

Diversity-Oriented Synthesis of 1-Substituted 4-Aryl-6-oxo-1,6-dihydropyridine-3-carboxamides.

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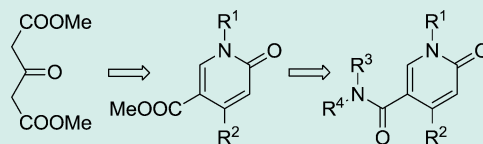
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Supporting Information

ABSTRACT: A simple five-step diversity-oriented synthesis of 1-substituted 4-aryl-6-oxo-1,6-dihydropyridine-3-carboxamides was developed. Treatment of dimethyl 2-((dimethylamino)methylidene)-3-oxopentanedioate with twenty primary amines gave 1-substituted methyl 4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylates. Transformation into the corresponding 4-tosyloxy and 4-chloro derivatives, followed by Suzuki–Miyaura arylations gave a series of eleven N-substituted methyl 4-aryl-6-oxo-1,6-dihydropyridine-3-carboxylates. Combinatorial screening was employed to establish suitable reaction conditions for Suzuki–Miyaura arylation of N-alkylpyridones. Hydrolysis of the esters followed by parallel solution-phase amidation of the corresponding carboxylic acids with primary and secondary amines furnished a library of seventeen final products.

KEYWORDS: parallel synthesis, cyclization, pyridones, Suzuki–Miyaura arylation, amidation



INTRODUCTION

Heterocyclic compounds are important scaffolds for the preparation of compound libraries for medicinal and pharmaceutical applications.^{1–4} Within this context, the 2-pyridone system is a useful core for derivatization and, hence, preparation of biologically active compounds. For example, 2-pyridone containing compounds have recently been prepared as MCH1R antagonists,⁵ 11 β -hydroxysteroid dehydrogenase 1 inhibitors,⁶ P2X7 purinoceptor modulators,⁷ inhibitors of cyclooxygenases and 5-lipoxygenase,⁸ dopamine D3 receptor antagonists,⁹ and antibiotics.¹⁰ Therefore, synthesis of libraries of novel 2-pyridone derivatives and their fused analogues is of particular interest.

Nicotinamide (vitamin B₃) is an important pyridine derivative and a large number of its derivatives and analogues have been prepared, so far. However, 1,4-disubstituted 6-oxo-1,6-dihydropyridine-3-carboxamides that are unsubstituted at positions 2 and 5 are almost unexplored group of nicotinamide derivatives. To the best of our knowledge, only two compounds of this particular type are known.^{11,12} The first one is N'-functionalized 2-(5-carbamoyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)acetic acid, that has been prepared as chemokine modulator quite routinely by a three step derivatization of commercially available 6-hydroxy-4-trifluoromethylnicotinic acid.¹¹ The second one, N'-substituted 4-(3-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide, has been prepared as farnesyltransferase inhibitor in five-step synthesis including pyridone ring formation. The synthesis comprises Heck-type arylation of diethyl glutaconate, formylation, cyclization with methylamine, hydrolysis of the ester, and amidation.^{12a}

Within our long-term studies on enaminones as versatile reagents in heterocyclic synthesis,¹³ a part of our research has been focused on the synthesis of fused pyridones¹⁴ from pyridineacetic acid derivatives^{13,15} and on the synthesis of 1,4-dihydropyridines¹⁶ by cyclocondensations of bis-enaminones with primary amines^{13,17} including parallel solution-phase approach.^{15,18} For the synthesis of dihydropyridine derivatives, dimethyl acetone-1,3-dicarboxylate (**1**)¹⁹ has been found as particularly useful starting material.^{17a,b,d,18} Recently, we reported a simple one-pot transformation of **1** with ammonia and aliphatic primary amines into methyl 1-alkyl-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylates.²⁰ In extension, we focused our attention on parallel preparation and transformations of 6-oxo-1,6-dihydropyridine derivatives with 4-aryl-6-oxo-1,6-dihydropyridine-3-carboxamides **11** as target compounds. Herein, we report a novel five-step synthesis of **11** (Scheme 1) comprising a enaminone-based preparation of methyl 4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylates **4** from primary amines **3**{1–20} (Figure 1), transformations into the corresponding tosylates **5** and chloro analogues **6**, Suzuki–Miyaura arylation of **5** and **6** with arylboronic acids **7**{1–4} (Figure 2), followed by hydrolysis of methyl 4-aryl-6-oxo-1,6-dihydropyridine-3-carboxylates **8**, and parallel amidations of the so-formed carboxylic acids **9** with aliphatic amines **3**{20–27} (Figure 1) to furnish title carboxamides **11** (Scheme 1).

