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Practical neutral aromatic nitration with nitrogen dioxide in the presence of heterogeneous catalysts under moderate oxygen pressure

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Abstract—A practical neutral aromatic nitration process using nitrogen dioxide in the presence of $FeCl_3 \cdot 6H_2O$ under 40–100 psig of oxygen was developed, and nitration of several aromatic compounds, including the deactivated nitrobenzene, was performed in a successful manner. The correlation of reaction rate with equivalents nitrogen dioxide, oxygen pressure, amount of catalyst and temperature was investigated through the nitration of benzene. Following the optimization of reaction conditions, the nitration of benzene was scaled up to 476 mol. Furthermore, inorganic solid catalysts with pore size over 5 Å and surface area over 100 m^2/g were applied to newly developed neutral nitration.

Keywords: Neutral aromatic nitration; nitrogen dioxide; oxygen; $FeCl_3 \cdot 6H_2O$; scale-up; inorganic solid catalysts.

INTRODUCTION

Aromatic nitration is one of the essential organic reactions because nitro aromatic compounds are used as the precursors to a wide range of valuable compounds such as pharmaceuticals, agrochemicals, dyes, explosives, etc. [1, 2]. Although in the past decades, a huge number of efforts have been made to find more efficient and clean nitration route [3–12], the long historic mixed-acid protocol using a mixture of nitric and sulfuric acid is utilized as the most common way in an industrial area thus far. Among them, the aromatic nitration using nitrogen dioxide (NO_2) and molecular oxygen (O_2) in the presence of a catalyst can be taken into account as

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one of the promising alternatives [13, 14]. The use of NO_2 and O_2 in place of nitric acid and sulfuric acid has attracted a lot of attention, especially in large scale. First, a neutral reaction condition can provide a safe and non-corrosive operation and also minimize the irritating oxidative side products. Second, the use of nitrogen oxide (NO_2 and NO) can save costs in manufacturing nitric acid. In particular, no use of sulfuric acid, causing a large amount of wastewater, can construct an environmentally benign process. However, in terms of reactivity, this method is not so strong compared with the conventional mixed acid nitration. Therefore, a longer reaction time is required and the nitration of deactivated arenes showed a low conversion even though a large excess of NO_2 was used [13]. Moreover, use of specially designed catalysts can give rise to high costs on a very large scale.

Here, we report a practical aromatic nitration methodology using nitrogen dioxide and pressurized oxygen in the presence of iron(III) chloride six hydrate ($FeCl_3 \cdot 6H_2O$). In addition, a pilot-scale test of this nitration and a use of inorganic solid catalysts in place of transition metal salt will be described.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. All reagents were reagent grade and they are purified prior to use if necessary. Chlorobenzne, nitrobenzene and $FeCl_3 \cdot 6H_2O$ were purchased from Aldrich. Benzene, toluene and chlorobenzene were obtained from Oriental Chemical. Nitrogen dioxide and oxygen were used as obtained in a cylinder and they were $>99.9\%$ in purity. All nitration products were known and identified by direct comparison with authentic samples. In gas chromatography (GC), a HP-5 column (5% Ph Me silicone, 10 m $\times$ 2.65 μm film thickness) and FID (flame ionization detector) detector were used for GC (680D gas chromatograph, Young-In Scientific). Detected peaks from GC were quantified with integrating software (Donam system, dsCHROM).

Typical procedure of the neutral nitration

A typical procedure is exemplified by the preparation of nitrobenzene. In an autoclave (*ca.* 300 ml) fitted with a gas inlet and a vent tube were placed benzene (0.1 mol, 8.9 ml), NO_2 (2.5 equiv, 0.25 mol) and $FeCl_3 \cdot 6H_2O$ (1 mol% NO_2, 2.5 mmol). To remove air present in the free volume of the reactor, the mixture was cooled to 0°C in an ice bath and briefly purged with oxygen. Oxygen was introduced into the autoclave through an inlet tube with stirring at room temperature and the total pressure was adjusted to 60 psig. Oxygen was supplied to the autoclave at regular intervals to keep the total pressure of the reactor. After 1.5 h, the reaction was interrupted by vent and the autoclave was purged with nitrogen to remove traces

of NO_2. After the catalyst was filtered off, pure nitrobenzene was obtained by the usual work-up procedure as follows; the organic layer was separated, washed with water, and dried over magnesium sulfate. The final isolated nitrobenzene was analyzed by NMR.

