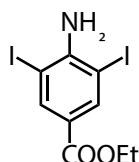


Organic Chemistry (MSE 211)

Synthesis and Purification of Ethyl 4-Amino-3,5-diiodobenzoate

1. Introduction



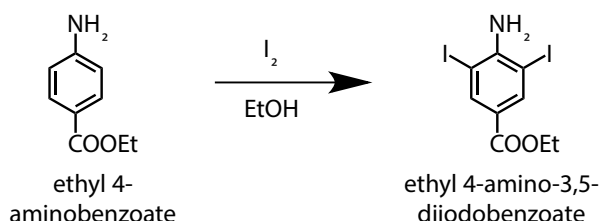
Iodination of aromatic compounds is highly relevant, as the resulting target compounds constitute important intermediates in modern synthetic chemistry. Although the reactivity of I_2 in common electrophilic aromatic substitution reactions is low compared to Br_2 , the combination of iodine and silver sulfate provides sufficient reactivity under mild conditions at room temperature, as exemplified by the synthesis of ethyl 4-amino-3,5-diiodobenzoate.

See also: Chapter 4.5 of the class.

Reading Recommendation: McMurry, 7th ed., chapters 21.2-21.5; Clayden, Chapter 12

2. General Principle of the Synthesis

The preparation of ethyl 4-amino-3,5-diiodobenzoate is an electrophilic aromatic substitution reaction, taking place twice in the ortho-positions of the amino group. The product, which exhibits poor solubility in ethanol, is collected and separated from further impurities by extraction and finally purified by recrystallization.



3. Required Equipment

- A 250 mL round-bottom flask

- A DrySin® with heating plate and magnetic stirrer
- Graduated cylinder
- TLC chamber and TLC silica gel (on aluminium foil)
- Separating funnel
- Reflux condenser
- Büchner funnel
- Spatula and other glassware

4. Experimental Procedure

Iodine (10 mmol) and silver sulfate (10 mmol) are dissolved in 75 mL EtOH in a 250 mL round-bottomed flask. Ethyl 4-aminobenzoate (4.8 mmol) is added and the reaction mixture is stirred at room temperature. The reaction is followed by TLC control every 5 min using dichloromethane/petrol ether (2:1) as the eluent. A precipitate forms during the reaction. When the reaction is finished, 50 mL dichloromethane (DCM) is added and the suspension is filtered over cotton. The filtrate is extracted with a saturated aqueous solution $NaHCO_3$ (50 mL) and three times with a saturated aqueous solution of $Na_2S_2O_3$ (3 x 50 mL). The DCM solution is dried over Na_2SO_4 transferred into a 50 mL round bottom flask, and then evaporated by distillation under vacuum.

5. Purification

The crude product is recrystallized from ethanol (20 mL). The collected crystals are dried in the oven (100 °C).

6. Control of the Purity

6.1 Melting Point Measurement

The melting point of the dry sample is measured and compared with the literature value (148 °C).

6.2 Thin Layer Chromatography

Check the purity of the product by thin layer chromatography (TLC). Determine the R_F -value.

6.3 ^1H -NMR Spectroscopy

Analyse the ^1H -NMR spectrum of the target compound dissolved in d^6 -DMSO. Assign the ^1H -NMR signals to the protons of ethyl 4-amino-3,5-diiodobenzoate. Determine the coupling constants.

7. End of the Manipulation

1/ 4-Amino-3,5-diiodobenzoate is stored in a glass vial that is labelled with the compound name, student name, and date.

2/ All starting materials are put back into the retention trays.

3/ The glassware is cleaned, dried, and put back in place:

- Remaining traces of organic chemical compounds are removed by rinsing the flask with a minimum of solvent (for example acetone), which is subsequently disposed as non-halogenated organic solvent waste in case of ethyl 4-aminobenzoate and as halogen containing organic solvent waste in case of the product.
- Traces of iodine are treated with saturated aqueous thiosulfate solution and disposed as aqueous waste.
- Being free of any chemical contamination, the dirty glassware is washed with a conventional detergent and rinsed thoroughly. It is then rinsed with deionized water to avoid the presence of limestone. It is possible to dry the glassware with acetone.
- All the glassware used is placed back into its original location. Any defective part is signalled to the assistant.

4/ The fume hood is tidied up. All electrical appliances are unplugged. Ventilation and lighting of the hood are switched off.

5/ The sink is cleaned.

6/ All waste contaminated with chemicals (absorbent paper, etc.) is collected in specific recovery cans, according to the indications of the assistants.

Learning Objective: Thin Layer Chromatography

Chromatographic methods are widely applied in organic chemistry, particularly for compound isolation, analysis, or following the progress of a reaction.

Chromatography is based on the continuous exchange of chemical compounds between a mobile phase (solvent) and a stationary phase (most common: silica gel). Depending on the distribution coefficient, compounds move with a different rate along the direction of flow.

Adsorption, i.e. an interaction between a stationary phase and a compound, is fundamental for thin layer chromatography (TLC). The chemical structure, in particular differences in polarity and hydrogen bonding capability, has a major impact on the adsorption behaviour of a compound, which in turn is also strongly influenced by the solvent. Given a defined solvent composition, a compound can accordingly be characterized by the so called retention factor (R_F -value) that is the ratio of migration distance of the compound and migration distance of the solvent front.

In practice, the sample of interest is dissolved in a solvent of low polarity and placed as a small spot on the lower corner of the TLC plate. The TLC plate is placed into a chamber that contains the eluent. Capillary forces move the eluent from the bottom to the top of the TLC plate. When finished, the solvent front is marked and the R_F -value determined, which should ideally be 0.3-0.5.

UV-light is the most common source for sample detection. Commercial TLC plates are often coated with a fluorescence indicator and fluoresce upon UV-irradiation. Compounds that absorb the incoming UV-light (for example, aromatic compounds) appear as dark spots on the plate. Using short-wave UV-light, the compound may inherently fluoresce itself.

TLC is highly suitable for following the progress of a reaction. Comparing the R_F -value of starting compounds, potential intermediates, and products allows to qualitatively determine the degree of the chemical conversion.

8. To be Addressed in the Protocol

- 1.) Give a detailed reaction mechanism including the elementary steps. Explain the regioselectivity.

- 2.) Compare the reactivity of starting material and potential intermediates.
- 3.) Which compounds are separated during the extraction and washing step?
- 4.) Which side product(s) can you imagine to be formed? Which spectroscopic methods can be applied to exclude them?

Be sure you have also completed the prelab protocol with the relevant safety information (**BEFORE** the lab course).