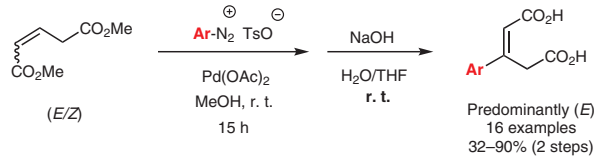
Synthesis D. Dar'in et al. Paper

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

Dmitry Dar'in[a]
Grigory Kantin[a]
Olga Bakulina[a]
Raivis Žalubovskis[b]
Mikhail Krasavin *[a,1]

[a] Saint Petersburg State University, Saint Petersburg 199034, Russian Federation
m.krasavin@spbu.ru
[b] Latvian Institute of Organic Synthesis, Riga 1006, Latvia



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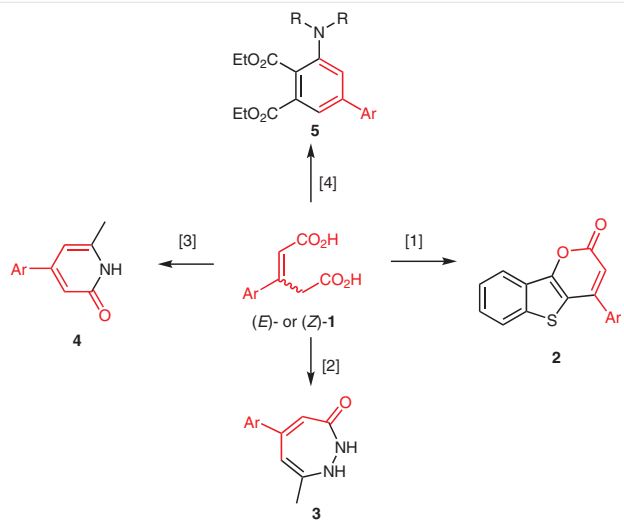
Abstract For the preparation of compound libraries of Michael acceptors with tunable reactivity toward nuclophilic selenocysteine residue of thioredoxin reductase, a range of 3-arylglutaconic acids were required. The existing methods at the time had limited scope or involved several steps. A hitherto 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(1*H*,3*H*)-diones has been exemplified.

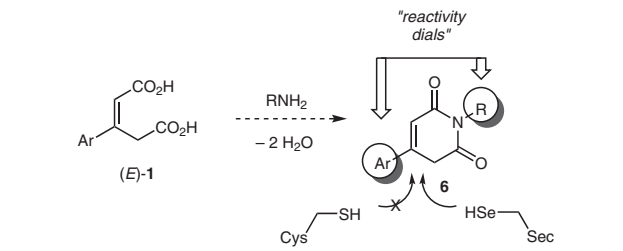
Key words arylpent-2-enedioic acids, glutaconic acid, diazonium tosylate, Pd-catalyzed coupling, regiospecificity, ester hydrolysis, imide synthesis



Scheme 1 Illustrative uses of 3-arylglutaconic acids as building blocks in organic synthesis

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

In our research program directed at developing selective inhibitors of selenocycteine enzyme thioredoxin reductase (TrxR),[6] we envisioned 3-arylglutaconic imides **6** (possibly derived from (*E*)-**1**[7]) to act as potential Michael acceptors for the reactive selenol of the Sec (selenocysteine) residue[8] 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).



Scheme 2 3-Arylglutaconic imides **6** as Michael acceptors with tunable reactivity

