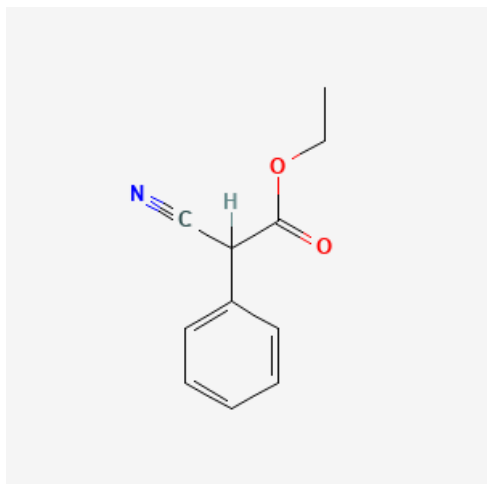


Ethyl Phenylcyanoacetate Synthesis (.5M)

Summary

Ethyl phenylcyanoacetate is an alpha-substituted cyanoacetate ester that consists of ethyl cyanoacetate bearing an alpha-phenyl substituent. It is an alpha-substituted cyanoacetate ester and an ethyl ester.



Name(s)	Ethyl phenylcyanoacetate, α-phenylcyanoacetic ester
Formula	C ₁₁ H ₁₁ NO ₂
Molar mass	189.21 g·mol ⁻¹
Density	1.09 g/mL at 25 °C [3.4]
Boiling point	275 °C [3.4]
Melting point	115-116 °C [3.4]
Appearance	liquid @ 20 °C [3.4]
Odor	
Hazards	Harmful (Xn) [3.4]

Reagents

- Absolute ethanol - 300 mL
- Sodium metal - 12 g
- Diethyl carbonate - 300 mL
- Toluene - 280 to 330 mL
- Benzyl cyanide - 58.5 g
- Distilled water - 400 mL

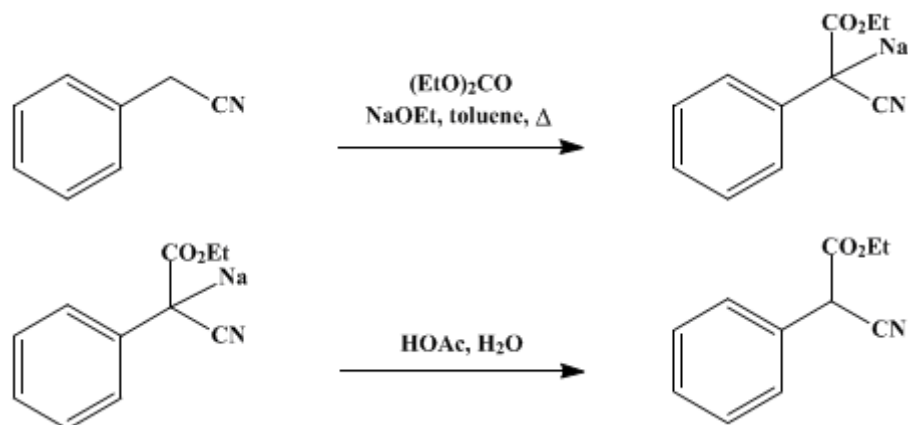
- Calcium chloride, anhy. (drying agent)
- Magnesium sulfate, anhy. (drying agent)

Equipment

- 1x L 3 neck RBF
- 1x 500 mL RBF
- Distillation equipment (condenser, head, vacuum adaptor)
 - Pig/cow adaptor for the last fractional distillation step.
 - 3x 50 to 100mL RBF's for receiving flasks
- Vacuum pump and/or aspirator
- 250 mL addition funnel
- 500 mL separatory funnel
- 1 L beaker

Procedure

The procedure is taken from the OrgSyn synthesis^[1.1] and is done on the same scale (.5 M based on BnCN). It starts out with the preparation of sodium ethoxide in a 1L RBF, followed by a vacuum distillation to get as much of the ethanol off as possible. Then benzyl cyanide is reacted with an excess of diethyl carbonate in the presence of the fresh sodium ethoxide to form the **α -phenylcyanoacetic ester**.



