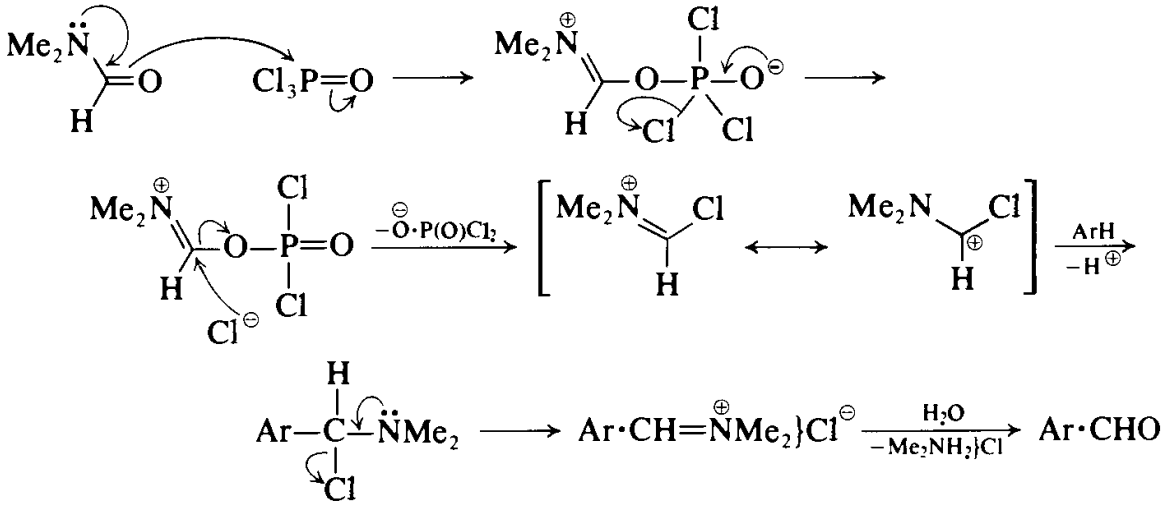
One alternative which avoids the use of the hazardous hydrogen cyanide is passing dry hydrogen chloride either into a mixture of zinc cyanide, aluminium chloride, the hydrocarbon or phenolic ether and a solvent (such as tetrachloroethane or benzene), or into a mixture of zinc cyanide, the phenol and anhydrous ether or benzene. The zinc cyanide is converted by the hydrogen chloride into hydrogen cyanide (which reacts *in situ*), and zinc chloride which is known to be an effective catalyst in this reaction. A second alternative, which is applicable to hydrocarbons only, is to use acetone cyanohydrin as an *in situ* source of hydrogen cyanide.[47] The preparation of 2,4,6-trimethylbenzaldehyde (mesitaldehyde) from mesitylene and the related cognate preparations (Expt 6.113) provides a varied range of examples.

Certain reactive aromatic hydrocarbons are formylated by dimethylformamide in the presence of phosphorus oxychloride (the Vilsmeier reaction, e.g. 9-formylanthracene, Expt 6.114). This method can also be used with advantage for the formylation of π-excessive heteroaromatic systems (e.g. 2-formylthiophene, cognate preparation in Expt 6.114).



A generally applicable method of formylation involves the reaction of an aromatic hydrocarbon and dichloromethyl methyl ether under Friedel–Crafts conditions (cf. Section 6.11.1, p. 1006). The intermediate chloroacetal (1) thus formed is readily hydrolysed to the corresponding aldehyde (e.g. *p*-t-butylbenzaldehyde, Expt 6.115).

