



Johnson Matthey
Catalysts

Halonitroaromatics

The selective hydrogenation of a halonitroaromatic to the corresponding haloaminoaromatic is a key transformation in the pharmaceutical and fine chemical industries. There are currently over 15,000 published haloheteroaromatic structures in drug discovery. Halogen containing structures (usually chlorine) promote lipophilicity and aid in drug transport into cells. The classic synthetic route to these molecules involves electrophilic substitution to give a halonitro moiety, with subsequent selective catalytic hydrogenation of the nitro group.

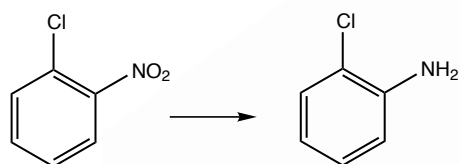
Typically, heterogeneous Platinum catalysts are preferred for these reactions as Palladium catalysts generally cause high levels of dehalogenation. The extent of dehalogenation depends on the halogen (I > Br > Cl > F), and its position on the aromatic ring with respect to the nitro group being

hydrogenated (ortho > para > meta). Acidity in the form of acid addition or an acidic catalyst will tend to inhibit dehalogenation. The use of various modifiers has been reported to increase selectivity. These include sulfur containing compounds, MgO and organic bases. A number of promoters have been used to either increase the rate of halonitroaromatic hydrogenations or to limit the amount of accumulated hydroxylamine intermediate.

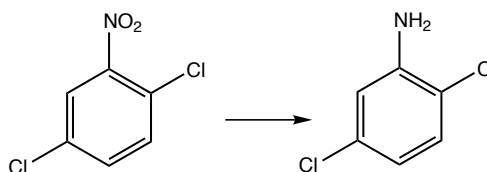
Efficient reduction of halonitroaromatics to haloaminoaromatics depends on the selection of the most active and selective catalyst, and an optimized set of reaction conditions. For Johnson Matthey Catalysis and Chiral Technologies, this need has led to the design and development of a new range of more active and selective catalysts for this transformation.

Model Reactions

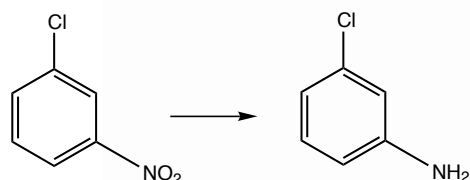
The selective reductions of 1-chloro-2-nitrobenzene, 1-chloro-3-nitrobenzene, 1-chloro-4-nitrobenzene, 1,4-dichloro-2-nitrobenzene and 1-bromo-2-nitrobenzene were selected and investigated.



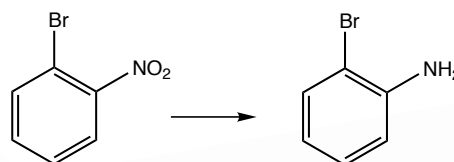
1-chloro-2-nitrobenzene



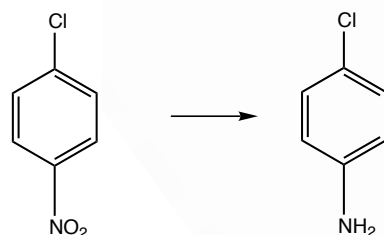
1,4-dichloro-2-nitrobenzene



1-chloro-3-nitrobenzene



1-bromo-2-nitrobenzene



1-chloro-4-nitrobenzene

Standard Reaction Conditions:

Temperature: 25 and 40°C

Pressure: 80 and 150 psi

Catalyst Loading: 2 and 5% wrt substrate for 1% Pt/C catalysts

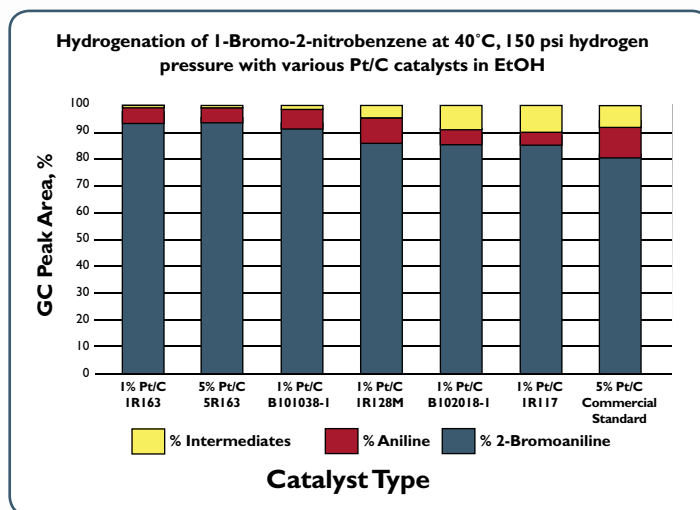
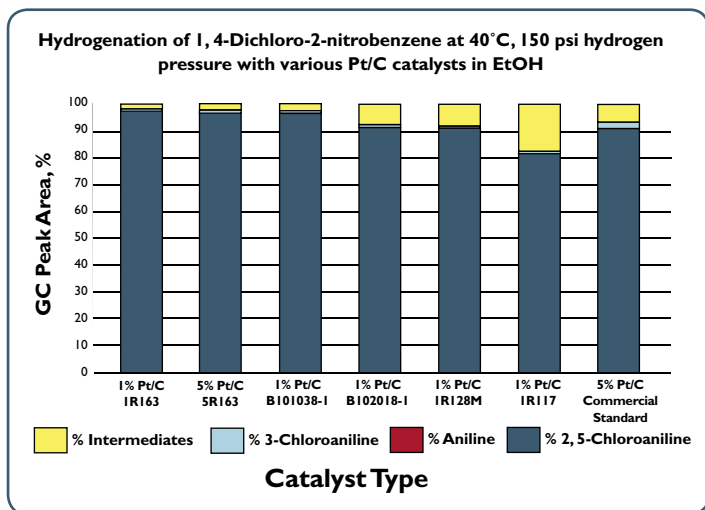
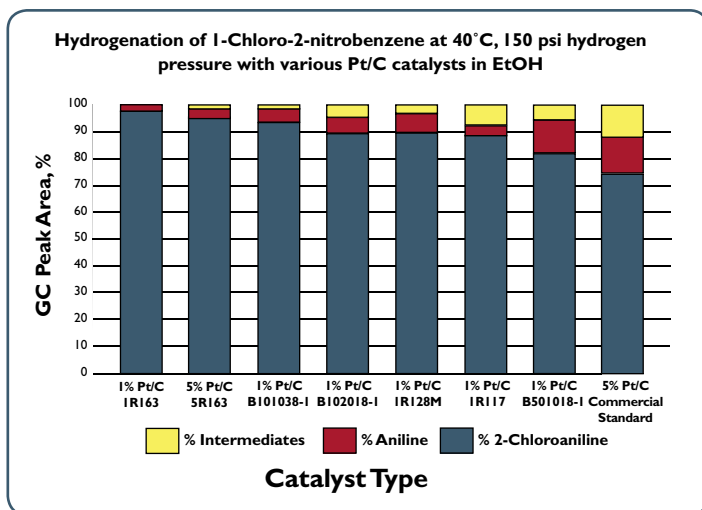
Screening: Biotage Endeavor 8 x 10 ml reactor system

Reaction Monitoring: H₂ uptake, GC and/or HPLC

Catalyst Activity and Selectivity

A wide range of 1% Pt/C and 5% Pt/C catalysts were screened under the standard reaction conditions for each reaction. Both catalyst activity and selectivity were found to be dependent on catalyst type, with the recently developed Pt/C catalysts exhibiting higher activity and selectivity than a current 5% Pt/C commercial catalyst standard. For the most active Pt/C catalysts, reactions proceeded with complete

conversion to the haloamine product. For catalysts exhibiting slower reaction rates, intermediate hydroxylamines were observed. Under otherwise equivalent conditions, higher levels of dehalogenation were observed with the 1-bromo-2-nitrobenzene substrate than the 1-chloro-2-nitrobenzene substrate.