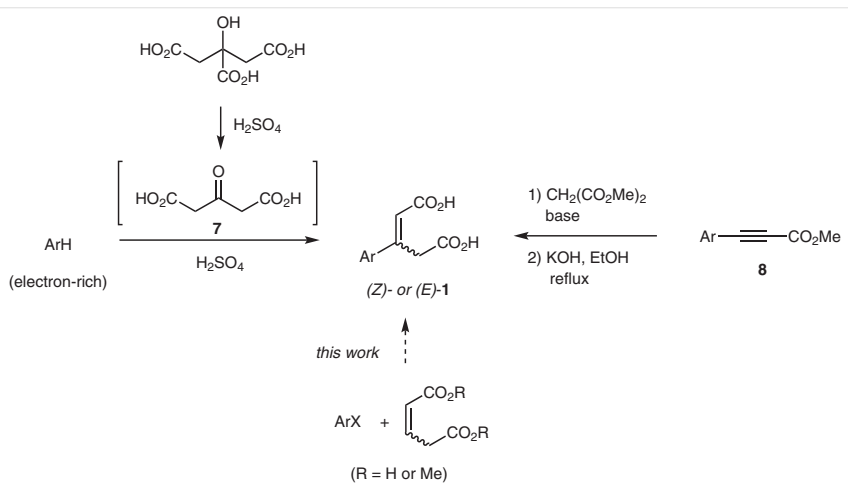
However, while the range of available primary amines (both aromatic and aliphatic) is distinctly wide, only seventeen 3-arylglutaconic acids **1** are registered in SciFinder as commercially available[10] and those exclusively contain electron-rich aryl groups. The known methods for the preparation of **1** are limited, on the one hand, to Fridel–Crafts-type alkylation of electron-rich aromatics with keto acid **7** (generated, in turn, from oxidation–decarboxylation of citric acid under the reaction conditions).[11] 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,[12] potentially allowing for greater diversity of aromatic groups in **1**, involves conjugate addition of dimethyl malonate anion to 3-arylpropiolic 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[13] arylation of glutaconic acids with arenediazonium species,[14] which has been amply exemplified for a number of β-substituted acrylates.[15] Herein, we present the results of our study.

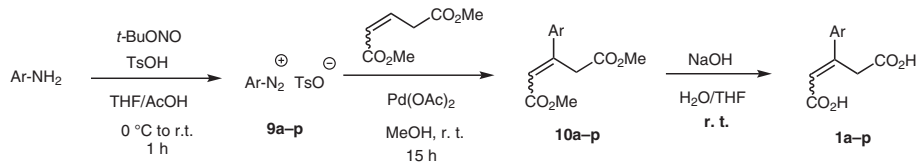
Arenediazonium salts were recognized by Matsuda and co-workers as exceptionally reactive partners for the Heck reaction.[16] This finding not only linked the Matsuda–Heck reaction to a vaster (compared to that of aryl halides and triflates) reagent space of commercially available anilines but also extended the reaction's scope to include partners previously considered poorly reactive or altogether unreactive (such as β-substituted acrylates, vide supra).[17]

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.[18] 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.[19] 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*-butyl nitrite 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 glutaconate (sold as a ~6.7:1 mixture of *E*- and *Z*-isomers according to ^{1}H 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 ^{1}H 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 glutaconate) 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 Two approaches to 3-arylglutaconic acids **1** featured in the literature at the onset of this study, and the direct arylation approach investigated in this work



Scheme 4 Preparation of 3-arylglutaconic acids **1a–p**

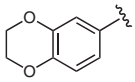
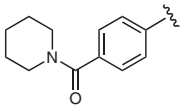
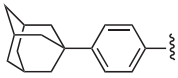
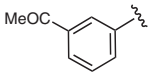
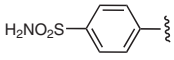
versed (Scheme 4, Table 1). It should be noted that attempted direct arylation of glutaconic acid did not produce satisfactory results.