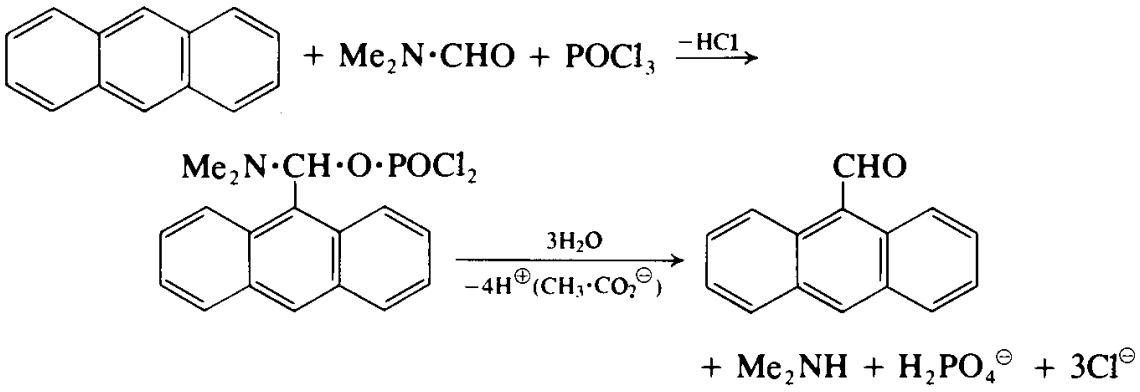
$$ArH + Cl_2CHOMe \xrightarrow[-HCl]{TiCl_4} \underset{(1)}{Ar{\cdot}CH(OMe)Cl} \xrightarrow{H_2O} Ar{\cdot}CHO + MeOH$$

The procedure is of value for the formylation of polycyclic aromatic and heteroaromatic systems, phenols and phenolic ethers.

Phenols are smoothly converted into phenolic aldehydes by reaction with chloroform in the presence of base (the Reimer–Tiemann reaction). This overall formylation reaction is of interest in that it involves the generation from chloroform and alkali of the reactive intermediate, dichlorocarbene (2). This effects electrophilic substitution in the reactive phenolate ions giving the benzylidene dichloride (3) which is hydrolysed by the alkaline medium to the corresponding hydroxyaldehyde. The phenolic aldehyde is isolated from the reaction medium after acidification.

to cool somewhat and pour the reaction mixture with stirring into excess of dilute hydrochloric acid; the imine hydrochloride separates as a heavy precipitate. Reflux the mixture for half an hour in order to decompose the imine hydrochloride and steam distil. Separate the organic layer in the distillate, dry with a little anhydrous magnesium sulphate and distil off the benzene. Continue distillation with an air bath and collect the anisaldehyde as a fraction which has a b.p. 246–248 °C; the yield is 35 g (92%). If required the product may be redistilled under reduced pressure, b.p. 134–135 °C/12 mmHg. The i.r. spectrum is given on p. 301; the p.m.r. spectrum should be recorded and interpreted.

Experiment 6.114 9-FORMYLANTHRACENE (*9-Anthraldehyde*)



Equip a 500-ml three-necked flask with a sealed stirrer unit, a reflux condenser and a dropping funnel. Assemble the apparatus on a water bath in a fume cupboard. Place in the flask a mixture of 17.8 g (0.1 mol) of anthracene (1), 19 g (20 ml, 0.26 mol) of dimethylformamide and 20 ml of *o*-dichlorobenzene (2), and charge the dropping funnel with 27 g (16 ml, 0.175 mol) of phosphorus oxychloride; close the condenser and dropping funnel with calcium chloride guard-tubes. Start the stirrer, run in the phosphorus oxychloride steadily and then heat on a boiling water bath for 2 hours. Cool the reaction flask in an ice–salt bath and neutralise the contents to Congo red by running in aqueous sodium acetate solution (about 100 g of the trihydrate in 175 ml of water are required). Dilute with more water to about 2 litres and allow the mixture to stand at 0 °C for 2 hours. Filter off the yellow crystalline product and recrystallise it from aqueous acetic acid; the yield of 9-formylanthracene is 12 g (58%), m.p. 104 °C.

Notes. (1) Good quality material should be used; commercial fluorescent grade of m.p. *c.* 215 °C is suitable.

(2) The use of *o*-dichlorobenzene as a solvent is recommended. If the reaction is carried out in excess dimethylformamide alone, the product is contaminated with unreacted anthracene. It is then best to extract the crude material with cold methanol, remove the anthracene by filtration and recover the product by dilution with water.

