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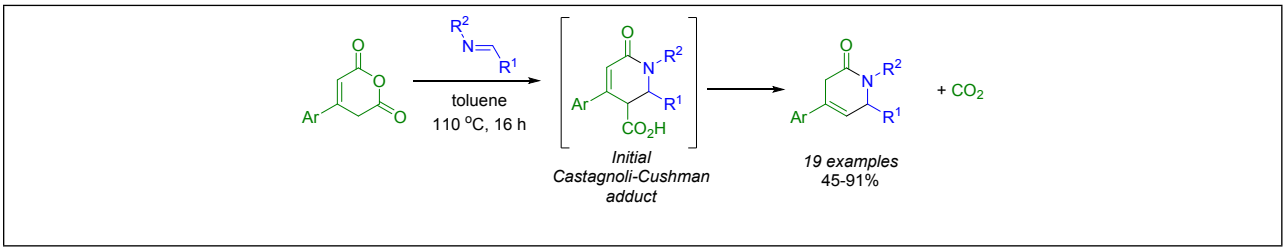
Further Insight into the Castagnoli–Cushman-type Synthesis of 1,4,6-Trisubstituted 1,6-Dihydropyridin-2-(3*H*)-ones from 3-Arylglutaconic Acid Anhydrides

Andrei Firsov, Olga Bakulina, Dmitry Dar'in, Natalia Guranova, and Mikhail Krasavin*

Saint Petersburg State University, Saint Petersburg 199034, Russian Federation

ABSTRACT: The earlier reported three-component Castagnoli–Cushman-type synthesis of 1,4,6-trisubstituted 1,6-dihydropyridin-2-(3*H*)-ones from 3-arylglutaconic acids, primary amines and aromatic aldehydes has been further investigated. It was shown to proceed *via* 3-arylglutaconic anhydrides which, in turn, were found to give superior results in the two-component reactions with imines. The initial formation of the Castagnoli–Cushman carboxylic acids was shown to be the case and their decarboxylation was found to follow a complex, 'forked' pathway, which was confirmed by deuterium incorporation experiments.



The reaction between imines **1** and α-C-H dicarboxylic acid anhydrides **2** offers a remarkably facile and often diastereoselective entry into polysubstituted lactams **3** bearing a carboxylic acid functionality. The reaction was discovered over 45 years ago by Castagnoli and Cushman[1] and has been recently dubbed the Castagnoli–Cusman reaction (or the CCR).[2] The ability of the cyclic anhydride to 'enolize' has a direct bearing on the rate of the CCR.[3] This ability, in turn, can be increased by introducing electron-withdrawing substituents[4] or heteroatoms[5] at the α-position of the cyclic anhydride. Alternatively, resonance stabilization of the anhydride's enol form can provide a strong driving force for the enolization and the resulting CCR.[6] Recently, we investigated a new type of highly reactive cyclic anhydrides for the CCR, namely, those of 3-

arylglutaconic acids **5**.[7] Anhydrides **4** are highly enolizable due to its being a 'vinylogous malonate' in which the enol form **4′** is effectively stabilized by conjugation to the other carbonyl group (the nearby aryl group, likely providing additional stabilization). A rather convenient variant of the CCR involves the preparation of a cyclic anhydride from the respective dicarboxylic acid *in situ* either under the influence of various dehydrating agents[8] or *via* azeotropic removal of water.[9] In the reaction of 3-arylglutaconic acids **5** with primary amines and aromatic aldehydes under the azeotropic reflux with toluene (proceeding, presumably, *via* the formation of the requisite imine *in situ* and cyclodehydration **5→4**), the sole product of the reaction was 4,6-diaryl-1,6-dihydropyridin-2(*3H*)-one **6** and not anticipated carboxylic acid **7**, i. e. decarboxylation with concomitant double bond migration took place (Figure 1). In our initial report on this new reaction, a tentative mechanism for the formation of **6** was proposed which postulated the initial involvement of 3-arylglutaconic anhydride **5** and subsequent decarboxylation of **7** due to steric crowding.[10] Both postulates needed to be tested and probed experimentally and thus we undertook a more in-depth investigation of the reaction course in order to verify the said mechanistic hypothesis. Herein, we report the results of our latest findings in this regard.

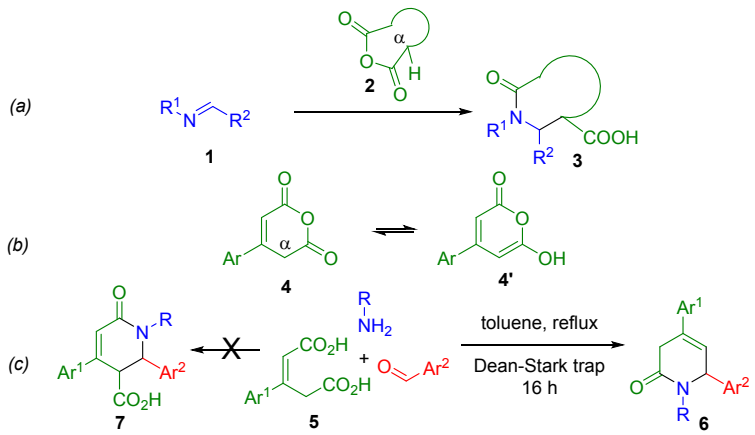
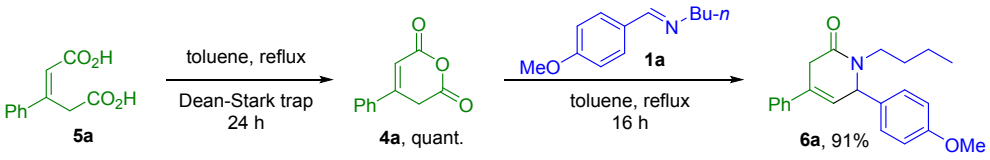


Figure 1. (a) The Castagnoli–Cushman reaction; (b) resonance stabilization of the enol form **4′** of 3-arylglutaconic anhydride **4**; (c) unusual formation of 4,6-diaryl-1,6-dihydropyridin-2(*3H*)-one **6** in the three-component reaction of **5** with aldehydes and amines.

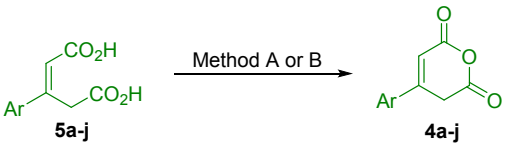
Establishing that the formation of 3-arylglutaconic anhydrides **4** indeed took place under the reaction conditions shown in Figure 1c was rather straightforward as 3-phenylglutaconic acid **5a** gave nearly quantitative yield of respective anhydride **4a** on refluxing in toluene with azeotropic removal of water over 24 h. Moreover, addition of imine **1a** to the toluene solution of **4a** and continued heating at reflux over 16 h delivered the same 1,6-dihydropyridin-2(*3H*)-one **6a** as was obtained previously[10] in the three component reaction of **5a** with the same aldehyde and amine components as form **1a**, albeit with nearly two-fold improvement of the yield: from 50%[10] to 91% (Scheme 1).



