Flexible Entry into 3-Arylpent-2-enedioic Acids via Heck–Matsuda Arylation of Dimethyl Glutaconate with Arenediazonium Tosylates

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Received: 27.12.2018
Accepted after revision: 29.01.2019
Published online: 25.02.2019
DOI: 10.1055/s-0037-1611211; Art ID: ss-2018-z0867-op

Abstract For the preparation of compound libraries of Michael acceptors with tunable reactivity toward nucleophilic selenocysteine residue of thioredoxin reductase, a range of 3-arylglutaconic acids were required. The existing methods at the time had limited scope or involved several steps. A hitherto undescribed protocol for direct palladium(II) acetate-catalyzed arylation of glutaconic acid dimethyl ester at position 3 has been developed with a diverse set of arenediazonium tosylates followed by hydrolysis. This generally good-yielding two-step sequence displayed a propensity to deliver E-configured coupling products while compounds mostly featured in the literature were predominantly Z-configured. The possibility for preparing a library of 4-arylpyridine-2,6(1H,3H)-diones has been exemplified.

Key words arylpent-2-enedioic acids, glutaconic acid, diazonium tosylate, Pd-catalyzed coupling, regiospecificity, ester hydrolysis, imide synthesis

The potential of 3-arylpent-2-enedioic acids 1 (hereafter referred to as 3-aryglutaconic acids) as building blocks for synthetic chemistry is illustrated by the synthesis of benzothiophene-fused pyranones 2,1,2-benzodiazepinones 3,4 4-aryl-2-pyridones 4,4 and polysubstituted benzenes 5 (Scheme 1).

In our research program directed at developing selective inhibitors of selenocyteine enzyme thioredoxin reductase (TrxR),6 we envisioned 3-arylgutaconic imides 6 (possibly derived from (E)-1) to act as potential Michael acceptors for the reactive selenol of the Sec (selenocysteine) residue8 whose reactivity can be tuned so as not to affect the abundant group of enzymes where cysteine (Cys, i.e., the less reactive thiol) is crucial for catalytic activity. While examples of β-alkyl,β-aryl-substituted Michael acceptors similar to 6 reacting with thiol nucleophiles are known,9 the electrophilicity of 6 is likely to depend strongly on the nature of the Ar and R substituents. Thus, if these substituents are varied within a wide range, a situation where 6 does not react with thiols but continues to form adducts with selenols, can be identified (Scheme 2).
However, while the range of available primary amines (both aromatic and aliphatic) is distinctly wide, only seventeen 3-arylglutaconic acids 1 are registered in SciFinder as commercially available and those exclusively contain electron-rich aryl groups. The known methods for the preparation of 1 are limited, on the one hand, to Friedel–Crafts-type alkylation of electron-rich aromatics with keto acid 7 (generated, in turn, from oxidation–decarboxylation of citric acid under the reaction conditions). While this method is relatively straightforward (and is, therefore, reflected by the products in the commercial domain), its scope is clearly limited to the introduction of electron-rich aromatic groups. An alternative method, potentially allowing for greater diversity of aromatic groups in 1, involves conjugate addition of dimethyl malonate anion to 3-arylpipolic acid esters 8 followed by global hydrolysis and decarboxylation. Direct arylation of glutaconic acid, which would offer the level of flexibility varying the pendant aryl groups in 1 (and, ultimately, in 6), is lacking in the literature (Scheme 3).

In this work, we set off to investigate the Heck arylation of glutaconic acids with arenediazonium species, which has been amply exemplified for a number of β-substituted acrylates. Herein, we present the results of our study.

Arenediazonium salts were recognized by Matsuda and co-workers as exceptionally reactive partners for the Heck reaction. This finding not only linked the Matsuda–Heck reaction to a vaster (as compared to that of aryl halides and triflates) reagent space of commercially available anilines but also extended the reaction's scope to include partners previously considered poorly reactive or altogether unreactive (such as β-substituted acrylates, vide supra). In terms of selecting a suitable counterion for the arenediazonium cations, our efforts were guided by the recently reported convenient preparation and use of arenediazonium tosylates. Not only are they more stable toward chemical decomposition and explosion compared to conventionally used tetrafluoroborates, they are more cleanly prepared by diazotization of respective anilines in the presence of p-toluenesulfonic acid in a variety of polar organic solvents and even water. Hence preparing various arenediazonium tosylates 9 and testing them in the Heck–Matsuda arylation of glutaconic acid dimethyl ester became our primary objective.

