Regioselective dinitration of simple aromatics over zeolite Hβ/nitric acid/acid anhydride systems

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Abstract
Various nitration systems comprising nitric acid, acid anhydride and zeolite Hβ in the absence of solvent are described. Direct double nitration of toluene with a nitric acid, propanoic anhydride and zeolite Hβ system has been developed to give 2,4-dinitrotoluene in 98% yield, with a 2,4-:2,6-dinitrotoluene ratio of 123:1. This system also nitrates activated mono-substituted benzenes (anisole and phenetole) and moderately activated mono-substituted benzenes (ethylbenzene and propylbenzene) to give mainly 2,4-dinitro derivatives. The zeolite can be recovered, regenerated and reused to give almost the same yield as that given when fresh zeolite is used.

Keywords: Dinitration, acid anhydride, propionic anhydride, propanoyl nitrate, mono-substituted benzenes, zeolite Hβ, regioselectivity

Introduction

Electrophilic aromatic substitution reactions are often involved in the synthesis of valuable chemicals. However, the commercial syntheses of these compounds still rely on technologies that were developed many years ago. Many suffer serious disadvantages, including the requirement for the use of large quantities of mineral or Lewis acids as activators, which on work-up could generate large quantities of toxic and corrosive waste by-products. They also often involve use of stoichiometric quantities of toxic or otherwise unpleasant reagents and/or suffer from poor yields and/or production of mixtures of regioisomers with low regioselectivity.[1-4]

The development of clean and environmentally benign processes for the regioselective production of *para*-disubstituted compounds has attracted the attention of many researchers. The use of solids, and in particular recyclable heterogeneous zeolite catalysts, can play an

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important role in the enhancement of product selectivities.[5-11] We have reported the successful use of zeolites in various electrophilic aromatic substitution reactions.[12-14] We have shown that the zeolites can be used in greener *para*-regioselective reactions including nitration,[15-21] alkylation,[22,23] acylation,[24,25] halogenation[26,27] and methanesulfonylation[28] reactions.

The production of many industrially important chemicals, such as polyurethanes, agrochemicals, explosives, dyes, pharmaceuticals and fragrances,[29,30] is highly dependent on the use of 2,4-dinitrotouene (2,4-DNT) as a crucial intermediate. Unfortunately, dinitration of toluene with mixed acids provides a mixture of 2,4- and 2,6-dinitrotoluenes with low selectivity (typically, 2,4-/2,6-DNT = 4). Several attempts have been made to improve the process by the use of solids as catalysts.[31-36] For example, 2,4-DNT was produced in 85% yield with a 2,4-:2,6-dinitritoluene ratio of 9 when nitration of toluene was carried out with nitric acid and acetic anhydride over claycop.[29,30] However, the process required a large excess of nitric acid and the use of carbon tetrachloride as a solvent. A better 2,4-/2,6-DNT ratio (14) was reported with nitric acid over a zeolite β catalyst.[37]

We have shown that dinitration of toluene with nitric acid and trifluoroacetic anhydride (TFAA) over zeolite Hβ gave 2,4-DNT in 92% yield with a 2,4-:2,6-dinitrotoluene (2,6-DNT) ratio of 25.[21] An even better yield (96%) of 2,4-DNT and greater regioselectivity (2,4-/2,6-DNT ratio = 70) were obtained when the reaction was conducted in two stages in which trifluoroacetic anhydride (TFAA) was added only in the second stage.[21] However, the toxicity of trifluoroacetic anhydride and its volatility and cost may render it unattractive for commercial processes. We have therefore sought to find a more attractive alternative.[38] We have already given a preliminary account of some of the results.[39] We now report the full details of the study and the successful double nitration of mono-substituted benzenes to give the corresponding 2,4-dinitro derivatives.

Results and Discussion

Initially, zeolite Hβ (SiO_2/Al_2O_3 = 25; 0.5 g) was added to stirred, cold (0 °C) nitric acid (70 mmol, 100%). Acetic anhydride (100 mmol) was added to the mixture in a dropwise manner, which generates acetyl nitrate *in situ* (Scheme 1). Toluene (35 mmol) was then carefully added dropwise to the stirred cold mixture over *ca.* 10 minutes. The major products of the nitration reaction were 2-nitrotoluene (2-NT, **2**), 3-nitrotoluene (3-NT, **3**), 4-nitrotoluene (4-NT, **4**), 2,4-dinitrotoluene (2,4-DNT, **5**) and 2,6-dinitrotoluene (2,6-DNT, **6**) (Scheme 2).

$$(MeCO)_2O + HNO_3 \rightleftharpoons MeC(O)ONO_2 + MeCO_2H$$

Scheme 1. Generation of acetyl nitrate.