Source data

Sodium ethoxide is prepared from 12.0 g. (0.52 g. atom) of sodium and 300 ml. of anhydrous ethanol in a 1-l. three-necked round-bottomed flask fitted with a reflux condenser carrying a calcium chloride tube. After the sodium has dissolved completely, the condenser is arranged for distillation under reduced pressure and the excess ethanol is removed by heating the flask on a steam bath while the system is maintained at the pressure obtained with an ordinary aspirator (Note 1). As rapidly as possible, after removal of the ethanol, the flask is fitted with a rubber-sealed stirrer, a dropping funnel, a distilling head containing a thermometer, and a condenser arranged for distillation into a flask protected by a calcium chloride tube.

There are then added 300 ml. (292 g., 2.5 moles) of dry diethyl carbonate, 80 ml. of dry toluene, and 58.5 g. (0.50 mole) of phenylacetonitrile (Note 2). The flask is heated, with good stirring, and the cake of sodium ethoxide soon dissolves. When distillation has started, dry toluene is added dropwise at about the same rate that the distillate is collected. Approximately 200–250 ml. of toluene should be added in a period of 2 hours (Note 3) while stirring and distillation are continued. The mixture is cooled and transferred to a 1-l. beaker. After addition of 300 ml. of cold water, the aqueous phase is acidified with 35–40 ml. of acetic acid. The layers are separated and the water solution is extracted with three 75-ml. portions of ether. The organic solutions are combined, washed with 100 ml. of water, and dried over anhydrous magnesium sulfate. The low-boiling solvents are removed by distillation at atmospheric pressure, and the residue is distilled under reduced pressure through a short (15-cm.) Vigreux column. After a 1–5 g. forerun, the product is collected at 125–135°/3–5 mm. (Note 4). The yield is 66–74 g. (70–78%).

Serialized Procedure

- To a **3 neck 1L RBF** fitted with a **reflux condenser and drying tube** was added **300 mL of dried ethanol**, followed by the addition of **12g of clean sodium metal**. The sodium should be added in portions to prevent any unwanted frothing of the reaction. Once the sodium has completely reacted and no more solids are seen, the reflux condenser was rearranged to prepare for a simple vacuum distillation.
- A vacuum is pulled and the mixture is brought to a boil to distill off as much ethanol as possible. The temperature in the flask should not exceed 90–100 °C.
 - The success of this procedure is dependent upon the quality of the sodium ethoxide. The ethanol should be dried before use, and the sodium ethoxide should not be heated to a temperature higher than 90–100°.
 - The ethanol distilled off can be saved and re-used, as it is now perfectly dry.
- As quickly as possible once the ethanol is removed, to the distillation flask was added **300 mL of dry diethyl carbonate, 80 mL of dry toluene** and **58.5 g of benzyl cyanide**. Then a pressure equalizing addition funnel is charged with **200–250 mL of dry toluene** and attached to the distillation flask. The receiving flask is swapped out with another flask that is protected by a calcium chloride drying tube.
 - Once the 300 mL of diethyl carbonate is added to the flask, the solid sodium ethoxide cake can be crushed up and mixed around with a glass rod to help get it into solution faster.
- The flask is now heated with vigorous stirring. The solid sodium ethoxide should soon go into solution and the distillation should begin.
- When distillation has started, dry **toluene** is added dropwise at about the same rate that the distillate is collected. Approximately 200–250 mL of toluene should be added in a period of 2 hours while stirring and distillation are continued.
 - Any ethanol remaining in the sodium ethoxide, together with the ethanol produced during the reaction, is removed during this period. The progress of the carbethoxylation reaction can be followed by temperature readings. During the first half of the heating period distillation usually occurs at a vapor temperature of 80–85°, but as the reaction nears completion and the ethanol is removed, the temperature rises to 110–115°. Near the end of the period, the sodium salt of ethyl phenylcyanoacetate appears as a precipitate.
- Once distillation is complete, the mixture is cooled and transferred to a 1-l. beaker.
- To the beaker is added 300 mL of cold distilled water. The aqueous phase is acidified with **35–40 mL of acetic acid**.
 - Note:** Since this says "the aqueous phase", I'm assuming it implies that the aqueous phase was separated from the organic phase first.

8. Using a separatory funnel, the layers are separated and the water solution is extracted with three **75-mL portions of ether**.
9. The organic solutions are combined, washed with 100 mL of water, and dried over anhydrous magnesium sulfate.
10. The low-boiling solvents are removed by distillation at atmospheric pressure, and the residue is fractionally distilled under vacuum. After a 1–5 g. forerun, the product is collected at 125–135°/3–5 mm. (Note 4). The yield is 66–74 g. (70–78%).
 - Other observed boiling points are 129–131°/3 mm., 145–150°/7–8 mm. The product is a colorless liquid, n_{D25}
11. The yield is 66–74 g. (70–78%).