Halogen Position Effects

The effect of halogen position on the aromatic ring with respect to the nitro group being hydrogenated was examined through the evaluation of equivalent catalysts with each of the four chloro containing model substrates. For the three mono chloro nitrobenzene substrates, dehalogenation

increased in the following order relative to halogen position: meta < para < ortho. For the dichloronitrobenzene substrate, the halogen ortho to the nitro group was lost more readily than the halogen meta to the nitro group. Results were independent of catalyst type.

Halogen Position Effect on Reaction Selectivity

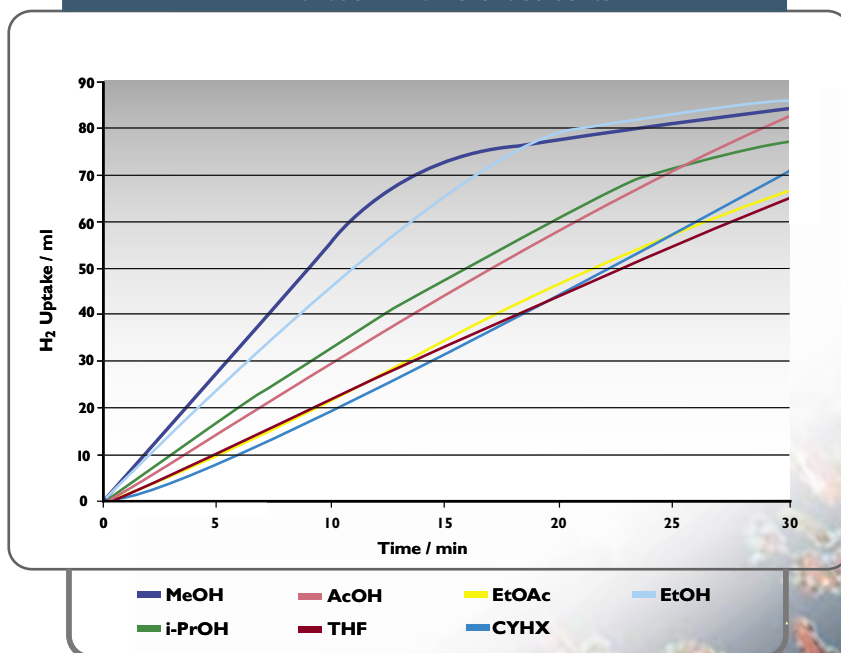
| Catalyst Type | 1-Chloro-2-nitrobenzene | | 1-Chloro-3-nitrobenzene | | 1-Chloro-4-nitrobenzene | |
|-----------------------------|-------------------------|-----------|-------------------------|-----------|-------------------------|-----------|
| | % 2-Chloroaniline | % Aniline | % 3-Chloroaniline | % Aniline | % 4-Chloroaniline | % Aniline |
| 1% Pt/C IRI163 | 98 | 1.9 | 98 | 0.3 | 98 | 1.1 |
| 5% Pt/C 5RI163 | 95 | 3.1 | 97 | 0.3 | 97 | 1.5 |
| 1% Pt/C BI01038-I | 95 | 4.0 | 97 | 0.5 | 95 | 3.4 |
| 1% Pt/C BI02018-I | 90 | 5.6 | 98 | 0.9 | 92 | 6.4 |
| 1% Pt/C IRI128M | 90 | 6.4 | 97 | 0.5 | 92 | 6.6 |
| 1% Pt/C IRI117 | 89 | 4.5 | 98 | 0.3 | 94 | 3.4 |
| 5% Pt/C Commercial Standard | 76 | 14 | 92 | 1.0 | 85 | 12 |

Reaction Conditions: EtOH Solvent, 40°C, 150 psi H₂, 5 weight percent catalyst, 30 minute reaction time.