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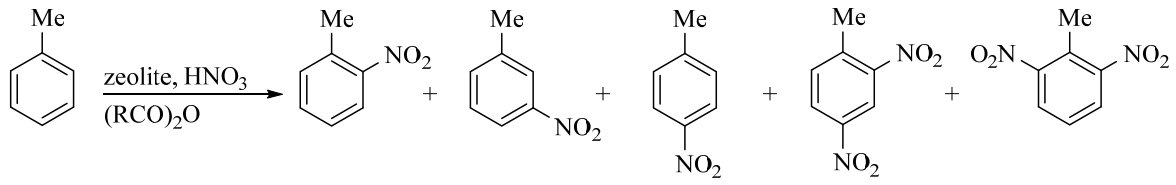

Scheme 2. Nitration of toluene (**1**) with a $HNO_3/(RCO)_2O$/zeolite system.

The GC results indicated that **5** was produced in 28% yield along with **6** (0.8%) and mononitrotoluenes **2–4** (67%). Therefore, we undertook a more detailed study of the reaction in order to optimize the process. We independently varied the quantities of zeolite, nitric acid and acetic anhydride, the time of reaction and the reaction temperature. A small selection of the results is given in Table 1.

Table 1. Optimization of dinitration of toluene (**1**; Scheme 2) using HNO_3 and acetic anhydride over zeolite Hβ[a]

Hβ:HNO_3:Ac_2O (g:mol eq:mol eq)	Temp/ Time (ºC/h)	Yield (%)[b,c]					**5/6** ratio[d]
		2	**3**	**4**	**5**	**6**	
0.5:2.0:2.9	20/16	9.0	3.0	55	28	0.8	35
0.5:2.0:2.9	20/16	11	2.3	68	18	0.6	30
2.0:2.0:2.9	20/16	0.1	2.1	36	54	0.6	92
2.0:2.0:2.9	20/0.5	11	2.3	68	18	0.6	30
2.0:2.0:2.0	20/16	0.9	2.1	43	49	0.8	60
2.0:2.9:2.0	20/16	0.4	2.5	28	63	1.3	50
2.0:3.4:4.3	20/16	0.1	2.0	21	76	1.3	58
2.0:4.0:4.9	20/16	—	1.4	11	84	1.3	64
2.0:3.4:4.3	50/16	0.3	2.1	34	63	1.4	45

[a] Reactions carried out using toluene (3.22 g, 35 mmol), nitric acid (100%), acetic anhydride and Hβ (SiO_2/Al_2O_3 = 25) in the stated quantities under the stated conditions of time and temperature. [b] By quantitative GC using hexadecane (1.0 g) as internal standard. [c] Isomer yields reported to two significant figures when more than 1%. [d] Ratio calculated directly from GC data and not from the rounded figures in the Table.

It was found that increasing the amount of catalyst increased the rate of reaction, that excess of both nitric acid and acetic anhydride also resulted in increased rate of reaction, and that the ratio of 2,4-DNT (**5**) to 2,6-DNT (**6**) increased as the extent of reaction increased, a consequence of the fact that all of the **6** resulted from conversion of 2-NT (**3**), which was consumed quickly, whereas a large proportion of **5** arose from conversion of 4-NT (**4**), which reacted much more

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slowly. However, despite extensive experimentation, the best yield of **5** obtained was only 84% and a significant proportion (around 14%) of under-nitrated species, predominantly **4**, remained. Even after addition of fresh zeolite, nitric acid and acetic anhydride to this reaction mixture the yield of **5** increased only to 89%, with almost 9% of under-nitrated species still remaining. Therefore, attention was turned to the nature of the zeolite in an attempt to improve the situation. The zeolite fulfils two important roles in the reaction: (i) it acts as an acid catalyst, to protonate the acetyl nitrate leading to generation of a nitronium ion, the active nitrating agent; (ii) it constrains the transition state for the reaction of the substrate with the nitronium ion, which influences the relative ease of reaction at different sites in the substrate, leading to changes in regioselectivity. Both of these processes depend on the structural nature of the zeolite.

Zeolites are aluminosilicates having a lattice structure bearing one negative charge for each aluminum atom in the framework. This lattice charge is counterbalanced by cations, which are mostly located within the zeolite pores, where most of the surface area is found. When the cation is a proton, the zeolite surface is acidic (and ammonium forms of zeolites lose ammonia during calcination to give proton forms). The acid strength depends on both the lattice structure (how the atoms of the lattice are located with respect to each other) and the Si/Al ratio (how many acid sites there are and how far apart from each other they are). For any particular lattice structure, increasing the Si/Al ratio results in fewer acid sites but of greater acid strength.

