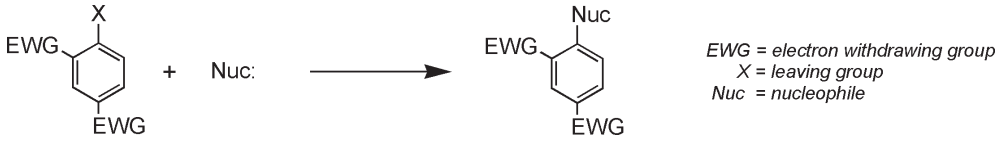
Experiment
1

Nucleophilic aromatic substitution

Introduction

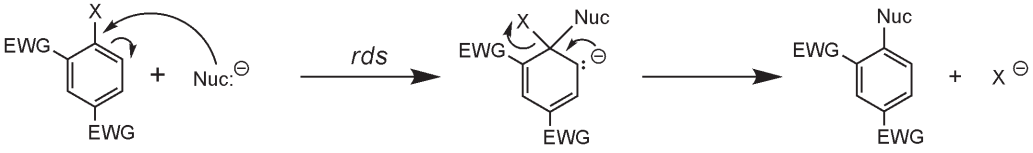
S_NAr reactions are used on an industrial scale for the preparation of pharmaceuticals.

Nucleophilic aromatic substitution (S_NAr) reactions offer a useful way to functionalize an aromatic ring. The high π–electron density of an aromatic ring results in predominant reactivity towards electrophiles; however, if the aromatic ring is activated with electron withdrawing groups (EWG) ortho and/or para to a good leaving group, a nucleophilic substitution reaction is possible. Halogens are the most common leaving groups for S_NAr reactions and functional groups such as $-NO_2$, $-SO_2R$, $-NR_3$, $-CF_3$ and -CN are electron withdrawing enough to render the aromatic ring susceptible to reaction with an electron-rich nucleophile, such as an amine.



The two-step mechanism is supported by the isolation of many Meisenheimer salts. Evidence for a rate determining first step comes from the observation that fluoroaromatics undergo nucleophilic substitution much more rapidly than their iodo- counterparts, despite the fact that I^- is a much better leaving group than F^-.

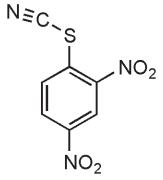
The reaction follows an addition-elimination two-step reaction sequence. It is generally accepted that the first step, in which a tetrahedral cyclohexadienyl anion called a Meisenheimer complex is formed, is the rate-determining step (rds). This is generated by the addition of the nucleophile to the carbon bearing the leaving group. Subsequent elimination of the halogen substituent (leaving group) leads to regeneration of the aromaticity in the ring.



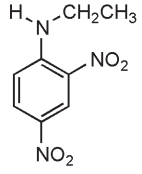
Meisenheimer complex

Thiocyanates are salts and esters of thiocyanic acid HSC ≡ N. They are some of the compounds responsible for the spicy taste in radishes and black mustard.

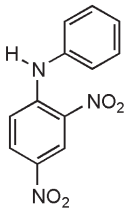
In this experiment, one of three nucleophiles (potassium thiocyanate, ethylamine, or aniline) is used to substitute for the bromine on 1-bromo-2,4-dintrobenzene. The three possible products from the S_NAr with 1-bromo-2,4-dinitrobenzene are all highly-colored crystalline solids, and are as follows:



2,4-dinitrophenyl thiocyanate

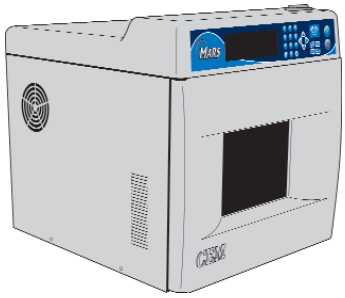


2,4-dinitro-*N*-ethylaniline



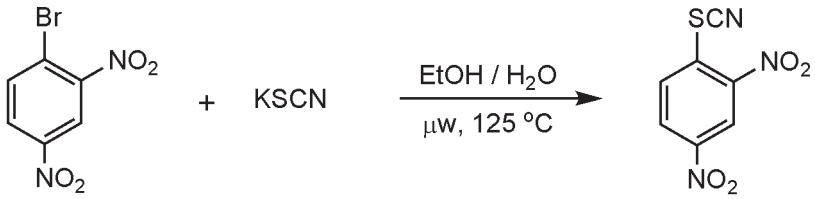
2,4-dinitrodiphenylamine

Experimental procedure



Microwave Unit: MARS

Procedure for 2,4-dinitrophenyl thiocyanate:



Reagents used:

Reagent	MW (g/mol)	mmol	Mass (g)	Density (g/mL)	Vol (mL)	MP / BP (°C)
1-bromo-2,4-dinitrobenzene	247	1.20	0.296			71-73
potassium thiocyanate	97.2	4.80	0.467			173
ethanol					4.0	
water					1.0	

The reactions are run using ethanol or a water–ethanol mixture as the solvent. This makes it a clean reaction and the product is easy to isolate.

SAFETY PRECAUTIONS:

1-Bromo-2,4-dinitrobenzene is classified as an irritant. Potassium thiocyanate is a toxic compound. This reaction should not be attempted in a sealed reaction vessel without temperature control.

Refer to Chapter 3 for more detailed instructions on setting up and safely securing your HP-500 vessel as well as information on programming the MARS System.

1-Bromo-2,4-dinitrobenzene (0.296 mg, 1.20 mmol), potassium thiocyanate (0.467 mg, 4.80 mmol), ethanol (4.0 mL) and water (1.0 mL) are placed in an HP-500 Teflon® microwave reaction vessel containing a magnetic stir bar. NOTE: The final volume must be at least 5 mL. The reaction vessel is inserted into the protective sleeve, fitted with the vessel top and load disk, and then placed into the vessel frame. The pre-set torque wrench is used to tighten the nut on top of the frame before placing it on the microwave turntable. Note the position the vessel occupies. The reaction control vessel (position #1) is connected to the temperature thermocouple and, if applicable, to the pressure sensor. The microwave is programmed using the ramp-to-temperature method to heat to 125 °C over a 2-minute period and then held at this temperature for 20 minutes. The solution is then allowed to cool for 5 minutes, or until it is below 50°C before removing from the microwave unit.

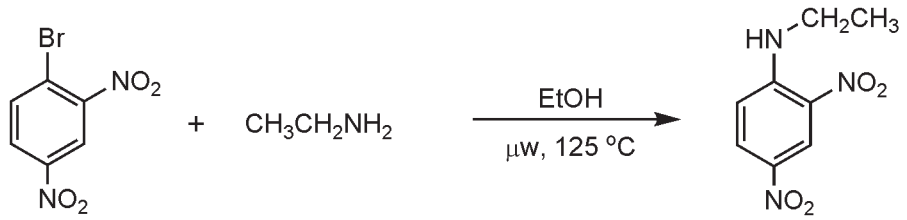
CAUTION: The vessel may still be hot to the touch.

The vessel is vented by loosening the blue nut. It is then removed from the frame and its protective sleeve. The reaction mixture is cooled in an ice bath to initiate crystallization. Once crystallization is complete, the product can be collected by vacuum filtration and washed with cold solvent. The brightly colored crystalline

product can then be dried on a clay plate. When the product is dry, the melting point should be determined and compared to that in the literature. The crude product can be re-crystallized from 95% ethanol and characterized by IR, ^{1}H-NMR and/or ^{13}C-NMR spectroscopy. The purity can be determined by TLC using 40% ethyl acetate/hexanes as eluent.

Procedure for 2,4-dinitro-*N*-ethylaniline:

No water is added; ethanol is the only solvent used.



Reagent	MW (g/mol)	mmol	Mass (g)	Density (g/mL)	Vol (mL)	MP / BP (°C)
1-bromo-2,4-dinitrobenzene	247	1.20	0.298			71-73
ethylamine (70% aqueous)	45.1	4.80	0.308	0.796	0.380	17
ethanol					5.0	

SAFETY PRECAUTIONS:

1-Bromo-2,4-dinitrobenzene is classified as an irritant. Ethylamine (70% aqueous) is flammable and corrosive. This reaction should not be attempted in a sealed reaction vessel without temperature control.

