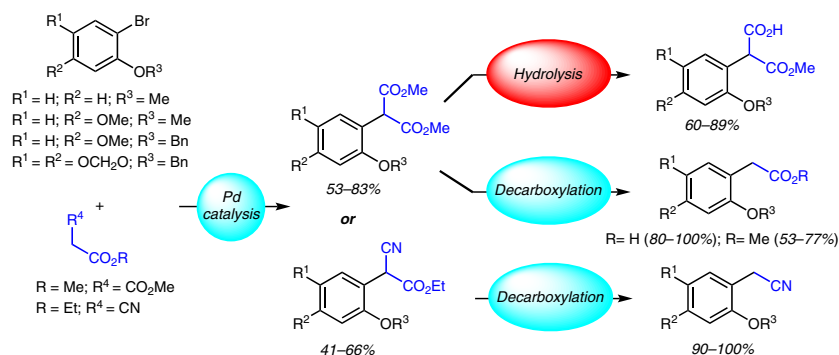


Palladium-Catalyzed α -Arylation of Dimethyl Malonate and Ethyl Cyanoacetate with *o*-Alkoxybromobenzenes for the Synthesis of Phenylacetic Acid, Esters and Phenylacetonitriles

José F. Cívicos^aPaulo R. R. Costa^{*a}Jorge L. O. Domingos^{*b}

^a Instituto de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, 21941-590, Rio de Janeiro, RJ, Brazil
prccosta2011@gmail.com

^b Dep. Química Orgânica, Instituto de Química, Centro de Tecnologia e Ciências, Universidade do Estado do Rio de Janeiro, 20550-900, Rio de Janeiro, RJ, Brazil



Received: 28.07.2017

Accepted after revision: 01.08.2017

Published online: 22.08.2017

DOI: 10.1055/s-0036-1588550; Art ID: so-2017-d0023-op

License terms:

Abstract α -Aryl malonate and α -aryl cyano acetate moieties are found in the structures of many bioactive compounds. They are also key intermediates for the synthesis of many compounds such as isoflavonoids. In this work, we synthesized these compounds, with different patterns of substitution, starting with the palladium-catalyzed reaction of *o*-alkoxybromoarenes with dimethyl malonate or ethyl cyanoacetate. Under the conditions applied, moderate to good yields of arylmalonate monoesters, phenylacetic esters or acids, and benzylnitrile derivatives were obtained.

Key words α -aryl malonates, α -aryl- α -cyanoacetates, α -arylation reactions, palladium catalysis, decarboxylation

α -Aryl malonates are found as substructures in bioactive compounds such as isoquinoline-1,3-dione, an HIV-1 integrase inhibitor,¹ and in barbiturates such as alphenal.² They can also be used as intermediates for the synthesis of 3-hydroxy-2-phenylpropanoic acid derivatives, through the reduction of one carboxylate group, to obtain tropic acid derivatives such as the tropane alkaloid scopolamine, an antiemetic drug.³ The decarboxylation reaction of α -aryl dicarbonyl compounds leads to α -phenylacetic acids, which are found for example in the structure of ibuprofen (anti-inflammatory activity),⁴ in UPF523 (active in the CNS),⁵ and in JSTX-3 (a neurotoxin found in spider venom).⁶ They have also been used in the total synthesis of isoflavonoids such as cajanol and daidzein.⁷ Phenylacetonitriles are used in the synthesis of isoflavonoids,⁸ and reduction of the nitrile

group gives rise to phenylethylamines.⁹ These are found in pharmaceuticals such as the antiarrhythmic verapamil and the anticancer drug anastrozole.¹⁰ The structures of these compounds are shown in Figure 1.

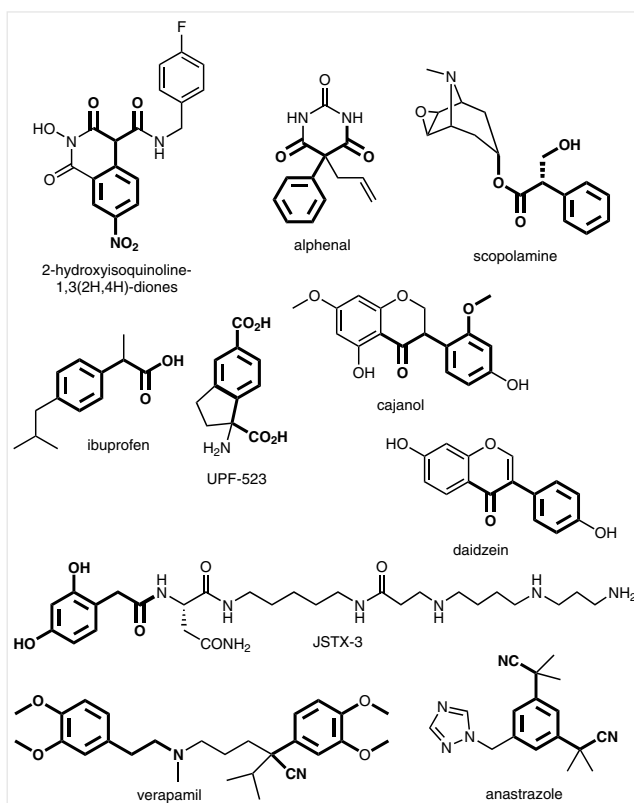


Figure 1 Bioactive compounds with α -arylmalonate, phenylacetic and benzylnitrile moieties

The alkylation of malonates is a useful approach to prepare intermediates in organic synthesis.¹¹ However, this approach is limited to primary and secondary alkyl halides and halobenzenes substituted with electron-withdrawing groups.¹² Our interest lies in the synthesis of oxygenated α -aryl carbonyl structures, which are used as precursors of isoflavonoid natural products, and these compounds cannot be prepared through the S_NAr approach.¹² In this paper, we report the synthesis of α -arylmalonates (**1**; $R^1 = R^2 = \text{alkyl}$) and α -arylcynoacetates **5** by α -arylation of malonates and cyanoacetates with aryl halides and their transformations into the desired compounds **2–6**, as shown in Figure 2.