Scheme 1. Preparation of 3-phenylglutaconic anhydride (**4a**) and its reaction with imine **1a**.

Encouraged by this remarkable improvement of the yield we reasoned that, while the three-component synthesis of 1,6-dihydropyridin-2(*3H*)-ones **6** (Figure 1c) carries an obvious convenience from the standpoint of array synthesis, greater yield (and possibly broader scope) might be achieved in two-component reactions such as **4a→6a**. The latter approach of course would require that anhydrides **4** and imines **1** be prepared in two separate (albeit distinctly straightforward) chemical operations. To investigate the yield and scope advantages of the two-component reactions of **4** with **1**, several 3-arylglutaconic anhydrides **4a-j** were prepared from respective 3-arylglutaconic acids **5a-j**[7] as depicted in Scheme 2. Only with three acids (**5a-c**) full conversion was achieved on simple reflux in toluene (Method A), leading to nearly quantitative yields. For the rest of acids (**5d-j**) the reaction stalled and the full conversion was not achieved even after 72 h, likely due to limited solubility of these acids in toluene. However, we found it possible to achieve full conversion of these starting materials and excellent yields of the respective anhydrides **4d-j** by performing cyclodehydration of the former in ethyl acetate at

ambient temperature using trifluoroacetic anhydride (TFAA) as the dehydrating agent (Method B).



5a-j **4a-j**

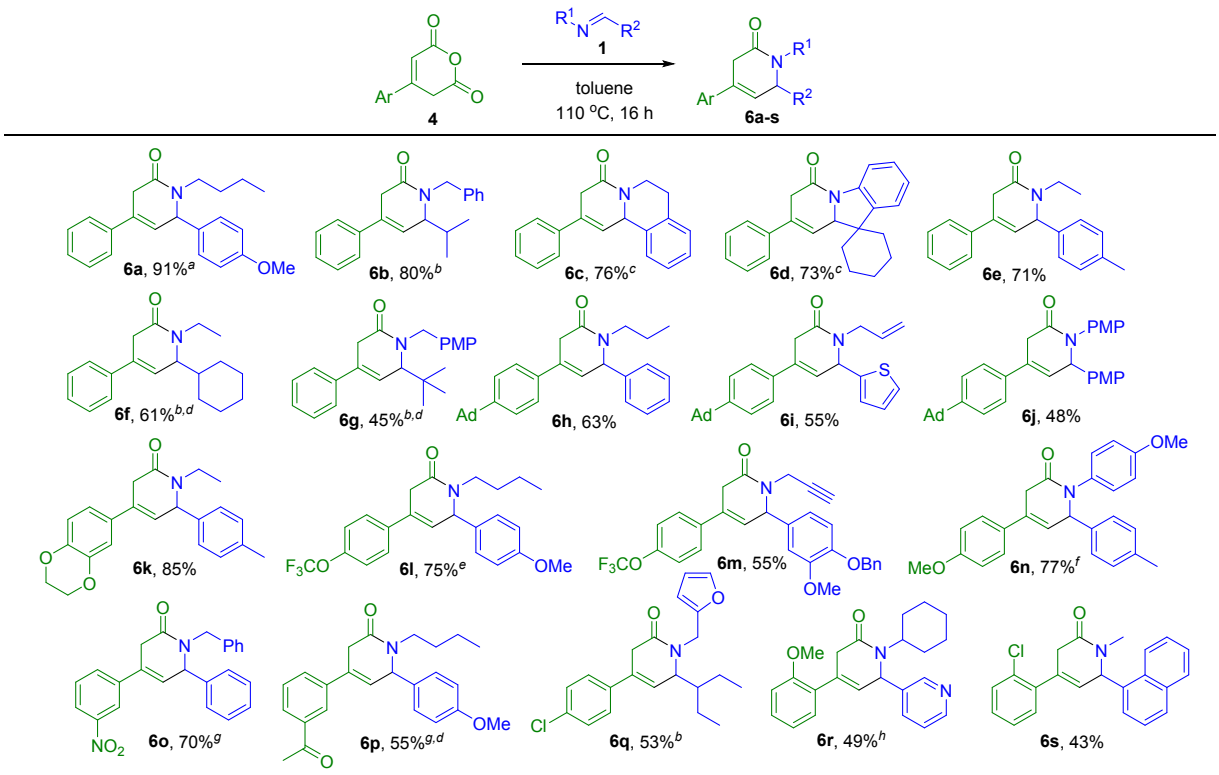
4a, Ar = Ph, quant.[a]
4b, Ar = 4-$MeOC_6H_4$, 90%[a]
4c, Ar = 4-ClC_6H_4, 94%[a]
4d, Ar = 2-ClC_6H_4, 91%[b]
4e, Ar = 3,4-$(OCH_2CH_2O)C_6H_3$, 93%[b]
4f, Ar = 4-$CF_3OC_6H_4$, 91%[b]
4g, Ar = 3-$O_2NC_6H_4$, 81%[b]
4h, Ar = 3-AcC_6H_4, 97%[b]
4i, Ar = 2-$MeOC_6H_4$, 90%[b]
4j, Ar = 4-AdC_6H_4, 86%[b]

Scheme 2. Preparation of 3-arylglutaconic anhydrides **4a-j** (Ad = 1-adamantyl): [a]Method A: toluene, reflux, Dean-Stark trap, 24 h; [b]Method B: EtOAc, TFAA, r. t., 2 days.

With the diverse selection of 3-arylglutaconic anhydrides **4a-j** at hand, we proceeded to investigate possible advantages of the two-component reaction **4**+**1**→**6** with respect to the product yield and substrate scope, compared to the three-component reaction of **5**.[10] The results of these studies are presented in Scheme 3.

Even a brief examination of these results reveals a number of advantages of the two-component (**4**+**1**→**6**) reaction format in comparison to the earlier investigated three-component reaction (**5**→**6**). Besides the marked improvement of the product yield (from 50% to 91% for **6a**, from 37% to 77% for **6n**), the reaction for the first time tolerated the use of imines derived from aliphatic aldehydes (**6b**, **6f-g**, **6q**), including 'enolizable' ones (i. e. α-C-H), as well as from electron-deficient heterocyclic aldehydes (**6r**). In addition, cyclic imines (**6c-d**) as well 3-arylglutaconic inputs (acids or respective anhydrides) containing electron-withdrawing substituents in the aromatic portion (**6o-p**) were investigated in these two-component reactions for the first time and proved successful. Notably, attempts to run the reactions with respective diacids (**5g-h**) in the three-component format failed. Notably, it was subsequently discovered that in some cases (**6f-g**, **6p**), moderate yields of the reaction could be significantly improved by

changing the solvent to DMSO. However, this approach carries the inconvenience of removing DMSO as a solvent during the product isolation.