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]

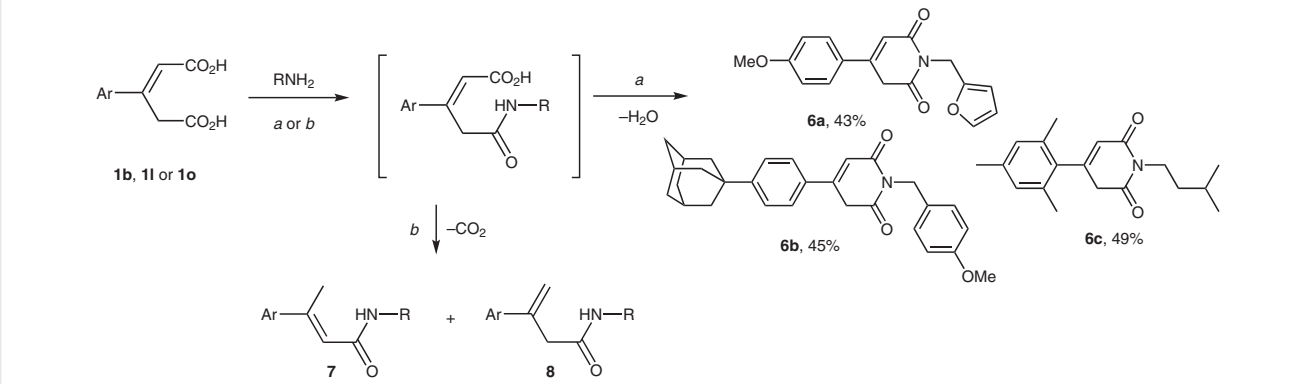
Having gained access to a range of *E*-configured 3-arylglutaconic acids **1** that had not been featured in the literature, we were keen to apply some of them in the synthesis of 3-arylglutaconic imides **6**. Examples of direct **1** → **6** conversion involving direct thermal[7] or mixed anhydride[22] activation have been sporadically reported in the literature. We successfully achieved the synthesis of imides **6a–c** in moderate yield from 3-arylglutaconic acids **1b**, **1l**, and **1o**, respectively, in refluxing toluene employing azeotropic removal of water. Notably, attempts to use thermal activation[7] 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 **6a**(**c**). The formation of the latter was accompanied by the accumulation of unwanted mixtures of decarboxylation products **7a**(**c**) and **8a**(**c**), as observed by ^{1}H NMR spectroscopy. From this mixture, pure amides **7a** and **7c** were isolated chromatographically and characterized (Scheme 5). Attempted preparation of compounds **6** from diacarboxylic acids **1** using acetic anhydride[22] was similarly ineffective.

In conclusion, we have described a novel, flexible approach to 3-arylglutaconic acids via direct Heck–Matsuda arylation of dimethyl glutaconate with arenediazonium tosylate 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-arylglutaconic 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.

Table 1 3-Arylglutaconic Acids **1a–p** Synthesized in this Work

Compound	Ar	Yield (%)[a]	*E*/*Z* ratio
1a	Ph	58[b]	*E* only
1b	4-MeOC$_6$H$_4$	58[b]	*E* only
1c	4-F$_3$CC$_6$H$_4$	85[b]	*E* only
1d	2-MeOC$_6$H$_4$	46[b]	3:1
1e	4-FC$_6$H$_4$	66[b]	*E* only
1f	4-O$_2$NC$_6$H$_4$	45[b]	*E* only
1g	3-O$_2$NC$_6$H$_4$	55[b]	*E* only
1h	4-F$_3$COC$_6$H$_4$	73[b]	12:1
1i	2-ClC$_6$H$_4$	63[c]	1:1.3
1j		55[b]	*E* only
1k		32[b]	10:1
1l		90[c]	20:1
1m	3,5-(F$_3$C)$_2$C$_6$H$_3$	63[c]	20:1
1n		57[c]	>20:1
1o	mesityl	89[c]	1:1.3
1p		82[c]	5:1[d]

[a] Isolated yields over 2 steps (from dimethyl glutaconate).
[b] Analytically pure product obtained as a precipitate on acidification of the alkaline solution after hydrolysis of **10**.
[c] Analytically pure product obtained as a precipitate on acidification of the alkaline solution after hydrolysis of **10** followed by extraction.
[d] Pure *E*-isomer was obtained in 41% yield by crystallization from MeCN.