The detailed lattice structure (the size of apertures, whether channels are linear or whether they intersect to create larger cavities and multiple transport routes within the pores) influences how likely individual reaction pathways are to occur, by allowing/inhibiting access to reagents (aperture size), by favoring some transition states over others (cavity dimensions) and by influencing the ability of products to escape from the pores (aperture size and channel structure). In order to check whether the zeolite Hβ (SiO_2:Al_2O_3 = 25) used in reactions thus far was the most effective catalyst, a range of different zeolites was screened for efficacy in the nitration of toluene (**1**; Scheme 2) with HNO_3 and acetic anhydride. The properties of the commercial zeolites used in this study are recorded in Table 2 and the yields obtained when they were used in the two-stage procedure that had produced the highest yield previously are recorded in Table 3.

Zeolites H-ZSM-5 (a medium pore zeolite) and HM (which has large apertures but linear channels and no large cavities) gave very low yields of **5**, implying that the reaction probably did not take place to any significant extent within the pores of these zeolites. It was probably catalysed non-selectively by acidic sites on the external surface of the zeolite, but the low number of such sites would have led to a very low rate for the second nitration step.

HY and Hβ (both of which have large apertures and 3D intersecting channels with large cavities) were found to be the most effective catalysts in terms of yields of **5**. The differences in yields obtained with different samples of HY can be understood in terms of the number and strengths of the acidic sites, which are associated with the Al centres in the lattice. When there is a low SiO_2/Al_2O_3 ratio, there are many acidic sites, but the acid strength of each site is low. It appears that the strength of the acid sites in HY (SiO_2/Al_2O_3 = 5.1) was too low to catalyse the dinitration reaction, but that by a SiO_2/Al_2O_3 ratio of 30 the strength of the acid sites was great

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enough to catalyse the reaction, while the relatively large number of such sites ensured a reasonable rate. For the sample with SiO_2/Al_2O_3 ratio of 80 the rate was less, even though the strength of the sites was greater, because of the small number of acid sites available, and this led to a lower yield at the time when the reaction was stopped.

Table 2. Typical properties of the commercial zeolites used[42]

Zeolite	Product code	SiO_2/Al_2O_3 ratio	Nominal cation form	Na_2O (wt%)	Pore diameter (Å)	Surface area (m^2/g)
HZSM-5	CBV 3024E	30	NH_4	0.05	5.3 x 5.6 and 5.1 x 5.5	400
HZSM-5	CBV 28014	280	NH_4	0.05	5.3 x 5.6 and 5.1 x 5.5	400
HM	CBV 21A	20	NH_4	0.08	6.5x7.0	500
HM	CBV 90A	90	H	0.05	6.5x7.0	500
HY	CBV 400	5.1	H	2.80	7.4x7.4	730
HY	CBV 720	30	H	0.03	7.4x7.4	780
HY	CBV 901	80	H	0.03	7.4x7.4	700
Hβ	CP 814E*-25	25	NH_4	0.05	6.6x7.7 and 5.5 x 5.6	680
Hβ	CP 811E-75	75	NH_4	0.05	6.6x7.7 and 5.5 x 5.6	650
Hβ	CP 811E-150	150	NH_4	0.05	6.6x7.7 and 5.5 x 5.6	720
Hβ	CP 811C-300	300	NH_4	0.05	6.6x7.7 and 5.5 x 5.6	620

[a] Pore volume was calculated using the formula: $= 4\pi(D_i/2)^3/3$, where D_i represents the maximum included sphere diameter (Å).[42]

When zeolite Hβ (SiO_2/Al_2O_3 = 25) was used, 88% of **5** was produced and there was a decrease in the yield as the acidity of the catalyst was increased (SiO_2/Al_2O_3 = 75–300). The trends in the results were consistent with the high *para*-selectivity reported in mono-nitration of toluene with acetyl nitrate over zeolite Hβ,[21] for which the high *para*-selectivity has been attributed to steric hindrance of the surface-bound acetyl nitrate complex.[40,41] It is clear from Table 7 that the best catalyst among all the zeolites tried was zeolite Hβ (SiO_2/Al_2O_3 = 25), the key one that was selected from the beginning of the project. Therefore, it seemed that the best procedure for this system had already been found.

It was clear that a system comprising nitric acid, acetic anhydride and zeolite Hβ could effect 2,4-dinitration of toluene with excellent regioselectivity, but despite extensive experimentation we have been unable to find conditions that bring about complete conversion of 4-NT into 2,4-DNT. Therefore, our attention was next turned to the use of different acid anhydrides, which on reaction with nitric acid should generate the corresponding acyl nitrates (Scheme 3).

$$(RCO)_2O + HNO_3 \rightleftharpoons RC(O)ONO_2 + RCO_2H$$

Scheme 3. Generation of acyl nitrates.