Solvent Effects

Solvents can have a marked influence on both the reaction rate and the selectivity to the desired haloamine product. In general, aprotic solvents inhibit dehalogenation and protic solvents tend to increase reaction rate. A series of commonly employed solvents, MeOH, EtOH, i-PrOH, THF, ethyl acetate, acetic acid and cyclohexane were screened under standard reaction conditions using a number of top performing catalysts for each reaction. Reaction rates were fastest in MeOH, EtOH and i-PrOH, slightly slower in acetic acid, and slowest in ethyl acetate, THF and cyclohexane. Highest reaction selectivities were obtained in cyclohexane.

Hydrogenation of 1-Chloro-2-nitrobenzene at 25° C, 80 psi hydrogen pressure using 1% Pt/C BI01038-I in different solvents



Reaction Temperature and Pressure Effects

In general, loss of halogen is favored by higher reaction temperatures and retarded by increasing hydrogen pressure. For each of the reactions, a range of reaction temperatures (25, 30, 35, 40 and 50°C) and pressures (40, 60, 80, 100, 120 and 150 psi hydrogen) were investigated. Increasing reaction temperature increased the amount of dehalogenation. For the pressure range examined, increasing reaction pressure reduced the reaction time required for full conversion of the hydroxylamine intermediate to the desired haloamine product.

Catalyst Percent Metal and Loading

For each of the reactions, several catalyst percent metals and catalyst loadings (1, 2 and 5 dry weight percent catalyst to substrate for 1% Pt/C catalysts) were investigated. For each reaction increasing catalyst loading increased reaction rate

and conversion to the haloamine product. At equal metal loadings, little rate differences were observed between equivalent 1% and 5% Pt/C catalysts; however selectivity to the desired haloamine product was slightly better with the 1% Pt/C catalysts.

Reaction Modifier Effects

The effect of the addition of several commonly employed reaction modifiers (MgO, morpholine, H₃PO₃, NaCl) on catalyst activity and selectivity was examined for several of the model substrates with the better performing catalyst types. The addition of an optimized number of molar equivalents of MgO and morpholine were found to improve reaction selectivity. The addition of H₃PO₃ was found to decrease reaction rate. The addition of NaCl did not improve reaction selectivity.

| Reaction Modifier Effect on Reaction Selectivity | | | | |
|--|------------------------|-------------------------|-----------|-----------------|
| | | 1-Chloro-2-nitrobenzene | | |
| Catalyst Type | Modifier | % 2-Chloroaniline | % Aniline | % Intermediates |
| 1% Pt/C IRI63 | None | 98 | 1.9 | 0.4 |
| | 0.01 Equiv MgO | 99 | 0.5 | 0.5 |
| | 0.02 Equiv MgO | 99 | 0.7 | 0.2 |
| | 0.04 Equiv MgO | 98 | 1.8 | 0.1 |
| | 0.005 Equiv Morpholine | 99 | 1.2 | 0.1 |
| | 0.04 Equiv Morpholine | 100 | 0.1 | 0.0 |
| | 0.13 Equiv Morpholine | 97 | 0.0 | 2.9 |

Reaction Conditions: EtOH Solvent, 40°C, 150 psi H₂, 5 weight percent catalyst, 30 minute reaction time.

Recommendations

| | |
|-------------------|--|
| Catalyst: | 1% Pt/C BI01038-1, BI02018-1, IRI63; 5% Pt/C 5RI63 |
| Solvent: | MeOH, EtOH, Cyclohexane |
| Temperature: | 20 - 40°C |
| Pressure: | 60 – 150 psi |
| Catalyst loading: | 1 to 5% wrt substrate |

Summary

The hydrogenation of halonitroaromatics to haloaminoaromatics can be achieved using heterogeneous Pt/C catalysts. A range of highly active and selective catalysts are available for the transformation. A variety of solvents, temperatures, pressures, catalyst loadings and reaction modifiers should be evaluated to arrive at an optimized set of reaction conditions.

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Our Halonitroaromatic Catalyst Kit contains 5 grams of each recommended catalyst