Scheme 5 Attempted (*a*) and successful (*b*) preparation of 3-arylglutaconic imides **6a–c**. *Reagents and conditions*: a) toluene, reflux, Dean–Stark trap, 16 h; b) MW, 180 °C, toluene 1 h.

NMR spectroscopic data were recorded on a 400 MHz (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) spectrometer in $CDCl_3$ and DMSO-d_6 and were referenced to residual solvent signals (δ_H = 7.26 and 2.50; δ_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 glutaconate (*E*/*Z* mixture) was purchased from Fluka and used as received. Microwave-assisted reactions were performed using Biotage Initiator+ reactor.

3-Arylglutaconic 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·H_2O (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 in one portion. 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_2O (150 mL) and the mixture was stirred for 30 min. The precipitate of **9** (crystalline in all cases except for **9d**) was separated, washed with Et_2O, and dried in vacuo.

The crude aryl diazonium tosylate **9** thus obtained was dissolved or suspended in MeOH (30 mL). Dimethyl glutaconate (1.45 mL, 10.0 mmol) and $Pd(OAc)_2$ (112 mg, 0.5 mmol) were successively added while stirring. After stirring at r.t. for 15 h, the mixture was concentrated under reduced pressure and partitioned between CH_2Cl_2 (40 mL) and H_2O (25 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was briefly fractionated on SiO_2 using CH_2Cl_2 or CH_2Cl_2–acetone (5:1) as eluent. Fractions containing arylation product were pooled and concentrated to give compound **10** of at least 90% purity (according to ^{1}H NMR analysis). It was used in the next step without further purification.

To a stirred solution of the above compound **10** in THF (10 mL) was added a solution of NaOH (1.0 g, 25.0 mmol) (or an equiv amount of LiOH in case of **10k**) in H_2O (15 mL) and the mixture was stirred at r.t. for 16 h (or 5 h in case of **10k**). The resulting mixture was washed with Et_2O (30 mL) and the organic layer was extracted with H_2O (5 mL). The combined aqueous phases were acidified with concd HCl to pH ~2 and stirred in an ice bath for 1 h. The solid precipitates formed were collected by filtration, washed with ice-cold H_2O, and air-dried.

The oil-like precipitates (**1i**, **1l–p**) were extracted with EtOAc (2 × 30 mL), dried (Na_2SO_4), filtered, and evaporated to dryness to give analytically pure title compounds.

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

Yield: 1.40 g (58%); white solid; mp 141.5–144.1 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 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): δ = 171.7, 167.7, 150.8, 140.7, 129.6, 129.1, 126.9, 120.3, 36.3.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{11}H_9O_4^-$: 205.0506; found: 205.0502.

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

Yield: 1.48 g (58%); beige solid; mp 161.7–163.0 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 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): δ = 171.9, 167.9, 160.6, 150.4, 132.7, 128.3, 118.1, 114.5, 55.7, 36.0.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{12}H_{11}O_5^-$: 235.0612; found: 235.0609.

(*E*)-3-[4-(Trifluoromethyl)phenyl]pent-2-enedioic Acid (1c)

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

^{1}H NMR (400 MHz, DMSO-d_6): δ = 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): δ = 171.6, 167.4, 149.3, 144.9, 129.6 (q, *J* = 32.0 Hz), 127.8, 125.9 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 271.4 Hz), 122.4, 36.3.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{12}H_8F_3O_4^-$: 273.0369; found: 273.0367.

(*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): δ (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); δ (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).

^{13}C NMR (100 MHz, DMSO-d_6): δ (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; δ (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.

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

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

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.37 (br s, 2 H), 7.64–7.54 (m, 2 H), 7.24 (t, *J* = 8.8 Hz, 2 H), 6.22 (s, 1 H, HC=), 4.12 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7, 167.6, 163.1 (d, *J* = 246.8 Hz), 149.8, 137.1 (d, *J* = 3.2 Hz), 129.2 (d, *J* = 8.4 Hz), 120.3, 116.0, 115.8, 36.3.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{11}H_8FO_4^-$: 223.0401; found: 223.0401.