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Scheme 1. General Synthetic Route

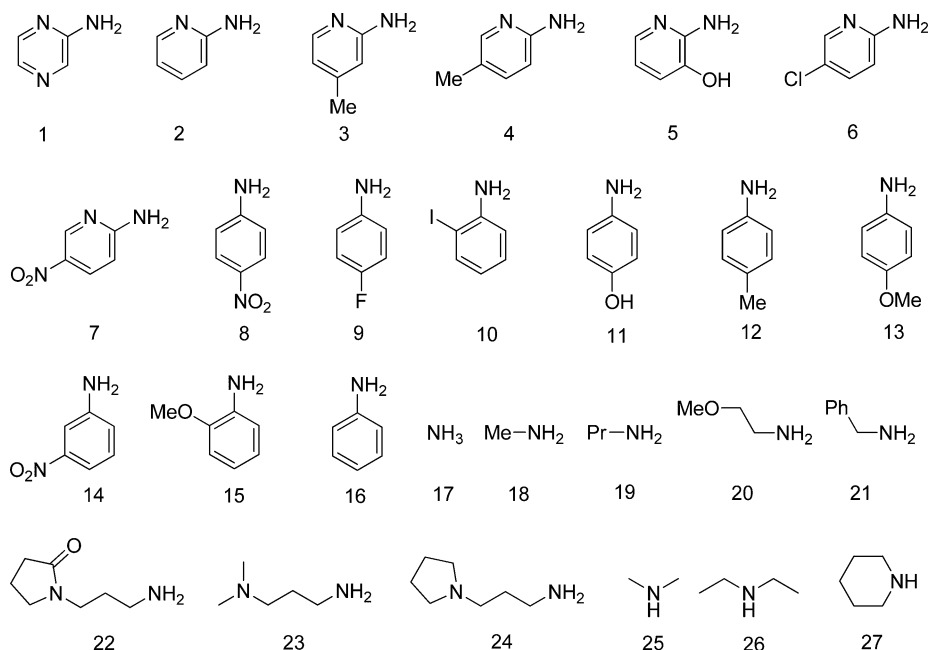
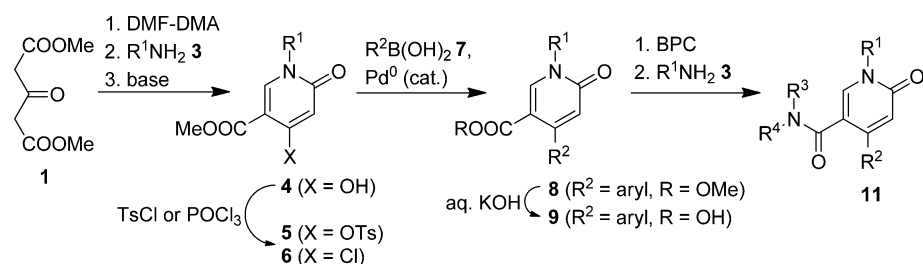


Figure 1. Diversity reagents 3{1–20} used for cyclization of enaminone 2 and diversity reagents 3{20–27} used for amidation of carboxylic acids 9.