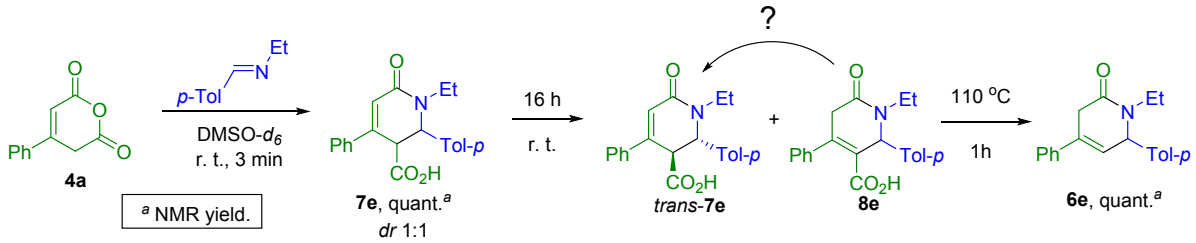


[a]*cf.* yield in the three-component format: 50%[10]; [b]successful reactions with aliphatic aldehyde-derived imines (including α-C-H) which did not work in the three-component format[10]; [c]the first examples of this reaction with cyclic imines; [d]the yield of the reaction run in DMSO, respective yields obtained in toluene: **6f** – 38%, **6g** – 29%, **6p** – 55%; [e]the yield of the reaction run on 3.3 mmol scale: 72%; [f]*cf.* yield in the three-component format: 37%[10]; [g]3-arylglutaconic acids with electron-withdrawing substituents are not tolerated in the three-component reactions[10]; [h]electron-deficient aldehydes (such as pyridine-3-carboxaldehyde) did not work in the three-component reactions.[10]

Scheme 3. Two-component reaction of 3-arylglutaconic anhydrides **4** with imines **1**.

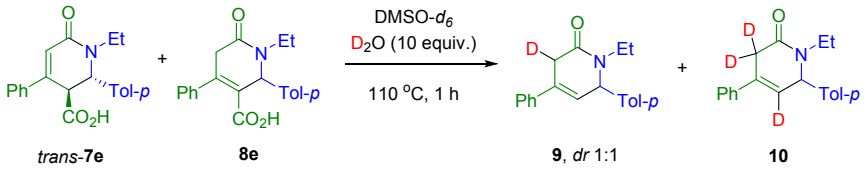
Having confirmed the intermediacy of 3-arylglutaconic anhydrides **4** *en route* to 1,6-dihydropyridin-2(*3H*)-ones **6**, we focused on investigating the course of the reaction in order to confirm that the formation of the initial Castagnoli–Cushman carboxylic acids **7** does indeed take place and that it is their decarboxylation that ultimately leads to the isolated products **6**. In order to be able to follow the reaction course at ambient temperature (so as to detect CCR adducts **7**), we tried replacing toluene (in which 3-arylglutaconic anhydrides are poorly soluble) with other polar solvents (chlorobenzene, THF, chloroform, acetone, acetonitrile and DMSO) amongst which DMSO was found most suitable for further experiments.

The reaction of anhydride **4a** and imine **1e** (which had given 71% yield of compound **6e** when conducted at 110 °C in toluene, Scheme 3) was followed by ^{1}H NMR in DMSO-d_6 at room temperature. We were pleasantly surprised to observe a full conversion to the CCR carboxylic acid **7e**, albeit with no diastereoselectivity, in only 3 min, thus making this reaction one of the fastest examples of the CCR known.[3] This result unequivocally confirmed the intermediacy of CCR adducts **7** *en route* to **6**. However, attempted isolation of *cis/trans*-**7e** failed as this mixture of diastereomers continued to gradually transform itself at room temperature into a mixture of compound **8e** (presumably originating from one of the diastereomers of **7e** *via* double bond migration) and the other diastereomer of **7e** which remained unchanged (*trans* stereochemistry was assigned to it based on the differences in vicinal coupling constants, in analogy with many other CCR adducts where this difference allows distinguishing the *cis* or *trans* isomers reliably[3,8a]). Full conversion to the mixture of *trans*-**7e** and **8e** (the sole components of the reaction mixture that point) was achieved in 16 h at room temperature whereupon it remained unchanged (Scheme S1). This mixture was isolated in 64% (relative to **4a**) and fully characterized by 1D and 2D NMR spectroscopy as well as HRMS. Unfortunately, all attempts to separate this mixture by HPLC or to convert it to ester or amide derivatives, as well as to oxidize it with DDQ, failed as they only resulted in decomposition. In contrast, raising the temperature above 40 °C already led to a noticeable accumulation of end-point 1,6-dihydropyridin-2(*3H*)-one **6e**. Full conversion and quantitative NMR yield of **6e** were obtained from the *trans*-**7e**/**8e** mixture in only 1 h at 110 °C (Scheme 4).



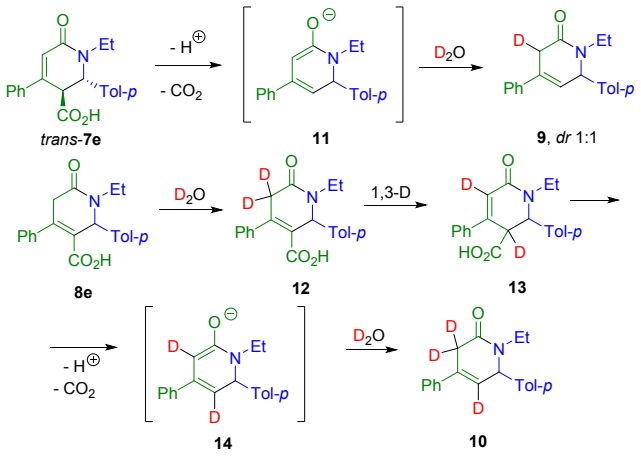
Scheme 4. Following the course of the reaction between **4a** and **1e** by ^{1}H NMR.

The observed transformations could be rationalized by the presumed ability of compound *trans*-**7e** to undergo decarboxylation into **6e** directly, while **8e** (essentially, a cinnamic acid) would need to be tautomerized into **7e** (*cis* or *trans*) first, before losing a CO_2 molecule. In order to trace the course of these transformations and possibly gain evidence for the above preliminary mechanistic interpretation, we heated the mixture of *trans*-**7e** and **8e**, generated and isolated as described above, at 110 °C in DMSO-d_6 in the presence of 10 equiv. of D_2O. Within 1h, the decarboxylation was complete and a 1:1 mixture of mono- and tris-deuterated compounds **9** and **10** formed in quantitative NMR yield (Scheme 5 and Scheme S2).