Table 3. Nitration of toluene (**1**; Scheme 2) with HNO_3 and acetic anhydride over various zeolites[a]

Zeolite	SiO_2/Al_2O_3	Yield (%)[b,c]					**5/6** ratio[d]
		2	**3**	**4**	**5**	**6**	
H-ZSM-5	30	54	2.4	42	3.2	—	—
H-ZSM-5	280	59	2.6	39	—	—	—
HM	20	57	3.1	40	—	—	—
HM	90	54	3.1	39	4.6	—	—
HY	5.1	58	4.1	37	—	—	—
HY	30	14	2.2	5.1	72	5.1	14
HY	80	30	2.1	12	52	4.3	13
Hβ	25	—	—	12	88	—	—
Hβ	75	—	2.0	21	77	—	—
Hβ	150	2.1	2.2	38	56	—	—
Hβ	300	13	2.2	38	46	—	—

[a] Reactions carried out using toluene (3.22 g, 35 mmol), nitric acid (100%, 7.56 g, 120 mmol), acetic anhydride (15.30 g, 150 mmol) and zeolite (2.0 g) overnight at room temperature and then nitric acid (1.89, 30 mmol) and acetic anhydride (3.83 g, 37.5 mmol) were added for the second step and the reaction mixture was stirred for a further 2 h at 50 °C. [b,c,d] See footnotes b, c and d to Table 1.

We have previously shown that trifluoroacetic anhydride (TFAA) is much more active than acetic anhydride for the double nitration of toluene.[20] However, the reaction conditions used in that study were different from those used in the present study. Therefore, the reaction of toluene (**1**) with TFAA and nitric acid was conducted under conditions similar to those used with acetic anhydride. The results showed that the reaction was rapid and gave almost complete conversion to dinitrotoluenes, but that the regioselectivity was much poorer than with acetic anhydride (around 87% **5** and 12% **6**, with only traces of **4**).

It appeared that the high reactivity of trifluoroacetyl nitrate led to a significant proportion of the reaction taking place without the beneficial effects of the zeolite catalysis.

Therefore, it was of interest to investigate the reactions with acyl nitrates of intermediate reactivity and a range of chlorinated acetic anhydrides was investigated to see whether one of those would provide an acyl nitrate with an appropriate level of both activity and selectivity. Since some of the chlorinated acetic anhydrides are solid, it was necessary to use a solvent (dichloromethane; DCM) for reactions in which they were involved. In order to allow proper comparison, the solvent was used for the other cases also. Reactions were conducted for short reaction times (10–30 min) over zeolite Hβ (SiO_2/Al_2O_3 = 25) under otherwise identical reaction conditions. The results obtained are recorded in Table 4.

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Table 4. Dinitration of toluene (**1**; Scheme 2) with chloroacetic anhydrides/HNO_3/zeolite Hβ[a]

Anhydride (R)	t (min)	Yield (%)[b,c]					**5/6** ratio[d]
		2	**3**	**4**	**5**	**6**	
CH_3	30	4.2	2.1	38	51	1.6	32
$ClCH_2$	10	6.4	1.1	31	57	2.7	21
$ClCH_2$	30	0.2	0.2	2.3	93	4.0	23
$ClCH_2$	60	—	0.4	0.6	97	2.3	45
Cl_2CH	30	—	0.0	—	98	1.8	54
Cl_3C	10	2.7	0.9	22	68	6.0	11
Cl_3C	30	—	—	7.9	85	6.3	14

[a] Reaction carried out using toluene (3.22 g, 35 mmol), nitric acid (100%, 7.56 g, 120 mmol), acid anhydride (120 mmol), DCM (10 mL) and zeolite Hβ (2.0 g) at 50 °C for the stated reaction time. [b,c,d] See footnotes b, c and d to Table 1.

The order of reactivity, as indicated by the overall yields of DNTs under identical conditions (*e.g.* 30 ºC), was dichloroacetic>chloroacetic>trichloroacetic>acetic. Trichloroacetic anhydride is intrinsically more reactive than dichloroacetic anhydride, so it might have been expected to produce the highest yields of dinitrotoluenes. However, trichloroacetic anhydride is the most sterically hindered of the group and this may restrict the nitrating reagent from forming within or entering the zeolite pores. This could also explain the observation that trichloroacetic anhydride resulted in the lowest selectivity for formation of 2,4-DNT, since a higher proportion of the reaction would have occurred outside the pores. The differences in selectivity between the other anhydrides were not major, especially when the effects of the different levels of conversion are considered, but dichloroacetic anhydride gave the highest regioselectivity (**5/6** = 54 after 30 min). However, chloroacetic anhydride still gave a very good yield of 2,4-DNT under appropriate conditions and is much cheaper than dichloroacetic anhydride.