Cognate preparation. ***2-Formylthiophene*** (*thiophene-2-aldehyde*). Use 21 g (19.3 ml, 0.25 mol) of thiophene, 23 g (24 ml, 0.315 mol) of dimethylformamide and 80 ml of 1,2-dichloroethane as solvent. Cool to 0 °C, add 48 g (29 ml, 0.313 mol) of phosphorus oxychloride slowly with stirring, and then heat, carefully at first, and then under reflux for 2 hours. Cool, pour on to crushed ice, neutralise with sodium acetate (*c.* 200 g of the hydrate), separate the

organic phase and extract the aqueous phase with ether. Wash the combined organic phases with aqueous sodium hydrogen carbonate, dry over magnesium sulphate and remove the solvent on a rotary evaporator. Distil the residue under reduced pressure and collect the 2-formylthiophene as a fraction of b.p. 85–86 °C/16 mmHg; yield 20 g (71%). Record the p.m.r. spectrum (CCl_4, TMS) and assign the signals which appear at δ 7.12 (t, 1H), 7.67 (d, 2H), and 9.86 (s, 1H), bearing in mind that the protons on C_3 and C_5 appear equivalent (cf. furan-2-aldehyde, cognate preparation in Expt 6.133).

Experiment 6.115 *p*-t-BUTYLBENZALDEHYDE

$$Ph{\cdot}CMe_3 \xrightarrow[TiCl_4]{Cl_2CH{\cdot}O{\cdot}Me} p\text{-}Me_3C{\cdot}C_6H_4{\cdot}CHO$$

Equip a 250-ml three-necked flask with a thermometer, reflux condenser, dropping funnel (protected with a calcium chloride guard-tube) and magnetic stirrer, and attach a gas absorption trap to the top of the condenser; assemble the apparatus in the fume cupboard. Place 15.1 g (0.12 mol) of t-butylbenzene (Expt 6.5) and 60 ml of dry dichloromethane (Section 4.1.5, p. 399) in the flask and cool to 0–5 °C in an ice–salt bath. To the stirred solution add 38 g (22 ml, 0.2 mol) of titanium (IV) chloride rapidly from the dropping funnel (2 to 3 minutes); the mixture becomes orange. Then add 11.5 g (0.1 mol) of dichloromethyl methyl ether (Expt 5.71) (**CAUTION**) during 20 minutes to the stirred and cooled solution. Hydrogen chloride is evolved after the first few drops of the ether are added. Stir the mixture for 5 minutes after completion of the addition, remove the cooling bath, allow the mixture to warm to room temperature (about half an hour) and then heat at 35 °C for 15 minutes. Pour the mixture into a separating funnel containing 100 g of ice and shake thoroughly. Separate the lower organic layer and extract the aqueous layer with three 25 ml portions of dichloromethane. Wash the combined dichloromethane extracts with three 25 ml portions of water, add a crystal of hydroquinone to prevent oxidation of the aldehyde and dry over magnesium sulphate. Filter the solution, remove the solvent by flash distillation and distil the residue under reduced pressure through a short fractionating column. The fraction which distils at 52 °C/4 mmHg is t-butylbenzene; collect the *p*-t-butylbenzaldehyde as a fraction of b.p. 98 °C/4 mmHg; the yield is 10.8 g (67%).

Experiment 6.116 SALICYLALDEHYDE

$$PhOH \xrightarrow[\ominus OH]{CHCl_3} o\text{- and } p\text{-}HO{\cdot}C_6H_4{\cdot}CHO$$

Equip a 1-litre three-necked flask with an efficient double surface reflux condenser, a mechanical stirrer and a thermometer, the bulb of which is within 2 cm of the bottom of the flask. Place a warm solution of 80 g of sodium hydroxide in 80 ml of water in the flask, add a solution of 25 g (0.266 mol) of phenol (**CAUTION**) in 25 ml of water and stir. Adjust the temperature inside the flask to 60–65 °C (by warming on a water bath or by cooling, as may be found necessary); do not allow the crystalline sodium phenoxide to separate out. Introduce 60 g (40.5 ml, 0.5 mol) of chloroform (**CAUTION**) in three portions at intervals of 15 minutes down the condenser.

