Efficient Synthesis of New 8-Aryl Tricyclic Pyridinones

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Abstract: New tricyclic pyridinones were synthesized from 6-bromo-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine in four steps involving a Suzuki–Miyaura cross-coupling reaction and a direct olefination with diethyl ketomalonate as key steps. Subsequent one-pot reduction–cyclization provided new ethyl 8-aryl-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3′,2′-*d*]imidazole-3-carboxylates.

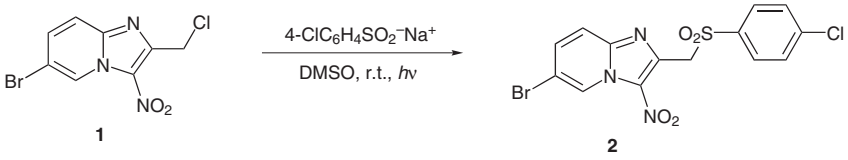
Key words: Suzuki–Miyaura cross-coupling, sulfones, diethyl methylenemalonate, nitro reduction, pyridin-2-ones

Pyridin-2(1*H*)-ones are attractive and important reagents in organic synthesis.[1] Among fused pyridin-2(1*H*)-one derivatives with pharmacological activities, tricyclic pyridinones have been the subject of several recent reports. Indeed, they are interesting intermediates in the synthesis of important drugs or drug candidates [e.g. the antitumor agent (+)-camptothecin,[2] benzodiazepine receptor ligands,[3–5] or subtype-selective $GABA_A$ receptor antagonists[6]]. Various syntheses of tricyclic pyridinones have been developed to find new compounds with enhanced biological activities.[7]

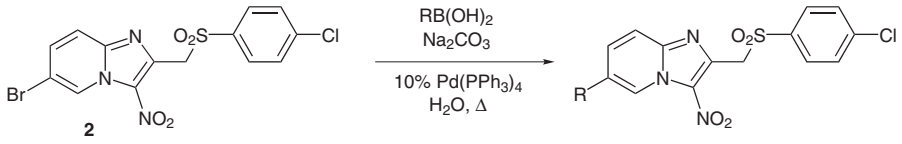
In continuation of our program directed towards the study of Suzuki–Miyaura reaction[8] in 2-arylsulfonylmethyl-6-halo-3-nitroimidazo[1,2-*a*]pyridine series and the reactivity of sulfonyl carbanion derivatives with diethyl ketomalonate involving an original direct olefination,[9] we report herein an original and efficient four-step synthesis of new 8-aryl tricyclic pyridinones. These potentially bioactive pyridinones for the treatment of central nervous system disorders[10,11] were synthesized from 6-bromo-3-nitroimidazo[1,2-*a*]pyridine bearing the 4-chlorophenylsulfonylmethyl group in an *ortho*-like position to the nitro group.

The first step is the synthesis of 6-bromo-2-(4-chlorophenylsulfonyl)methyl-3-nitroimidazo[1,2-*a*]pyridine (**2**), which was performed by reaction of sodium 4-chlorobenzenesulfinate and 6-bromo-2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine (**1**) in DMSO. In the presence of two equivalents of sodium 4-chlorobenzenesulfinate and under photostimulation in DMSO, **1** reacts only at the chloromethyl position with good yield probably following a S_N2 mechanism[12,13] (Scheme 1).

Several new sulfonyl derivatives **3a**–**g** were obtained from **2** by cross-coupling reactions with some arylboronic acids in aqueous medium (Scheme 2). The 4-chlorosulfonyl compound **2** with bromine atom in 6-position was reacted with arylboronic acids according to Suzuki–Miyaura reaction in water using $Pd(PPh_3)_4$ as catalyst. This method required 10 mol% of $Pd(PPh_3)_4$ as catalyst, 5 equivalents of Na_2CO_3 as base and 1.3 equivalents of aryl-



Scheme 1



Scheme 2

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boronic acid.[13] A large amount of base was employed because of the easy formation of the sulfonyl anion of **2**. The formation of the sulfonyl anion in basic medium allows a better solubility of the reagent in water, which allows the cross-coupling reaction to proceed in aqueous medium.