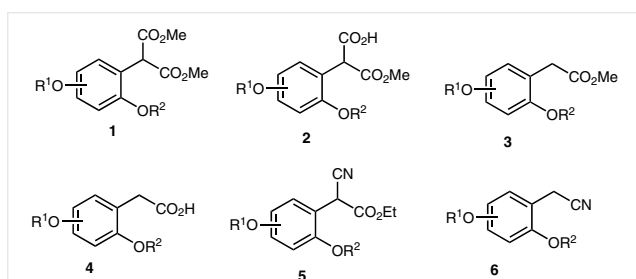
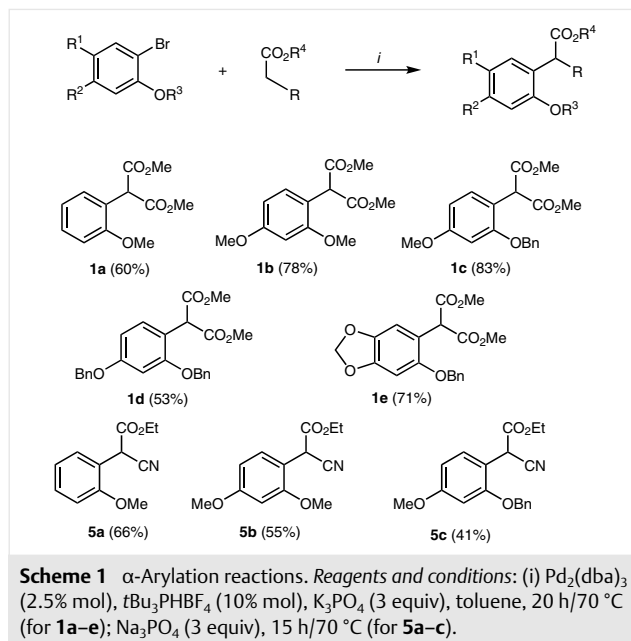


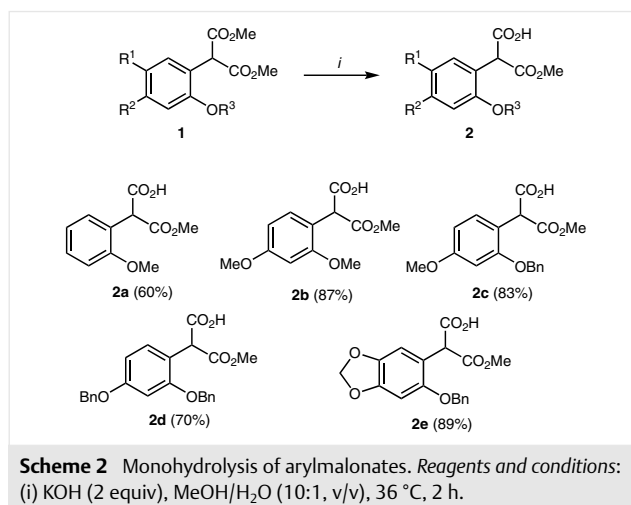
Figure 2 α -Arylmalonates, phenylacetic acid derivatives, and phenylacetonitriles synthesized in this work

The α -arylation reaction of carbonyl compounds has been studied since the early eighties, and more extensively and independently studied by Buchwald, Hartwig and Miura.¹³ Since then, various metal catalysts, ligands, and conditions have been developed for this reaction.¹⁴ Our approach was based on the α -arylation of malonates and cyanoacetates catalyzed by palladium. Although these reactions have been well studied, little attention has been given to the use of the more sterically hindered *o*-alkoxy-bromoarenes as the arylating agents, leading to compounds of type **1** and **5**. In addition, very few oxygenation patterns at the aromatic ring have been examined using these α -arylations.

The α -arylation step was optimized using the reaction of *o*-bromoanisole and dimethyl malonate or ethyl cyanoacetate (Scheme 1). After 20 h at 70 °C in toluene in the presence of $Pd_2(dba)_3$, the corresponding arylmalonate **1a** was obtained in 60% yield.¹⁵ Aryl-cyano acetate **5a** was prepared, under the same conditions (15 h), in 66% yield (Scheme 1).¹⁶ Both compounds were purified by flash column chromatography. Other *O*-protected bromoarenes were used under the same conditions and the α -arylmalonates **1b–e** and α -arylcynoacetates **5b,c** were obtained in yields ranging from 41 to 83% (Scheme 1). By using this methodology, we were able to prepare derivatives that were *O*-benzylated in the *ortho*-position (41–83%), which is a protecting group that can be removed under less drastic conditions than those used to remove methyl groups.¹⁷ This is the first time that compounds **1c**, **1d** and **5c** have been synthesized.

