Honors Cup Synthetic Proposal

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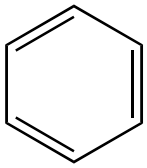
Title: Synthesis of Benzaldehyde from Benzene

Introduction: Benzaldehyde is an interesting target compound for a three-step synthesis given its widespread application, among others, as an industrial solvent and commercial food flavoring. Its recurrence in nature is evident in extracts of apricot, cherry, and various nuts. Benzaldehyde is characterized by its distinctive almond scent and is, as a result, a key intermediate in various perfumes and dyes.

In addition to its noteworthy application in industrial products, benzaldehyde's structural simplicity as an aromatic compound lends to a straightforward synthesis from benzene.

Overall synthetic reaction scheme:

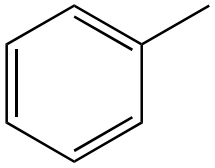
A



benzene

$\xrightarrow[AlCl_3]{CH_3Cl}$

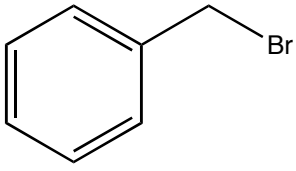
B



toluene

$\xrightarrow[\text{dibenzoyl peroxide (cat.)}]{\text{N-Bromophthalimide}}$

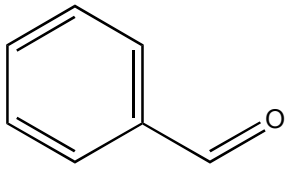
C



bromomethyl-benzene

$\xrightarrow[\text{reflux}]{H_2O_2,\ EtOH}$

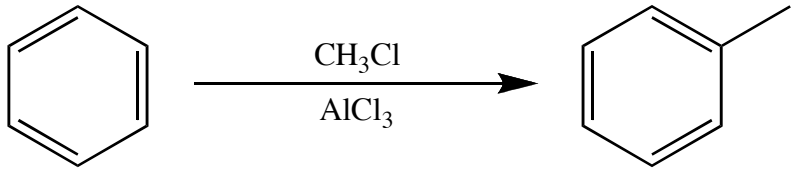
X



benzaldehyde

Step 1

Synthetic transformation 1:



benzene toluene

Experimental 1:

Anhydrous aluminum chloride (73.5242 g, 551.404 mmol) was weighed into a weighing boat in the fume hood and transferred to a clean round bottom flask with a magnetic stir bar. The flask was outfitted with a Claisen adaptor, a dropping funnel, stopper, and a condenser vented to a gas trap (Figure 1). Benzene (43.072 grams) was added to the flask. The water aspirator was turned on and an excess of chloromethane was added to the flask slowly. The reaction was controlled, in part, by an ice bath to reduce the boiling. The solution within the reaction flask was cautiously and slowly poured into a 100 mL beaker containing about 10 g of ice. The aqueous/organic mixture is rapidly stirred using a magnetic stirrer while solid sodium chloride was added. After saturating the aqueous layer, the mixture is put into to a separatory funnel without the salt. The organic layer is separated and transferred to a 100 mL Erlenmeyer flask and dried over anhydrous magnesium sulfate. The dried organic layer is placed into a clean round bottom flask for further purification by distillation.

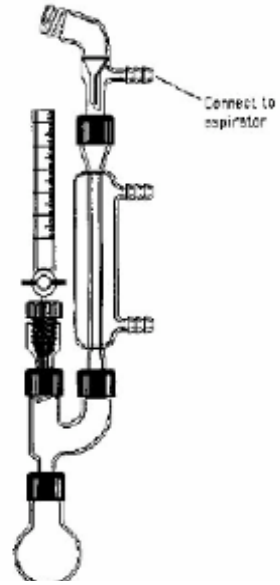


Figure 1: Reaction Vessel

Because the resulting aromatic compound in the reaction is highly reactive, methylation is not limited to one site. However, separation of the desired monosubstituted product through distillation was possible; Table 1 catalogues the boiling point ranges for all of the substituted products. Distillation of the organic mixture at approximately 115^{o} C isolated the toluene from its more substituted counterparts.