tion. Transfer the mixture to a large separatory funnel, allow to stand and remove the small quantity of unsaponified material which separates as an upper oily layer. Place the aqueous solution of sodium propylacetoacetate in a 3-litre two-necked flask fitted with a small separatory funnel and a wide bent delivery tube connected to a condenser set for downward distillation. Add 150 ml of 50 per cent by weight sulphuric acid (*d.* 1.40) slowly through the separatory funnel with shaking; a vigorous evolution of carbon dioxide occurs. When the latter has subsided, heat the reaction mixture slowly to the boiling point and distil slowly until the total volume is reduced by about one-half; by this time all the hexan-2-one should have passed over. The distillate contains the ketone, ethanol and small quantities of acetic and valeric acids. Add small portions of solid sodium hydroxide to the distillate until it is alkaline and redistil the solution until 80–90 per cent has been collected; discard the residue.

Separate the ketone layer from the water, and redistil the latter until about one-third of the material has passed over. Remove the ketone after salting out any dissolved ketone with potassium carbonate (2). Wash the combined ketone fractions four times with one-third the volume of 35–40 per cent calcium chloride solution in order to remove the alcohol. Dry over 15 g of anhydrous calcium chloride; it is best to shake in a separatory funnel with 1–2 g of the anhydrous calcium chloride, remove the saturated solution of calcium chloride as formed, and then allow to stand over 10 g of calcium chloride in a dry flask. Filter and distil. Collect the hexan-2-one at 126–128 °C. The yield is 71 g (67%).

Notes. (1) The addition of the ethanol to the sodium, although attended by a very vigorous reaction which must be carefully controlled, is preferable to the reverse procedure of adding the sodium in small pieces to the ethanol. The latter method is longer and has the further disadvantage that it necessitates frequent handling and exposure to the air of small pieces of sodium.

(2) A more complete recovery of the ketone from the aqueous solution may be obtained by repeated distillation of the aqueous layer until no appreciable amount of ketone is found in the distillate. The procedure outlined is, however, quite satisfactory.

Cognate preparation. ***Heptan-2-one.*** Use 34.5 g (1.5 mol) of sodium, 1 litre of super-dry absolute ethanol, 195 g (1.5 mol) of redistilled ethyl acetoacetate and 225 g (177 ml, 1.63 mol) of dry butyl bromide (Expt 5.54). This yields 280 g of crude or 200 g (72%) of pure ethyl butylacetoacetate, b.p. 112–116 °C/16 mmHg. Upon hydrolysis 105 g (80%) of heptan-2-one, b.p. 149–151 °C, are isolated.

Experiment 5.96 CYCLOHEXYL METHYL KETONE

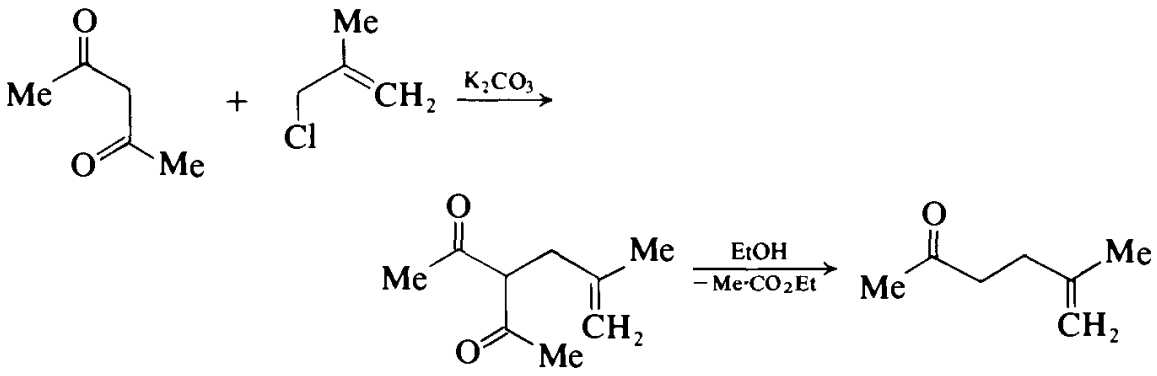
$$C_6H_{11}\cdot COCl + [CH(CO_2Et)_2]MgOEt \longrightarrow$$