Synthesis Notes

Preparation

- The ethanol was dried by reacting it with a small amount of sodium (approximately 1g per 1L of ethanol), then distilled and stored over sieves.
- The toluene and diethyl carbonate were both distilled and stored over sieves.
- The benzyl cyanide was distilled.

Synthesis

- A three neck 1L RBF was first rinsed out with pure ethanol, then to it was added 300mL of absolute ethanol and a medium sized oval stir bar. A reflux condenser was attached to the middle neck with cold water running through it. A drying tube with anhydrous calcium chloride was mounted on top of the condenser.
- The sodium was added in chunks from 2 to 3.88g in weight and only when the previous chunk had entirely reacted and no more solids were observed. The total sodium added ended up closer to 13 g than 12 g. Once all the sodium was added, the reaction flask was allowed to cool down to prepare for the vacuum distillation.
 - sodium portions: 2.01, 2.08, 2.89, 3.88, 2.09 = 12.95 g
- The flask was setup for simple vacuum distillation with a K-type thermocouple submerged in the NaOEt solution to keep track of the temperature. A vacuum was pulled via aspirator and the temperature was turned up. As the solution boiled at 35.6 °C and had a rather excessive amount of bumping. Some of the ethoxide splashed up into the distillation head. The walls of the RBF were almost entirely covered in ethoxide making it difficult to determine the level of ethoxide left.
- Once the rate of ethanol coming over had slowed down to just 1 drop every 3–4 seconds, the heating mantle was lowered and the heat turned off. The aspirator was left on as the reaction flask cooled. The perfectly white solidified ethoxide was observed on the bottom of the 1L RBF.
 - In an attempt to cool the reaction flask down faster, a cold water bath was used, but this caused an excessive amount of suck back from the aspirator and was abandoned quickly.
- Once the flask had cooled down to ~43 °C, the vacuum was released slowly, and the setup was reconfigured for simple distillation, the receiving flask was swapped out with a clean two neck 1L RBF with a drying tube, and a new clean distillation head equipped with a thermometer well was swapped out.
- The toluene/BnCN/DEC mixture was added to the reaction flask, and pretty much immediately the color went from perfectly white to mostly yellow with a hint of brown. The stir bar was entrapped in the solidified ethoxide and was freed using a stirring stick. A 250 mL pressure

entrapped in the solidified enoxide and was freed using a stirring stick. A 200 mL pressure equalizing addition funnel was added to the distillation flask and charged with 250 mL of dry toluene.

- Once everything was setup, stirring was turned on and the heat was turned on to a medium/low heat.
- Pretty soon it was brought to a boil, and it became evident that foam would be one of the main concerns. At times, the foam reached about 12 mm below the bottoms of the side necks on the flask, and to some extent could be dealt with using the stirring speed.
- Once the distillate started to come over, the toluene addition began and at approximately the same rate. The majority of the distillate came over at 116-117 °C.
- The distillation took about 1.45 hours in total. At the end, the level in the distillation flask seemed to be a bit too low and some toluene was added, and the flask was allowed to cool.
 - **Note:** This is probably what fucked everything up. I shouldn't have let it get so low.
- At this point, the distillation flask was semi-solid colored from yellow to orange and brown.
- The flask was purged with argon (probably totally unnecessary) and stoppered to be processed on a later date.
- [The next day] The mass inside the reaction vessel was pretty mush solid (despite adding about 30mL of toluene right when the heat was turned off), so it wasn't going to be possible to just pour this out into a 1L flask. 300 mL of cold distilled water was added right to the reaction vessel, and after some shaking to liberate the stir bar, two layers formed. The top layer is presumably the residual toluene.
- After shaking and letting it settle, it became apparent that the toluene layer was pretty small and there was some undissolved chunks. I assume that there should still be enough toluene in there to perform a separation and pull out anything soluble in the toluene. So about 30-40 mL of toluene was added and the mixture was shaken a bit more and left to separate.
- After the layers had separated, the bottom aqueous layer was separated using the separatory funnel. The organic layer was washed with about 20 mL of distilled water. The water separated to the bottom in a clear phase, even after being shaken a bit, seemingly indicating that not much else in the organic phase was soluble in the toluene phase.
- The aqueous phase containing our crude product was washed with toluene.
- The two phases were poured off into separate containers. The aqueous phase was washed with about 35-40 mL of toluene (far too much) twice, the toluene from the second wash was crystal clear. The toluene washes were poured off into a separate container.
- The pH of the aqueous layer was determined to be strongly alkaline.
- 42 mL of glacial acetic acid was slowly added to the aqueous phase inside a 500mL GL45 bottle. Upon the first addition of 15 mL AcOH a very noticeable color change took place going from orange to a very light beige color (still opaque). The beige layer also settled to the top half of the mixture. The mixture was agitated with a stirring rod to mix the two phases and turned the entire mixture to a color between the two (a very light orange color). The remaining AcOH was added incrementally while checking the pH in between additions. There was a noticeable amount of effervesce after each addition and during the agitation. Once all the AcOH was added, the acidity of the solution read ~2 and had cleared up entirely and retained a yellow color.
- A stir bar was added to the container and stirred at 250 RPM until no more effervesce was observed.
- The product was extracted from the aqueous phase using 75 mL of ether in three separate extractions.