Systemic Name	BP (°C)	Distillation Range (°C)
Methylbenzene (Toluene)	110.6	110.6
1,2-Dimethylbenzene	144	
1,3-Dimethylbenzene	139	138 – 144
1,4-Dimethylbenzene	138.3	
1,2,3-Trimethylbenzene	175	
1,3,5-Trimethylbenzene	165	165 – 175
1,2,4-Trimethylbenzene	169	
1,2,3,4-Tetramethylbenzene	205	
1,2,4,5-Tetramethylbenzene	197	197 – 205
1,2,3,5-Tetramethylbenzene	198	
Pentamethylbenzene	231	231
Hexamethylbenzene	264	264

Table 1: Distillation Ranges From Toluene to Hexamethylbenzene

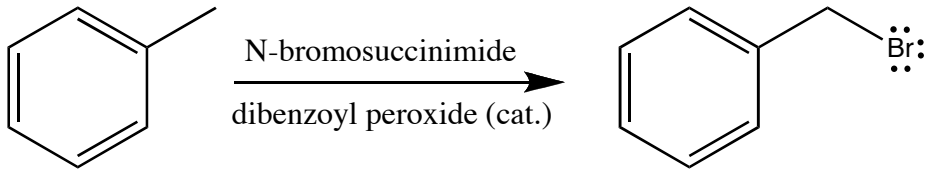
Modifications: Starting masses for aluminum chloride and benzene (substrate) are greater to accommodate low yields; procedure adapted from 216H Friedel-Crafts laboratory literature

Expected yield:
The chemical conversion of benzene to toluene with chloromethane and aluminum chloride results in a 1.5 percent yield (~0.762 grams) as can be best counterbalanced with excess benzene.

Safety, disposal and green issues (1):
- Gloves, goggles, and aprons must be worn at all times in the laboratory
- Benzene is a carcinogenic agent and severe eye, skin, and respiratory irritant
- Chloromethane is highly toxic if inhaled and must be handled carefully under a fume hood
- Aluminum chloride is a skin, eye, and respiratory irritant and, when combined with water, forms hydrogen chloride – a highly corrosive compound
- Toluene is flammable and is highly hazardous if ingested; avoid direct contact and inhalation
- In compliance with local regulations, benzene must be appropriately disposed into an organic waste container; chloromethane and aluminum chloride are halogenated waste products.

Step 2

Synthetic transformation 2:



toluene bromomethyl-benzene

Experimental 2:
Using the toluene recovered from the first step of the experimental, benzyl bromide was synthesized by means of adding N-bromosuccinimide (NBS). A TLC analysis was first necessary to confirm the relative purity of the starting material in this second step by means of a co-spot with pure toluene. A TLC was also run to check for the precursor, benzene, as a complement to IR and NMR spectroscopic analyses.

In the first step, 5-10 mole percent of the catalyst dibenzoyl peroxide is added to the N-bromosuccinimide (1.472 g, 8.271 mmol) as a dry mixture in a beaker. The resulting mixture was then added to the toluene solution to allow for a peroxide-catalyzed reaction. Another round of distillation was applied to separate the reagents and product; vaporization of the former at approximately 115^{o}C left the latter separate (b.p. 198^{o}C - 199^{o}C). Subsequent characterization by TLC, IR, and NMR for the benzyl bromide product was conducted to assess relative purity.

Modifications: The use of ferric chloride/sulfuric acid was abandoned in favor of only the peroxide-catalyzed reaction.

Expected yield:
The reaction from toluene provided a 64% yield of benzyl bromide (~0.905 grams).