Pilot scale operation of the neutral nitration of benzene

In a 200-l autoclave reactor equipped with safety rupture were placed benzene (467 mol, 36.14 kg) and $FeCl_3 \cdot 6H_2O$ (1.15 mol% NO_2, 0.8 kg). NO_2 (0.55 equiv, 267 mol, 11.81 kg) was inhaled under reduced pressure into the reactor. Oxygen was introduced into the reactor until the total pressure of the reactor reached 40 psig. Periodically, aliquots of reaction mixture were withdrawn for GC analysis. The remaining iron in final reaction mixture was determined by ICP. Details of the process are shown in Fig. 1.

Neutral nitration in the presence of inorganic solid catalysts

In an autoclave (*ca.* 300 ml) fitted with a gas inlet and a vent tube were placed benzene (0.1 mol, 8.9 ml), NO_2 (10 equiv, 1.0 mol) and catalyst (2.0 g). To remove air present in the free volume of the reactor, the mixture was cooled to 0°C in an ice bath and briefly purged with oxygen. Oxygen was introduced into the autoclave through an inlet tube with stirring at room temperature and the total pressure was adjusted to 40 psig. Oxygen was supplied to the autoclave at regular intervals to keep the total pressure of the reactor constant. The reaction was interrupted by vent and the autoclave was purged with nitrogen. After the catalyst was filtered off, pure nitrobenzene was obtained by the usual work-up procedure. The final isolated nitrobenzene was analyzed by NMR.

RESULTS AND DISCUSSION

In order to increase the solubility of oxygen, a moderate pressure was employed. With regard to possible risk, a temperature and total pressure were carefully checked against literature data [15, 16]. Based on the preliminary screening of commercial transition metal salts, including Fe(II), Fe(III), Co(III), Cu(II), Mn(III), Ce(III) and Ce(IV) salts, $FeCl_3 \cdot 6H_2O$ was chosen as most reliable catalyst. With 2.5 equiv NO_2 and 1.0 mol% $FeCl_3 \cdot 6H_2O$ under 60 psig of oxygen, the nitration of benzene was completed within 1 h (Table 1, entry 1). On the other hand, unless oxygen was pressurized, the reaction was very slow. Toluene underwent the nitration with 4.5 equiv of NO_2 at an initial pressure of 40 psig. Mononitration was completed within 0.5 h to give three isomeric nitrotoluenes ($o/m/p$ = 55:1:44). When oxygen was pressurized to 100 psig and the reaction temperature was elevated to 60°C, dinitration proceeded to more than 98% conversion after 3 h to give a mixture of isomeric dinitrotoluenes (2,4/2,6 = 83:17; Table 1, entry 2). Under

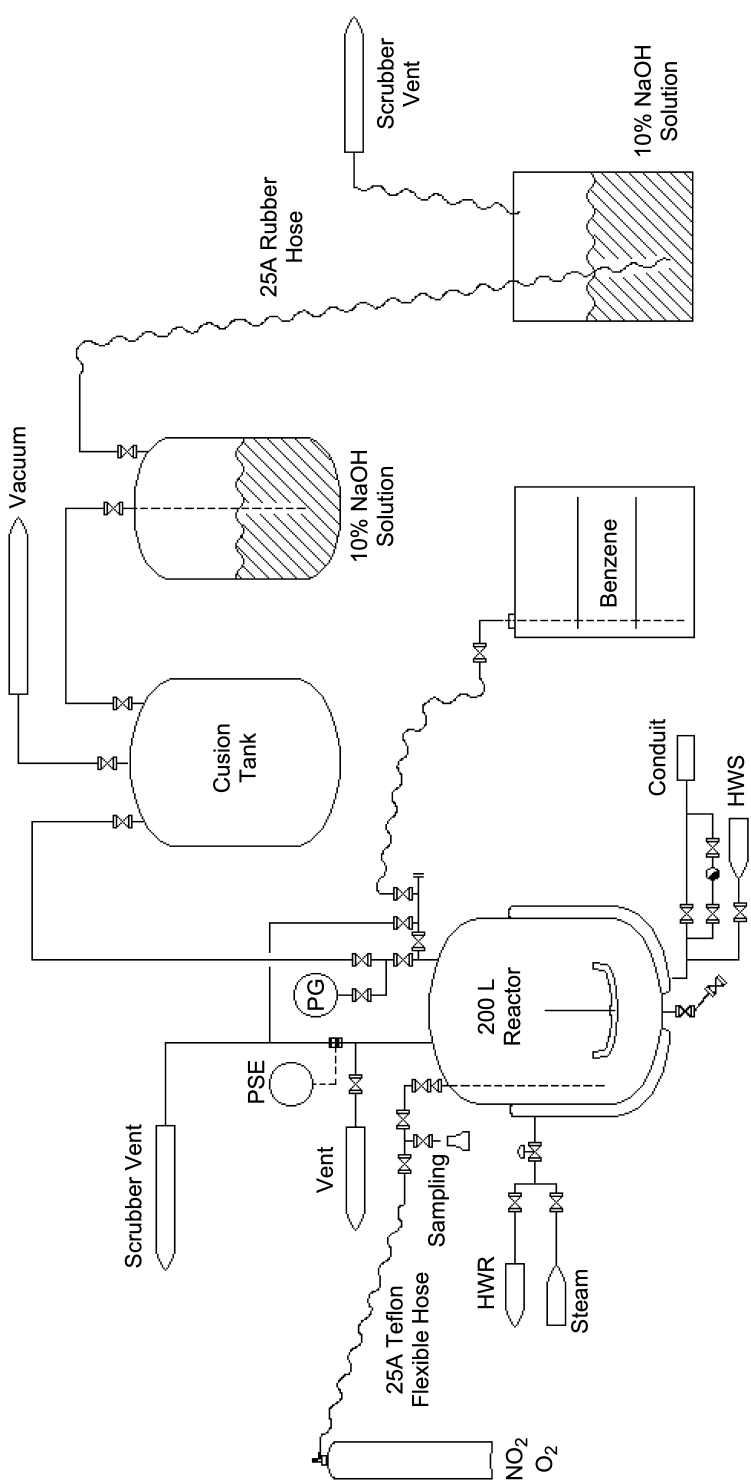
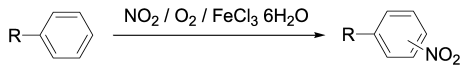