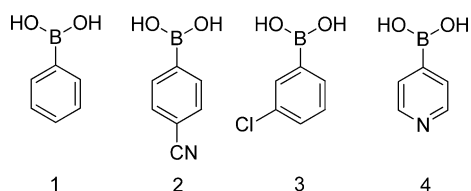


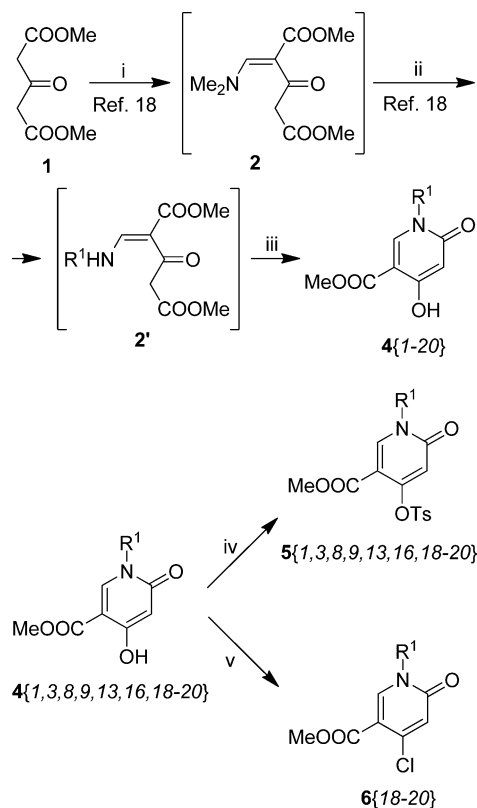
Figure 2. Diversity reagents 7{1–4} used for Suzuki–Miyaura arylations.

RESULTS AND DISCUSSION

Following modified literature procedures,^{18,20} commercially available dimethyl acetone-1,3-dicarboxylate (**1**) was first transformed with *N,N*-dimethylformamide dimethylacetal (DMF-DMA) into the enaminone **2**. Acid-catalyzed parallel treatment of **2** with primary amines **3**{1–20} gave the intermediates **2'**{1–20},¹⁸ which were directly (without isolation) cyclized into **4** by treatment with methanolic potassium hydroxide. Acidification and evaporation of the reaction mixtures followed by extraction of the products **4** from the solid residues with a 2:5 mixture of methanol and ethyl acetate, filtration, and evaporation furnished analytically pure methyl 1-aryl-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylates **4**{1–20} in 40–80% yield. Further parallel treatment of 4-hydroxypyridones **4**{1,3,8,9,13,16,18–20} with tosyl chloride in DMF in the presence of triethylamine and 4-dimethylami-

nopyridine (DMAP) at 95 °C furnished the corresponding tosylates **5**{1,3,8,9,13,16,18–20} in 18–87% yield. Similarly, parallel chlorination of the pyridones **4**{18–20} in refluxing phosphorus oxychloride afforded the chloro analogues **6**{18–20} in 60–57% yield (Scheme 2, Table 1). It is noteworthy, that triflates and bromides should be better coupling partners in subsequent Suzuki–Miyaura reactions than the corresponding tosylates **5** and chlorides **6**. Unfortunately, attempts to obtain the corresponding triflate and bromide from pyridone **4**{18} failed. [Simplicity and cost-effectiveness of the cross-coupling method were also important to us. Preparation of triflates and bromides was not studied further for the following reasons: (a) the reagents, TiF_2O and POBr_3 , are approximately ten times more expensive than TsCl and POCl_3 ; (b) the solid TsCl is much easier to handle than TiF_2O , which is a moisture-sensitive liquid; (c) excess POCl_3 (bp 106 °C) is easily removable by evaporation using a diaphragm pump, while POBr_3 (bp 192 °C) is not; (d) tosylates are more convenient to use, since they are usually crystalline and hydrolytically more stable than triflates.]

Suzuki–Miyaura cross-coupling of the corresponding tosylates **5** with arylboronic acids **7** (Figure 2) was then studied. Reaction conditions were first optimized for the reaction of 1-phenyltosylate **5**{16} with phenylboronic acid **7**{1} and $\text{Pd}(\text{PPh}_3)_4$ as catalyst. Reaction in refluxing *tert*-butanol in the presence of potassium phosphate afforded the corresponding cross-coupling product **8**{16/1} in 10% yield.