Given that a reasonable conversion and excellent selectivity had been achieved with acetic anhydride it was also of interest to see how other simple aliphatic anhydrides would compare and therefore dinitration of toluene (**1**) was investigated with systems comprising such anhydrides, nitric acid and zeolite Hβ for 4 h at 50 °C. The anhydrides chosen were propionic, butyric, valeric, isobutyric and pivalic anhydrides. The results obtained are reported in Table 5.

Two significant trends can be deduced from Table 5; (i) there was a strong diminution in yield with increased branching, suggesting that branching discouraged the corresponding active nitrating agents from gaining access to or forming within the pores; and (ii) the yield and 2,4-DNT selectivity with straight chain anhydrides peaked at propionic anhydride. The observed selectivity in the latter series depends significantly on the extent of reaction, since 2-NT is converted quickly to a mixture of DNTs while 4-NT is converted more slowly, but specifically to 2,4-DNT, so the differences observed do not imply substantial differences in intrinsic selectivity. However, the rate differences were quite marked, with propionic anhydride giving a much higher

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yield (94%) of **5** than either acetic anhydride or the longer chain anhydrides. Propionic anhydride is less polar than acetic anhydride, which might encourage the reaction to take place to a greater extent inside the pores of the zeolite. However, on that basis alone it would be expected that the even longer chain butyric and valeric anhydrides would also give high yields, but this was not the case. It could be that the reactions with the longer chain anhydrides are slower because of lower diffusion rates within the pores of the zeolite. In order to test this possibility, the reaction using valeric anhydride was studied over a longer reaction period (8 h) and the yield of **5** increased to 83%. However, these results are still not as good as those obtained by use of propionic anhydride for a shorter reaction time.

Table 5. Dinitration of toluene (Scheme 2) with $(RCO)_2)O/HNO_3$/zeolite Hβ[a]

Anhydride (R)	Yield (%)[b,c]					**5/6** ratio[d]
	2	**3**	**4**	**5**	**6**	
Me	—	1.8	27	69	1.3	53
Et	—	0.9	4.6	94	1.0	85
Pr	7.1	1.3	29	59	2.4	25
Bu	2.3 (1.9)[e]	4.1 (2.7)[e]	24 (8.6)[e]	67 (81)[e]	1.5 (3)[e]	45 (27)[e]
i-Pr	22	2.1	44	31	0.7	2.0
t-Bu	45	1.3	47	5.5	0.0	1.1

[a] Reactions carried out using toluene (3.22 g, 35 mmol), nitric acid (100%, 7.56 g, 120 mmol), acid anhydride (120 mmol) and zeolite Hβ (2.0 g) at 50 °C for 4 h. [b,c,d] See footnotes b, c and d to Table 1.[e] Figures in parentheses are for 8 h reaction.

Several other representative anhydrides were tested under similar conditions. No 2,4-DNT was produced when the reaction was carried out using phthalic, maleic or benzoic anhydride in the presence of DCM as a solvent. By contrast, succinic anhydride produced **5** in 85% yield with a **5/6** ratio of 10 under similar reaction conditions, reflecting that conjugation of the carbonyl groups of the anhydride moiety reduces the electrophilicity of the anhydride group.

Clearly, propionic anhydride was the most attractive candidate for further study, which was unexpected. Optimization of the propionic anhydride system was undertaken in a manner analogous to that used with acetic anhydride in an attempt to push the reaction to completion to produce **5** in even greater yield. The best result was obtained by stirring toluene, 3.4 mole equivalents of nitric acid, 3.7 mole equivalents of propionic anhydride and zeolite Hβ (2.0 g for 35 mmol of toluene) for 4 h at 50 °C, which according to GC of the crude product mixture produced **5** in 98% yield and **6** in 0.8% yield (a **5/6** ratio of 123) along with traces of **3** (0.4%) and **4** (0.8%).

Pure 2,4-DNT was isolated in 94% yield by simply filtering, washing the zeolite with solvent, concentrating the mother liquor, and recrystallization from diethyl ether. For large scale work solvent extraction of the zeolite would probably be unnecessary, since residual

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product could be removed from the zeolite by filtration under reduced pressure, but to ensure that all products were accounted for, in this work the zeolite was fully extracted. Also, for larger scale work the propionic acid by-product could be recovered by direct evaporation from the crude reaction product mixture after removal from the zeolite, making it easily available for conversion back into anhydride if required.

Interestingly, the combined yield of dinitrotoluenes was 82% even after 5 minutes at 50 ºC, at which point the 2,4-:2,6-DNT ratio was around 74 and already there was virtually no residual 2-nitrotoluene, showing how rapidly it reacted to give dinitrotoluenes. The 4-nitrotoluene reacted more slowly, so that the yield of DNTs and the selectivity for 2,4-DNT both rose over time after the first few minutes. It is likely that the apparent disappearance of products derived from 3-nitrotoluene reflects inability to measure trace quantities of several different compounds.