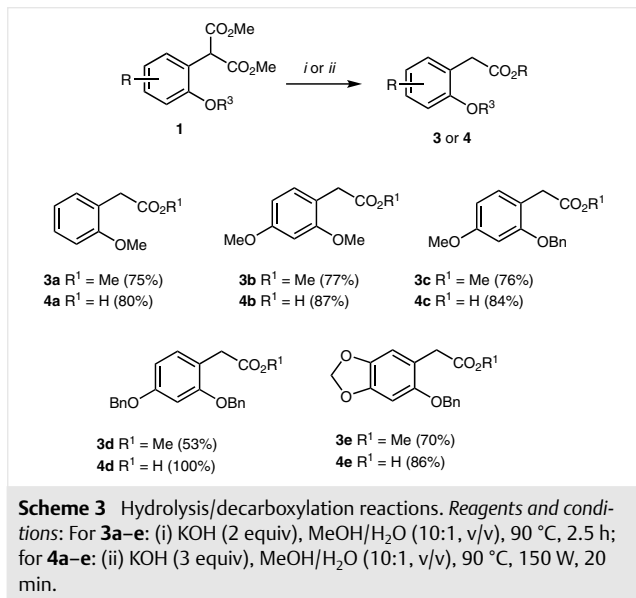


The monohydrolysis of arylmalonates has been described under basic or acidic conditions.¹⁸ In our hands, in the presence of KOH in THF– H_2O at 0 °C the arylmonomethyl malonate **2a** was obtained in low yield as a mixture with the unreacted arylmalonate and the decarboxylation product. The same outcome was observed when KOH/MeOH at 35 °C was used. However, the desired product **2a** was obtained in good yield when KOH was used in a mixture of MeOH/ H_2O (10:1, v/v), at 36 °C after 2 h (Scheme 2). Under the same conditions, arylmalonates **1b–e** were hydrolyzed to the corresponding aryl monomethyl malonates **2b–e** in yields ranging from 70 to 89%.

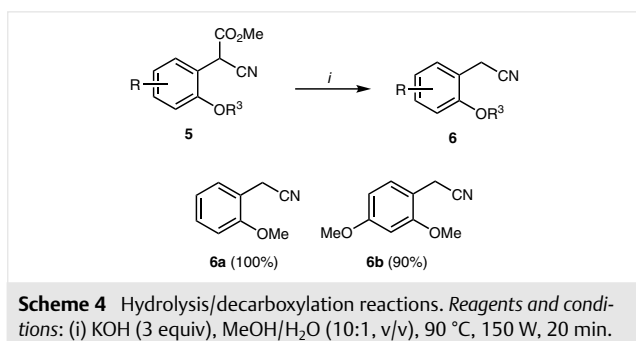


The one-pot hydrolysis followed by decarboxylation was successfully used to obtain, selectively, either arylacetate esters or the arylacetic acids, by changing the reaction

conditions. When the temperature was increased to 80 °C, methyl esters of arylacetates **3a–e** were obtained in moderate to high yields (Scheme 3). By increasing the amount of base from 2 to 3 equivalents and raising the temperature to 90 °C, under microwave irradiation, arylacetic acids **4a–e** were produced in high yields (80–100%) (Scheme 3).



The hydrolysis/decarboxylation of aryl-cyanoacetates **5** was performed under the same conditions and benzyl-nitriles **6a–b** were obtained in high yields (Scheme 4).



In conclusion, selected products from palladium-catalyzed α -arylation reactions of dimethyl malonates and ethyl cyanoacetates with bromoarenes were obtained in moderate to good yields. Some of these compounds, with the benzyl protecting group on the phenol functionality (**1c**, **1d**, **5c**),^{19,20} were obtained for the first time in this work.

The arylmalonates could be transformed directly into the phenylacetic acids or the corresponding methyl esters (**3a–e**, **4a–e**). Arylacetonitriles **6a–b** could also be prepared from arylcyanoacetates **5a–c** through one-pot hydrolysis followed by decarboxylation.

¹H NMR (400 MHz) and ¹³C NMR (75 MHz) spectra were obtained with a Varian Gemini-200 with CDCl₃ as solvent and TMS as internal standard unless otherwise stated. High-resolution mass spectra were obtained at 70 eV by electron impact with direct insertion on a Micromass MM12F. Analytical TLC was performed on Merck aluminum sheets with silica gel 60 F₂₅₄. For flash chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. Melting points were determined with a Fisatom 430 apparatus and are uncorrected.

Arylation of Dimethyl Malonate with Aryl Bromides; General Procedure

Dimethyl malonate (1 mmol), aryl bromide (1.1 mmol), [HP(tBu)₃]BF₄ (0.10 mmol), Pd₂(dba)₃ (0.025 mmol), and K₃PO₄ (3.0 mmol) were placed in a 25 mL round-bottomed flask with a magnetic stirrer. The flask was closed with a septum, the contents were placed under an argon atmosphere and anhydrous toluene (5.0 mL) was added. The heterogeneous mixture was stirred at 70 °C and the reaction was monitored by TLC. Upon complete consumption of the aryl bromide, the crude reaction mixture was filtered through a plug of Celite®, extracted with EtOAc (3 × 10 mL), washed with brine, dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (1:9, EtOAc/hexanes).

Dimethyl 2-(2-Methoxyphenyl)malonate (**1a**)²¹

Yield: 0.143 g (60%); yellow oil; *R*_f 0.16 (1:9, EtOAc/hexanes).

¹H NMR (CDCl₃, 400 MHz): δ = 7.36–7.28 (m, 2 H), 6.97 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.90 (d, *J* = 8.1 Hz, 1 H), 5.16 (s, 1 H), 3.82 (s, 3 H), 3.75 (s, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 169.0, 156.8, 129.5, 129.4, 121.5, 120.7, 110.7, 55.6, 52.7, 50.7.

Dimethyl 2-(2,4-Dimethoxyphenyl)malonate (**1b**)

Yield: 0.209 g (78%); brown solid; mp 60–62 °C; *R*_f 0.26 (1:9 EtOAc/hexanes).

¹H NMR (CDCl₃, 400 MHz): δ = 7.25 (d, *J* = 8.5 Hz, 1 H), 6.50 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.46 (d, *J* = 2.3 Hz, 1 H), 5.07 (s, 1 H), 3.79 (s, 6 H), 3.74 (s, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 169.3, 168.9, 160.8, 157.8, 130.1, 113.9, 104.5, 98.6, 55.6, 55.3, 52.7, 50.1, 48.9.