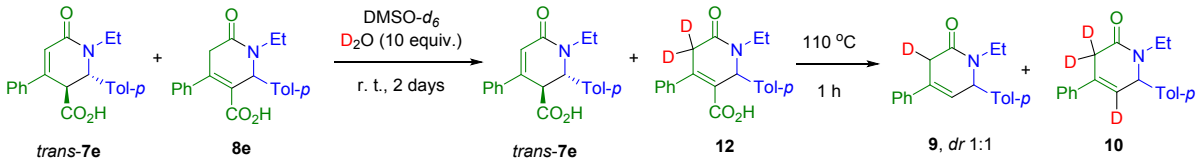
Scheme 5. Decarboxylation of the *trans*-**7e**/**8e** mixture in the presence of D_2O.

Mechanistically, the formation of **9** and **10** can be rationalized as follows and, therefore, it confirms the above hypothesis regarding the course of decarboxylation of the *trans*-**7e**/**8e** mixture. Notably, it is also consistent with the preliminary mechanistic picture proposed in the previous report on the preparation of 1,6-dihydropyridin-2(*3H*)-ones **6**.[10] Monodeuterated compound **9** (obtained as a 1:1 mixture of diastereomers) most likely arises from direct decarboxylation of *trans*-**7e** whereby the intermediate enolate **11** is re-protonated by D_2O in non-diastereoselective fashion. Compound **8e**, being essentially a vinylogous variant of malonic acid monoamide, contains a highly acidic methylene group which is likely to undergo deuterium exchange to give bis-deuterated compound **12**. Subsequently (and much in line of our initial hypothesis), this compound had to undergo an allylic proton transposition in order to be set for decarboxylation. This process resulted in the formation of **13** which, upon decarboxylation and re-protonation of intermediate enolate **14**, delivered the observed tris-deuterated compound **10** (Scheme 6). All structural assignments are consistent with the ^1H NMR and HRMS data.



Scheme 6. Mechanistic rationale for the formation of compounds **9** and **10**.

We further tested this mechanistic interpretation by exposing the mixture of *trans*-**7e** and **8e** to D_2O (10 equiv.) in DMSO-d_6 at ambient temperature. To our delight, as prognosticated in the above mechanistic reasoning, **8e** underwent a complete deuterium exchange over 2 days to give bis-deuterated compounds **12** while *trans*-**7e** remained intact. Ultimately, when the temperature was raised to 110 °C, the mixture of *trans*-**7e** and **12** rapidly (over 1 h) and quantitatively converted to a mixture of **9** and **10**, thus confirming the correctness of the mechanistic picture outlined above, which involves a 'forked' decarboxylation pathway, ultimately leading to 1,6-dihydropyridin-2(*3H*)-ones **6** (Scheme 7 and Schemes S3,S4).



Scheme 7. Successive incorporation of deuterium *en route* to **9** and **10**.

In summary, we have investigated the earlier discovered three-component synthesis of 4,6-disubstituted 1,6-dihydropyridin-2-(3*H*)-ones *via* a Castagnoli–Cushman-type reaction of 3-arylglutaconic acids with amines and aldehydes, accompanied by decarboxylation. Firstly, the reaction was shown to involve cyclodehydration of the diacids to the respective cyclic

anhydrides. The latter, when prepared and isolated, were shown to give superior results in a two-component reaction with imines, compared to the earlier reported three-component reaction, both in terms of the yield and reagent scope. Further investigation of the reaction path leading to 1,6-dihydropyridin-2-(3*H*)-ones, particularly with respect to the alleged decarboxylation of the initial Castagnoli–Cushman carboxylic acid adduct, revealed that both diastereomers of the latter are rapidly formed in the reaction mixture. However, each diastereomer then follows a different decarboxylation pathway, which was confirmed by ^{1}H NMR monitoring of the deuterium incorporation in the final product as the result of decarboxylation in the presence of D_2O. These findings validate the reaction of 3-arylglutaconic anhydrides with imines as a convenient and high-yielding method to prepare rare[11] 4,6-disubstituted 1,6-dihydropyridin-2-(3*H*)-ones and reveal intriguing mechanistic details underlying the reaction path that leads to the formation of these heterocyclic products.

EXPERIMENTAL SECTION

General. NMR spectroscopic data were recorded with 400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for $^{13}C\{^{1}H\}$) and 500 spectrometer (500.03 for ^{1}H and 125 MHz for $^{13}C\{^{1}H\}$) in DMSO-d_6 and in $CDCl_3$ and were referenced to residual solvent proton signals (δH = 2.50 and 7.26 ppm, respectively) and solvent carbon signals (δC = 39.5 and 77.0 ppm, respectively). Mass spectra were recorded with a HRMS-ESI-qTOF spectrometer (electrospray ionization mode, positive ions detection). Flash column chromatography on silica was performed with Biotage Isolera Prime instrument using Biotage SNAP KP-Sil 25g cartridges. TLC was performed with Macherey- Nagel «Alugram Sil G/UV254» plates. Melting points were determined with a Stuart SMP50 instrument in open capillary tubes and are uncorrected. All reactions were performed in air, unless otherwise noted. Toluene was distilled from sodium and stored over MS 4Å. Ethyl acetate and DMSO were dried over MS 4Å.

General procedure for synthesis of 4-aryl-2*H*-pyran-2,6(3*H*)-diones (4a-j).

Method A. Corresponding dicarboxylic acid[7] (5 mmol) was suspended in toluene (100 mL) and heated at reflux in an oil bath with azeotropic removal of water using a Dean-Stark trap. After 24 h, the reaction mixture was concentrated *in vacuo* and the residue was thoroughly washed with hexane. The solid residue thus obtained was separated by filtration and dried *in vacuo* to give analytically pure compounds **4a-c**.

Method B.[5] To a stirred suspension of dicarboxylic acid (5 mmol) in dry ethyl acetate (30 mL) trifluoroacetic anhydride (12.5 mmol, 2.5 equiv.) was added in one portion at room temperature. After stirring for 2 days, the resulting mixture was concentrated *in vacuo* and the residue was thoroughly washed with hexane, followed by filtration and drying of the solids *in vacuo* to afford pure compounds **4d-j**. All compounds **4** were stored at 5 °C in sealed screw-cap vials.

*4-Phenyl-2H-pyran-2,6(3H)-dione (**4a**)*

Yield 0.94 g, 100%. Beige solid. The ^{1}H and ^{13}C NMR spectra matched literature data.[12]

*4-(4-Methoxyphenyl)-2H-pyran-2,6(3H)-dione (**4b**).*

Yield 0.98 g, 90%. Beige solid. The ^{1}H and ^{13}C NMR spectra matched literature data.[13]

*4-(4-Chlorophenyl)-2H-pyran-2,6(3H)-dione (**4c**)*

Yield 1.04 g, 94%; beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J = 8.3 Hz, 2H), 7.65 – 7.50 (m, 2H), 6.84 (s, 1H), 4.16 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.4, 161.7, 153.3, 136.7, 133.4, 129.4, 129.1, 111.9, 33.9.