Reactions were also conducted in various solvents (cyclohexane, chloroform, 1,2-dichloroethane, propanoic acid or excess propanoic anhydride). However, use of solvent invariably brought about a decrease in yield of dinitrotoluenes (DNTs), presumably as a result of the lower concentrations of reacting species, and in all cases except for propanoic anhydride the 2,4-:2,6-DNT ratio was also somewhat lower, consistent with the reduced extent of reaction of 4-nitrotoluene. Therefore, the addition of solvent to the nitration system has no advantages on either selectivity or yield and is not necessary.

In order to check on the possibility of reuse of the zeolite, it was recovered following extraction of the products and was regenerated by heating overnight in air at 450 °C. Nitration reactions were then conducted under identical conditions using the recovered zeolite. The reaction was repeated seven times using the same batch of catalyst, but later reactions were scaled down somewhat due to small losses of zeolite during recovery. The results (Table 6) showed that under the standard conditions there was only a slight decrease (to 94%) in the yield of **5** even after using the same zeolite seven times, and the selectivity was virtually the same. In total, around 43 g of **5** was produced by using just 2.0 g of zeolite Hβ by using it seven times with calcination after every individual reaction.

In a second series of reactions, the zeolite was reused without calcination at a high temperature. The fresh zeolite was separated from the mixture after the first reaction and was washed with acetone several times to extract the products. The zeolite was then dried in an oven at 60 °C under reduced pressure overnight and was then reused in a reaction. The results obtained are recorded in Table 7.

It is clear from the results in Table 7 that there was a significant decrease (9%) in the yield of **5** after the first reuse of non-calcined zeolite. Also, the **5/6** ratio dropped substantially from 123 to 80 after the first reuse, consistent with the fact that it was specifically the conversion of **4** into **5** that had reduced. Thereafter, however, the results showed a fairly consistent activity of the zeolite after its first use, although there may be a slight increase in the amount of **6** formed, resulting in lower selectivity, with increased number of uses of the zeolite. The relatively constant results after the first reuse suggest that the zeolite was being reactivated in the oven to a

certain extent, but that something was retained by the zeolite when it was heated only at 60 °C, and that the retained material had a deleterious effect on the zeolite activity. It was thought to be possible that a fixed amount of propionic acid was strongly retained by the zeolite at 60 °C and that this could have caused the partial deactivation.

Table 6. Efficiency of recycled calcined zeolite in dinitration of toluene (**1**; Scheme 2)[a,b]

Run	Yield (%)[b,c]					**5/6** ratio[d]
	2	**3**	**4**	**5**	**6**	
1	—	0.4	0.6	98	0.8	123
2	—	0.4	1.6	97	0.5	195
3	—	0.6	2.5	96	0.6	160
4	—	0.7	3.2	95	0.5	190
5	0.4	0.5	3.0	95	0.9	106
6	—	0.8	3.0	95	0.8	119
7	—	0.8	4.1	94	0.8	118

[a] Zeolite calcined at 450 °C. [b] The initial reaction was carried out using toluene (3.22 g, 35 mmol), propanoic anhydride (16.91 g, 130 mmol), nitric acid (100%, 7.56 g, 120 mmol) and zeolite Hβ (2.0 g) at 50 °C for 4 h. Each subsequent reaction was scaled down according to the amount of zeolite recovered (there were small physical losses of zeolite during recovery). [b,c,d] See footnotes b, c and d to Table 1.

Table 7. Efficiency of recycled non-calcined zeolite in dinitration of toluene (**1**; Scheme 2)[a]

Runs	Yield (%)[b,c]					**5/6** ratio[d]
	2	**3**	**4**	**5**	**6**	
1	—	0.4	0.6	98	0.8	123
2	— (—)[e]	0.9 (0.8)[e]	9.5 (6.7)[e]	89 (91)[e]	1.1 (1.3)[e]	80 (70)[e]
3	—	1.2	13	85	1.4	60
4	—	1.1	11	87	1.4	62
5	—	1.2	11	86	1.4	61
6	3.4	1.7	18	74	1.7	44
7	—	1.3	10	88	1.7	52

[a] Initial reaction carried out using toluene (3.22 g, 35 mmol), nitric acid (100%, 7.56 g, 120 mmol), propionic anhydride (16.91 g, 130 mmol) and zeolite Hβ (2.0 g) at 50 °C for 4 h; subsequent reactions were scaled down due to small physical losses of zeolite during recovery, but were carried out under otherwise similar conditions with the same sample of zeolite after reactivation at 60 ºC overnight. [b,c,d] See footnotes b, c and d to Table 1. [e] Figures in parentheses are for a reaction conducted under similar conditions except with a different batch of once-used zeolite that had been reactivated at 60 °C under reduced pressure for 48 h instead of around 16 h.