Figure 1. Process diagram of pilot scale nitration of benzene. HWR, hot water recirculating return; HWS, hot water supply; PG, pressure gauge; PSE, pressure safety element.

Table 1.
Neutral nitration of aromatic compounds using NO_2/pressurized O_2/$FeCl_3 \cdot 6H_2O$



Entry	Substrate	Total pressure (psig)	NO_2 (equiv)	$FeCl_3 \cdot 6H_2O$ (mol%)	Time (h)	Conversion (%)	Isomer ratio (%)	
							$o/m/p$	2,4/2,6
1	Benzene	60	2.5	1	1.5	99	—	—
2	Toluene	100	4.5	1	3.5	99 (98)	—	83:17
3	Chlorobenzene	80	2.5	5	3	>99	34:0:66	—
4	Nitrobenzene	100	4.5	5	6	>99	12:85:3	—

All reactions were performed without any solvent at ambient temperature. Conversion percentage in parentheses was based on dinitrotoluene. Isomer ratio was determined by GC. Initial pressure of toluene was 40 psig: after 0.5 h, oxygen was injected to 100 psig and the reaction temperature was elevated to 60°C. The reaction temperature for nitrobenzene was elevated to 60°C.

similar conditions, chlorobenzene was quantitatively converted to a mixture of two isomeric nitrochlorobenzenes ($o/p = 34{:}66$) within 3 h (Table 1, entry 3). Even the deactivated nitrobenzene was quantitatively nitrated within 6 h using 4.5 equiv NO_2 under 100 psig oxygen at 60°C to afford three isomeric dinitrobenzenes ($o/m/p =$ 12:85:3; Table 1, entry 4).

The effect of the reaction factors, such as partial pressure of oxygen, amount of NO_2 and $FeCl_3 \cdot 6H_2O$, and temperature, was investigated employing mononitration of benzene as a model reaction. From the results, it was found that over 2.0 equiv NO_2 was required to complete conversion of benzene. The nitration with 1.0 equiv of NO_2 resulted in a final conversion of 57% and the extra 7% was considered to be due to nitric acid produced during the reaction. As expected the reaction rate was enhanced when the partial pressure of oxygen was increased (Table 2, runs 4–7) and it was proportional to the amount of catalyst in the range of 0.5 to 1.0 mol% (Table 2, runs 8–10). In addition, the reaction rate doubled as the temperature rose by 10°C (Table 2, runs 12–14).

In order to optimize a pilot-scale reaction, middle-size scale reproduction tests were carried out three times. On expecting that 50% of benzene would be converted to nitrobenzene, benzene (0.4 mol) was treated with 1.0 equiv NO_2 and 1.1 mol% $FeCl_3 \cdot 6H_2O$ under 60 psig oxygen. A constant level of pressure was maintained for 3 h at room temperature. In each run, nitrobenzene was prepared in conversion of 58% (first run), 64% (second run) and 67% (third run) from GC, respectively.