The reaction was carried out by refluxing a mixture of 6-bromo-2-(4-chlorophenyl)sulfonylmethyl-3-nitroimidazo[1,2-*a*]pyridine (**2**), arylboronic acid, $Pd(PPh_3)_4$, and Na_2CO_3 in water, from 2–3.5 hours, until the disappearance of starting materials as monitored by TLC. No organic solvent or co-solvent was used or investigated. Although the reaction mixtures were non-homogeneous and aggregated, the overall yields were good. Some yields appeared to suffer from difficulties in the extractive work-up. Moreover, the aggregation coupled with the high surface tension of water, diminishes the surface contact between hydrophobic species and water molecules.[14] Under these conditions **3a**–**g** were obtained in moderate to good yields (Scheme 2, Table 1) and the structure of the boronic acid had little influence on the yield, even if the best yields were obtained with boronic acids bearing an electron-withdrawing group (Table 1, entries 4 and 5). Furthermore, no by-product was observed from a possible cross-coupling reaction with the chlorine atom on the *p*-sulfonyl group.

The arylsulfonyl derivatives **3a**–**g** prepared by the Suzuki–Miyaura cross-coupling reaction were studied for the reactivity of the sulfonyl carbanion with diethyl ketomalonate. Compounds **3a**–**g** were metalated in DMSO under argon at room temperature by reaction with 60% NaH for 1 hour and reacted with diethyl ketomalonate at room temperature for 12 to 24 hours. After work-up and purification, this reaction led directly to diethyl methylenemalonate derivatives **4a**–**g** in moderate yields as expected and not to the β-alkoxysulfones (Scheme 3, Table 2).

Table 1 Cross-Coupling Reactions of **2** with Arylboronic Acids[a]

Entry	R	Product	Time (h)	Yield (%)
1	C_6H_5	**3a**	3	60
2	2-$CH_3C_6H_4$	**3b**	2	70
3	4-$CH_3OC_6H_4$	**3c**	2	56
4	4-FC_6H_4	**3d**	3.5	73
5	3-$CF_3C_6H_4$	**3e**	3	70
6	2-naphthyl	**3f**	3	67
7	1-naphthyl	**3g**	3	67

[a] Conditions: catalyst $Pd(PPh_3)_4$ (10 mol%), 6-bromo-2-(4-chlorophenyl)sulfonylmethyl-3-nitroimidazo[1,2-*a*]pyridine (1 equiv), arylboronic acid (1.3 equiv), Na_2CO_3 (5 equiv), H_2O, 100 °C.

Table 2 Reactions of Sulfonyl Carbanions with Diethyl Ketomalonate[a]

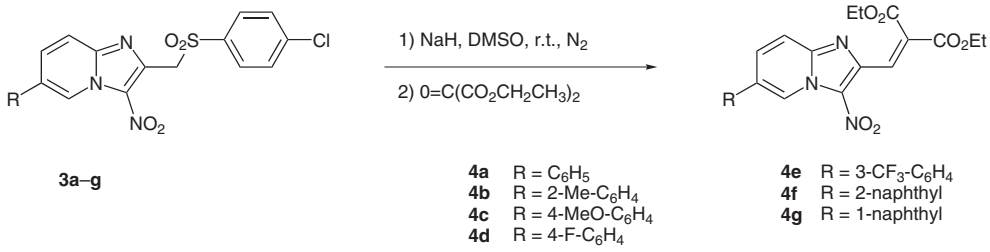
Entry	R	Product	Time (h)	Yield (%)
1	C_6H_5	**4a**	24	35
2	2-$CH_3C_6H_4$	**4b**	24	35
3	4-$CH_3OC_6H_4$	**4c**	24	50
4	4-FC_6H_4	**4d**	24	31
5	3-$CF_3C_6H_4$	**4e**	12	31
7	2-naphthyl	**4f**	24	32
8	1-naphthyl	**4g**	24	35

[a] Conditions: 6-aryl-2-(4-chlorophenyl)sulfonylmethyl-3-nitroimidazo[1,2-*a*]pyridine (1 equiv), diethyl ketomalonate (1.5 equiv), NaH (1.1 equiv), and DMSO. All reactions are performed at r.t. under N_2 and irradiated with a fluorescent lamp (60 W).

The analogous sulfonyl carbanions of 6-aryl-3-nitro-2-phenylsulfonylmethylimidazo[1,2-*a*]pyridine[13] and 6-aryl-3-nitro-2-(tosylmethyl)imidazo[1,2-*a*]pyridine[13] were found as reactive as the sulfone derivatives **3a**–**g** under these experimental conditions. The chlorine or hydrogen atom or the methyl group as substituent in the *para* position to the sulfonyl group does not seem to have a strong effect on the reactivity.