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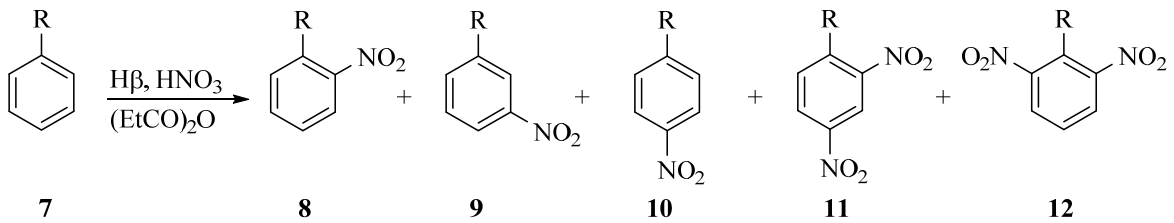
It was therefore desirable to know if the zeolite could be fully reactivated again by calcination. Therefore, the same batch of zeolite that had been used in all the experiments reported in Table 7 was reactivated by calcination at 450 °C overnight and reused again under similar conditions. The results suggested that zeolite which had not previously been recalcined could recover almost its original activity level by such calcination. Therefore, by reactivation of the zeolite at 60 °C rather than by calcination there is potential to produce a very large quantity of **5** with the same batch of zeolite, since the zeolite can be recovered and reused many times before its activity is significantly damaged, and if necessary the full activity can be restored by calcination at high temperature.

Several mono-substituted benzenes **7**, including ones that are activated (anisole, phenetole), moderately activated (ethylbenzene, propylbenzene), and moderately deactivated (fluorobenzene, chlorobenzene, bromobenzene), were subjected to the nitrating system under the same conditions as those optimized for toluene. Reactions were worked up and product compositions determined by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy (since not all expected products were to hand for use as GC standards). The calculated mass balances were consistent with the total weights of products obtained (Table 8).



Scheme 4. Nitration of mono-substituted benzenes **7** with a $HNO_3/(EtCO)_2O/H\beta$ system.

Table 8. Nitration of mono-substituted benzenes **7** (Scheme 4)[a]

Entry	R	Yield (%)[b]					Mass balance
		8	**9**	**10**	**11**	**12**	(%)[c]
1	OMe	trace	trace	trace	97	1	98[d]
2	OEt	trace	trace	trace	96	1	97[d]
3	Me	—	0.4	0.8	98	0.8	100[e]
4	Et	7	trace	17	73	trace	97
5	Pr	5 (3)[f]	trace	31 (7)[f]	61 (89)[f]	trace	97 (99)[f]
6	F	7	trace	85	5	—	97
7	Cl	2	—	92	2	2	98
8	Br	2	—	92	2	2	98

[a] Propanoic anhydride (16.91 g, 130 mmol) was added to a stirring mixture of nitric acid (100%, 7.56 g, 120 mmol) and zeolite Hβ (2.00 g) at 0 °C and the mixture was stirred for 5 min. Substituted benzene (35 mmol) was added dropwise and the mixture was allowed to warm to

room temperature then stirred at 50 °C for 4 h under a calcium chloride guard tube. (The order of addition was found not to be important for halobenzenes, but it was important for the more reactive substrates.) The mixture was allowed to cool to room temperature and the catalyst was removed by filtration and washed with acetone (3 × 10 mL). Water (30 mL) and DCM (30 mL) were added to the combined filtrate and washings and the layers were separated. The aqueous layer was extracted with DCM (20 mL) and the organic layers were combined. The combined organic extract was washed with aq. saturated $NaHCO_3$ solution (30 mL) and water (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. [b] By weight of crude product and its ^{1}H NMR spectrum. [c] The sum of the calculated percentage yields of nitro products based on weight of product and its ^{1}H NMR spectrum. [d] Traces of other dinitro compounds, possibly arising from 3-nitro derivative, were also seen. [e] Yields of isomers calculated by use of quantitative GC. [f] When 4.00 g of Hβ was used.

In no case other than toluene was there evidence of a significant quantity of 3-nitro compound. All reactions appeared to be extremely selective for formation of 2,4-dinitro isomer or 4-mononitro derivative. Highly active anisole and phenetole produced excellent yields of the corresponding 2,4-dinitro derivatives (97 and 96%, respectively). 2,6-Dinitroanisole and 2,6-dinitrophenetole were produced in very low yields (1%) along with small quantities of other nitrated products.