HRMS: *m/z* calcd for C₁₃H₁₆O₆: 268.0947; found: 268.0946.

Dimethyl 2-(2-(Benzyloxy)-4-methoxyphenyl)malonate (**1c**)

Yield: 0.285 g (83%); yellow solid; mp 61–63 °C; *R*_f 0.21 (1:9 EtOAc/hexanes).

¹H NMR (CDCl₃, 400 MHz): δ = 7.40–7.32 (m, 4 H), 7.30 (dd, *J* = 6.0, 2.7 Hz, 1 H), 7.25 (d, *J* = 8.1 Hz, 1 H), 6.51 (s, 1 H), 6.49 (d, *J* = 2.4 Hz, 1 H), 5.12 (s, 1 H), 5.02 (s, 2 H), 3.73 (s, 3 H), 3.68 (s, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 169.3, 160.8, 157.0, 136.6, 130.2, 128.64, 128.0, 127.3, 114.5, 105.0, 99.9, 70.4, 55.5, 52.8, 50.7.

HRMS: *m/z* calcd for C₁₉H₂₀O₆: 344.1260; found: 344.1259.

Dimethyl 2-(2,4-Bis(benzyloxy)phenyl)malonate (**1d**)

Yield: 0.223 g (53%); yellow solid; mp 103–105 °C; *R*_f 0.16 (1:9 EtOAc/hexanes).

¹H NMR (CDCl₃, 400 MHz): δ = 7.42–7.29 (m, 8 H), 7.24 (q, *J* = 4.5 Hz, 2 H), 7.14 (d, *J* = 8.1 Hz, 1 H), 6.60 (d, *J* = 2.2 Hz, 1 H), 6.58 (dd, *J* = 8.4, 2.3 Hz, 1 H), 5.12 (s, 1 H), 5.03 (s, 2 H), 5.01 (s, 2 H), 3.71 (s, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 169.4, 160.1, 157.1, 139.5, 136.8, 136.6, 128.8, 128.7, 128.2, 128.1, 127.8, 127.7, 127.3, 123.0, 106.0, 100.8, 70.4, 70.3, 52.83, 52.83, 50.8.

HRMS: m/z calcd for $\text{C}_{25}\text{H}_{24}\text{O}_6$: 420.1573; found: 420.1572.

Dimethyl 2-(6-(Benzyloxy)benzo[d][1,3]dioxol-5-yl)malonate (1e)

Yield: 0.254 g (71%); brown solid; mp 87–89 °C; R_f 0.10 (1:9 EtOAc/hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ = 7.39–7.29 (m, 5 H), 6.88 (s, 1 H), 6.57 (s, 1 H), 5.90 (s, 2 H), 5.16 (s, 1 H), 5.00 (s, 2 H), 3.71 (s, 6 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 169.0, 151.3, 148.1, 141.7, 136.6, 128.5, 128.1, 127.4, 127.2, 114.1, 109.2, 109.2, 101.4, 96.4, 96.3, 71.7, 52.8, 52.7, 50.7, 50.5.

HRMS: m/z calcd for $\text{C}_{19}\text{H}_{18}\text{O}_7$: 358.1053; found: 358.1052.

Arylation of Ethyl Cyanoacetate with Aryl Bromides; General Procedure

Ethyl cyanoacetate (1.1 mmol), aryl bromide (1.0 mmol), $[\text{HP}(\text{tBu})_3]\text{BF}_4$ (0.10 mmol), $\text{Pd}_2(\text{dba})_3$ (0.025 mmol, and Na_3PO_4 (3.0 mmol) were placed in a 25 mL round-bottom flask. The flask was closed with a septum, the contents were placed under an argon atmosphere and anhydrous toluene (5.0 mL) was added. The heterogeneous reaction mixture was stirred at 70 °C and monitored by TLC. Upon complete consumption of the aryl bromide, the crude reaction mixture was filtered through a plug of Celite®, extracted with EtOAc (3 × 10 mL), washed with brine, dried with anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (1:9 EtOAc/hexanes).

Ethyl 2-Cyano-2-(2-methoxyphenyl)acetate (5a)²²

Yield: 0.144 g (66%); yellow oil; R_f 0.12 (1:9 EtOAc/hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ = 7.36 (dd, J = 12.2, 4.5 Hz, 2 H), 6.99 (t, J = 7.5 Hz, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 5.03 (s, 1 H), 4.24 (dd, J = 7.2, 4.2 Hz, 2 H), 3.84 (s, 3 H), 1.27 (t, J = 7.1 Hz, 2 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 165.1, 156.4, 130.6, 129.3, 120.9, 119.0, 115.8, 111.0, 62.8, 55.6, 38.1, 24.5, 13.8.

Ethyl 2-Cyano-2-(2,4-dimethoxyphenyl)acetate (5b)²³

Yield: 0.137 g (55%); red brown oil; R_f 0.13 (1:9 EtOAc/hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ = 7.39 (ddd, J = 12.3, 6.6, 1.4 Hz, 2 H), 7.01 (td, J = 7.6, 0.9 Hz, 1 H), 6.94 (d, J = 8.2 Hz, 1 H), 5.03 (s, 1 H), 4.27 (qd, J = 7.1, 1.4 Hz, 2 H), 3.87 (s, 3 H), 1.32–1.27 (m, 3 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 165.5, 161.7, 157.5, 130.0, 116.2, 111.5, 104.9, 98.9, 62.9, 55.7, 55.5, 37.6, 14.0.

