]		33	67	
			B	90		26	74	
c	Br	F	A	88		30	68	
			B	91		28	72	
d	OMe	F	A	98		92		8
			B	94		29	9	62
e	Me	F	A	96		10	90	
			B	72		7	51[g]	
f	Me	Cl	A	99		25	75	
			B	87		many products[h]		
g	Me	Br	A	99		19	81	
			B	91		many products[h]		
h	Me	Me	A	>99	32		44[i]	
			B	80	55		35	

[a] Equation 4 depicts the new method (method A). [b] Method A: 90% HNO₃ (35 mmol), H⁺β (1 g), Ac₂O (53 mmol), 0 °C, 30 min. Method B: HNO₃ (90%, 35 mmol), H₂SO₄ (98%, 35 mmol), **5** (35 mmol), 0 °C, 30 min. [c] All yields are of isolated products. The identity of the products was established by GC, ¹H NMR, ¹³C NMR, and ¹⁹F NMR. [d] Proportions of the isomers as determined by ¹H NMR. [e] These reactions were conducted for 3 h. The figure in parentheses is for a reaction in which H⁺β (2 g) was used. [f] The figure in parentheses is for a 3 h reaction. [g] Eight products were present in the mixture as seen by ¹⁹F NMR, but they could not all be identified from the spectra of the mixture. [h] The mixture of products was too complex to interpret. [i] 3,4-Dimethyl-1-acetoxybenzene (23%) was also formed. In the case of *o*-xylene **6** = **9** and **7** = **8**.

represent the highest para selectivities yet achieved in high-yielding nitration reactions for the entire range of substrates. An attempt was also made to nitrate a deactivated substrate, nitrobenzene, using the new nitrating system, but even when the reaction temperature was raised to 50 °C, the yield was only 13% after 2 h, and although the proportion of the para isomer (7%) was higher than normal, the major product (92%) was still the meta isomer. Therefore, the present method has no particular advantages for the nitration of such substrates.

1,2-Disubstituted benzenes often present even more problems of selectivity in nitrations than do monosubstituted benzenes, and it was therefore of interest to see how the new system would behave in such cases. It was by no means clear that diffusion of substrates and/or products through the pores of the zeolite would be easy, nor that the more hindered transition states would easily form within the pores, but the reaction was tried, nevertheless, for a range of 1,2-disubstituted benzenes according to eq 4. The results are shown in Table 9 (method A), where they are also compared with the results of comparative reactions carried out under similar conditions with a mixture of sulfuric and nitric acids (method B).

As can be seen from Table 9, the new method has no selectivity advantages over the use of mixed acid for 1,2-dihalogenobenzenes, which are already quite selective for production of compounds of types **7** and **8**. However, the yields are sometimes a little better and the method offers the environmental advantage of avoiding a waste inorganic acid stream. In the cases of 2-fluoroanisole and the 2-halogenotoluenes, the new method shows a significant selectivity advantage over mixed acid. The method significantly reduces the number of products formed and so provides a synthetically useful method for the selective syntheses of a range of compounds of types **7** and **8**.

$$\text{(4)}$$
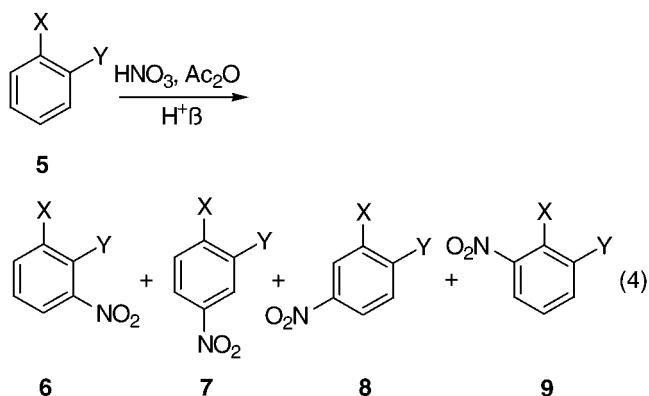
However, in the cases of 2-chloro- and 2-bromoanisoles (not shown in Table 9), the method gave a complex mixture of products similar to that obtained with mixed acid. It should be noted that none of the reactions (method A or method B) were optimized for the particular substrate, and it is possible that better results may be available by either method under appropriate conditions.