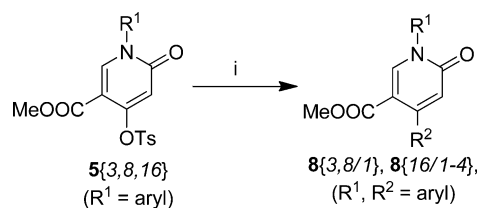
Scheme 2. Synthesis of Compounds 4–6^a

^aReaction conditions: (i) DMF-DMA, MeOH, r.t. (ref 18); (ii) R¹NH₂ 3{1–20}, MeOH, 37% HCl (1 equiv.), r.t. (ref 18); (iii) KOH, MeOH, reflux; (iv) TsCl, DMF, Et₃N, DMAP (cat.), 95 °C; (v) POCl₃, reflux.

Table 1. Experimental Data on Compounds 4–6^a

entry	compound	R ¹	yield (%)		
			4	5	6
1	4{1}, 5{1}	pyrazinyl	58 ^b	47 ^b	
2	4{2}	pyridin-2-yl	63 ^b		
3	4{3}, 5{3}	4-methylpyridin-2-yl	65 ^b	52 ^b	
4	4{4}	5-methylpyridin-2-yl	60 ^b		
5	4{5}	3-hydroxypyridin-2-yl	54 ^b		
6	4{6}	5-chloropyridin-2-yl	80 ^b		
7	4{7}	5-nitropyridin-2-yl	50 ^b		
8	4{8}, 5{8}	4-nitrophenyl	50 ^b	87 ^b	
9	4{9}, 5{9}	4-fluorophenyl	46 ^b	18 ^b	
10	4{10}	2-iodophenyl	45 ^b		
11	4{11}	4-hydroxyphenyl	45 ^b		
12	4{12}	4-methylphenyl	45 ^b		
13	4{13}, 5{13}	4-methoxyphenyl	60 ^b	36 ^b	
14	4{14}	3-nitrophenyl	48 ^b		
15	4{15}	2-methoxyphenyl	63 ^b		
16	4{16}, 5{16}	Ph	54 ^b	75 ^b	
17	4{17}	H	40 ^b		
18	4{18}–6{18}	Me	60 ^b	45 ^b	62 ^b
19	4{19}–6{19}	1-propyl	57 ^b	29 ^b	75
20	4{20}–6{20}	2-methoxyethyl	46 ^b	35 ^b	60

^aAll compounds were obtained in ≥80% purity (determined by LC-MS and ¹H NMR). ^bAnalytical purity was determined by elemental analysis. The found values for C, H, and N were within ±0.4% range with respect to the theoretical values.

Scheme 3. Synthesis of 1,4-Diarylpyridones 8 (Method A)^a

^aReaction conditions: (i) R²B(OH)₂ 7 (chemset 7), Pd(PPh₃)₄ (cat.), Cs₂CO₃, DMF–H₂O, 90 °C.

Table 2. Experimental Data on 1,4-Diarylpyridones 8^a

entry	compound	R ¹	R ²	yield (%)
1	8{3/1}	4-methylpyridin-2-yl	Ph	63
2	8{8/1}	4-nitrophenyl	Ph	82 ^b
3	8{16/1}	Ph	Ph	72 ^b
4	8{16/2}	Ph	4-cyanophenyl	67 ^b
5	8{16/3}	Ph	3-chlorophenyl	58 ^b
6	8{16/4}	Ph	pyridin-4-yl	50 ^b