Initial experiments involving preparation of 9 demonstrated that the arenediazonium salts were sufficiently pure to be used in the Heck–Matsuda arylation step without further purification. Thus, the syntheses of 1 were planned accordingly. Treatment of aniline with tert-butylnitrite in a 1:3 mixture of THF and glacial acetic acid led to the formation of the anticipated diazonium salt 9, which was isolated by filtration. Mild, ambient-temperature coupling of the latter with commercially available dimethyl glutarate (sold as a ~6.7:1 mixture of E- and Z-isomers according to 1H NMR analysis of the reagent received from the vendor) yielded, after brief fractionation on silica gel, the crude Heck–Matsuda coupling product 10. The latter was analyzed by 1H NMR spectroscopy to reveal its sufficiently high purity (so as not to necessitate further purification prior to subsequent hydrolysis), generally excellent yield (in the range 81–98%, except for 10k whose yield was estimated to be around 50%) and higher E/Z ratio (~10:1 throughout). Without further purification and characterization, esters 10 were subjected to alkaline hydrolysis to give pure 3-arylglutaconic acids 1 in moderate to excellent yields over two steps (from dimethyl glutarate) predominantly in the E-configured form (as assigned by NOESY spectroscopy, see the experimental section), except for products 1d, 1i, and 1o containing an o-substituted aryl group, in which the E/Z isomeric ratio was lower or even re-

![Scheme 3](image-url)
versed (Scheme 4, Table 1). It should be noted that attempted direct arylation of glutaric acid did not produce satisfactory results.

As it is evident from examples presented in Table 1, the arylation method reported herein displays a broad scope with respect to both electron-donating and electron-withdrawing groups in the aromatic portion and a good functional group tolerance with substituents such as carboxamide 1k, ketone 1n, and primary sulfonamide 1p remaining intact and not requiring protection. The fact that the arylation products 1 are obtained as a sole E-isomer (or are significantly enriched in it) is also notable as previously reported approaches have been reported to give significantly higher proportions of the Z-isomer.20,21

Having gained access to a range of E-configured 3-arylglutaric acids 1 that had not been featured in the literature, we were keen to apply some of them in the synthesis of 3-arylglutaric imides 6. Examples of direct 1 → 6 conversion involving direct thermal7 or mixed anhydride22 activation have been sporadically reported in the literature. We successfully achieved the synthesis of imides 6 in moderate yield from 3-arylglutaric acids 1b, 1l, and 1o, respectively, in refluxing toluene employing azotropic removal of water. Notably, attempts to use thermal activation7 of dicarboxylic acids 1b and 1o toward imide formation with respective amines at 180 °C under microwave irradiation in toluene resulted in a poor yield of target imides 6. The formation of the latter was accompanied by the accumulation of unwanted mixtures of decarboxylation products 7 and 8, as observed by 1H NMR spectroscopy. From this mixture, pure amides 7 and 7c were isolated chromatographically and characterized (Scheme 5). Attempted preparation of compounds 6 from dicarboxylic acids 1 using acetic anhydride22 was similarly ineffective.

In conclusion, we have described a novel, flexible approach to 3-arylglutaric acids via direct Heck–Matsuda arylation of dimethyl glutarate with arenediazonium tosylation salts catalyzed by Pd(II) acetate. The method proved convenient and practically simple while displaying a wider scope with respect to the aromatic groups, compared to the previously reported approaches, and a tendency to yield E-configured products. The latter can be employed directly in the preparation of 3-arylglutaric imides with independently variable elements of molecular periphery. These are intended as Michael acceptors with tunable reactivity as potential selective inhibitors of selenocysteine enzymes (such TrxR) not affecting the cell’s cysteinome.
NMR spectroscopic data were recorded on a 400 MHz (400.13 MHz for $^1H$ and 100.61 MHz for $^{13}C$) spectrometer in CDCl$_3$ and DMSO-$d_6$ and were referenced to residual solvent signals ($\delta_H = 7.26$ and 2.50; $\delta_C = 77.2$ and 39.5, respectively). Coupling constants, $J$ are reported in Hz. Mass spectra were recorded with a HRMS-ESI-qTOF spectrometer (electrospray ionization mode). Column chromatography was performed on silica gel 60 (230–400 mesh). Melting points were measured with SMP 50 and are not corrected. For TLC analysis UV254 silica gel coated plates were used (Merck). Dimethyl glutarate ($E/Z$ mixture) was purchased from Fluka and used as received. Microwave-assisted reactions were performed using Biotage Initiator+ reactor. ESI-HRMS analyses were performed with a Q-TOF instrument (Micromass, Manchester, UK). Yields are stated as isolated yields. 2D NMR spectra (HMQC, HMBC) were recorded on a Bruker $400$ MHz spectrometer.