The case of *o*-xylene was interesting because 3,4-dimethyl-1-acetoxybenzene (**10**) was formed in 23% yield alongside the products **6/9h** and **7/8h**. It is well-known that *o*-xylene is highly susceptible to ipso attack and, in acetic acid, the ipso nitration Wheland intermediate is attacked by acetate anion with loss of HNO₂ to give **10**.[11] In sulfuric acid some of the ipso-nitration Wheland intermediate undergoes rearrangement, leading ultimately to a substantial amount of **6/9h**. The new method, however, gives a significant reduction in the amount of **6/9h** + **10** and a corresponding increase in the amount of **7/8h** compared with the use of either of these methods or the use of nitric acid–acetic anhydride without zeolite.

3-Fluorotoluene, as a representative 1,3-disubstituted benzene, was tested in the new method and produced 3-fluoro-6-nitrotoluene (59%) and 3-fluoro-4-nitrotoluene (41%) in 95% yield. Nitration of thiophene with a mixture of nitric acid and acetic anhydride yields a mixture containing around 95% of the 2-nitro isomer and 5% of the 3-nitro isomer.[12] In contrast, thiophene was nitrated by the new method to give a crude product that appeared to contain about 56% of the 3-nitro isomer and 44% of the 2-nitro isomer in an overall yield of about 80%. Nitration of pyridine was unsuccessful by the new method, presumably because the pyridyl nitrogen was simply protonated to produce a salt, as with traditional methods. The new method clearly has its limitations, though optimization for any particular substrate may produce better results.

In view of all the results presented in Tables 8 and 9, it is clear that the new method offers high yields and outstanding regioselectivities for a whole range of mono-substituted and some 1,2-disubstituted benzenes, although as for all methods, there are limitations to its applicability. The added practical advantages that the method requires no solvent and uses only stoichiometric quantities of inexpensive reagents, that the only byproduct (acetic acid) is easily recovered, that there is no waste inorganic acid stream, and that direct reduced-pressure

(11) Fisher, A.; Read, A. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3691.
(12) Babasinian, V. S. In *Organic Synthesis*; Blatt, A. H., Ed.; Wiley & Sons: New York, 1943; Collect. Vol. II, p 466. See also: Blatt, A. H.; Bach, S.; Kresch, L. W. *J. Org. Chem.* **1957**, *22*, 1693.

Table 10. Calculated Concentrations of Components in the Mixtures Prepared by Brown and Watt[16]

proportion of HNO$_3$[a]	concns of components (mol/100 g)					total nitrate[b]
	HNO$_3$	H$_2$O	Ac$_2$O	AcONO$_2$	AcOH	
26	0	0	0.282	0.400	0.487	0.400
41	0.121	0	0	0.510	0.647	0.631
50	0.363	0	0	0.407	0.574	0.770
55	**0.498**	**0**	**0**	**0.350**	**0.532**	**0.847**
60	**0.632**	**0**	**0**	**0.292**	**0.492**	**0.924**
70	**0.900**	**0**	**0**	**0.177**	**0.411**	**1.078**
85.5	*1.316*	*0*	*0*	*0*	*0.284*	*1.316*

[a] Percentage of 97% HNO$_3$ in admixture with acetic anhydride, according to ref 16. Mixtures for which detonation occurred are highlighted in bold. The mixture which was presumed not to detonate is shown in italics. [b] Sum of numbers of moles of HNO$_3$ plus AcONO$_2$.