$$C_6H_{11}\cdot CO\cdot CH(CO_2Et)_2 \xrightarrow[-CO_2,\ -2EtOH]{H_3O^{\oplus}} C_6H_{11}\cdot CO\cdot Me$$

Place 10.7 g (0.44 mol) of magnesium turnings in a 1-litre three-necked round-bottomed flask, equipped with a sealed stirrer unit, a dropping funnel and a double surface reflux condenser each protected with a calcium chloride guard-tube. Add in one portion a mixture of 10 ml of absolute ethanol and 1 ml of carbon tetrachloride. Allow the reaction, which commences almost

immediately, to proceed for about 5 minutes and then add carefully 150 ml of sodium-dried ether (Section 4.1.*15*, p. 404). Site the flask in a warm-water bath and allow the reaction mixture to reflux gently while a solution of 70 g (0.44 mol) of diethyl malonate in 50 ml of dry ether is added with stirring. On completion of the addition, heat the mixture under reflux for about 3 hours or until all the magnesium has reacted. Then add with vigorous stirring a solution of 58 g (0.4 mol) of cyclohexanecarbonyl chloride (Expt 5.138) in 50 ml of dry ether. Heat the reaction mixture under reflux for 2 hours and then cool and acidify with 50 ml of dilute sulphuric acid. Separate the ether layer and extract the residual aqueous solution with two 50 ml portions of ether. Wash the combined ether extracts with water and evaporate the solvent on a rotary evaporator. To the residue add a solution of 120 ml of glacial acetic acid, 15 ml of concentrated sulphuric acid and 80 ml of water and heat under reflux for 5 hours. Cool the reaction mixture, basify by the careful addition of 100 ml of 20 per cent sodium hydroxide solution and extract the solution with four 50 ml portions of ether. Dry the combined ether extracts over sodium sulphate and remove the ether on a rotary evaporator. Distil the crude product at atmospheric pressure through a short fractionating column. The yield of cyclohexyl methyl ketone of b.p. 178–180 °C is 35 g (70%).

Experiment 5.97 5-METHYLHEX-5-EN-2-ONE



Equip a 1-litre two-necked round-bottomed flask with a sealed stirrer unit and a reflux condenser protected with a guard-tube containing anhydrous calcium sulphate. Place in the flask 500 ml of anhydrous ethanol, 75 g (0.75 mol) of freshly distilled pentane-2,4-dione (b.p. 136–137 °C) (Expt 5.102), 63.4 g (0.70 mol) of 3-chloro-2-methylpropene (methallyl chloride) and 96.8 g (0.70 mol) of anhydrous potassium carbonate. Heat the stirred mixture under gentle reflux for 16 hours. Allow the mixture to cool a little and replace the condenser by a still-head and condenser arranged for downward distillation. Distil the stirred mixture until about 370 ml of ethanol and the ethyl acetate formed during the reaction has collected, then cool the residue and add sufficient ice-water to dissolve the suspended salts (about 550 ml is required). Transfer to a separatory funnel and extract with three 200 ml portions of ether. Wash the combined extracts with two 100 ml portions of saturated aqueous sodium chloride and then dry the ethereal solution over anhydrous sodium sulphate. Filter, and remove the ether by flash distillation. Fractionally distil the residue using a well-lagged fractionating column of about 12 cm length filled with glass helices. Collect the unsaturated ketone as a fraction of b.p. 148–153 °C; (mainly 148–150 °C) (1). The yield of 5-