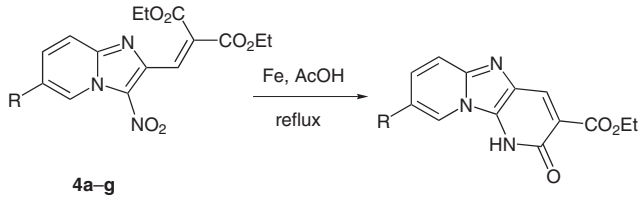
This study also shows an enhanced reactivity of 6-arylsulfonyl carbanion derivatives with diethyl ketomalonate, as disclosed recently[9] in the direct Julia olefination used for the preparation of the 3-nitroimidazo[1,2-*a*]pyridines bearing the diethyl methylenemalonate group in the 2-position. This enabled the preparation of the precursors **4** of the desired functionalized tricyclic pyridinones **5**.

Finally, taking into account the high degree of functionalization of the pyridinone precursors (malonic acid diethyl ester, conjugated double bond, nitro group, heterocyclic ring with nucleophilic heteroatom) we chose a mixture of iron powder in glacial acetic acid as the reducing agent.[15]



Scheme 3

After refluxing diester derivatives **4a–g** in glacial acetic acid with an excess of iron powder (28 equiv) for 2–24 hours, and work-up, the target lactams **5a–g** were obtained in moderate to good yields in a one-pot reduction-cyclization reaction (Scheme 4, Table 3).



4a–g

5a R = C_6H_5
5b R = 2-Me-C_6H_4
5c R = 4-MeO-C_6H_4
5d R = 4-F-C_6H_4
5e R = 3-CF_3-C_6H_4
5f R = 2-naphthyl
5g R = 1-naphthyl

Scheme 4

Table 3 Reduction Reactions of the Nitro Group and Cyclization of the Resulting Amino Derivatives[a]

Entry	R	Product	Time (h)	Yield (%)
1	C_6H_5	**5a**	24	68
2	2-$CH_3C_6H_4$	**5b**	24	31
3	4-$CH_3OC_6H_4$	**5c**	2	46
4	4-FC_6H_4	**5d**	24	42
5	3-$CF_3C_6H_4$	**5e**	24	30
7	2-naphthyl	**5f**	24	30
8	1-naphthyl	**5g**	4	44

[a] Conditions: diethyl 2-(6-aryl-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene)malonate (1 equiv), iron powder (28 equiv), glacial AcOH, 115 °C.

In conclusion, an efficient method for the preparation of new ethyl 8-aryl-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3′,2′-*d*]imidazole-3-carboxylates has been developed on the basis of palladium-mediated coupling of arylboronic acid and reaction of sulfonyl carbanions with diethyl ketomalonate. Moreover, we have shown the functional compatibility of the 4-chlorophenylsulfonylmethyl group in *ortho*-like position of the nitro group in the Suzuki reaction with 6-bromo-2-(4-chlorophenylsulfonyl)methyl-3-nitroimidazo[1,2-*a*]pyridine (**2**).

Melting points were determined with a B-540 Büchi melting point apparatus. 200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR spectra were recorded on a Bruker ARX 200 spectrometer in $CDCl_3$ solution at the Faculté de Pharmacie de Marseille. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm with respect to $CHCl_3$ 7.26 ppm (^{1}H) and 76.9 ppm (^{13}C). Elemental analyses were carried out at the Centre de Microanalyses de la Faculté des Sciences et Techniques de Saint-Jérôme and at the Service Central d'Analyse du Centre National de la Recherche Scientifique de Vernaison. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC analyses were performed on 5 cm × 10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate solvent. 6-Bromo-2-(chloromethyl)-3-nitroimidazo [1,2-*a*]pyridine (**1**) was prepared as previously described.[13]

6-Bromo-2-(4-chlorophenyl)sulfonylmethyl-3-nitroimidazo[1,2-*a*]pyridine (2)

To a solution of sodium 4-chlorobenzenesulfinate (4.09 g, 20.6 mmol) in DMSO (45 mL) under N_2, was added **1** (3.0 g, 10.3 mmol) and the mixture was irradiated with a tungsten lamp (60 W) . The mixture was stirred at r.t. for 3 h. After the disappearance of **1** (monitored by TLC), the mixture was poured into an ice-water mixture. The precipitated solid was collected by filtration and dried in the air to give after purification by recrystallization from toluene 2.66 g (60%) of **2** as white solid; mp 220 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.12 (s, 2 H), 7.48–7.55 (m, 2 H), 7.69–7.94 (m, 4 H), 9.54 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.7, 112.6, 119.1, 127.7, 129.6, 129.8, 134.7, 137.5, 139.2, 141.1, 143.3.