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1-Bromo-2,4-dinitrobenzene (0.298 mg, 1.20 mmol, 1 eq.), ethylamine (0.380 mL, 4.80 mmol), ethanol (4.0 mL) and water (1.0 mL) are placed in an HP-500 Teflon® microwave reaction vessel containing a magnetic stir bar. NOTE: The final volume must be at least 5 mL. The reaction vessel is inserted in to the protective sleeve, fitted with the vessel top and load disk, and then placed into the vessel frame. The pre-set torque wrench is used to tighten the nut on top of the frame before placing it on the microwave turntable. Note the position the vessel occupies. The reaction control vessel (position #1) is connected to the temperature thermocouple and, if applicable, to the pressure sensor. The microwave is programmed using the ramp-to-temperature method to heat to 125 °C over a 2-minute period and then held at this temperature for 5 minutes. The solution is then allowed to cool for 20 minutes, or until it is below 50 °C before removing fromthe microwave unit.

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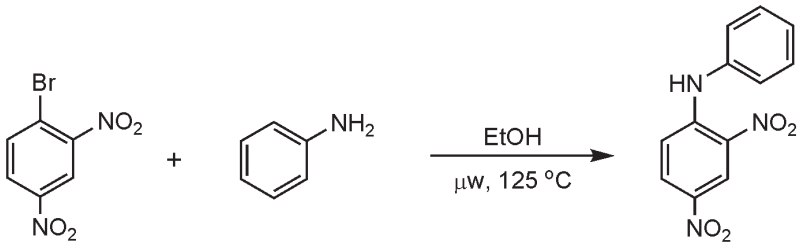
Procedure for 2,4-dinitrodiphenylamine:

No water is added; ethanol is the only solvent used.



Reagent	MW (g/mol)	mmol	Mass (g)	Density (g/mL)	Vol (mL)	MP / BP (°C)
1-bromo-2,4-dinitrobenzene	247	1.20	0.296			71-73
aniline	93.1	4.80	0.450	1.022	0.440	184
ethanol					5.0	

SAFETY PRECAUTIONS:

1-Bromo-2,4-dinitrobenzene and aniline are classified as irritants. Aniline is a toxic compound. This reaction should not be attempted in a sealed reaction vessel without temperature control.

Refer to Chapter 3 for more detailed instructions on setting up and safely securing your HP-500 vessel as well as information on programming the MARS System.

1-Bromo-2,4-dinitrobenzene (0.296 mg, 1.20 mmol), aniline (0.440 mL, 4.80 mmol), and ethanol (5.0 mL) are placed in an HP-500 Teflon® microwave reaction vessel containing a magnetic stir bar. NOTE: The final volume must be at least 5 mL. The reaction vessel is inserted in to the protective sleeve, fitted with the vessel top and load disk, and then placed into the vessel frame. The pre-set torque wrench is used to tighten the nut on top of the frame before placing it on the microwave turntable. Note the position the vessel occupies. The reaction control vessel (position #1) is connected to the temperature thermocouple and, if applicable, to the pressure sensor. The microwave is programmed using the ramp-to-temperature method to heat to 125 °C over a 2-minute period and then held at this temperature for 5 minutes. The solution is then allowed to cool for 20 minutes, or until it is below 50 °C before removal from the microwave unit.

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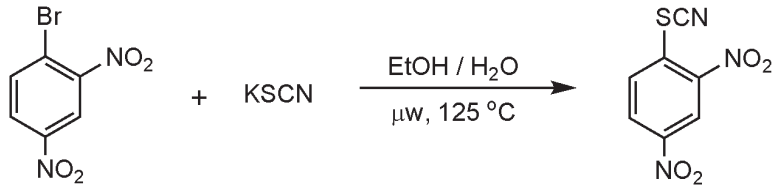
Experimental procedure

Microwave Unit: Discover

Procedure for 2,4-dinitrophenyl thiocyanate:



Reagents used:

Reagent	MW (g/mol)	mmol	Mass (g)	Density (g/mL)	Vol (mL)	MP / BP (°C)
1-bromo-2,4-dinitrobenzene	247	1.20	0.298			71-73
potassium thiocyanate	97.2	4.80	0.467			173
ethanol					2.5	
water					0.5	