- The organic layers were combined and dried with anhydrous calcium chloride which seemed to solidify rather quickly indicating that there was still water left in the organic phase. The ether was poured off into a separate flask and dried with magnesium sulfate.
- It was then realized that the organic phase should have been washed with 100 mL of distilled water before being dried with the magnesium sulfate. Thus, the magnesium sulfate was filtered off, the ether was washed with distilled water, separated off using a separatory funnel, and dried with magnesium sulfate.
- The organic phase was filtered directly into a 250 mL amber GL45 bottle for temporary storage. Even though the workup was done using 3x 75 mL of ether, plus ~25mL total for the washings (250 mL total), the current volume is only about 175mL. This could be due to the quick rate at which ether evaporates.
- [Next day] The ether was distilled off using a hot water bath. Everything came over between 34.6 and 36.5 °C. Unfortunately, almost everything came over.
- When the distillation rate dropped quite a bit, the hotplate was lowered and the residual mixture in the flask was pipetted into a vial and **weighed out at 7.5 g and orange/amber in color** (while still having a slightly ether like smell, indicating not all ether was removed yet).
- Considering the prep being followed (done on the same scale) mentions having about 66–74 g worth of purified ethyl ester at the end, having only 7.4 g of crude product is a clear indication of failure. 7.4g isn't even enough to move onto purification via distillation. But it may be enough to characterize it to determine if the prep was a complete synthesis failure or if I just managed to get a piss poor yield out of it. (characterization TBD)

Takeaways/To Research

1. Do some calculations to determine just how much ethanol should be distilled off (based off of how much of the EtOH got turned into NaOEt). This would help monitor the progress of removing the ethanol from the mixture.
2. If a cold water bath is desired to aid in cooling the reaction flask down quickly, it may be idea to put a stopcock, check valve or drying trap between the aspirator and takeoff adapter, or use the KNF vacuum pump instead.
3. Grease the stopcock joints on the addition funnels when attaching it to a vacuum distillation setup. The vacuum being pulled caused a stream of bubbles to form from the stopcock in the 500mL pressure equalizing addition funnel (which at the time was erroneously attributed to off-gassing).
4. Remember to wash the ether with water, and use magnesium sulfate if possible (Read the instructions!)
5. The ether evaporated rather quickly, it was about 75 mL less in volume than expected. Benzene could possibly be used as an alternative.
6. Only 7.4 g of crude product was left over after the ether was distilled off. This is up to 10x less than the upper amount mentioned in the source material^[1.1].

References

1. Synthesis Procedures

1. OrgSyn - [ETHYL PHENYLCYANOACETATE](#)

2. JACS - [Alkyl Carbonates in Synthetic Chemistry. III. Condensation with Nitriles.Synthesis](#)

1. Pubchem [Ethyl phenylcyanoacetate, 97% \(Ethyl phenylcyanoacetate, 97% of a-Cyano Esters\)](#)

2. Pubchem

1. [Ethyl phenylcyanoacetate](#)

3. MSDS

1. Fishersci [Ethyl phenylcyanoacetate, 97%](#)
2. Sigma-Aldrich [Ethyl phenylcyanoacetate](#)
3. TCI [Ethyl Phenylcyanoacetate](#)
4. Chemical Book [4553-07-5\(ETHYL PHENYLCYANOACETATE\) Product Description](#)

4. Wikipedia

1. [Diethyl carbonate](#)

5. https://youtu.be/5oAZyhPx_ws