distillation of the reaction mixture gives the separated nitration product and leaves the catalyst in the reaction flask ready for reuse, mean that the method should be attractive for larger-scale operation. Therefore, it is particularly important that safety factors should be explicitly considered.[13]
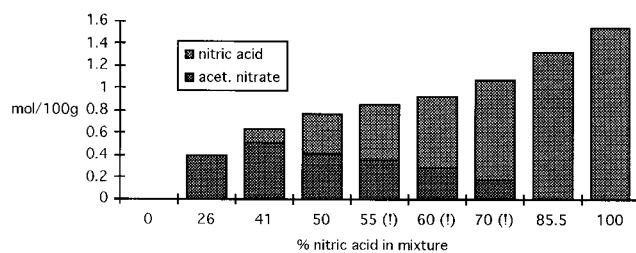
Safety

Nitration reactions are notoriously dangerous, and current commercial nitration procedures can lead to buildup of dangerous residues.[14] Pure acetyl nitrate can be distilled under reduced pressure (bp 22 °C/70 mmHg) but explosively decomposes at atmospheric pressure at 60 °C.[15] Therefore, it is generally handled in solvent or produced in situ from acetic anhydride and nitric acid. Such mixtures are in commercial use, but there are still potential dangers.

To try to quantify the dangers empirically, Brown and Watt fitted various mixtures of nitric acid (97%) and acetic anhydride with a priming charge and detonator and fired them.[16] Samples containing more than 55% (w/w) of the nitric acid (97%) detonated, whereas those with 50% or less did not, even under these extreme conditions. Also, Brown and Watt assumed that mixtures containing more than about 85% of the nitric acid would be stable. This corresponds to the level at which the water present in the nitric acid would just about convert all of the acetic anhydride into acetic acid, thereby precluding the generation of any acetyl nitrate.

Assuming that the anhydride reacts with any water present to give acetic acid, then with nitric acid to give acetyl nitrate (eq 2), we have calculated the concentrations of components in the mixtures of Brown and Watt (Table 10) and plotted out the results for the nitrate components (Figure 1).

From these results, two key features appear to lead to a mixture becoming explosively unstable to a priming charge: (a) the total amount of "nitrate" in the mixture should exceed about 0.77 mol/100 g; and (b) the mixture should contain at least some of a sensitive form of nitrate, such as acetyl nitrate. The critical amounts may also depend on the scale and geometry of the reaction vessel, and additional dangers may arise from the exothermic reaction of water with acetic anhydride or from changes

(13) Olah, G. A. Letter to the editor. *Chem. Br.* **1996**, August, 21.
(14) See, for example: *Chem. Ind. (London)* **1994**, 488.
(15) See ref 1a, p 43.
(16) Brown, T. A.; Watt, J. A. C. *Chem. Br.* **1967**, 504.

Figure 1. Amounts of nitrate components (mol in 100 g mixture) in mixtures of Brown and Watt.[16] The mixtures marked (!) could be detonated.

Table 11. Calculated Concentrations of Components during Mixing of Zeolite β/Nitric Acid with Acetic Anhydride According to the Recommended Procedure[a]

amt Ac$_2$O (mL)	H$_2$O (mol/100 g)	HNO$_3$ (mol/100 g)	AcONO$_2$ (mol/100 g)	AcOH (mol/100 g)	total nitrate (mol/100 g)
0	0.397	1.020	0	0	1.020
0.5	0.213	0.884	0	0.262	0.884
1.0	0.072	0.779	0	0.463	0.779
1.5	0	0.658	0.039	0.582	0.697
2.0	0	0.502	0.129	0.620	0.631
2.5	0	0.372	0.203	0.651	0.575
3.0	0	0.264	0.265	0.678	0.529
3.5	0	0.172	0.318	0.701	0.490
4.0	0	0.092	0.364	0.720	0.456
4.5	0	0.023	0.404	0.736	0.427
5.0	0	0	0.401	0.713[b]	0.401

[a] 2.5 g of HNO$_3$ to 1.0 g of Hβ then addition of the acetic anhydride. [b] Plus 0.038 mol Ac$_2$O/100 g.
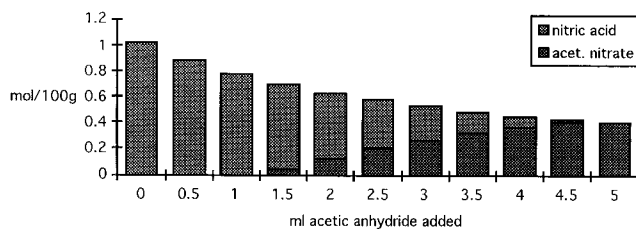
Figure 2. Amounts of nitrate components (mol in 100 g mixture) as acetic anhydride is added to a mixture of zeolite (1.0 g) and 90% nitric acid (2.5 g).