SAFETY PRECAUTIONS:

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1-Bromo-2,4-dinitrobenzene (0.298 g, 1.20 mmol), potassium thiocyanate (0.467 g, 4.80 mmol), ethanol (2.5 mL) and water (0.5 mL) are added to a 10-mL glass microwave reaction vessel containing a stir bar. The reaction vessel is sealed with a cap and then placed into the microwave cavity. The pressure device is put in place on top of the reaction vessel and the unit programmed to heat the reaction mixture to 125 °C and hold it for 5 minutes. After the reaction is complete and the vessel has cooled to below 50 °C, the pressure device can be removed and the vessel may be taken from the microwave cavity.

CAUTION: The tube may still be hot to the touch.

The sealed reaction vessel and its contents are cooled in an ice bath to initiate crystallization. The brightly-colored crystalline product can be collected by vacuum filtration, washed with cold ethanol, and dried on a clay plate. When the product is dry, the melting point should be determined and compared to that in the literature. The crude product can be re-crystallized from 95% ethanol and characterized by IR, ^{1}H-NMR and/or ^{13}C-NMR spectroscopy. The purity can be determined by TLC using 40% ethyl acetate/hexanes as eluent.

Procedure for 2,4-dinitro-*N*-ethylaniline:

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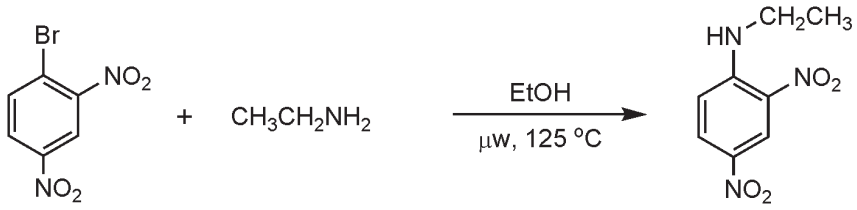

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ethylamine (70% aqueous)	45.1	4.80	0.308	0.796	0.380	17
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Procedure for 2,4-dinitrodiphenylamine:

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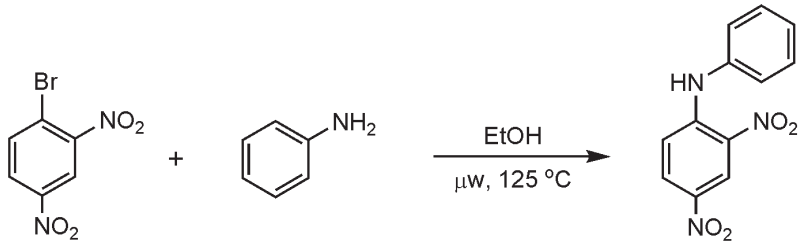

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aniline	93.1	4.80	0.450	1.022	0.440	(184)
ethanol					3.0	

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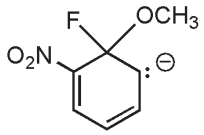
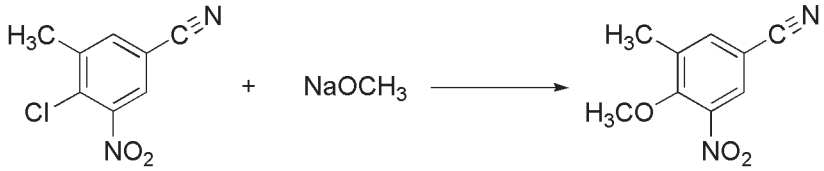
Lab Questions

1. Draw all the possible resonance structures for the Meisenheimer complex below.



2. The introduction lists a number of functional groups that are considered electron withdrawing. Explain why they are classified as electron withdrawing groups in the context of aromatic chemistry.

3. In the following reaction scheme, identify all of the following: nucleophile, leaving group, and electron withdrawing group.



4. Why is cold solvent used to wash your product rather than room temperature or hot solvent?

5. Which bromine in 1,2-dibromo-4-nitrobenzene would be substituted by a nucleophile?