

Simple Synthesis of Arylsuccinic Acids

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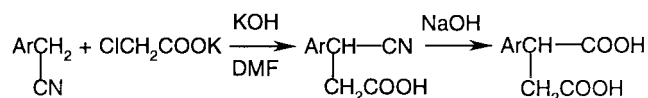
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Abstract: Alkylation of arylacetonitriles with potassium chloroacetate proceeds selectively leading to 3-cyano-3-arylpropionic acids, which are directly hydrolyzed to arylsuccinic acids.

Key words: alkylations, hydrolysis, nitriles, propionic acid, succinic acid

Aryl succinic acids are important intermediates in organic synthesis particularly in medicinal chemistry.¹ The most important method of synthesis of these acids consists in the condensation of aromatic aldehydes with ethyl malonate and addition of cyanide anion to produce arylidene-malonates. Hydrolysis and decarboxylation of the intermediate 3-cyano-3-arylpropionates gave arylsuccinic acids.² Other reported methods, such as addition of BrZnCH₂COOEt to nitrostyrenes and subsequent oxidative Nef reaction,³ alkylation of arylacetonitriles with bromoacetal followed by hydrolysis and oxidation,⁴ or alkylation of the dianion of phenylacetic acid with lithium iodoacetate,⁵ etc.⁶ are without practical value. An attractive possibility of synthesis of arylsuccinic acids appears to be phase-transfer catalyzed (PTC) alkylation of arylacetonitriles with isopropyl chloroacetate and hydrolysis of the produced 3-aryl-3-cyanopropionates. Unfortunately, this process is not selective and produces, in addition to the monoalkylation product, the product of dialkylation – diisopropyl 3-phenyl-3-cyano-glutarate in substantial quantity,⁷ even when the nitrile is used in excess.

We have expected that alkylation of phenylacetonitrile with salts of chloroacetic acid should proceed with high selectivity because of the negatively charged substituent, which would decrease substantially the CH acidity of the product and so avoid the dialkylation. Indeed treatment of phenylacetonitrile in DMF with potassium chloroacetate and solid powdered KOH resulted in a mild exothermic reaction giving the expected salt of 3-cyano-3-phenylpropionic acid which can be easily isolated upon acidification. Direct hydrolysis of the reaction mixture gave phenylsuccinic acid in excellent yield (Scheme). The reaction also proceeded with other arylacetonitriles to give the corresponding arylsuccinic acids.



Scheme Ar = C₆H₅, 4-ClC₆H₄, 2,4-Cl₂C₆H₃, 2-CH₃C₆H₄, 4-BrC₆H₄

To a stirred suspension of anhyd K₂CO₃ (8 g, 0.06 mol) in DMF (20 mL), chloroacetic acid (4.7 g, 0.05 mol) was added. From the resulting suspension, DMF (approx. 10 mL) was distilled off under reduced pressure at approx. 54 °C /30 mm Hg. The suspension was cooled to r.t. and DMF (30 mL) followed by phenylacetonitrile (5.86 g, 0.05 mol) were added. Powdered KOH (5.8 g, 0.1 mol) was added in portions at 20–25 °C. The reaction mixture was stirred further for 2 h at 20–25 °C, and the solvent was completely distilled off under reduced pressure at approx. 54 °C /30 mm Hg. The solid residue was dissolved in H₂O (approx. 20 mL) and the solution was extracted with hexane (2 × 10 mL). The aqueous layer containing potassium 3-cyano-3-phenylpropionate was further elaborated in two ways giving 3-cyano-3-phenylpropionic acid and phenylsuccinic acid.

3-Cyano-3-phenylpropionic Acid

The aqueous layer was acidified with HCl and extracted with EtOAc (2 × 10 mL). Evaporation of the solvent gave an oily residue (slowly solidified) which was recrystallized from benzene to give 3-cyano-3-phenylpropionic acid (4.75 g, 81%).

Mp 82 °C (Lit.⁸ mp 74–76 °C).

¹H NMR (200 MHz, DMSO-*d*₆): δ = 2.5 (m, 1H, *J*_{a'a} = 16.6 Hz, *J*_{a'b} = 5.1 Hz, *H*_a, CH₂), 2.9 (m, 1H, *J*_{aa'} = 16.6 Hz, *J*_{ab} = 9.5 Hz, *H*_{a'}, CH₂), 3.8–3.9 (m, 1H, *J*_{ba} = 9.5 Hz, *J*_{ba'} = 5.1 Hz, CH), 7.5 (m, 5H, C₆H₅), 12.2 (s, 1H, COOH).

¹³C NMR (DMSO-*d*₆): δ = 37.2, 40.7, 46.8, 126.7, 127.5, 128.3, 140.2, 172.7, 173.7.

Phenylsuccinic Acid

To the aqueous layer, NaOH (20%, 15 mL) was added and the mixture was refluxed for approx. 16 h. Upon cooling, the reaction mixture was acidified with HCl (38%), the precipitated acid was filtered with suction, and dried to give phenylsuccinic acid (5.14 g, 85%).

Mp 162–163 °C (Lit.² mp 163–164 °C).

¹H NMR (CD₃COCD₃): δ = 2.6 (m, 1H, *J*_{a'a} = 17.1 Hz, *J*_{a'b} = 5.1 Hz, *H*_a, CH₂), 3.1 (m, 1H, *J*_{aa'} = 17.1 Hz, *J*_{ab} = 10.1 Hz, *H*_{a'}, CH₂), 4.0–4.1 (m, 1H, *J*_{ba} = 10.1 Hz, *J*_{ba'} = 5.1 Hz, CH), 7.3 (m, 5H, C₆H₅), 12.4 (s, 2H, COOH).

¹³C NMR (CD₃COCD₃): δ = 37.8, 46.8, 127.0, 127.6, 128.5, 138.5, 172.5, 173.8.³

Other arylsuccinic acids were prepared in this way from the corresponding arylacetonitriles: 2-chlorophenyl-succinic acid 82.5%, mp 159–160 °C (Lit.⁹ mp 161–162 °C); 2,4-dichloro phenyl-succinic acid 84%, mp 175 °C (Lit.¹⁰ 175 °C); 2-methylphenyl-succinic acid 83.2%, mp 183–184 °C (Lit.¹¹ mp 184–185 °C); 4-bromophenyl-succinic acid 84.6%, mp 211–212 °C (Lit.¹² 211–212 °C).

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