Finally, a pilot-scale nitration of benzene was performed in a 200-l reactor. On expecting 25% conversion of benzene, 36.14 kg (467 mol) benzene was treated with 11.81 kg (0.55 equiv) NO_2 and 0.8 kg (1.15 mol% NO_2) $FeCl_3 \cdot 6H_2O$ under 40 psig oxygen to afford nitrobenzene in conversion of 16% (3 h), 26% (5 h) and 34% (8 h), respectively (Fig. 2). 0.67 ppm Fe(III) ion was contained in the resulting crude product and this impurity could be eliminated up to approximately 93% by simple extraction with water.

Table 2.
Correlation of reaction rates with reaction factors in neutral nitration of benzene using NO_2/pressurized $O_2/FeCl_3 \cdot 6H_2O$

Run	NO_2 (equiv)	O_2 (psig)	$FeCl_3 \cdot 6H_2O$ (mol%)	Temperature (°C)	Time (min)[a]	Reaction rate (k_{obs})[b]
1	1.0	40	1.0	30	120 [c]	1.26×10^{-2}
2	2.0	40	1.0	30	90	2.60×10^{-2}
3	3.0	40	1.0	30	50	3.76×10^{-2}
4	2.0	20	1.0	30	120	1.73×10^{-2}
5	2.0	30	1.0	30	100	1.94×10^{-2}
6	2.0	40	1.0	30	90	2.60×10^{-2}
7	2.0	60	1.0	30	80	2.91×10^{-2}
8	2.0	40	0.05	30	120	1.43×10^{-2}
9	2.0	40	0.75	30	110	1.86×10^{-2}
10	2.0	40	1.0	30	90	2.60×10^{-2}
11	2.0	40	1.5	30	85	2.65×10^{-2}
12	2.0	40	1.0	30	120	2.60×10^{-2}
13	2.0	40	1.0	40	90	4.36×10^{-2}
14	2.0	40	1.0	50	50	1.20×10^{-1}

[a] The time when benzene was completely consumed.
[b] The conversion yields of nitrobenzene (C) *versus* the reaction time (t) were observed at regular intervals. The graph for each factor resulted in a pattern of pseudo-first-order kinetics to give an exponential curve corresponding to $C = C_\infty \cdot e^{-kt}$ and the rate constants (k_{obs})were calculated from the curves. All correlation factors were above 0.9.
[c] The time when 40% of benzene was converted to nitrobenzene.

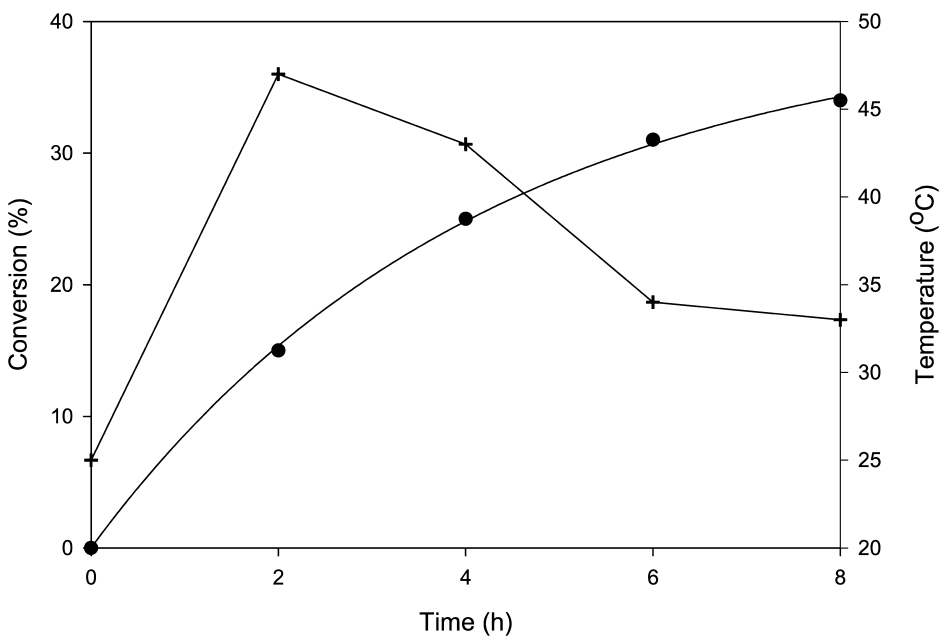


Figure 2. Reaction profile of pilot scale nitration of benzene. (●) Conversion of benzene, (+) temperature.