*4-(2-Chlorophenyl)-2H-pyran-2,6(3H)-dione (**4d**)*

Yield 1.01 g, 91%; beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 7.7, 1.6 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.31 – 7.26 (m, 1H), 6.35 (t, J = 1.9 Hz, 1H), 3.93 (d, J = 1.8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.4, 159.8, 154.1, 134.7, 131.4, 131.4, 130.7, 129.1, 127.6, 117.8, 35.3.

*4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2H-pyran-2,6(3H)-dione (**4e**)*

Yield 1.14 g, 93%**;** beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.08 (m, 2H), 6.98 (d, J = 9.3 Hz, 1H), 6.52 (t, J = 1.7 Hz, 1H), 4.39 – 4.29 (m, 4H), 3.87 (d, J = 1.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.9, 160.4, 151.8, 147.2, 144.1, 126.8, 119.8, 118.2, 115.3, 110.1, 64.7, 64.2, 33.2.

*4-(4-(Trifluoromethoxy)phenyl)-2H-pyran-2,6(3H)-dione (**4f**)*

Yield 1.24 g, 91%; beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 2H), 7.42 – 7.34 (m, 2H), 6.62 (t, *J* = 1.7 Hz, 1H), 3.93 (d, *J* = 1.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.2, 159.9, 151.7 (q, *J* = 1.8 Hz), 151.1 (d, *J* = 65.2 Hz), 132.1, 127.9, 121.4, 112.8, 33.3.

*4-(3-Nitrophenyl)-2H-pyran-2,6(3H)-dione (**4g**)*

Yield 0.94 g, 81%; beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 7.8 Hz,1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 4.27 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 166.1, 161.5, 152.4, 148.8, 136.4, 133.5, 131.0, 126.0, 121.9, 113.8, 34.0.

*4-(3-Acetylphenyl)-2H-pyran-2,6(3H)-dione (**4h**)*

Yield 1.12 g, 97%; beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 6.70 (s, 1H), 3.98 (s, 2H), 2.69 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.9, 164.2, 159.9, 151.7, 138.0, 134.4, 131.6, 130.2, 129.9, 125.7, 113.3, 33.4, 26.7.

*4-(2-Methoxyphenyl)-2H-pyran-2,6(3H)-dione (**4i**)*

Yield 0.98 g, 90%; beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 – 7.43 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.62 (t, *J* = 1.7 Hz, 1H), 4.12 (d, *J* = 1.7 Hz, 2H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 166.7, 161.8, 157.8, 154.0, 132.7, 129.8, 124.1, 121.3, 114.6, 112.7, 56.2, 35.4.

*4-(4-(Adamantan-1-yl)phenyl)-2H-pyran-2,6(3H)-dione (**4j**)*

Yield 1.39 g, 86%; beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.45 (m, 4H), 6.62 (d, *J* = 1.8 Hz, 1H), 3.93 (d, *J* = 1.7 Hz, 2H), 2.15 (s, 3H), 1.95 (s, 6H), 1.90 – 1.71 (m, 6H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$) δ 165.0, 160.4, 156.1, 152.6, 130.8, 126.1, 126.0, 110.9, 42.9, 36.7, 36.6, 33.3, 28.8.

General procedure for synthesis of pyridin-2(3*H*)-ones 6a-s.

Method A. 3-Arylglutaconic anhydride (1 mmol) was placed in a screw-cap vial and suspended in dry toluene (2 mL) at room temperature followed by addition of the corresponding imine (1.05 mmol). The resulting mixture was heated at 110 ^oC in an oil bath for 16 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to provide pure compounds **6a-e,h-o,q-s**.

Method B. To a stirred solution of arylglutaconic anhydride (1 mmol) in DMSO (2 mL) in a screw-cap vial the corresponding imine (1.05 mmol) was added at room temperature. The

resulting mixture was heated at 110 °C in an oil bath for 16 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and water (15 mL). The organic layer was separated, washed with water (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography to provide pure compounds **6f,g,p**.

*1-Butyl-6-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyridin-2(3H)-one (**6a**).*

Yield 305 mg (91%). Obtained NMR spectra were in accordance with the previously published data[10].

*1-Benzyl-6-isopropyl-4-phenyl-1,6-dihydropyridin-2(3H)-one (**6b**).*

Yield 244 mg (80%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 – 7.48 (m, 2H), 7.42 – 7.23(m, 8H), 6.24 (dd, *J* = 4.9, 2.6 Hz, 1H), 5.20 (d, *J* = 15.2 Hz, 1H), 4.21 (d, *J* = 15.2 Hz, 1H), 3.97 (dt, *J* = 5.0, 2.1 Hz, 1H), 3.46 (dt, *J* = 21.0, 3.3 Hz, 1H), 3.29 (dd, *J* = 21.0, 2.3 Hz, 1H), 2.36 – 2.23 (m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.9, 138.5, 138.2, 134.4, 129.0, 128.9 (2C), 128.3, 128.0, 127.5, 125.5, 119.0, 62.7, 46.5, 34.6, 31.6, 19.4, 15.8. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}NO$ 306.1852; Found 306.1855

*2-Phenyl-6,7-dihydro-3H-pyrido[2,1-a]isoquinolin-4(11bH)-one (**6c**).*

Yield 209 mg (76%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); white solid, mp 111-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.45 – 7.33 (m, 3H), 7.32 – 7.26 (m, 3H), 7.23 (td, *J* = 7.1, 6.7, 1.9 Hz, 1H), 6.61 (dt, *J* = 3.4, 1.6 Hz, 1H), 5.53 (*pseudo*-q, *J* = 4.3 Hz, 1H), 4.88 – 4.78 (m, 1H), 3.49 (ddd, *J* = 21.3, 5.0, 1.8 Hz, 1H), 3.40 (ddd, *J* = 21.2, 4.3, 1.5 Hz, 1H), 3.23 – 3.07 (m, 2H), 2.95 – 2.81 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.6, 136.7, 135.1, 133.5, 129.2, 129.0, 128.7, 128.2, 127.2, 126.8, 126.7, 125.2, 124.7, 119.6, 57.2, 40.4, 34.1, 28.4. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{17}NONa$ 298.1202; Found 298.1202.