in composition that develop during aging of nitric acid−acetic anhydride mixtures.[17]

The levels of compounds formed during mixing in the new procedure have been calculated (Table 11), and the nitrate components have been plotted (Figure 2). As can be seen, the total nitrate exceeds 0.77 mol/100 g only during the initial stages of mixing, when no acetyl nitrate is formed. We nevertheless maintained the temperature at or below ambient until the reaction with the substrate was over, by which time little or no acetyl nitrate remained, and the total "nitrate" level was also well below 0.77 mol/100 g. The mixture could then be safely distilled under reduced pressure. We have performed over 200 experiments using this procedure and have experienced no problems.

Although the procedure developed here has been consistently safe on the scale used, it is possible that at a considerably larger scale problems might be encountered as a result of variables such as locally poor mixing, localized heating, or mechanical stress. Organizations which undertake large-scale nitrations should carry out

(17) Dingle, L. E. *Chem. Br.* **1968**, 136. See also: Urben, P. G. *J. Chem. Educ.* **1992**, *69*, 344.

thorough safety testing on any procedure under consideration. We urge great care in scaling up any nitration procedure.

Conclusion

Zeolite H$^+\beta$ is an effective catalyst for the nitration of monosubstituted aromatic substrates by acetic anhydride–nitric acid mixtures. Benzene, alkylbenzenes, and halogenobenzenes are nitrated in quantitative yields with excellent para selectivities using a stoichiometric quantity of nitric acid and enough acetic anhydride to convert all the nitric acid into acetyl nitrate and all the water into acetic acid. Dinitro compounds are not formed in any significant amounts, and the best para regioselection is obtained, at least in the case of toluene, by the addition of the reagents in the order nitric acid/zeolite, acetic anhydride, substrate. Under such conditions, the para regioselectivities obtained from a range of substrates (Table 8) are generally the best ever obtained in high-yielding reactions. Furthermore, the method has a number of practical advantages (no solvent; moderate temperature; easy separation by direct vacuum distillation of both the only byproduct, acetic acid, and the reaction product; and easy recycling of the catalyst) that should make it highly attractive for commercial application. Patent protection has therefore been sought,[9] and the safety of the process has been considered in detail. The method also offers advantageous regioselectivity compared with traditional methods for nitration of some 1,2-disubstituted benzenes (Table 9).

Experimental Section

Preparation of the Proton Form of Zeolite β. The zeolite (CP806), as supplied by PQ Zeolites Ltd., was calcined at 600 °C for 12 h to remove the organic template. The zeolite was then stirred in a refluxing solution (1 M) of aqueous ammonium acetate (10 mL/g) for 1 h. After filtration and a second exchange, to ensure complete ion exchange, the zeolite was again filtered and then calcined at 600 °C overnight, cooled, and ground to a fine powder. It was reheated to 400 °C for 2 h immediately prior to use.

Nitration Procedure: Investigative Experiments. Nitric acid (0.25 g, 70%, 2.5 mmol), acetic anhydride (20 mL), 3A molecular sieves (0.2 g), zeolite (0.1 g), toluene (0.23 g, 2.5 mmol), and hexadecane (0.3 g, 1.3 mmol) as internal standard were mixed together in the desired order and stirred at room temperature. The reaction was sampled at regular intervals and analyzed by GC. Later it was found that the excess of acetic anhydride could be reduced and the molecular sieves omitted from the mixture with only minor modifications to the procedure. Such a procedure was therefore adopted for preparative experiments (see below).