(*E*)-3-(4-Nitrophenyl)pent-2-enedioic Acid (1f)

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

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.57 (br s, 2 H), 8.24 (d, *J* = 8.8 Hz, 2 H), 7.81 (d, *J* = 8.9 Hz, 2 H), 6.36 (s, 1 H, HC=), 4.16 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.5, 167.3, 148.7, 147.9, 147.3, 128.4, 124.1, 123.4, 36.2.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{11}H_8NO_6^-$: 250.0346; found: 250.0347.

(*E*)-3-(3-Nitrophenyl)pent-2-enedioic Acid (1g)

Yield: 1.38 g (55%); yellow solid; mp 149.3–151.6 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.56 (br s, 2 H), 8.30 (t, *J* = 1.9 Hz, 1 H), 8.24 (ddd, *J* = 8.2, 2.2, 0.8 Hz, 1 H), 8.00 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1 H), 7.71 (t, *J* = 8.0 Hz, 1 H), 6.36 (s, 1 H, HC=), 4.18 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.6, 167.3, 148.6, 148.5, 142.5, 133.5, 130.7, 124.1, 122.7, 121.6, 36.3.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{11}H_8NO_6^-$: 250.0346; found; 250.0345.

(*E*/*Z*)-3-[4-(Trifluoromethoxy)phenyl]pent-2-enedioic Acid (1h)

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

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.44 (br s, 2 H), 7.67 (d, *J* = 8.9 Hz, 2 H), 7.40 (d, *J* = 8.2 Hz, 2 H), 6.26 (s, 1 H, HC=), 4.13 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.6, 167.5, 149.3, 149.2 (q, *J* = 1.8 Hz), 139.9, 129.0, 121.4, 121.3, 120.5 (q, *J* = 256.8 Hz), 36.3.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{12}H_8F_3O_5^-$: 289.0318; found: 289.0314.

(*E*/*Z*)-3-(2-Chlorophenyl)pent-2-enedioic Acid (1i)

Yield: 1.52 g (63%); *E*/*Z* 1:1.3; beige viscous oil, slowly solidified on standing.

^{1}H NMR (400 MHz, DMSO-d_6): δ (*E*) = 9.32 (br s, 2 H, 2 × CO_2H), 7.43–7.38 (m, 1 H), 7.35–7.31 (m, 1 H), 7.30–7.25 (m, 2 H), 6.08 (s, 1 H, HC=), 4.07 (s, 2 H, CH_2); δ (*Z*) = 7.43–7.38 (m, 1 H), 7.32–7.29 (m, 1 H), 7.28–7.22 (m, 1 H), 7.21–7.17 (m, 1 H), 6.20 (t, *J* = 1.0 Hz, 1 H, HC=), 3.52 (d, *J* = 1.0 Hz, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ (*E*) = 175.8, 171.1, 152.5, 140.3, 131.4, 130.2, 130.0, 129.9, 127.0, 123.6, 38.5; δ (*Z*) 175.2, 169.7, 150.2, 137.2, 130.8, 129.4, 129.35, 129.32, 126.6, 123.0, 43.7.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{11}H_8ClO_4^-$: 239.0106; found: 239.0103.

(*E*)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)pent-2-enedioic Acid (1j)

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

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.27 (br s, 2 H), 7.10–6.98 (m, 2 H), 6.94–6.81 (m, 1 H), 6.16 (s, 1 H, HC=), 4.34–4.20 (m, 4 H), 4.09 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.8, 167.8, 150.1, 144.9, 143.7, 133.7, 120.1, 118.6, 117.6, 115.6, 64.7, 64.5, 36.0.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{13}H_{11}O_6^-$: 263.0550; found: 263.0559.