*8'-Phenyl-7',9a'-dihydro-6'H-spiro[cyclohexane-1,10'-pyrido[1,2-a]indol]-6'-one (**6d**).*

Yield 240 mg (73%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); white solid, mp 181-183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.41 (d, *J* = 7.1 Hz, 2H), 7.34 (dd, *J* = 8.5, 6.6 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H), 6.25 (s, 1H), 4.57 – 4.40

(m, 1H), 3.54 (ddd, *J* = 20.9, 6.4, 2.6 Hz, 1H), 3.37 (dt, *J* = 20.7, 2.8 Hz, 1H), 1.98 (dd, *J* = 21.0, 12.1 Hz, 2H), 1.88 – 1.70 (m, 3H), 1.57 – 1.23 (m, 5H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.5, 140.6 (d, *J* = 15.2 Hz), 138.4, 134.9, 128.7, 128.2, 127.5, 125.2, 124.7, 124.2, 71.4, 47.0, 36.1, 33.0, 32.2, 25.7, 23.2, 21.0. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{23}NONa$ 352.1672; Found 352.1672.

*1-Ethyl-4-phenyl-6-(p-tolyl)-1,6-dihydropyridin-2(3H)-one (**6e**).*

Yield 207 mg (71%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.36 (ddd, *J* = 7.6, 6.6, 1.5 Hz, 2H), 7.35 – 7.28 (m, 1H), 7.23 – 7.13 (m, 4H), 6.14 (ddd, *J* = 4.2, 2.1, 1.1 Hz, 1H), 5.13 (d, *J* = 4.0 Hz, 1H), 3.92 (dq, *J* = 14.3, 7.2 Hz, 1H), 3.58 (ddd, *J* = 21.3, 4.1, 2.1 Hz, 1H), 3.50 (ddd, *J* = 21.2, 3.6, 1.2 Hz, 1H), 2.90 (dq, *J* = 14.1, 7.1 Hz, 1H), 2.37 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 167.0, 138.0, 137.9, 137.5, 130.4, 129.7, 128.6, 128.0, 127.0, 125.0, 121.8, 62.7, 39.4, 34.0, 21.1, 12.2. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{21}NONa$ 314.1515; Found 314.1513.

*6-Cyclohexyl-1-ethyl-4-phenyl-1,6-dihydropyridin-2(3H)-one (**6f**).*

Yield 173 mg (61%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 4H), 7.35 – 7.31 (m, 1H), 6.17 (dd, *J* = 4.8, 1.5 Hz, 1H), 4.01 (t, *J* = 4.1 Hz, 1H), 3.89 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.37 – 3.31 (m, 2H), 3.21 (dq, *J* = 14.0, 7.1 Hz, 1H), 1.95 – 1.53 (m, 7H), 1.37 – 0.88 (m, 7H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 168.0, 138.4, 134.2, 128.6, 127.9, 125.0, 119.5, 63.2, 43.1, 40.0, 35.0, 30.1, 26.7, 26.3, 26.0, 25.9, 12.8. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{25}NONa$ 306.1828; Found 306.1836.

*6-(tert-Butyl)-1-(4-methoxybenzyl)-4-phenyl-1,6-dihydropyridin-2(3H)-one (**6g**).*

Yield 157 mg (45%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 4H), 7.35 – 7.32 (m, 1H), 7.15 – 7.09 (m, 2H), 6.89 – 6.82 (m, 2H), 6.29 (dd, *J* = 5.7, 1.8 Hz, 1H), 5.72 (d, *J* = 15.1 Hz, 1H), 4.03 (d, *J* = 15.1 Hz, 1H), 3.84 – 3.73 (m, 4H), 3.48 (s, 2H), 1.07 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.5, 158.8, 138.4, 134.9, 129.3, 128.6, 127.9, 125.1, 122.2, 114.0, 66.3, 55.2, 50.2, 41.5, 36.3, 27.4. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{27}NO_2Na$ 372.1934; Found 372.1933.

*4-(4-(Adamantan-1-yl)phenyl)-6-phenyl-1-propyl-1,6-dihydropyridin-2(3H)-one (**6h**).*

Yield 268 mg (63%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); grey solid, mp 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 6H), 7.27 – 7.23 (m, 2H), 6.15 (dt, *J* = 3.3, 1.5 Hz, 1H), 5.15 (*pseudo*-q, *J* = 3.9 Hz, 1H), 3.89 (ddd, *J* = 13.5, 9.7, 6.2 Hz, 1H), 3.64 – 3.47 (m, 2H), 2.71 (ddd, *J* = 13.6, 9.6, 5.3 Hz, 1H), 2.15 – 2.07 (m, 4H), 1.92 (d, *J* = 2.9 Hz, 6H), 1.86 – 1.73 (m, 6H), 1.72 – 1.44 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.5, 151.5, 140.7, 134.9, 130.4, 129.0, 128.1, 127.0, 125.1, 124.6, 120.8, 63.3, 46.2, 43.1, 36.7, 36.1, 33.9, 28.9, 20.2, 11.4. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{35}NONa$ 448.2611; Found 448.2630.

*4-(4-(Adamantan-1-yl)phenyl)-1-allyl-6-(thiophen-2-yl)-1,6-dihydropyridin-2(3H)-one (**6i**).*
Yield 234 mg (55%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); yellow solid, mp 152 – 154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 4H), 7.33 – 7.26 (m, 1H), 7.02 (dd, *J* = 3.5, 1.3 Hz, 1H), 6.98 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.23 (dt, *J* = 4.7, 1.5 Hz, 1H), 5.80 (dddd, *J* = 17.6, 10.1, 7.7, 4.2 Hz, 1H), 5.45 (*pseudo*-q, *J* = 3.7 Hz, 1H), 5.28 – 5.14 (m, 2H), 4.85 (ddt, *J* = 15.4, 3.9, 1.8 Hz, 1H), 3.56 (dt, *J* = 3.1, 1.8 Hz, 2H), 3.38 (dd, *J* = 15.4, 7.7 Hz, 1H), 2.18 – 2.07 (m, 3H), 1.93 (d, *J* = 2.9 Hz, 6H), 1.87 – 1.72 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1, 151.7, 144.4, 134.8, 132.4, 131.5, 126.7, 125.9, 125.8, 125.2, 124.8, 120.3, 118.0, 56.9, 45.8, 43.1, 36.7, 36.2, 34.0, 28.9. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{31}NOSNa$ 452.2019; Found 452.2005.

*4-(4-(Adamantan-1-yl)phenyl)-1,6-bis(4-methoxyphenyl)-1,6-dihydropyridin-2(3H)-one (**6j**).*
Yield 249 mg (48%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); grey solid, mp 224 - 226 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.06 – 7.00 (m, 2H), 6.92 – 6.87 (m, 2H), 6.86 – 6.78 (m, 4H), 6.30 – 6.25 (m, 1H), 5.35 (*pseudo*-q, *J* = 3.8 Hz, 1H), 3.79 (d, *J* = 3.9 Hz, 6H), 3.77 – 3.64 (m, 2H), 2.18 – 2.10 (m, 3H), 1.95 (d, *J* = 2.8 Hz, 6H), 1.81 (qd, *J* = 12.1, 6.0 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.7, 159.4, 158.5, 151.6, 134.9, 133.4, 132.2, 130.6, 129.2, 128.9, 125.2, 124.7, 121.0, 114.4, 114.0, 66.8, 55.3, 55.2, 43.1, 36.8, 36.2, 34.4, 28.9. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{37}NO_3Na$ 542.2666; Found 542.2665.