Safety, disposal and green issues (2):
- Gloves, goggles, and aprons must be worn at all times in the laboratory
- Toluene is flammable and is highly hazardous if ingested; avoid direct contact and inhalation
- NBS is a skin, eye, and respiratory irritant and should not be ingested
- Dibenzoyl peroxide has a flash point at 104° F and directed contact should be avoided with the skin and eyes; inhalation and ingestion are also unsafe
- Benzyl bromide is a lachrymator and severe skin, respiratory, and eye irritant
- Toluene and dibenzoyl peroxide must be disposed into the appropriate organic waste receptacles; NBS must be discarded with halogenated compounds

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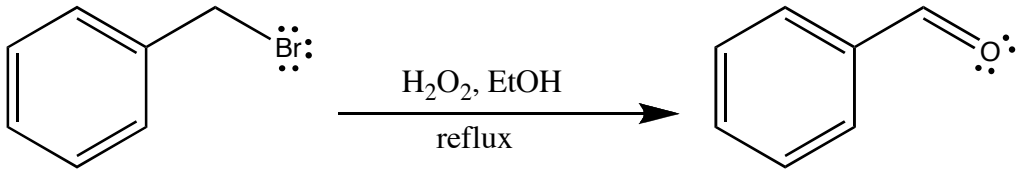
Step 3

Synthetic transformation 3:



bromomethyl-benzene benzaldehyde

Experimental 3:
The benzyl bromide (bromomethyl-benzene) recovered from the previous step had undergone oxidation to yield the target compound, benzaldehyde.

Prior to the oxidative work-up, a hot plate/magnetic stirrer was set up in the fume hood. In the first step, 5.293 mL of 30% hydrogen peroxide was added to an Erlenmeyer flask already containing a magnetic stir bar. Thereafter, 39.701 mL of ethanol was slowly added to the hydrogen peroxide. Finally, the benzyl bromide product was added to the solution and heated under reflux for 3 hours. The resulting solution was allowed to cool to room temperature.

TLC analysis was applied to test for the presence of benzyl bromide and to co-spot with the pure product. The boiling points of benzyl bromide and benzaldehyde are 198-199°F and 178.1°F respectively; distillation of the solution at the 180° degree range allowed for the separation of the two organic compounds where the latter vaporized and condensed first.

IR and NMR spectroscopic analyses were subsequently performed on the recovered product in confirmation of functional groups and chemical shifts.

Modifications: The approximate heat of vaporization was modeled for distillation given a buffer of 20 degrees between the relative boiling points of the two compounds. Ethanol and hydrogen peroxide volumes are increased to accommodate the greater substrate and reagent quantities.

Expected yield:
The oxidation step should result in an 89% approximate yield of benzaldehyde (~0.5 grams).

Safety, disposal and green issues (3):
- Gloves, goggles, and aprons must be worn at all times in the laboratory
- Reactions heated under reflux must be carefully maintained at a steady boiling
- Benzyl bromide is a lachrymator and severe skin, respiratory, and eye irritant
- Benzaldehyde is an eye, skin, and respiratory irritant – avoid contact/ingestion
- Hydrogen peroxide is highly corrosive; avoid contact with eyes and skin and do not inhale
- Ethanol is highly flammable and can cause skin irritation – direct contact should be avoided
- All glassware must be cleaned with acetone and dried along with the magnetic stir bar
- The hot plate must be turned off and left to cool prior to storage
- Benzyl bromide must be disposed into a halogen-only waste container; benzaldehyde, ethanol, and hydrogen peroxide should be disposed into appropriate organic waste containers

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Overall budget:

Chemical	Supplier	Cost	Amt. Needed	Total
Benzene	Aldrich	$26.00 per 100 mL	43.071 grams	$12.75
CH_3Cl	Aldrich	$114.00 per 500 g	55.681 grams	$12.70
$AlCl_3$	Aldrich	$52.80 per 1 kg	73.524 grams	$3.88
Toluene*	Aldrich	$21.00 per 100 mL	-	-
NBS	Aldrich	$8.90 per 5 g	1.472 grams	$2.62
Dibenzoyl Peroxide	Aldrich	$64.40 per 500 g	0.200 grams	$0.03
Benzyl Bromide*	Aldrich	$19.50 per 25 g	-	-
H_2O_2 (30%)	Aldrich	$42.20 per 500 mL	5.293 mL	$0.45
Ethanol	Aldrich	$32.00 per 100 mL	39.701 mL	$12.70
Benzaldehyde*	Aldrich	$9.70 per 2 g	-	-

* Compounds necessary for TLC co-spotting – not crucial to synthesis

Total costs per synthesis: $45.13

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