Ethyl 2-(2-(Benzyloxy)-4-methoxyphenyl)-2-cyanoacetate (5c)

Yield: 0.139 g (41%); yellow oil; R_f 0.14 (1:9 EtOAc/hexanes).

^1H NMR (CDCl_3 , 500 MHz): δ = 7.44–7.37 (m, 4 H), 7.33 (dd, J = 13.5, 7.8 Hz, 2 H), 6.54 (d, J = 6.9 Hz, 2 H), 5.08 (q, J = 11.5 Hz, 2 H), 4.95 (s, 1 H), 4.15 (q, J = 7.0 Hz, 2 H), 3.80 (s, 3 H), 1.19 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 165.5, 161.7, 156.6, 136.1, 130.3, 128.8, 128.8, 128.7, 128.7, 128.2, 127.4, 116.2, 111.8, 105.2, 100.1, 70.5, 62.9, 55.5, 38.0, 13.9.

HRMS: m/z calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4$: 325.1314; found: 325.1314.

Selective Monohydrolysis of Dimethyl Arylmalonates; General Procedure

Dimethyl arylmalonate (1.0 mmol) and KOH (2.0 mmol), followed by MeOH (1.0 mL) and H_2O (0.1 mL) were placed in a 25 mL round-bottom flask with a magnetic stirrer. The mixture was stirred at 36 °C for 2 h, then the reaction was quenched by the addition of water (5 mL). Unreacted ester was removed by EtOAc extraction (2 × 5 mL) and the carboxylic acid was obtained by acidification of the aqueous phase to pH 2 with 10% HCl, extracted with EtOAc (3 × 5 mL), washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated on a rotary evaporator.

3-Methoxy-2-(2-methoxyphenyl)-3-oxopropanoic Acid (2a)

Yield: 0.134 g (60%); brown oil.

^1H NMR (CDCl_3 , 500 MHz): δ = 7.22 (d, J = 7.5 Hz, 1 H), 7.20–7.15 (m, 1 H), 6.81 (t, J = 7.4 Hz, 1 H), 6.77 (d, J = 8.2 Hz, 1 H), 6.40 (s, 1 H), 4.90 (s, 1 H), 3.67 (s, 3 H), 3.57 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 173.1, 169.6, 156.8, 129.8, 129.8, 121.4, 120.8, 110.9, 55.7, 53.0, 50.9.

HRMS: m/z calcd for $\text{C}_{11}\text{H}_{12}\text{O}_5$: 224.0685; found: 224.0684.

2-(2,4-Dimethoxyphenyl)-3-methoxy-3-oxopropanoic Acid (2b)²⁴

Yield: 0.221 g (87%); pale-brown solid; mp 108–110 °C.

^1H NMR (CDCl_3 , 500 MHz): δ = 7.26 (d, J = 3.4 Hz, 1 H), 6.51 (dd, J = 8.5, 2.4 Hz, 1 H), 6.47 (d, J = 2.3 Hz, 1 H), 4.92 (s, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.76 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 173.8, 169.7, 160.9, 157.8, 130.4, 113.6, 104.7, 98.7, 55.7, 55.4, 52.9, 50.3.

2-(2-(Benzyloxy)-4-methoxyphenyl)-3-methoxy-3-oxopropanoic Acid (2c)

Yield: 0.274 g (83%); pale-brown solid; mp 165–167 °C.

^1H NMR (CDCl_3 , 500 MHz): δ = 8.98 (s, 1 H), 7.35 (q, J = 7.9 Hz, 4 H), 7.31–7.23 (m, 2 H), 6.62–6.38 (m, 2 H), 5.04 (s, 1 H), 5.03 (s, 2 H), 3.76 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 171.5, 171.0, 161.1, 156.9, 136.3, 131.0, 128.7, 128.2, 127.4, 114.4, 105.2, 100.2, 70.6, 55.5, 53.2, 50.7.

HRMS: m/z calcd for $\text{C}_{18}\text{H}_{18}\text{O}_6$: 330.1103; found: 330.1103.

2-(2,4-Bis(benzyloxy)phenyl)-3-methoxy-3-oxopropanoic Acid (2d)

Yield: 0.284 g (70%); pale-brown solid; mp 90–92 °C.

^1H NMR (CDCl_3 , 500 MHz): δ = 7.50–7.24 (m, 11 H), 6.69–6.54 (m, 2 H), 5.08–4.96 (m, 4 H), 4.87 (s, 1 H), 3.71 (s, 3 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 171.5, 170.3, 160.5, 156.8, 136.7, 136.3, 128.8, 128.7, 128.3, 128.2, 128.2, 127.8, 127.7, 127.5, 127.4, 114.8, 106.1, 100.9, 70.6, 70.4, 53.2, 50.6.

HRMS: m/z calcd for $\text{C}_{24}\text{H}_{22}\text{O}_6$: 406.1416; found: 406.1416.

2-(6-(Benzyloxy)benzo[d][1,3]dioxol-5-yl)-3-methoxy-3-oxopropanoic Acid (2e)

Yield: 0.306 g (89%); yellow oil.

^1H NMR (CDCl_3 , 400 MHz): δ = 8.51 (s, 1 H), 7.43–7.23 (m, 5 H), 6.88 (s, 1 H), 6.57 (s, 1 H), 5.91 (s, 2 H), 5.09 (s, 1 H), 5.00 (s, 2 H), 3.72 (s, 3 H).

^{13}C NMR (CDCl_3 , 125 MHz): $\delta = 172.5, 170.1, 151.4, 148.5, 141.8, 136.5, 128.8, 128.74, 128.68, 127.5, 127.4, 113.8, 109.8, 101.7, 96.4, 71.8, 53.1, 50.8$.