Anal. Calcd for $C_{14}H_9BrClN_3O_4S$: C, 39.04; N, 9.76; H, 2.11. Found: C, 39.37; N, 10.00; H, 2.24.

Cross-Coupling Reaction of Heteroaryl Bromides with Arylboronic Acids; 2-(4-Chlorophenyl)sulfonylmethyl-3-nitro-6-phenylimidazo[1,2-*a*]pyridine (3a); Typical Procedure

A mixture of phenylboronic acid (180 mg, 1.48 mmol) with **2** (500 mg, 1.16 mmol), $Na_2CO_3·10H_2O$ (1.66 g, 5.80 mmol) and $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol) in demineralized H_2O (20 mL) was refluxed for 2–3.5 h (Table 1). After disappearance of **2** (monitored by TLC), the mixture was cooled and the solid was collected by filtration and dried in the air. The crude product was purified by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 9:1) and recrystallized from *i*-PrOH, to give 298 mg (60%) of **3a** as yellow solid; mp 192 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.17 (s, 2 H), 7.44–7.96 (m, 11 H), 9.56 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.9, 118.4, 125.0, 127.4, 129.2, 129.5, 129.6, 130.0, 131.7, 132.1, 135.6, 137.8, 139.5, 141.0, 144.2.

Anal. Calcd for $C_{20}H_{14}ClN_3O_4S$: C, 56.14; H, 3.30; N, 9.82. Found: C, 56.46; H, 3.35; N, 9.74.

2-(4-Chlorophenyl)sulfonylmethyl-6-(2-methylphenyl)-3-nitroimidazo[1,2-*a*]pyridine (3b)

Cross-coupling reaction of 2-methylphenylboronic acid (160 mg, 1.18 mmol) with **2** (400 mg, 0.93 mmol), $Na_2CO_3·10H_2O$ (1.33 g, 4.64 mmol) and $Pd(PPh_3)_4$ (0.10 g, 0.09 mmol) gave, after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 9:1) and recrystallization from *i*-PrOH, 288 mg (70%) of **3b** as black solid; mp 193 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 5.19 (s, 2 H), 7.28–7.40 (m, 4 H), 7.54 (d, *J* = 8.3 Hz, 2 H), 7.68 (dd, *J* = 1.6, 9.1 Hz, 1 H), 7.84–7.90 (m, 3 H), 9.36 (dd, *J* = 1.0, 1.6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.4, 56.9, 117.7, 126.5, 126.6, 129.2, 129.6, 129.9, 130.0, 131.0, 132.3, 133.6, 135.7, 135.8, 137.9, 139.4, 141.0, 144.0.

Anal. Calcd for $C_{21}H_{16}ClN_3O_4S$: C, 57.08; H, 3.65; N, 9.51. Found: C, 57.00; H, 3.73; N, 9.26.

2-(4-Chlorophenyl)sulfonylmethyl-6-(4-methoxyphenyl)-3-nitroimidazo[1,2-*a*]pyridine (3c)

Cross-coupling reaction of 4-methoxyphenylboronic acid (230 mg, 1.51 mmol) with **2** (500 mg, 1.16 mmol), $Na_2CO_3·10H_2O$ (1.66 g, 5.80 mmol) and $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol), gave after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc,

9:1) and recrystallization from *i*-PrOH, 300 mg (56%) of **3c** as yellow solid; mp 160 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 5.16 (s, 2 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.9 Hz, 2 H), 7.81 (d, *J* = 8.8 Hz, 2 H), 7.85–7.92 (m, 2 H), 9.51 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.5, 56.9, 115.0, 118.3, 124.3, 127.8, 128.5, 129.5, 129.9, 131.5, 131.8, 137.7, 139.4, 141.0, 144.0, 160.5.