Table 3.
Neutral nitration of benzene in the presence of various inorganic solid catalysts

Catalyst	Conversion (%)	Catalyst	Conversion (%)
Silica (70–230 mesh)	>99	α-Alumina	7
Silica (14–20 mesh)	97	γ-Alumina	>99
Kieselguhr	9	Sodium mordenite	99
Magnesium silicate	98	Zeolite X	99
Siliceous earth	99	Zeolite Y	99
Sand (70–230 mesh)	3	Zeolite A	32
Celite	5	Pearlite	99
Molecular Sieve 4A	5	Kaoline	>99

Benzene (0.1 mol), NO_2 (10 equiv) and oxygen (40 psig) were used for each reaction. Kaoline is a sort of clay collected in Koryung area (South Korea).

Inspired by the recent work by Smith *et al.* [8, 17–20], inorganic solid catalysts were examined for the application to newly developed neutral nitration. These inorganic solid catalysts would provide an opportunity for aromatic nitration to meet environmental economics owing to the easy workup, superior recycling, low price, and non-corrosive nature. Various readily available inorganic solids were tested with the nitration of benzene as model reaction. From the results, we could believe that an active surface area is critical to the catalyst property. The candidates with a small surface area below 100 m^2/g, such as α-alumina, kieselguhr, sand and celite, did not play an efficient role as catalysts. Interestingly, even if a surface area is sufficient, molecular sieve 4A with too small pore size couldn't catalyze the reaction, which is probably caused by an obstacle to an access of substrate. In a structural point of view, zeolite X or Y with micropores surrounded by 12 oxygen atoms showed better conversion yield compared with zeolite A surrounded by 8 oxygen atoms. The results are summarized in Table 3.

CONCLUSIONS

A neutral aromatic nitration process was developed using NO_2 and pressurized oxygen in the presence of catalyst. Several nitro aromatic compounds were obtained in high conversion yields under the neutral condition. After investigating the effects of the reaction factors, the nitration of benzene was scaled-up to 476 mol. Furthermore, a wide range of inorganic solid catalysts with pore size over 5 Å and surface area over 100 m^2/g could be replaced as promising catalysts in a successful manner.

REFERENCES

1. G. A. Olah, R. Malhotra and S. C. Narang, *Nitration: Methods and Mechanisms.* VCH, New York, NY (1989).

2. L. F. Albright, R. V. C. Carr and R. J. Schmitt, *ACS Symposium Series, Volume 623.* American Chemical Society, Washington, DC (1996).
3. A. Cornelis, A. Gerstmans and P. Laszlo, *Chem. Lett.*, 1839 (1988).
4. D. B. Akolekar, G. Lemay, A. Sayari and S. Kaliaguine, *Res. Chem. Intermed.* **21**, 7 (1995).
5. J. M. Riego, Z. Sedin, J. M. Zaldivar, N. C. Marziano and C. Tortato, *Tetrahedron Lett.* **37**, 513 (1996).
6. H. Firouzabadi, N. Iranpoor and M. A. Zolfigol, *Synth. Commun.* **27**, 3301 (1997).
7. F. J. Waller, A. G. M. Barrett, D. C. Braddock and D. Ramprasad, *Chem. Commun.*, 613 (1997).
8. K. Smith, A. Musson and G. A. DeBoos, *J. Org. Chem.* **63**, 8448 (1998).
9. S. Samajdar, F. F. Becker and B. K. Banik, *Tetrahedron Lett.* **41**, 8017 (2000).
10. B. M. Choudary, M. Sateesh, M. L. Kantam, K. K. Rao, K. V. R. Prasad, K. V. Raghavan and J. A. R. P. Sarma, *Chem. Commun.*, 25 (2000).
11. X. Peng and H. Suzuki, *Org. Lett.* **3**, 3431 (2001).
12. K. K. Laali and V. J. Gettwert, *J. Org. Chem.* **66**, 35 (2001).
13. H. Suzuki, S. Yonezawa, N. Nonoyama and T. Mori, *J. Chem. Soc., Perkin Trans. 1*, 2385 (1996).
14. X. Peng, N. Fukui, M. Mizuta and H. Suzuki, *Org. Biomol. Chem.* **1**, 2326 (2003).
15. R. W. Van Dolah, *Chem. Eng. Progr.* **3**, 32 (1969).
16. A. B. Quakenbush, US Patent No. 5,245,092 (1993).
17. K. Smith, T. Gibbins, R. W. Millar and R. P. Claridge, *J. Chem. Soc., Perkin Trans. 1*, 2753 (2000).
18. K. Smith, S. Almeer and S. J. Black, *Chem. Commun.*, 1571 (2000).
19. K. Smith, S. Almeer and C. Peters, *Chem. Commun.*, 2748 (2001).
20. K. Smith, S. Almeer, S. J. Black and C. Peters, *J. Mater. Chem.* **12**, 3285 (2002).