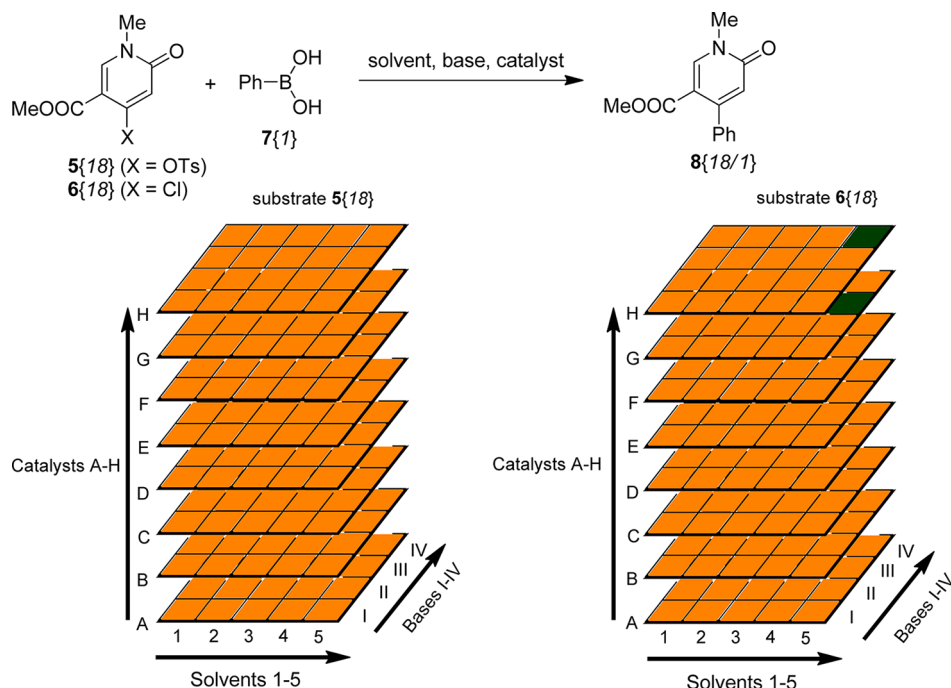
^aAll compounds were obtained in ≥80% purity (determined by LC-MS and ¹H NMR). ^bAnalytical purity was determined by elemental analysis. The found values for C, H, and N were within ±0.4% range with respect to the theoretical values.

Next, reaction in aqueous DMF in the presence of cesium carbonate at 65 °C gave 8{16/1} in 47% yield, while at 90 °C 8{16/1} was obtained in 72% yield. Under microwave irradiation at 90 °C, the yield was almost identical (71%). Next, parallel cross-coupling of the representative 1-phenyl-tosylate 5{16} with arylboronic acids 7{1–4} and reactions of 5{3} and 5{8} with phenylboronic acid 7{1} was performed. Reactions were carried out in aqueous DMF, Pd(PPh₃)₄ as catalyst, and cesium carbonate at 90 °C followed by extraction and purification of the crude products by filtration through a short plug of silica gel to give 1,4-diarylpyridones 8 in 50–82% yield. Out of six pyridones 8, five were analytically pure, while compound 8{3,1} was also >80% pure according to ¹H NMR and LC-MS (Method A, Scheme 3, Table 2).

To our surprise, neither the 1-alkyl tosylates 5{18–20}, nor the chloropyridones 6{18–20}, underwent cross-coupling with phenylboronic acid 7{1}. Several attempts to carry out these reactions by variation of reaction conditions (substrate, solvent, base, and catalyst) were futile as well. To prepare the 1-alkyl substituted pyridones 8, extensive combinatorial screening for suitable reaction conditions with respect to the substrate, solvent, base, and catalyst was performed. A series of 320 Suzuki–Miyaura cross-coupling reactions were carried out, comprising combinations of one reagent 7{1}, two substrates 5{18} and 6{18}, five solvents 1–5, four bases I–IV, and eight catalysts A–H. Parallel screening reactions were carried out at 60 °C on a 12 × 0.1 mmol scale in 2 mL glass vials using a standard magnetic stirrer/heater equipped with aluminum block with 12 positions and temperature controller. The reactions were monitored by TLC and by change of color. In the two successful cross-couplings, progress of the reaction was detected when the initially orange-brown reaction mixture turned dark green with precipitation of colloidal palladium black (Scheme 4).

Out of 320 reactions, just two of them gave the desired cross-coupling product 8{18/1}: (a) reaction of the chloride 6{18} in DMF, with KOH–MeOH as base, and PdCl₂/P(*p*-tolyl)₃ as

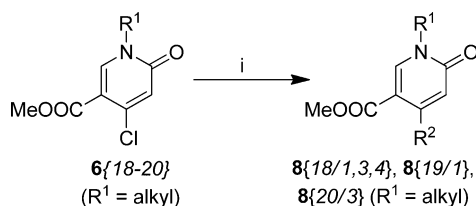
Scheme 4. Screening for Reaction Conditions for Arylation of 1-Alkylpyridones 5 and 6



Solvents 1-5: MeOH (1), *n*-PrOH (2), *t*-BuOH (3), MeCN (4), DMF (5)