Anal. Calcd for $C_{21}H_{16}ClN_3O_5S$: C, 55.08; H, 3.52; N, 9.18. Found: C, 55.28; H, 3.63; N, 9.32.

2-(4-Chlorophenyl)sulfonylmethyl-6-(4-fluorophenyl)-3-nitroimidazo[1,2-*a*]pyridine (3d)

Cross-coupling reaction of 4-fluorophenylboronic acid (210 mg, 1.50 mmol) with **2** (500 mg, 1.16 mmol), $Na_2CO_3·10H_2O$ (1.66 g, 5.80 mmol), $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol), gave after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 9:1) and recrystallization from *i*-PrOH, 380 mg (73%) of **3d** as yellow solid; mp 265 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.18 (s, 2 H), 7.20–7.29 (m, 2 H), 7.50–7.89 (m, 8 H), 9.55 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.9, 116.4, 116.8, 118.5, 124.9, 128.4, 129.1, 129.3, 129.6, 129.9, 131.1, 131.5, 131.7, 131.8, 137.7, 139.6, 141.0, 144.1, 163.4.

Anal. Calcd for $C_{20}H_{13}ClFN_3O_4S$: C, 53.88; H, 2.94; N, 9.42. Found: C, 54.05; H, 3.17; N, 9.35.

2-(4-Chlorophenyl)sulfonylmethyl-3-nitro-6-[3-(trifluoromethyl)phenyl]imidazo[1,2-*a*]pyridine (3e)

Cross-coupling reaction of 3-(trifluoromethyl)phenylboronic acid (290 mg, 1.52 mmol) with **2** (500 mg, 1.16 mmol), $Na_2CO_3·10H_2O$ (1.66 g, 5.80 mmol) and $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol), gave after purification by column chromatography (silica gel, eluent: $CHCl_3$) and recrystallization from *i*-PrOH, 400 mg (70%) of **3e** as beige solid; mp 224 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.18 (s, 2 H), 7.51–7.94 (m, 10 H), 9.61 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.9, 118.8, 124.9, 125.0, 125.4, 126.4, 129.6, 129.9, 130.2, 130.6, 130.7, 130.8, 131.2, 132.1, 136.6, 137.7, 139.8, 141.1, 144.2.

Anal. Calcd for $C_{21}H_{13}ClF_3N_3O_4S$: C, 50.87; H, 2.64; N, 8.47. Found: C, 51.17; H, 2.88; N, 8.38.

2-(4-Chlorophenyl)sulfonylmethyl-6-(naphthalen-2-yl)-3-nitroimidazo[1,2-*a*]pyridine (3f)

Cross-coupling reaction of naphthalen-2-ylboronic acid (260 mg, 1.51 mmol) with **2** (500 mg, 1.16 mmol), $Na_2CO_3·10H_2O$ (1.66 g, 5.80 mmol) and $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol), gave after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 9:1) and recrystallization from *i*-PrOH, 370 mg (67%) of **3f** as yellow solid; mp 262 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.20 (s, 2 H), 7.51–8.10 (m, 13 H), 9.71 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 57.0, 117.7, 124.6, 125.4, 126.5, 127.1, 127.2, 128.0, 128.8, 129.6, 129.7, 130.0, 131.4, 133.8, 133.9, 134.3, 137.9, 139.5, 141.1, 144.2.

Anal. Calcd for $C_{24}H_{16}ClN_3O_4S$: C, 60.31; H, 3.37; N, 8.79. Found: C, 60.56; H, 3.48; N, 8.61.

2-(4-Chlorophenyl)sulfonylmethyl-6-(naphthalen-1-yl)-3-nitroimidazo[1,2-*a*]pyridine (3g)

Cross-coupling reaction of naphthalen-1-ylboronic acid (260 mg, 1.51 mmol) with **2** (500 mg, 1.16 mmol), $Na_2CO_3·10H_2O$ (1.66 g, 5.80 mmol), $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol), gave after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 9:1) and recrystallization from EtOAc, 370 mg (67%) of **3g** as yellow solid; mp 246 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.21 (s, 2 H), 7.49–8.02 (m, 13 H), 9.52 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 57.0, 117.7, 124.6, 125.4, 126.5, 127.1, 127.2, 128.0, 128.8, 129.6, 129.7, 130.0, 131.4, 133.8, 133.9, 134.3, 137.9, 139.5, 141.1, 142.2.