(*E*/*Z*)-3-[4-(Piperidine-1-carbonyl)phenyl]pent-2-enedioic Acid (1k)

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

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.41 (br s, 2 H), 7.59 (d, *J* = 8.3 Hz, 2 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 6.28 (s, 1 H, HC=), 4.13 (s, 2 H, CH_2), 3.58 (br s, 2 H), 3.29 (br s, 2 H), 1.75–1.35 (m, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7, 168.8, 167.6, 150.0, 141.4, 137.5, 127.4, 126.9, 121.0, 48.4 (br s), 42.8 (br s), 36.2, 26.4 (br s), 25.7 (br s), 24.5.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{18}NO_5^-$: 316.1179; found: 316.1176.

(*E*)-3-{4-[(3r,5r,7r)-Adamantan-1-yl]phenyl}pent-2-enedioic Acid (1l)

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

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.32 (br s, 2 H), 7.48 (d, *J* = 8.6 Hz, 2 H), 7.39 (d, *J* = 8.7 Hz, 2 H), 6.23 (s, 1 H, HC=), 4.12 (s, 2 H, CH_2), 2.08–2.04 (m, 3 H), 1.88–1.85 (m, 6 H), 1.77–1.72 (m, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.8, 167.8, 152.5, 150.6, 137.7, 126.7, 125.5, 119.3, 42.9, 36.6, 36.2, 36.1, 28.7.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{23}O_4^-$: 339.1602; found: 339.1600.

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

Yield: 2.15 g (63%); *E*/*Z* = 20:1; colorless solid; mp 164.1–165.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.59 (br s, 2 H), 8.18 (s, 2 H), 8.12 (s, 1 H), 6.44 (s, 1 H, HC=), 4.24 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7, 167.2, 147.7, 143.7, 131.0 (q, *J* = 33.0 Hz), 128.1–127.6 (m), 124.0, 123.7 (q, *J* = 273.0 Hz), 123.3–122.6 (m), 36.2.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{13}H_7F_6O_4^-$: 341.0243; found: 341.0234.

(*E*)-3-(3-Acetylphenyl)pent-2-enedioic Acid (1n)

Yield: 1.41 g (57%); pale beige solid; mp 160.0–162.0 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.43 (br s, 2 H), 8.05 (t, *J* = 1.8 Hz, 1 H), 8.01–7.94 (m, 1 H), 7.80 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1 H), 7.57 (t, *J* = 7.8 Hz, 1 H), 6.32 (s, 1 H, HC=), 4.17 (s, 2 H, CH_2), 2.62 (s, 3 H, $COCH_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 198.2, 171.7, 167.5, 150.1, 141.2, 137.6, 131.5, 129.6, 129.2, 126.4, 121.4, 36.3, 27.3.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{13}H_{11}O_5^-$: 247.0601; found: 247.0601.

(*E*/*Z*)-3-Mesitylpent-2-enedioic Acid (1o)

Yield: 2.21 g (89%); *E*/*Z* = 1:1.3; colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ (*E*) = 12.27 (br s, 2 H, 2 × CO_2H), 6.85 (s, 2 H), 5.72 (s, 1 H, HC=), 3.73 (s, 2 H, CH_2), 2.21 (s, 3 H), 2.18 (s, 6 H); δ (*Z*) = 12.27 (br s, 2 H, 2 × CO_2H), 6.80 (s, 2 H), 6.14 (t, *J* = 1.3 Hz, 1 H, HC=), 3.18 (d, *J* = 1.3 Hz, 2 H, CH_2), 2.21 (s, 3 H), 2.09 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (*E*) = 171.0, 167.3, 151.3, 139.1, 136.9, 136.7, 128.7, 123.8, 39.8, 20.9, 20.1; δ (*Z*) = 171.2, 166.3, 150.0, 135.9, 134.5, 133.6, 128.2, 122.4, 44.3, 21.0, 19.6.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{14}H_{15}O_4^-$: 247.0965; found: 247.0968.