HRMS: m/z calcd for $\text{C}_{18}\text{H}_{16}\text{O}_7$: 344.0896; found: 344.0896.

Synthesis of α -Arylacetates; General Procedure

Dimethyl arylmalonate (1.0 mmol) and KOH (2.0 mmol), followed by MeOH (1.0 mL) and H_2O (0.1 mL) were placed in a 25 mL round-bottom flask with a magnetic stirrer. The mixture was stirred at 80 °C for 2.5 h, then the reaction was quenched by the addition of water (5 mL). The α -arylacetate was removed by EtOAc extraction (3×5 mL) and the carboxylic acid was obtained by acidification of the aqueous phase to pH 2 with 10% HCl, extracted with EtOAc (3×5 mL), washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated on a rotary evaporator.

Methyl 2-(2-Methoxyphenyl)acetate (3a)²⁵

Yield: 0.135 g (75%); yellow oil.

^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.27\text{--}7.22$ (m, 1 H), 7.16 (d, $J = 7.4$ Hz, 1 H), 6.90 (t, $J = 7.2$ Hz, 1 H), 6.86 (d, $J = 8.2$ Hz, 1 H), 3.80 (s, 3 H), 3.67 (s, 3 H), 3.62 (s, 2 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 172.41, 157.55, 130.92, 128.65, 123.03, 120.56, 110.52, 55.50, 51.98, 35.83$.

Methyl 2-(2,4-Dimethoxyphenyl)acetate (3b)²⁶

Yield: 0.162 g (77%); yellow oil.

^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.08$ (d, $J = 8.6$ Hz, 1 H), 6.48–6.41 (m, 2 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.56 (s, 2 H).

^{13}C NMR (CDCl_3 , 125 MHz): $\delta = 172.7, 160.3, 158.5, 131.2, 115.5, 104.1, 98.6, 55.5, 55.4, 51.9, 35.1$.

Methyl 2-(2-(Benzyloxy)-4-methoxyphenyl)acetate (3c)²⁷

Yield: 0.217 g (76%); brown oil.

^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.45\text{--}7.28$ (m, 5 H), 7.11 (d, $J = 8.2$ Hz, 1 H), 6.52 (d, $J = 2.2$ Hz, 1 H), 6.47 (dd, $J = 8.2, 2.3$ Hz, 1 H), 5.05 (s, 2 H), 3.78 (s, 3 H), 3.63 (s, 3 H), 3.61 (s, 2 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 172.75, 160.22, 157.54, 137.00, 131.36, 128.61, 127.93, 127.19, 115.92, 104.54, 99.91, 70.04, 55.50, 51.95, 35.55$.

Methyl 2-(2,4-Bis(benzyloxy)phenyl)acetate (3d)²⁸

Yield: 0.192 g (53%); yellow solid; mp 78–80 °C (lit. 74.5–75 °C).

^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.44\text{--}7.28$ (m, 10 H), 7.10 (d, $J = 8.3$ Hz, 1 H), 6.60 (d, $J = 2.2$ Hz, 1 H), 6.54 (dd, $J = 8.2, 2.3$ Hz, 1 H), 5.02 (d, $J = 4.0$ Hz, 4 H), 3.62 (s, 3 H), 3.61 (s, 2 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 172.7, 159.4, 157.5, 136.9, 136.9, 131.3, 128.7, 128.5, 128.1, 127.9, 127.6, 127.1, 116.1, 105.5, 100.6, 70.2, 69.9, 51.9, 35.5$.

Methyl 2-(6-(Benzyloxy)benzo[d][1,3]dioxol-5-yl)acetate (3e)

Yield: 0.210 g (70%); white solid; mp 105–107 °C.

^1H NMR (CDCl_3 , 500 MHz): $\delta = 7.47\text{--}7.23$ (m, 5 H), 6.70 (s, 1 H), 6.56 (s, 1 H), 5.89 (s, 2 H), 4.99 (s, 2 H), 3.63 (s, 3 H), 3.58 (s, 2 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 172.5, 151.6, 147.4, 141.3, 137.0, 128.6, 128.0, 127.2, 115.6, 110.7, 101.3, 96.3, 71.3, 52.0, 35.8$.

HRMS: m/z calcd for $\text{C}_{17}\text{H}_{16}\text{O}_5$: 300.0998; found: 300.0997.

Synthesis of α -Arylacetic Acids; General Procedure

A 10-mL MW vessel was charged with dimethyl arylmalonate (0.20 mmol) and KOH (0.60 mmol), followed by MeOH (2.0 mL) and H_2O (0.2 mL). The vessel was sealed with a pressure lock, and the mixture was heated under microwave irradiation (150 W) at 90 °C for 20 min in a CEM Discover MW reactor. After cooling to r.t., the reaction mixture was extracted with EtOAc (3×10 mL), and the α -arylacetic acid was obtained by acidification of the aqueous phase to pH 2 with 10% HCl, extracted with EtOAc (3×5 mL), washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated on a rotary evaporator.

2-(2-Methoxyphenyl)acetic Acid (4a)²⁹

Yield: 0.026 g (80%); pale-brown solid; mp 115–117 °C (lit. 119–121 °C).

^1H NMR (CDCl_3 , 500 MHz): $\delta = 7.29\text{--}7.24$ (m, 1 H), 7.18 (d, $J = 7.3$ Hz, 1 H), 6.92 (t, $J = 7.4$ Hz, 1 H), 6.88 (d, $J = 8.2$ Hz, 1 H), 3.82 (s, 3 H), 3.66 (s, 2 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 178.2, 157.6, 131.1, 129.0, 122.4, 120.7, 110.6, 55.6, 35.9$.