Anal. Calcd for $C_{24}H_{16}ClN_3O_4S$: C, 60.31; H, 3.37; N, 8.79. Found: C, 60.13; H, 3.39; N, 8.85.

Reactions of Sulfonyl Carbanions with Diethyl Ketomalonate; Diethyl 2-(3-Nitro-6-phenylimidazo[1,2-*a*]pyridin-2-ylmethylene)malonate (4a); Typical Procedure

To a solution of **3a** (0.54 g, 1.27 mmol) in DMSO (10 mL) was added NaH (60% dispersion in mineral oil, 0.06 g, 1.40 mmol) under N_2 and the mixture was irradiated with a tungsten lamp (60 W). The mixture was stirred 1 h at r.t. and diethyl ketomalonate (0.33 g, 1.90 mmol) was added dropwise over a period of about 10 min. The mixture was stirred at r.t. for 24 h and then poured into ice-water mixture (200 mL). The aqueous solution was extracted with Et_2O (5 × 100 mL) and the combined organic extracts were washed with H_2O (2 × 20 mL) and dried ($MgSO_4$). Filtration and removal of the solvent on a rotary evaporator followed by a flash chromatography on silica gel (eluent: cyclohexane–EtOAc, 1:1) and recrystallization from *i*-PrOH gave 182 mg (35%) of **4a** as yellow solid; mp 205 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.1 Hz, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 7.48–7.66 (m, 5 H), 7.78 (dd, *J* = 0.9, 9.3 Hz, 1 H), 7.88 (dd, *J* = 1.7, 9.3 Hz, 1 H), 8.48 (s, 1 H), 9.60 (dd, *J* = 0.9, 1.7 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.1, 61.7, 62.1, 118.5, 124.8, 127.3, 129.1, 129.2, 129.4, 131.6, 131.8, 133.6, 135.7, 142.3, 144.1, 163.3, 165.6.

Anal. Calcd for $C_{21}H_{19}N_3O_6$: C, 61.61; H, 4.68; N, 10.26. Found: C, 61.98; H, 4.77; N, 10.38.

Diethyl 2-[6-(2-Methylphenyl)-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene]malonate (4b)

The reaction of sulfonyl derivative **3b** (90 mg, 0.2 mmol) with NaH (60%, 8.8 mg, 0.22 mmol) and diethyl ketomalonate (52 mg, 0.3 mmol) gave after purification by column chromatography (silica gel, eluent: cyclohexane–EtOAc, 1:1) and recrystallization from *i*-PrOH, 30 mg (35%) of **4b** as yellow solid; mp 153 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.1 Hz, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 2.31 (s, 3 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 7.29–7.39 (m, 4 H), 7.47 (q, *J* = 7.2 Hz, 2 H), 7.63 (dd, *J* = 1.7, 9.2 Hz, 1 H), 7.76 (dd. *J* = 0.9, 9.2 Hz, 1 H), 8.49 (s, 1 H), 9.37 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.1, 20.4, 61.8, 62.2, 117.8, 126.5, 129.1, 129.3, 130.0, 130.9, 132.1, 133.5, 133.7, 135.7, 135.8, 142.3, 144.0, 163.3, 165.7.

Anal. Calcd for $C_{22}H_{21}N_3O_6$: C, 62.41; H, 5.00; N, 9.92. Found: C, 62.00; H, 5.05; N, 9.83.

Diethyl 2-[6-(4-Methoxyphenyl)-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene]malonate (4c)

The reaction of sulfonyl derivative **3c** (330 mg, 0.72 mmol) with NaH (60%, 30 mg, 0.79 mmol) and diethyl ketomalonate (188 mg, 1.08 mmol) gave after purification by column chromatography (silica gel, eluent: cyclohexane–EtOAc, 1:1) and recrystallization from *i*-PrOH, 160 mg (50%) of **4c** as orange solid; mp 166 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.1 Hz, 3 H), 1.39 (t, *J* = 7.0 Hz, 3 H), 3.89 (s, 3 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.46 (q,

J = 7.1 Hz, 2 H), 7.05 (d, *J* = 8.9 Hz, 2 H), 7.56 (d, *J* = 8.8 Hz, 2 H), 7.75 (dd, *J* = 1, 9.3 Hz, 1 H), 7.86 (dd, *J* = 1.8, 9.3 Hz, 1 H), 8.48 (s, 1 H), 9.55 (dd, *J* = 0.9, 1.8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.1, 55.5, 61.7, 62.1, 114.9, 118.4, 124.2, 128.0, 128.5, 129.3, 131.5, 133.4, 142.2, 144.0, 160.5, 163.3, 165.7, 171.1.