*4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1-ethyl-6-(p-tolyl)-1,6-dihydropyridin-2(3H)-one (**6k**).*
Yield 297 mg (85%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.94 – 6.88 (m, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.02 (dt, *J* = 3.1, 1.5 Hz,

1H), 5.09 (*pseudo*-q, *J* = 4.0 Hz, 1H), 4.26 (s, 4H), 3.90 (dq, *J* = 14.2, 7.2 Hz, 1H), 3.50 (ddd, *J* = 21.3, 4.1, 2.1 Hz, 1H), 3.46 – 3.38 (m, 1H), 2.88 (dq, *J* = 14.1, 7.1 Hz, 1H), 2.36 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 167.1, 143.6, 143.5, 137.9, 137.6, 131.5, 129.7, 129.6, 127.0, 120.5, 118.1, 117.2, 114.0, 64.4, 64.3, 62.6, 39.4, 34.0, 21.1, 12.2. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{23}NO_3Na$ 372.1570; Found 372.1569.

*1-Butyl-6-(4-methoxyphenyl)-4-(4-(trifluoromethoxy)phenyl)-1,6-dihydropyridin-2(3H)-one (**6l**).*
Yield 314 mg (75%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2H), 7.23 – 7.14 (m, 4H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.13 (dt, *J* = 3.1, 1.5 Hz, 1H), 5.11 (*pseudo*-q, *J* = 3.9 Hz, 1H), 3.91 (ddd, *J* = 13.5, 9.5, 6.2 Hz, 1H), 3.83 (s, 3H), 3.54 (ddd, *J* = 21.2, 4.1, 2.0 Hz, 1H), 3.50 – 3.42 (m, 1H), 2.74 (ddd, *J* = 13.6, 9.5, 5.3 Hz, 1H), 1.64 – 1.44 (m, 2H), 1.35 – 1.23 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.8, 159.6, 148.88 (q, *J* = 1.8 Hz), 136.6, 132.1, 129.9, 128.2, 126.4, 122.7, 121.0, 120.4 (q, *J* = 257.4 Hz), 114.5, 62.5, 55.3, 44.1, 33.9, 29.0, 20.2, 13.8. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{24}F_3NO_3Na$ 442.1600; Found 442.1597.

Scale-up experiment was performed according to General procedure for preparation of compounds **6**, method A using anhydride **4f** (900 mg, 3.3 mmol), *N*-butyl-1-(4-methoxyphenyl)methanimine (631 mg, 3.3 mmol) and toluene (5 mL). Purification by column chromatography in acetone−*n*-hexane (2-20% of acetone) afforded 992 mg (72 %) of compound **6l**.

*6-(4-(Benzyloxy)-3-methoxyphenyl)-1-(prop-2-yn-1-yl)-4-(4-(trifluoromethoxy)phenyl)-1,6-dihydropyridin-2(3H)-one (**6m**).*
Yield 279 mg (55%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 4H), 7.42 – 7.37 (m, 2H), 7.36 – 7.31 (m, 1H), 7.25 – 7.20 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.85 – 6.76 (m, 2H), 6.17 (dd, *J* = 3.8, 1.9 Hz, 1H), 5.39 (*pseudo*-q, *J* = 4.0 Hz, 1H), 5.17 (s, 2H), 5.09 (dd, *J* = 17.4, 2.6 Hz, 1H), 3.89 (s, 3H), 3.64 – 3.40 (m, 2H), 3.31 (dd, *J* = 17.3, 2.5 Hz, 1H), 2.26 (t, *J* = 2.5 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 150.3, 149.0 (q, *J* = 1.8 Hz), 148.5, 136.9, 136.4, 131.8, 129.1, 128.6, 128.0, 127.2, 126.4, 122.3, 121.1, 120.3 (q, *J* = 256.9 Hz), 119.8, 114.2, 110.7, 78.3, 72.2, 71.1, 61.7, 56.2, 33.6, 32.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{25}F_3NO_4$ 508.1730; Found 508.1742.

*1,4-Bis(4-methoxyphenyl)-6-(p-tolyl)-1,6-dihydropyridin-2(3H)-one (**6n**).*

Yield 307 mg (77%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); beige foam. Obtained NMR spectra were in accordance to previously published data[10].

*1-Benzyl-4-(3-nitrophenyl)-6-phenyl-1,6-dihydropyridin-2(3H)-one (**6o**).*

Yield 269 mg (70%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (t, *J* = 2.1 Hz, 1H), 8.16 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.75 – 7.67 (m, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.47 – 7.31 (m, 6H), 7.28 – 7.23 (m, 4H), 6.30 – 6.22 (m, 1H), 5.70 (d, *J* = 14.8 Hz, 1H), 5.06 (*pseudo*-q, *J* = 3.9 Hz, 1H), 3.79 – 3.66 (m, 1H), 3.67 – 3.58 (m, 1H), 3.52 (d, *J* = 14.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.7, 148.6, 139.5, 139.2, 136.4, 130.7, 129.6, 129.4, 128.7, 128.7, 128.6, 128.4, 127.7, 127.1, 124.3, 122.8, 120.0, 61.7, 46.3, 33.7. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{20}N_2O_3Na$ 407.1366; Found 407.1370.

*4-(3-Acetylphenyl)-1-butyl-6-(4-methoxyphenyl)-1,6-dihydropyridin-2(3H)-one (**6p**).*

Yield 207 mg (55%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 1.8 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.22 – 7.16 (m, 2H), 6.94 – 6.90 (m, 2H), 6.29 – 6.17 (m, 1H), 5.21 – 5.05 (m, 1H), 3.98 – 3.88 (m, 1H), 3.83 (s, 3H), 3.60 – 3.51 (m, 2H), 2.74 (ddd, *J* = 14.0, 9.4, 5.4 Hz, 1H), 2.63 (s, 3H), 1.59 (s, 2H), 1.34 – 1.22 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.8, 166.9, 159.6, 138.4, 137.4, 132.1, 129.6, 129.4, 128.9, 128.2, 127.9, 124.7, 123.1, 114.5, 62.6, 55.3, 44.1, 33.9, 29.7, 29.0, 26.7, 20.2, 13.8. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{27}NO_3Na$ 400.1883; Found 400.1896.