3-Methoxy-4-nitrotolueneA. 5-L three-necked flask fitted with a mechanical stirrer was charged with 300 mL of 6 N NaOH. The solution was warmed to 40-50 O C and 60.0 g of 5-methyl-2-nitrophenol (Aldrich) was added in one portion. The solution was heated to ***80*** **"C** and dimethyl sulfate was rapidly added until the color changed from red to yellow. More base was added until the color changed back to red. The altemate addition of dimethyl sulfate and base was continued until no more red color was observed on addition of base. When the solution was allowed to cool, a yellow precipitate formed which was collected and recrystaked from 95% ethanol to give 58.9 g (90.0% yield) of yellow needles, mp 58-60 "C (lit.16 mp 62 **"C).**

Ethyl 4-Amino-3-methoxybenzoate(9). To a solution of 51.3 g of 3-methoxy-4nitrotoluene in 3.5 L of boiling water containing 25.0 g of Na2C03 was added 200 g of powdered KMnOl. The solution was refluxed for 1.5 h, filtered through diatomaceous earth, cooled to 0 "C, and acidified with dilute H2S04. The mixture was heated to dissolve the product, decolorized with charcoal, filtered, and allowed to cool and crystallize. The product was recrystallized from 95% ethanol, affording 60.5 g (100% yield) of 3-methosy-4nitrobenoic acid **as** colorless crystals, mp 230-233 "C (lit." mp 233 "C).

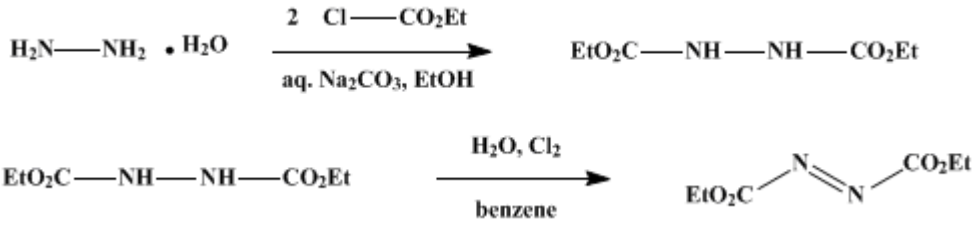
A solution containing 27.0 g of **3-methoxy-4-nitrobenzoic**a cid, 200 mL of absolute ethanol, 150 mL of benzene (dried over sodium), and 5 mL of concentrated H#04 was heated to reflux for 24 h. **A** Dean-Stark trap was used to remove the water of reaction. The solution was allowed to cool and then extracted with 100 mL of 10% aqueous Na2C03. The organic layer was dried over anhydrous Na2S04 and the solvent removed in vacuo, affording 29.6 g (95.9% yield) of ethyl 3-methoxy-4-nitrobenoate as a light tan residue. This residue was sufficiently pure for the next step; however, it could be recrystallized from benzenefpetroleum ether to give yellow needles, mp 93-94 "C (lit.'* mp 93 "C).

Ethyl **3-methoxy-4-nitrobenzoat**(**e**2 5.4 g) dissolved in 300 mL of 95% ethanol with 0.3 g of PgO catalyst added was placed in a Paar hydrogenation bottle and shaken at room temperature under 65 psi of H2 for 3 days. The catalyst was filtered off and the solvent removed in vacuo, affording 16.8 g (74.6% yield) of **9** as a colorless solid mp 81-83 "C; 'H NMR (CDC13 6 1.2 (t, 3 **H),** 3.7 ***(8,*** 3 H), 4.1 (9, 2 HI, 4.2 (q, 2 H), 6.5 (m, 2 H), **7.4** (d,

Organic Syntheses, Coll. Vol. 3, p.375 (1955); Vol. 28, p.58 (1948).

ETHYL AZODICARBOXYLATE

[Formic acid, azodi-, diethyl ester]



Submitted by Norman Rabjohn
Checked by H. J. Sampson and R. S. Schreiber.