(*E*)-3-(4-Sulfamoylphenyl)pent-2-enedioic Acid (1p)

Yield: 2.34 g (82%); *E*/*Z* = 5:1; colorless solid; pure *E*-diastereomer was isolated after recrystallization of diastereomeric mixture from MeCN; yield: 1.17 g (41%), colorless solid; mp 275.2–280.0 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.47 (br s, 2 H), 7.84 (d, *J* = 8.6 Hz, 2 H), 7.72 (d, *J* = 8.6 Hz, 2 H), 7.41 (s, 2 H, SO_2NH_2), 6.30 (s, 1 H, HC=), 4.15 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.6, 167.4, 149.5, 144.7, 144.0, 127.6, 126.4, 122.1, 36.2.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{11}H_{10}NO_6S^-$: 284.0223; found: 284.0221.

3-Arylglutaconic Imides 6a–c; General Procedure

To a solution of amine (1.1 mmol) in toluene (30 mL) was added diacid **1b**, **1l**, or **1o** (1 mmol) and the mixture was heated at reflux with a Dean–Stark trap for 16 h. Upon cooling to r.t., the mixture was concentrated and the respective title compound was isolated using flash column chromatography on silica gel eluting with $CHCl_3$.

1-(Furan-2-ylmethyl)-4-(4-methoxyphenyl)pyridine-2,6(1*H*,3*H*)-dione (6a)

Yield: 127 mg (43%); orange foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.42 (m, 2 H), 7.34 (dd, *J* = 2.0, 0.9 Hz, 1 H), 7.10–6.77 (m, 2 H), 6.58 (t, *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).

^{13}C NMR (101 MHz, $CDCl_3$): 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, 55.5, 36.0, 35.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_4$: 298.1074; found: 298.1064.

4-[4-(Adamantan-1-yl)phenyl]-1-(4-methoxybenzyl)pyridine-2,6(1*H*,3*H*)-dione (6b)

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

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (101 MHz, $CDCl_3$) 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.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{32}NO_3$: 442.2377; found: 442.2373.

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

Yield: 146 mg (49%); beige foam.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (101 MHz, $CDCl_3$): 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, 22.5, 21.0, 19.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{26}NO_2$: 300.1958; found: 300.1968.

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

A mixture dicaboxylic acid **1b** or **1o** (1 mmol) and amine (see below) (1 mmol) in toluene (3 mL) was heated at 180 °C for 1 h in a microwave reactor. Upon cooling to r.t., the reaction mixture was concentrated and subjected to column chromatography on silica eluting with $CHCl_3$.

Reaction of **1b** with 2-furylmethaneamine afforded 37 mg (12%) of **6a** and 77 mg (28%) of compounds **7a** and **8a** as 6.4:1 mixture (by ^{1}H NMR analysis). The latter was further purified by column chromatography using $CHCl_3$ as eluent to give 44 mg (16%) of pure **7a**.

(*E*)-*N*-(Furan-2-ylmethyl)-3-(4-methoxyphenyl)but-2-enamide (7a)

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

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (101 MHz, $CDCl_3$): 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.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{17}NO_3Na$: 294.1101; found: 294.1127.

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 ^{1}H NMR analysis). The latter was further purified by column chromatography using $CHCl_3$ as eluent to give 62 mg (23%) of pure **7c**.

(*E*)-*N*-Isopentyl-3-mesitylbut-2-enamide (7c)

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

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (s, 2 H), 5.54 (q, *J* = 1.5 Hz, 1 H), 5.41 (s, 1 H), 3.53–3.22 (m, 2 H), 2.39 (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).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 153.1, 140.9, 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.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{28}NO$: 274.2165; found: 274.2180.

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Supporting Information

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(1) Address correspondence to this author at the Laboratory of Chemical Pharmacology, Institute of Chemistry, Saint Petersburg State University, 26 Universitetskyi prospekt, Peterhof 198504, Russian Federation.
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