*4-(4-Chlorophenyl)-1-(furan-2-ylmethyl)-6-(pentan-3-yl)-1,6-dihydropyridin-2(3H)-one (**6q**).*

Yield 189 mg (53%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.25 (m, 5H), 6.41 – 6.25 (m, 2H), 6.07 (dd, *J* = 4.8, 1.9 Hz, 1H), 5.28 (d, *J* = 15.5 Hz, 1H), 4.29 – 4.16 (m, 2H), 3.45 – 3.27 (m, 2H), 1.80 (tq, *J* = 8.7, 3.9 Hz, 1H), 1.72 – 1.56 (m, 1H), 1.43 – 1.17 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 4H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.1, 150.5, 142.1, 136.8, 133.8, 132.5, 128.7, 126.2, 119.1, 110.5, 109.1, 59.9, 45.0, 39.8, 34.5, 23.2, 21.5, 12.3, 12.1. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{24}ClNO_2Na$ 380.1388; Found 380.1391.

*1-Cyclohexyl-4-(2-methoxyphenyl)-1,2-dihydro-[2,3'-bipyridin]-6(5H)-one (**6r**).*

Yield 177 mg (49%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.58 (m, 1H), 8.55 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.58 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.18 – 7.09 (m, 1H), 6.90 – 6.85 (m, 2H), 6.05 (ddd, *J* = 5.2, 2.1, 0.9 Hz, 1H), 5.23 (dt, *J* = 5.4, 2.9 Hz, 1H), 4.14 (tt, *J* = 11.7, 3.6 Hz, 1H), 3.82 (s, 3H), 3.52 (td, *J* = 2.9, 2.4, 1.5 Hz, 2H), 1.89 – 1.73 (m, 2H), 1.69 – 1.51 (m, 4H), 1.35 – 1.16 (m, 3H), 1.05 (tt, *J* = 12.8, 3.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.9, 159.7, 149.0, 147.8, 138.4, 134.2, 131.1, 129.8, 129.6, 126.2, 124.0, 119.8, 114.0, 58.4, 56.5, 55.3, 35.3, 31.1, 30.0, 26.1, 26.0, 25.4. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{27}N_2O_2$ 363.2067; Found 363.2065.

*4-(2-Chlorophenyl)-1-methyl-6-(naphthalen-1-yl)-1,6-dihydropyridin-2(3H)-one (**6s**).*

Yield 149 mg (43%), purification by flash chromatography (eluent: acetone+*n*-hexane, gradient: 2%−20% of acetone); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.08 (m, 1H), 8.01 – 7.89 (m, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.46 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.24 – 7.17 (m, 2H), 7.15 – 7.10 (m, 1H), 6.01 – 5.88 (m, 2H), 3.63 (ddd, *J* = 21.7, 4.2, 1.8 Hz, 1H), 3.52 (dd, *J* = 21.8, 3.6 Hz, 1H), 2.95 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.9, 138.6, 135.2, 134.2, 132.4, 132.3, 130.6, 129.9, 129.8, 129.3, 129.0, 128.8, 126.9, 126.7, 126.0, 125.9, 124.9, 122.1, 35.3, 32.8. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{18}ClNONa$ 370.0969; Found 370.0980.

*1-Ethyl-6-oxo-4-phenyl-2-(p-tolyl)-1,2,3,6-tetrahydropyridine-3-carboxylic acid and 1-ethyl-6-oxo-4-phenyl-2-(p-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid (**7e** + **8e**).*

To a stirred solution of of 4-phenyl-2*H*-pyran-2,6(3*H*)-dione (188 mg, 1 mmol) in DMSO (0.5 mL) *N*-ethyl-1-(*p*-tolyl)methanimine (154 mg, 1.05 mmol) dissolved in DMSO (0.5 mL) was added dropwise at room temperature (exothermic reaction, temperature should remain below 25 °C). After 24 h the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water twice, dried over Na_2SO_4, filtered and concentrated *in vacuo* at room temperature (T<25 °C to avoid decarboxylation). The residue was washed with cold diethyl ether (5 mL), filtered and dried to give a 1:1 mixture of compounds **7e** and **8e**.

Yield 215 mg (64%); beige solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 9.9 Hz, 7H), 7.18 (td, *J* = 4.0, 3.4, 1.7 Hz, 5H), 7.12 (d, *J* = 8.4 Hz, 6H), 6.48 (s, 1H), 5.51 (dd, *J* = 3.7, 2.0 Hz, 1H), 5.28 – 5.19 (m, 1H), 4.02 (dq, *J* = 14.3, 7.2 Hz, 1H), 3.90 (d, *J* = 1.4 Hz, 1H), 3.84 (dq, *J* = 14.3, 7.2 Hz, 1H), 3.68 (dd, *J* = 21.9, 3.6 Hz, 1H), 3.29 (dd, *J* = 21.9, 2.0 Hz, 1H), 2.92 (dq, *J* =

14.2, 7.2 Hz, 1H), 2.82 (dq, *J* = 14.1, 7.1 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 1.14 – 1.04 (m, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 173.0, 168.6, 166.8, 164.6, 143.9, 142.0, 139.1, 138.2, 137.8, 137.1, 136.0, 135.5, 129.7, 129.6, 129.4, 128.7, 128.3, 127.3, 126.8, 126.5, 126.2, 126.1, 121.3, 65.9, 62.6, 60.8, 50.5, 40.6, 40.0, 39.1, 21.1, 21.0, 15.2, 12.9, 12.3. (**7e** + **8e**): HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{21}NO_3Na$ 358.1414; Found 358.1425. The structure of these compounds was also confirmed by HMBC and HSQC spectra.

1-Ethyl-4-phenyl-6-(p-tolyl)-3,6-dihydropyridin-2(1H)-one-3-d (**9**) and 1-*ethyl-4-phenyl-6-(p-tolyl)-3,6-dihydropyridin-2(1H)-one-3,3,5-d_3* (**10**)

(9)+(10): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 – 7.38 (m, 9H), 7.34 (dd, *J* = 8.4, 6.5 Hz, 9H), 7.31 – 7.24 (m, 4H), 7.22 – 7.13 (m, 17H), 6.25 – 6.15 (m, 2H), 5.21 (s, 4H), 3.71 – 3.57 (m, 4H), 3.55 (d, *J* = 3.8 Hz, 1H), 3.25 (d, *J* = 3.1 Hz, 1H), 2.77 (dq, *J* = 14.0, 7.0 Hz, 4H), 2.26 (s, 12H), 0.94 (t, *J* = 7.1 Hz, 12H). **(9)+(10)**: ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.9, 138.2, 138.0, 137.9, 137.7, 129.9, 129.8, 129.0, 128.4, 127.5, 125.3, 124.7, 122.5, 62.1, 62.1, 21.1, 12.6.

(**9**): HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}DNO$ 293.1759; Found 293.1749

(**10**)**:** HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}D_3NO$ 295.1884; Found 295.1883

ASSOCIATED CONTENT

Supporting Information

Schemes S1-S4 and copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for compounds **4a-j, 6a-s, 7e+8e, 9+10**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail: m.krasavin@spbu.ru.

Notes

The authors declare no competing financial interest.

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