1. Procedure

A report has been received that a sample of ethyl azodicarboxylate decomposed upon attempted distillation with sufficient violence to shatter the distillation apparatus. It is possible that the explosion may have been due to over chlorination or to insufficient washing of the product with sodium bicarbonate solution. It is recommended that ethyl azodicarboxylate be distilled only behind a safety shield, and protected from direct sources of light.

A. *Ethyl hydrazodicarboxylate.* In a 2-l. three-necked flask, equipped with a mechanical stirrer, two 500-ml. dropping funnels, and a thermometer (Note 1), is placed a solution of 59 g. (1 mole) of 85% hydrazine hydrate in 500 ml. of 95% ethanol. The reaction flask is cooled by means of an ice bath. When the temperature of the solution has dropped to 10°, 217 g. (2 moles) of ethyl chloroformate is added dropwise with stirring at a rate sufficient to maintain the temperature between 15° and 20°. After one-half of the ethyl chloroformate has been introduced, a solution of 106 g. (1 mole) of sodium carbonate in 500 ml. of water is added dropwise simultaneously with the remaining ethyl chloroformate. The addition of these two reactants is regulated so that the temperature does not rise above 20° and so that the addition of the chloroformate is completed slightly in advance of the sodium carbonate in order to ensure a slight excess of ethyl chloroformate in the reaction mixture at all times.

After all the reactants have been added, the precipitate on the upper walls of the flask is washed down with 200 ml. of water and the reaction mixture is allowed to stir for an additional 30-minute period. The precipitate is then collected on a Büchner funnel, washed well with a total of 800 ml. of water, and dried in an oven at 80°. There is obtained 145–150 g. (82–85%) of ethyl hydrazodicarboxylate which melts at 131–133°. It is sufficiently pure (Note 2) for the preparation of ethyl azodicarboxylate.

B. *Ethyl azodicarboxylate.* A mixture of 100 g. (0.57 mole) of ethyl hydrazodicarboxylate, 500 ml. of benzene, and 500 ml. of water is placed in a 2-l. three-necked flask equipped with a mechanical stirrer and a gas inlet tube. The flask and contents are tared, the flask is placed in an ice bath, and a slow stream of chlorine is bubbled into the mixture with stirring. The temperature is maintained below 15°, and chlorine is introduced until the increase in weight amounts to 50–55 g. (Note 3). The flow of chlorine is stopped, and the reaction mixture is stirred until a clear, orange-colored benzene layer forms when the mixture is allowed to settle. The layers are separated, and the water layer is extracted once with benzene. The benzene solutions are combined and washed twice with 100-ml. portions of water, then with 100-ml. portions of 10% sodium bicarbonate solution until neutral (usually four to six washes are required), and twice more with water, and then are dried over anhydrous sodium sulfate. The benzene is removed under reduced pressure on a steam bath, and the residue is distilled in vacuum through a short indented column. After a small fore-run, the main fraction is collected at 107–111° /15 mm. There is obtained 80–82 g. (81–83%) of ethyl azodicarboxylate.

2. Notes

1. The thermometer and one of the funnels are fitted to a two-necked adapter; the thermometer scale must be such that the range between 10° and 20° is easily visible, preferably outside the flask, when the bulb is inserted in the liquid.

2. Ethyl hydrazodicarboxylate may be purified by crystallization from dilute ethanol; m.p. 134–135°

3. A larger excess of chlorine causes the formation of higher-boiling materials and lowers the yield of ethyl azodicarboxylate.

3. Discussion

Ethyl hydrazodicarboxylate can be prepared by the reaction of ethyl chloroformate with hydrazine hydrate[1] or hydrazine sulfate in the presence of potassium hydroxide.[2] It can be prepared also by the treatment of symmetrical hydrazinedicarboxylic acid diazide with ethanol.[3]

Ethyl azodicarboxylate can be prepared by treating ethyl hydrazodicarboxylate with concentrated nitric acid[2] or a mixture of concentrated and fuming nitric acid.[4,5]
This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 411
- Org. Syn. Coll. Vol. 5, 96
- Org. Syn. Coll. Vol. 3, 58
- Org. Syn. Coll. Vol. 5, 544