2-(2,4-Dimethoxyphenyl)acetic Acid (4b)³⁰

Yield: 0.034 g (87%); white solid; mp 90–92 °C (lit. 99–102 °C).

^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.08$ (d, $J = 7.8$ Hz, 1 H), 6.51–6.40 (m, 2 H), 3.80 (s, 6 H), 3.59 (s, 2 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 177.9, 160.5, 158.5, 131.4, 114.9, 104.3, 98.8, 55.6, 55.5, 35.2$.

2-(2-(Benzyloxy)-4-methoxyphenyl)acetic Acid (4c)³¹

Yield: 0.046 g (84%); pale-yellow solid; mp 115–117 °C.

^1H NMR (CDCl_3 , 500 MHz): $\delta = 7.41\text{--}7.28$ (m, 5 H), 7.11 (d, $J = 8.3$ Hz, 1 H), 6.52 (d, $J = 2.0$ Hz, 1 H), 6.48 (dd, $J = 8.2, 2.2$ Hz, 1 H), 5.05 (s, 2 H), 3.78 (s, 3 H), 3.64 (s, 2 H).

^{13}C NMR (CDCl_3 , 125 MHz): $\delta = 177.7, 160.3, 157.5, 136.9, 131.5, 128.7, 128.6, 127.9, 127.1, 127.1, 115.7, 104.6, 99.9, 70.1, 55.5, 35.7$.

2-(2,4-Bis(benzyloxy)phenyl)acetic Acid (4d)³²

Yield: 0.070 g (100%); pale-brown solid; mp 134–136 °C (lit. 137–137.5 °C).

^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.28\text{--}7.04$ (m, 1 H), 6.92 (d, $J = 7.2$ Hz, 1 H), 6.39 (s, 1 H), 6.28 (d, $J = 7.4$ Hz, 1 H), 4.77 (s, 1 H), 4.71 (s, 1 H), 3.38 (s, 1 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 177.4, 158.6, 157.2, 137.1, 131.4, 128.6, 128.5, 127.9, 127.8, 127.7, 127.2, 118.9, 105.7, 101.2, 70.1, 69.9, 29.8$.

2-(6-(Benzyloxy)benzo[d][1,3]dioxol-5-yl)acetic acid (4e)³³

Yield: 0.049 g (86%); brown solid; mp 119–122 °C.

^1H NMR (400 MHz, acetone- d_6): $\delta = 7.42$ (d, $J = 7.4$ Hz, 2 H), 7.34 (t, $J = 7.4$ Hz, 2 H), 7.29 (d, $J = 7.3$ Hz, 1 H), 6.71 (s, 1 H), 6.66 (s, 1 H), 5.86 (s, 2 H), 5.00 (s, 2 H), 3.54 (s, 2 H).

^{13}C NMR (CDCl_3 , 125 MHz): $\delta = 172.9, 152.6, 148.0, 142.0, 138.5, 129.5, 128.9, 128.8, 128.2, 127.9, 117.2, 111.5, 111.4, 102.0, 97.1, 71.7, 35.7$.

Synthesis of α -Arylacetonitriles; General Procedure

A 10-mL MW vessel was charged with ethyl arylcyanoacetate (0.20 mmol) and KOH (0.60 mmol), followed by MeOH (2.0 mL) and H_2O (0.2 mL). The vessel was sealed with a pressure lock, and the mixture

was heated under microwave irradiation (150 W) at 90 °C for 20 min in a CEM Discover MW reactor. After cooling to r.t., the reaction mixture was extracted with EtOAc (3 × 10 mL), and the α-arylacetonitrile was obtained by acidification of the aqueous phase to pH 2 with 10% HCl, extracted with EtOAc (3 × 5 mL), washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated on a rotary evaporator.

2-(2-Methoxyphenyl)acetonitrile (6a)³⁴

Yield: 0.029 g (100%); yellow oil.

¹H NMR (CDCl₃, 400 MHz): δ = 7.30 (dd, *J* = 15.9, 7.9 Hz, 2 H), 6.94 (t, *J* = 7.4 Hz, 1 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 3.82 (s, 3 H), 3.64 (s, 2 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 156.6, 129.4, 129.1, 120.6, 118.5, 118.0, 110.4, 55.3, 18.5.

2-(2,4-Dimethoxyphenyl)acetonitrile (6b)³⁵

Yield: 0.032 g (90%); white solid; mp 70–72 °C (lit. 76 °C).

¹H NMR (CDCl₃, 400 MHz): δ = 7.23 (d, *J* = 8.0 Hz, 1 H), 6.48 (d, *J* = 8.4 Hz, 2 H), 3.84 (s, 2 H), 3.81 (s, 2 H), 3.61 (s, 2 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 161.0, 157.8, 129.7, 118.5, 110.9, 104.3, 98.7, 55.6, 55.5, 18.2.

Funding Information

We thank the Brazilian agencies Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; BJT-2014), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1588550>.