3-Arylglutaric Acids 1a–p; General Procedure

To a stirred ice-cooled solution or suspension of the respective aniline (15.0 mmol) in THF (5 mL) was added a solution of $p$-TsOH$\cdot$H$_2$O (3.04 g, 16.0 mmol) in glacial AcOH (15 mL). The resulting suspension was stirred for 5 min whereupon $t$-BuONO (2.44 mL, 22.5 mmol) was added. The mixture was stirred at 0 °C for 20 min, the ice bath was removed, and the stirring was continued for 50 min at r.t. The resulting solution was poured into Et$_2$O (150 mL) and the mixture was stirred for 5 min whereupon the precipitate of 9 crystalline in all cases except for 9d was separated, washed with Et$_2$O, and dried in vacuo. The crude aryl diazonium tosylate thus obtained was dissolved or suspended in MeOH (30 mL). Dimethyl glutarate (1.45 mL, 10.0 mmol) and Pd(OAc)$_2$ (112 mg, 0.5 mmol) were successively added suspended in MeOH (30 mL). Dimethyl glutarate ($E/Z$ mixture) was purchased from Fluka and used as received. Microwave-assisted reactions were performed using Biotage Initiator+ reactor.

The oil-like precipitates (H, 11–p) were extracted with EtOAc (2 × 30 mL), dried (Na$_2$SO$_4$), filtered, and evaporated to dryness to give analytically pure title compounds.

(E)-3-Phenylpent-2-enedioic Acid (1a)

Yield: 1.48 g (58%); white solid; mp 161.5–163.0 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 12.35$ (br s, 2 H), 7.59–7.50 (m, 2 H), 7.46–7.35 (m, 3 H), 6.23 (s, 1 H, HC=), 4.13 (s, 2 H, CH$_2$).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 171.0, 167.9, 150.0, 140.7, 129.6, 129.1, 126.9, 120.3, 36.3$.

HRMS: $[M – H]^- \text{calcld for } C_{11}H_{9}O_4$: 205.0502; found: 205.0502.

(E)-3-(4-Methoxyphenyl)pent-2-enedioic Acid (1b)

Yield: 2.33 g (85%); pale yellow solid; mp 174.5–176.1 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 12.27$ (br s, 2 H), 7.51 (d, $J = 8.8$ Hz, 2 H), 6.97 (d, $J = 8.8$ Hz, 2 H), 6.19 (s, 1 H, HC=), 4.12 (s, 2 H, CH$_2$), 3.79 (s, 3 H, OCH$_3$).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 171.0, 167.9, 160.6, 150.4, 132.7, 128.3, 118.1, 114.5, 55.7, 36.0$.

HRMS: $[M – H]^- \text{calcld for } C_{12}H_{10}O_5$: 235.0612; found: 235.0609.

(E)-3-(4-Trifluoromethyl)phenylpent-2-enedioic Acid (1c)

Yield: 2.50 g (85%); pale yellow solid; mp 220–222 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 12.51$ (br s, 2 H), 7.83–7.69 (m, 4 H), 6.31 (s, 1 H, HC=), 4.15 (s, 2 H, CH$_2$).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 171.6, 167.4, 149.3, 144.9, 129.6$.


(E/Z)-3-(2-Methoxyphenyl)pent-2-enedioic Acid (1d)

Yield: 1.48 g (46%); $E/Z = 3:1$; beige solid.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ (major, $E$) = 12.19 (br s, 2 H), 7.35 (ddd, $J = 8.3, 7.4, 1.8$ Hz, 1 H), 7.19 (dd, $J = 7.5, 1.7$ Hz, 1 H), 7.04 (dd, $J = 8.4, 0.9$ Hz, 1 H), 6.96 (td, $J = 7.5, 1.0$ Hz, 1 H), 5.92 (s, 1 H, HC=), 3.95 (s, 2 H, CH$_2$), 3.78 (s, 3 H, OCH$_3$); $\delta$ (minor, $Z = 7.25$ (ddd, $J = 8.3, 7.4, 1.8$ Hz, 1 H), 7.02 (dd, $J = 7.6, 1.7$ Hz, 1 H), 6.98 (dd, $J = 8.3, 0.9$ Hz, 1 H), 6.87 (td, $J = 7.4, 1.0$ Hz, 1 H), 6.00 (t, $J = 1.0$ Hz, 1 H, HC=), 3.73 (s, 3 H, OCH$_3$), 3.36 (d, $J = 1.0$ Hz, 2 H, CH$_2$).
1H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) (major, E) = 171.3, 167.5, 156.6, 151.1, 130.8, 130.5, 130.0, 122.6, 121.0, 112.0, 55.9, 37.7; \(\delta\) (minor, Z) = 171.5, 166.7, 156.0, 147.7, 129.8, 129.4, 128.4, 123.2, 120.2, 111.5, 55.8, 44.1.