Bases I-IV: K₃PO₄ (I), NaOH (II), KOH (III), Cs₂CO₃ (IV)

Catalysts A-H: Pd(OAc)₂-PPh₃ (Catalyst A), PdCl₂-PPh₃ (Catalyst B), Pd(OAc)₂-P(naphthyl)₃ (Catalyst C), PdCl₂-P(naphthyl)₃ (Catalyst D), Pd(OAc)₂-(dicyclohexyl)(*N*-(2'-tolyl)indol-2-yl)phosphine (Catalyst E), Pd(OAc)₂-(dicyclohexyl)(*N*-(2'-tolyl)indol-2-yl)phosphine (Catalyst F), PdCl₂/P(*p*-tolyl)₃ (Catalyst G), Pd(PPh₃)₄-[PdCl(allyl)]₂ (Catalyst H).

Scheme 5. Synthesis of 1-Alkyl-4-arylpyridones 8 (Method B)^a

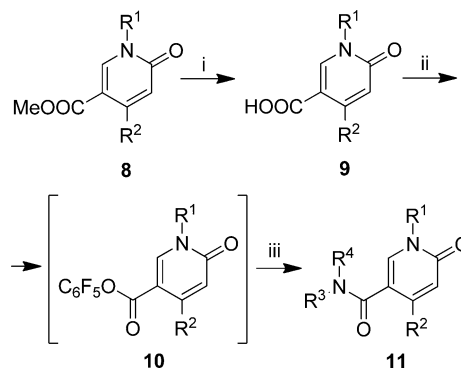
^aReaction conditions: (i) R²B(OH)₂ 7, Cs₂CO₃, DMF–H₂O, Pd(PPh₃)₄–[PdCl(allyl)]₂ (cat.), 55–65 °C.

Table 3. Experimental Data on 1-Alkyl-4-arylpyridones 8^a

entry	compound	R ¹	R ²	yield (%)
1	8{18/1}	Me	Ph	73 ^b
2	8{18/3}	Me	3-chlorophenyl	49
3	8{19/1}	1-propyl	Ph	61
4	8{20/3}	2-methoxyethyl	3-chlorophenyl	45

^aAll compounds were obtained in ≥80% purity (determined by LC-MS and ¹H NMR). ^bAnalytical purity was determined by elemental analysis. The found values for C, H, and N were within ±0.4% range with respect to the theoretical values.

catalyst and (b) reaction of the chloride 6{18} in DMF, Cs₂CO₃ as base, and combination of Pd(PPh₃)₄ and [PdCl(allyl)]₂ as the catalyst (Scheme 3). However, only the latter reaction was reproducible and, consequently, these conditions were finally employed for the preparation of five 1-alkyl-4-arylpyridones 8. In this manner, compounds 8{18/1,3}, 8{19/1},

Scheme 6. Synthesis of Compounds 9 and 11^a

^aReaction conditions: (i) 1 M KOH–MeOH, reflux; (ii) Et₃N, BPC, MeCN, r.t.; (iii) R³R⁴NH 3{20–27}, Et₃N, MeCN, r.t.

and 8{20/3} were obtained in 45–73% yield and in >80% purity (determined by LC-MS and ¹H NMR)(Method B, Scheme 5, Table 3).

Although our primary goal was to obtain the 4-arylpyridones 8, several attempts were also made to prepare the 4-alkyl and the 4-alkenyl substituted compounds 8 by cross-coupling of 5{16} and 6{18} with butyl-, isobutyl-, cyclopentyl-, and *trans*-styrylboronic acid, yet without success. Even under microwave irradiation formation of the corresponding cross-coupling products was not observed.