References

- (1) Suchaud, V.; Bailly, F.; Lion, C.; Calmels, C.; Andréola, M. L.; Christ, F.; Debyser, Z.; Cotellet, P. *J. Med. Chem.* **2014**, *57*, 4640.
- (2) Martin, J. R.; Godel, T.; Hunkeler, W.; Jenck, F.; Moreau, J.-L.; Sleight, A. J.; Widmer, U. *Psychopharmacological Agents*, In *Kirk-Othmer Encyclopedia of Chemical Technology*; **2000**.
- (3) Nocquet, P.-A.; Opatz, T. *Eur. J. Org. Chem.* **2016**, 1156.
- (4) Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8547.
- (5) Costantino, G.; Pellicciari, R. *J. Med. Chem.* **1996**, *39*, 3998.
- (6) Barslund, A. F.; Poulsen, M. H.; Bach, T. B.; Lucas, S.; Kristensen, A. S.; Strømgaard, K. *J. Nat. Prod.* **2011**, *74*, 483.
- (7) (a) Goel, A.; Kumar, A.; Hemberger, Y.; Raghuvanshi, A.; Jeet, R.; Tiwari, G.; Knauer, M.; Kureel, J.; Singh, A. K.; Gautam, A.; Trivedi, R.; Singh, D.; Bringmann, G. *Org. Biomol. Chem.* **2012**, *10*, 9583. (b) Basha, G. M.; Yadav, S. K.; Srinuvasarao, R.; Prasanthi, S.; Ramu, T.; Mangarao, N.; Siddaiah, V. *Can. J. Chem.* **2013**, *91*, 763.
- (8) (a) Vasquez-Martinez, Y.; Ohri, R. V.; Kenyon, V.; Holman, T. R.; Sepúlveda-Boza, S. *Bioorg. Med. Chem.* **2007**, *15*, 7408. (b) Liu, J.; Yang, Z.; Luo, S.; Hao, Y.; Ren, J.; Su, Y.; Wang, W.; Li, R. *Synth. Commun.* **2014**, *44*, 3296.
- (9) Delorme, D.; Gregor, V.; Roberts, E.; Sun, E. WO 9967203, **1999**; *Chem. Abstr.* **1999**, *132*, 49802
- (10) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.
- (11) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 2212. (b) Hoogenboom, B. E.; Ihrig, P. J.; Langsjoen, A. N.; Linn, C. J.; Mulder, S. D. *J. Chem. Educ.* **1991**, *68*, 689.
- (12) (a) Yoshida, M.; Maeyama, Y.; Shishido, K. *Tetrahedron* **2012**, *68*, 9962. (b) Deng, P.; Lei, Y.; Zheng, X.; Li, S.; Wu, J.; Zhu, F.; Ong, B. S.; Zhang, Q. *Dyes Pigm.* **2016**, *125*, 407. (c) Yoshikawa, M.; Kamisaki, H.; Kunitomo, J.; Oki, H.; Kokubo, H.; Suzuki, A.; Ikemoto, T.; Nakashima, K.; Kamiguchi, N.; Harada, A.; Kimura, H.; Taniguchi, T. *Bioorg. Med. Chem.* **2015**, *23*, 7138.
- (13) (a) Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932. (b) Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, 506. (c) Sakamoto, T.; Kato, E.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1664. (d) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (e) Hartwig, J. F.; Hamann, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (f) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740.
- (14) (a) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.
- (15) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.
- (16) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641.
- (17) Fernandes, T. A.; Domingos, J. L. O.; Rocha, L. I. A.; Medeiros, S.; Nájera, C.; Costa, P. R. R. *Eur. J. Org. Chem.* **2014**, 1314.
- (18) (a) Malki, F.; Touati, A.; Rahal, S.; Moulay, S. *Asian J. Chem.* **2011**, *23*, 961. (b) Niwayama, S.; Cho, H.; Lin, C. *Tetrahedron Lett.* **2008**, *49*, 4434. (c) Niwayama, S. *J. Org. Chem.* **2000**, *65*, 5834.
- (19) Luo, M.; Liu, X.; Zu, Y.; Fu, Y.; Zhang, S.; Yao, L.; Efferth, T. *Chem.-Biol. Interact.* **2010**, *188*, 151.
- (20) Skouta, R.; Li, C. J. *Tetrahedron Lett.* **2007**, *48*, 8343.
- (21) Baciocchi, E.; Dell'Aira, D.; Ruzziconi, R. *Tetrahedron Lett.* **1986**, *27*, 2763.
- (22) Gandi, V. R.; Lu, Y. *Chem. Commun.* **2015**, 16188.
- (23) *Daikin Kogyo Co. Ltd.* Jpn. Kokai Tokkyo Koho JP 59051251 A 19840324, **1984**; *Chem. Abstr.* **1984**, *101*, 72461
- (24) Kamijo, T.; Tsubaki, A.; Yamaguchi, T.; Hirata, K. Jpn. Kokai Tokkyo Koho JP 03024047 A 19910201, **1991**; *Chem. Abstr.* **1991**, *115*, 49430
- (25) Jaita, S.; Phakhodee, W.; Pattarawarapan, M. *Synlett* **2015**, 26, 2006.
- (26) Al-Maharik, N.; Botting, N. P. *Tetrahedron* **2004**, *60*, 1637.
- (27) van Aardt, T. G.; van Rensburg, H.; Ferreira, D. *Tetrahedron* **2001**, *57*, 7113.
- (28) Chiba, T.; Akizawa, T.; Matsukawa, M.; Nishi, M.; Kawai, N.; Yoshioka, M. *Chem. Pharm. Bull.* **1996**, *44*, 972.
- (29) Morton, A. A.; Brachman, A. E. *J. Am. Chem. Soc.* **1954**, *76*, 2973.
- (30) Bernier, D.; Brückner, R. *Synthesis* **2007**, 2249.
- (31) Gray, T. I.; Pelter, A.; Ward, R. S. *Tetrahedron* **1979**, *35*, 2539.
- (32) Shih, T. L.; Ruiz-Sanchez, J.; Mrozik, H. *Tetrahedron Lett.* **1987**, *28*, 6015.
- (33) Pinard, E.; Gaudry, M.; Hénot, F.; Thellend, A. *Tetrahedron Lett.* **1998**, *39*, 2739.
- (34) Tseng, K.-N. T.; Rizzi, A. M.; Szymczak, N. K. *J. Am. Chem. Soc.* **2013**, *135*, 16352.
- (35) Neill, K. G. *J. Chem. Soc.* **1953**, 3454.