Nitration Procedure: Preparative Experiments (N.B.: See Section on Safety). Nitric acid (2.5 g, 35 mmol) was mixed with H$^+\beta$ (1.0 g) and stirred in an ice–water bath for a few minutes. Stirring and cooling were maintained while acetic anhydride (5.0 mL, 53 mmol) was added (the temperature rose temporarily to about 12 °C during this process), followed by the substrate (35 mmol), dropwise. The cooling bath was removed, and the mixture was stirred for 30 min unless stated otherwise in the text. The acetic acid was removed by distillation

under reduced pressure (30 mmHg), and a second, lower-pressure distillation (0.2 mmHg) at temperatures up to about 70 °C was used to provide the products, leaving the catalyst behind in the reaction flask. The composition of the distilled product mixture was determined by both GC and NMR techniques, and where possible, the spectra were compared with those of authentic samples. Yields and isomer proportions are listed in Tables 8 and 9. Authentic samples were available for comparison with the products from the nitration of monosubstituted benzenes. NMR data for individual products from disubstituted benzenes are given below.

From Nitration of 1,2-Difluorobenzene (5a). 1,2-Difluoro-4-nitrobenzene (**7a**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.42 (1H, m), 8.12 (2H, m); ^{19}F NMR (CDCl$_3$, 400 MHz) δ −126.7 (1F, m), −133.1 (1F, m).

From Nitration of 2-Chlorofluorobenzene (5b). 2-Chloro-1-fluoro-4-nitrobenzene (**8b**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.34 (1H, m), 8.21 (2H, m), 8.35 (1H, m); ^{19}F NMR (CDCl$_3$, 400 MHz) δ −104.40. 1-Chloro-2-fluoro-4-nitrobenzene (**7b**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.63 (1H, m), 8.04 (2H, m); ^{19}F NMR (CDCl$_3$, 400 MHz) δ −110.31.

From Nitration of 2-Bromofluorobenzene (5c). 2-Bromo-1-fluoro-4-nitrobenzene (**8c**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.29 (1H, m), 8.22 (1H, m), 8.46 (1H, m). 1-Bromo-2-fluoro-4-nitrobenzene (**7c**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.77 (1H, m), 7.95 (2H, m).

From Nitration of 2-Fluoroanisole (5d). 2-Fluoro-4-nitroanisole (**7d**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.01 (3H, s), 7.05 (1H, m), 8.00 (1H, m), 8.09 (1H, m); ^{19}F NMR (CDCl$_3$, 400 MHz) δ −131.38. 2-Fluoro-6-nitroanisole (**9d**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.07 (3H, s), 7.07 (1H, m), 7.38 (1H, m), 7.60 (1H, m); ^{19}F NMR (CDCl$_3$, 400 MHz) δ −126.70.

From Nitration of 2-Fluorotoluene (5e). 2-Fluoro-5-nitrotoluene (**8e**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.20 (3H, s), 7.39 (1H, m), 7.88 (1H, m), 7.98 (1H, m); ^{19}F NMR (CDCl$_3$, 400 MHz) δ −113.40. 2-Fluoro-4-nitrotoluene (**7e**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.38 (3H, s), 7.15 (1H, m), 8.09 (2H, m); ^{19}F NMR (CDCl$_3$, 400 MHz) δ −106.50.

From Nitration of 2-Chlorotoluene (5f). 2-Chloro-5-nitrotoluene (**8f**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.41 (1H, d, *J* 8.4), 7.99 (1H, dd, *J* 8.4, 2.3), 8.15 (1H, d, *J* 2.3). 2-Chloro-4-nitrotoluene (**7f**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.48 (1H, d, *J* 8.7), 7.07 (1H, dd *J* 2.4, 8.7), 8.08 (1H, d, *J* 2.6).

From Nitration of 2-Bromotoluene (5g). 2-Bromo-5-nitrotoluene (**8g**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.39 (1H, d, *J* 8.4), 8.03 (1H, dd, *J* 8.4, 2.3), 8.31 (1H, d, *J* 2.3). 2-Bromo-4-nitrotoluene (**7g**): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.66 (1H, d, *J* 8.7), 7.86 (1H, dd *J* 2.6, 8.7), 8.05 (1H, d, *J* 2.7).