Finally, transformation of the esters 8 into the corresponding carboxamides 11 was performed (Scheme 6). Hydrolysis of the esters 8 was carried out in parallel with 1 M KOH in methanol

Table 4. Experimental Data on Compounds 9^a

entry	compound	R ¹	R ²	yield (%)
1	9{8/1}	4-nitrophenyl	Ph	95
2	9{16/1}	Ph	Ph	80
3	9{16/2}	Ph	4-cyanophenyl	83 ^b
4	9{16/3}	Ph	3-chlorophenyl	83 ^b
5	9{16/4}	Ph	pyridin-2-yl	65 ^b
6	9{18/1}	Me	Ph	98 ^b
7	9{18/3}	Me	3-chlorophenyl	94 ^b
8	9{19/1}	<i>n</i> -Pr	Ph	74 ^b
9	9{20/3}	MeO(CH ₂) ₂ -	3-chlorophenyl	82 ^b

^aAll products were obtained in ≥80% purity (determined by LC-MS and ¹H NMR). ^bAnalytical purity was confirmed by elemental analysis. The found values for C, H, and N were within ±0.4% range with respect to the theoretical values.

under reflux to afford analytically pure carboxylic acids 9 in 76–98% yield upon simple filtration workup (Scheme 6, Table 4).

Carboxylic acids 9{16/1,3} and 9{18/1,3} and amines 3{20,21,23} were chosen as model substrates for parallel amidation. In addition, five other amidations of the acids 9{16,18/1} and 9{20/3} with amines 3{22,24–27} were performed as well. The acids 9 were activated with bis(pentafluorophenyl) carbonate (BPC) to give the pentafluorophenyl esters 10, followed by treatment with aliphatic

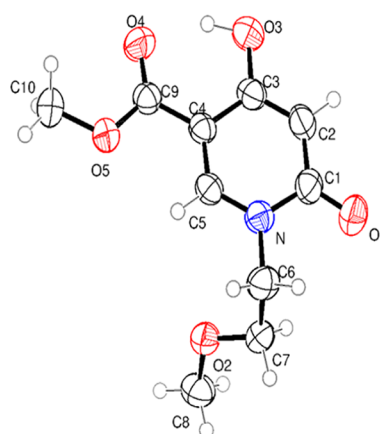


Figure 3. Molecular structure of compound 4{20}.

amines 3{20–27} (Figure 1) to furnish title compounds 11 in 48–98% yield. Since BPC-mediated amidation affords only volatile byproduct, it allows simple evaporative workup. Thus, all seventeen title compounds 11 were primarily isolated just by filtration of the reaction mixtures (to remove the precipitated ammonium salts) followed by thorough evaporation of the filtrates at 100 °C/0.01 Torr (Workup A). Ten products, compounds 11{16/1/20,23}, 11{16/3/20,21,23}, 11{18/1/

Table 5. Experimental Data on Compounds 11^a

Entry	Compound	R ¹	R ²	R ³ R ⁴ NH (3)	Workup	Yield (%)
1	11{16/1/20}	Ph	Ph	MeOCH ₂ CH ₂ NH ₂	A	96
2	11{16/1/21}	Ph	Ph	PhCH ₂ NH ₂	B	78 ^b
3	11{16/1/23}	Ph	Ph	Me ₂ NCH ₂ CH ₂ NH ₂	A	98
4	11{16/1/26}	Ph	Ph		B	48
5	11{16/3/20}	Ph	3-chlorophenyl	MeOCH ₂ CH ₂ NH ₂	A	91
6	11{16/3/21}	Ph	3-chlorophenyl	PhCH ₂ NH ₂	A	85 ^b
7	11{16/3/23}	Ph	3-chlorophenyl	Me ₂ NCH ₂ CH ₂ NH ₂	A	98
8	11{18/1/20}	Me	Ph	MeOCH ₂ CH ₂ NH ₂	A	87 ^b
9	11{18/1/21}	Me	Ph	PhCH ₂ NH ₂	A	84 ^b
10	11{18/1/22}	Me	Ph		B	57
11	11{18/1/23}	Me	Ph	Me ₂ NCH ₂ CH ₂ NH ₂	B	91 ^b
12	11{18/1/24}	Me	Ph		B	54 ^b
13	11{18/1/25}	Me	Ph		B	62 ^b
14	11{18/3/20}	Me	3-chlorophenyl	MeOCH ₂ CH ₂ NH ₂	A	83 ^b
15	11{18/3/21}	Me	3-chlorophenyl	PhCH ₂ NH ₂	A	80
16	11{18/3/23}	Me	3-chlorophenyl	Me ₂ NCH ₂ CH ₂ NH ₂	A	97
17	11{20/3/27}	MeO(CH ₂) ₂ -	3-chlorophenyl		B	92

^aAll products were obtained in ≥80% purity (determined by LC-MS and ¹H NMR). ^bAnalytical purity was confirmed by elemental analysis. The found values for C, H, and N were within ±0.4% range with respect to the theoretical values.