With ethylbenzene and propylbenzene, significant amounts (17–31%) of 4-nitro-1-alkylbenzenes remained after 4 hours, although relatively high yields of 2,4-dinitro-1-alkylbenzenes (61–73%) were obtained with outstanding selectivity (only trace amounts of the 2,6-isomers). The yield of 2,4-dinitro-1-propylbenzene increased to 89% under similar reaction conditions when the amount of zeolite used was doubled to 4 g, so it seems that longer-chain alkylbenzenes simply react more slowly, presumably because of more difficult diffusion through the pores and/or more restricted transition states within the pores of the zeolite. Halobenzenes produced very low yields of dinitro compounds (2–5%). Instead, 1-halo-4-nitrobenzenes were the main products. We have not optimized conditions for each substrate but longer reaction times, additional nitrating reagent, more catalyst and/or higher temperature might lead to high yields of 2,4-dinitro derivatives for the less active substrates.

Conclusions

Dinitration of toluene over a nitric acid, acetic anhydride and zeolite Hβ (SiO_2/Al_2O_3 = 25) system was optimised to give 2,4-dinitrotoluene (88%) along with 4-nitrotoluene (12%) but the reaction could not be caused to go to completion. However, dinitration of toluene (35 mmol) with nitric acid (120 mmol) and propanoic anhydride (150 mmol) over zeolite Hβ (2.0 g) gives 2,4-dinitrotoluene in 98% yield with a 2,4-:2,6- ratio around 123:1. This is easily the most selective quantitative double nitration of toluene ever recorded. Good yields and

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selectivities can also be obtained by use of chloroacetic and dichloroacetic anhydrides. Trifluoroacetic anhydride has also been previously reported, but propanoic anhydride is more attractive than trifluoroacetic anhydride in terms of selectivity, volatility, toxicity and cost. Since propanoic acid can be recovered and the zeolite can be reused several times, the method could be attractive for larger scale syntheses. It also works well for dinitration of activated substrates such as anisole and phenetole. Other alkylbenzenes give dinitro compounds in lower yields but high selectivity, while halobenzenes give mainly *para*-nitro derivatives.

Experimental Section

General. Commercial Hβ zeolites were purchased from Zeolyst International and were freshly calcined at 450 °C for a minimum of 6 h prior to use. Toluene was purchased from Fisher Scientific and nitric acid (100%) was purchased from BDH Laboratory Supplies. Other chemicals were purchased from Aldrich Chemical Company and used without further purification except for toluene and propanoic anhydride, which were distilled.

All GC analyses were carried out on a PU 4400 Gas Chromatograph (Philips) using a capillary ZB Carbowax column (30 m, 0.32 mm ID). The GC conditions used for analysis were: 35 °C for 0.5 min, ramped to 240 °C at 20 °C/min and held for 15 min. The injection temperature was 300 °C and the detection temperature 300 °C. Hexadecane was added as an internal standard to allow quantification. All of the expected products from nitration of toluene were purchased from Aldrich Chemical Company and used to determine retention times and response factors relative to hexadecane (average from four injections) for each product.

^{1}H NMR spectroscopy was the method of analysis for substrates other than toluene, for which diphenylmethane was used as a standard. The calculated mass balances were consistent with the total weights of products obtained.

Typical experimental procedure for the double nitration of toluene using nitric acid, propanoic anhydride and zeolite Hβ catalyst.

Propanoic anhydride (16.90 g, 130 mmol) was added to a stirring mixture of nitric acid (7.65 g, 100%, 120 mmol) and Hβ (2.0 g, SiO_2: Al_2O_3 = 25) at 0 °C and the mixture was stirred for 5 min at constant temperature. Toluene (**1**; 3.22 g, 35 mmol) was then added dropwise and the mixture was allowed to warm to room temperature. The flask was equipped with a water condenser fitted with a calcium chloride guard tube and the reaction mixture was heated at 50 °C for 4 h with stirring. The mixture was cooled to room temperature, analytical grade acetone (30 mL) was added and stirring was continued for 5 min. The zeolite was removed by suction filtration and washed with copious amounts of acetone. The mother liquors were combined, hexadecane (1.00 g) was added and the mixture was subjected to GC analysis.

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Purification of 2,4-dinitrotoluene (2,4-DNT; 5). The isolation procedure is for a reaction that did not have hexadecane added. At the end of the reaction, the mixture was allowed to cool to room temperature and the catalyst was removed by filtration and washed with analytical grade acetone (3 × 10 mL). Water (30 mL) and DCM (30 mL) were added to the combined filtrate and washings and the layers were separated. The aqueous layer was extracted with DCM (20 mL) and the organic layers were combined. The organic extract was washed with saturated aq. $NaHCO_3$ solution (30 mL) followed by water (30 mL), then dried ($MgSO_4$) and evaporated to constant weight under reduced pressure to give the crude product (6.34 g). The crude product was recrystallized from analytical grade acetone to give pure 2,4-dinitrotoluene (**5**; 5.99 g, 94%; >99% purity by GC).

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