HRMS m/z [M – H]– calcd for C\(_{12}\)H\(_{11}\)O\(_5\): 235.0601; found: 235.0598.

(Y(E,Z)-3-(4-Fluorophenyl)pent-2-enedioic Acid (1e))

Yield: 1.13 g (45%); yellow solid; mp 167.3–169.9 °C.

HRMS: [M – H]– calcd for C\(_{12}\)H\(_{11}\)O\(_5\): 171.1, 167.3, 147.3, 147.9, 147.3, 128.4, 124.1, 123.4, 36.2.

(Y(E,Z)-3-(3-Chlorophenyl)pent-2-enedioic Acid (1f))

Yield: 1.45 g (55%); pale beige solid; mp 206.8–208.4 °C (dec).


(E,Z)-3-(3,5-Bis(trifluoromethyl)phenyl)pent-2-enedioic Acid (1m)

Yield: 2.02 g (32%); E/Z = 10:1; colorless solid; mp 158.6–159.6 °C (dec.).

HRMS: [M – H]– calcd for C\(_{13}\)H\(_{11}\)F\(_6\)O\(_4\): 339.1602; found: 339.1600.

(E)-3-(4-Fluorophenyl)pent-2-enedioic Acid (1k)

Yield: 1.02 g (32%); E/Z = 10:1; colorless solid; mp 158.6–159.6 °C (dec.).

HRMS: [M – H]– calcd for C\(_{12}\)H\(_{11}\)O\(_5\): 235.0601; found: 235.0598.

(E)-3-(4-(Piperidine-1-carbonyl)phenyl)pent-2-enedioic Acid (1I)

Yield: 3.06 g (90%); pale beige solid; mp 204.0–206.8 °C (dec.).

HRMS: [M – H]– calcd for C\(_{21}\)H\(_{23}\)O\(_4\): 341.0179; found: 341.0176.

(E,Z)-3-(4-(Trifluoromethyl)phenyl)pent-2-enedioic Acid (1H)

Yield: 2.12 g (73%); E/Z = 12:1; colorless solid; mp 152.7–154.2 °C.

HRMS: [M – H]– calcd for C\(_{13}\)H\(_{11}\)F\(_3\)O\(_4\): 316.1176; found: 316.1174; A–G.

(E,Z)-3-(4-(3r,5r,7r)-Adamantan-1-yl)phenyl)pent-2-enedioic Acid

Yield: 1.48 g (66%); pale yellow solid; mp 150.9–151.7 °C.

HRMS: [M – H]– calcd for C\(_{14}\)H\(_{15}\)N\(_3\): 263.0550; found: 263.0559.
To a solution of amine (1.1 mmol) in toluene (30 mL) was added diacetoxy-1-(furan-2-ylmethyl)-3-(4-methoxyphenyl)but-2-enamide (6a) Yield: 27 mg (47%); colorless solid; mp 275.2–280.0 °C (dec.).

1H NMR (400 MHz, CDCl3): δ = 6.72–7.42 (m, 2 H), 7.34 (dd, J = 2.0, 0.9 Hz, 1 H), 7.10–6.77 (m, 2 H), 6.58 (l, J = 1.5 Hz, 1 H), 6.37 (dd, J = 3.2, 0.8 Hz, 1 H), 6.32 (dd, J = 3.3, 1.8 Hz, 1 H), 5.11 (s, 2 H), 3.87 (s, 3 H), 3.82 (d, J = 1.4 Hz, 2 H).

13C NMR (101 MHz, CDCl3): δ = 169.5, 165.2, 161.9, 150.2, 148.5, 142.0, 127.4, 127.2, 114.7, 114.6, 110.4, 109.0, 55.3, 36.0, 35.3.

HRMS: m/z [M – H]– calcd for C18H28NO: 274.2165; found: 274.2180.

1-Isopentyl-4-mesitylpyridine-2,6(1H,3H)-dione (6b)

Yield: 197 mg (45%); light yellow foam.

1H NMR (400 MHz, CDCl3): δ = 7.70–7.38 (m, 6 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.62 (d, J = 1.5 Hz, 1 H), 5.04 (s, 2 H), 3.82 (d, J = 1.6 Hz, 2 H), 3.80 (s, 3 H), 2.14 (pent, J = 3.1 Hz, 3 H), 1.94 (d, J = 2.9 Hz, 6 H), 1.87–1.74 (m, 6 H).