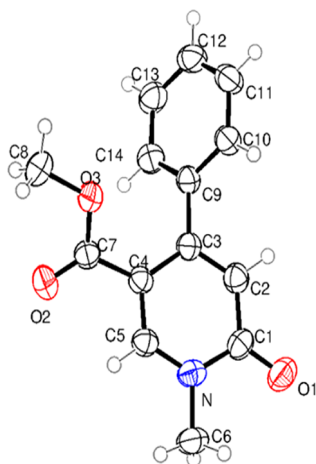


Figure 4. Molecular structure of compound 8{18/1}.

20,21}, and 11{18/3/20,21,23} were obtained in this way in 83–98% yield and in 80–98% purity. The purity of seven other products, 11{16/1/21,26}, 11{18/1/22–25}, and 11{20/3/27} was not satisfactory upon Workup A. These crude products were further purified by trituration with 1 M hydrochloric acid followed by extraction with ethyl acetate (Workup B) to give the corresponding purified products 11 in 48–92% yield and in 87–100% purity. Of the seventeen final library members 11, seven were $\geq 95\%$ pure as confirmed also by elemental analyses for C, H, and N (Scheme 6, Table S).

The structures and purities of novel compounds in chemsets 4–6, 8, 9, and 11 were determined by spectroscopic methods (IR, NMR, MS, HRMS), by LC-MS, and by elemental analyses for C, H, and N. Physical and spectral data for known compounds 4{17} and 4{18} were in agreement with the literature data.¹⁸ Characterization data for all compounds of chemsets 4–6, 8, 9, and 11 are given in the Supporting Information.

The structures of compounds 4{20} and 8{18/1} were determined by X-ray diffraction (Figures 3 and 4, see also the Supporting Information).

CONCLUSION

A five-step parallel solution-phase synthesis of 1-substituted 4-aryl-6-oxo-1,6-dihydropyridine-3-carboxamides 11 from dimethyl 3-oxopentanedioate (1) was developed. The synthesis starts with one-pot preparation of methyl 4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylates 4. O-tosylation or nucleophilic chlorination of 4-hydroxypyridines 4, followed by Suzuki–Miyaura cross-coupling of the corresponding tosyloxy- 5 or chloro derivatives 6 with arylboronic acids 7 gave 4-aryl-6-oxo-1,6-dihydropyridine-3-carboxylates 8 as the key-intermediates. Combinatorial screening was crucial for determining of the optimal reaction conditions for the synthesis of 1-alkyl-4-arylpriodones 8. Hydrolysis of the esters 8 followed by BPC-mediated parallel solution-phase amidation of the acids 9 gave the title compounds 11 in good yields and purities. Typical overall yield of the final carboxamides 11 obtained from the representative amines 3{20,21,23} and 1-arylcarboxylic acids 9{16/1,3} ($\sim 20\%$, $R^1 = \text{Ph}$, $R^2 = \text{Ar}$) and 8{18/1,3} ($\sim 15\%$, $R^1 = \text{Me}$, $R^2 = \text{Ar}$) shows that the method is somewhat more efficient for the preparation of the 1-aryl- than for the 1-alkyl substituted compounds. In summary, this method allows introduction of diverse substituents at three different positions:

N(1), C(4), and the carboxy group in the 6-oxo-1,6-dihydropyridine-3-carboxylic acid core. Hence, it offers an easy access to 1-substituted 4-aryl-6-oxo-1,6-dihydropyridine-3-carboxamides 11 and could also serve as a useful tool for the preparation of novel compound libraries for pharmaceutical and other practical applications.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and the representative spectra for chemsets 4–6, 8, 9, and 11. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written with contributions from all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

ABBREVIATIONS

BPC, bis(pentafluorophenyl) carbonate; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; DMF-DMA, *N,N*-dimethylformamide dimethylacetal; TLC, thin layer chromatography

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