13C NMR (101 MHz, CDCl3): δ = 169.9, 165.7, 159.0, 154.7, 148.9, 132.1, 130.7, 129.3, 125.7, 125.6, 116.2, 113.7, 55.2, 42.9, 41.9, 36.7, 36.5, 36.1, 28.8.


1-Isopentyl-3-(4-methoxyphenyl)pyridine-2,6(1H,3H)-dione (6c)

Yield: 146 mg (40%); beige foam.

1H NMR (400 MHz, CDCl3): δ = 6.93 (s, 2 H), 6.10 (t, J = 1.7 Hz, 1 H), 4.00–3.76 (m, 2 H), 3.48 (d, J = 1.7 Hz, 2 H), 2.32 (s, 3 H), 2.20 (s, 6 H), 1.76–1.58 (m, 1 H), 1.58–1.43 (m, 2 H), 1.00 (d, J = 6.6 Hz, 6 H).

13C NMR (101 MHz, CDCl3): δ = 170.0, 165.2, 152.9, 138.2, 133.9, 133.8, 128.6, 122.0, 38.5, 38.1, 36.7, 26.4, 24.5, 21.0, 19.6.


Microwave-Assisted Reaction of Dicarboxylic Acids 1b and 1o with Amines

A mixture dicarboxylic acid 1b or 1o (1 mmol) and amine (see below) in toluene (30 mL) was heated at 180 °C for 1 h in a microwave reactor. Upon cooling to rt, the reaction mixture was concentrated and subjected to column chromatography on silica gel eluting with CHCl3.

Reaction of 1b with 2-furylmethanamine afforded 37 mg (12%) of 6a and 77 mg (28%) of compounds 7a and 8a as 6:4:1 mixture (by 1H NMR analysis). The latter was further purified by column chromatography using CHCl3 as eluent to give 44 mg (16%) of pure 7a.

(E)-N-(Furan-2-ylmethyl)-3-(4-methoxyphenyl)but-2-enoic Acid (1p)

Yield: 44 mg (16%); light yellow foam.

1H NMR (400 MHz, CDCl3): δ = 7.47–7.34 (m, 3 H), 7.02–6.61 (m, 2 H), 6.34 (dd, J = 3.3, 1.9 Hz, 1 H), 6.27 (dd, J = 3.2, 0.8 Hz, 1 H), 6.00 (q, J = 1.3 Hz, 1 H), 5.97 (br s, 1 H), 4.53 (d, J = 5.6 Hz, 2 H), 3.83 (s, 3 H), 2.57 (d, J = 1.2 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 166.7, 160.01, 151.6, 151.0, 142.1, 134.8, 127.4, 117.7, 113.8, 110.5, 107.4, 55.3, 36.3, 17.5.

For NOESY spectrum, see Supporting Information.


Reaction of 1o with isopentylamine afforded 45 mg (15%) of 6c and 108 mg (40%) of compounds 7c and 8c as 5:7:1 mixture (by 1H NMR analysis). The latter was further purified by column chromatography using CHCl3 as eluent to give 62 mg (23%) of pure 7c.

(E)-N-Isopentyl-3-mesitylbut-2-enoic Acid (7c)

Yield: 62 mg (23%); light brown oil.

1H NMR (400 MHz, CDCl3): δ = 6.87 (s, 2 H), 5.41 (s, 1 H), 3.53–3.22 (m, 2 H), 2.30 (d, J = 1.5 Hz, 3 H), 2.29 (s, 3 H), 2.20 (s, 6 H), 1.74–1.57 (m, 1 H), 1.52–1.36 (m, 2 H), 0.96 (d, J = 6.6 Hz, 6 H).

13C NMR (101 MHz, CDCl3): δ = 166.5, 153.1, 149.0, 136.3, 133.9, 128.2, 121.8, 38.6, 37.7, 26.0, 22.5, 20.9, 19.6, 19.5.

For NOESY spectrum, see Supporting Information.


Funding Information

This work was supported by the Russian Foundation for Basic Research (project grant 18-515-76001) under «ERA.Net RUS plus» joint program grant RUS_ST2017-309 and State Education Development Agency of the Republic of Latvia (‘THIOREDIN’).

Acknowledgment

Research Centre for Magnetic Resonance and the Center for Chemical Analysis and Materials Research of Saint Petersburg State University Research Park for obtaining the analytical data.
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611211. Copies of 1H and 13C NMR spectra are provided.

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