Anal. Calcd for $C_{22}H_{21}N_3O_7$: C, 60.13; H, 4.82; N, 9.56. Found: C, 59.87; H, 4.86; N, 9.93.

Diethyl 2-[6-(4-Fluorophenyl)-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene]malonate (4d)

The reaction of sulfonyl derivative **3d** (300 mg, 0.67 mmol) with NaH (60%, 30 mg, 0.74 mmol) and diethyl ketomalonate (174 mg, 1.0 mmol) gave, after purification by column chromatography (silica gel, eluent: cyclohexane–EtOAc, 1:1) and recrystallization from *i*-PrOH, 89 mg (31%) of **4d** as yellow solid; mp 190 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.1 Hz, 3 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 7.19–7.28 (m, 2 H), 7.57–7.61 (m, 2 H), 7.71 (dd, *J* = 1.1, 9.3 Hz, 1 H), 7.85 (dd, *J* = 1.7, 9.3 Hz, 1 H), 8.48 (s, 1 H), 9.56 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.1, 61.8, 62.2, 116.4, 116.8, 118.6, 124.7, 129.1, 129.2, 130.9, 131.4, 131.9, 132.0, 133.7, 138.6, 142.4, 144.1, 164.5.

Anal. Calcd for $C_{21}H_{18}FN_3O_6$: C, 59.02; H, 4.25; N, 9.83. Found: C, 59.28; H, 4.39; N, 9.88.

Diethyl 2-[6-(3-Trifluoromethylphenyl)-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene]malonate (4e)

The reaction of sulfonyl derivative **3e** (350 mg, 0.7 mmol) with NaH (60%, 30 mg, 0.77 mmol) and diethyl ketomalonate (183 mg, 1.05 mmol) (reaction time 12 h) gave after purification by column chromatography (silica gel, eluent: cyclohexane–EtOAc, 1:1) and recrystallization from *i*-PrOH, 104 mg (31%) of **4e** as yellow solid; mp 150 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.2 Hz, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 4.48 (q, *J* = 7.2 Hz, 2 H), 7.67–7.90 (m, 6 H), 8.47 (s, 1 H), 9.62 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.1, 61.8, 62.3, 118.9, 123.3, 124.1, 125.2, 129.0, 130.1, 130.4, 130.7, 131.2, 132.1, 134.0, 136.7, 142.6, 144.1, 163.2, 165.6.

Anal. Calcd for $C_{22}H_{18}F_3N_3O_6$: C, 55.35; H, 3.80; N, 8.66. Found: C, 55.48; H, 3.81; N, 8.90.

Diethyl 2-[6-(Naphthalen-2-yl)-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene]malonate (4f)

The reaction of sulfonyl derivative **3f** (190 mg, 0.40 mmol) with NaH (60%, 17 mg, 0.44 mmol) and diethyl ketomalonate (104 mg, 0.60 mmol) gave after purification by column chromatography (silica gel, eluent: cyclohexane–EtOAc, 1:1) and recrystallization from *i*-PrOH, 59 mg (32%) of **4f** as yellow solid; mp 153 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.1 Hz, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.48 (q, *J* = 7.1 Hz, 2 H), 7.54–8.08 (m, 9 H), 8.49 (s, 1 H), 9.70 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.1, 61.8, 62.1, 118.5, 124.5, 125.0, 126.6, 127.0, 127.7, 128.3, 129.2, 129.4, 131.7, 132.8, 133.2, 133.4, 133.6, 142.3, 144.1, 163.3, 165.7.

Anal. Calcd for $C_{25}H_{21}N_3O_6$: C, 65.35; H, 4.61; N, 9.15. Found: C, 65.40; H, 4.65; N, 9.40.

Diethyl 2-[6-(Naphthalen-1-yl)-3-nitroimidazo[1,2-*a*]pyridin-2-ylmethylene]malonate (4g)

The reaction of sulfonyl derivative **3g** (70 mg, 0.15 mmol) with NaH (60%, 6.4 mg, 0.16 mmol) and diethyl ketomalonate (40 mg, 0.23 mmol) gave after purification by column chromatography (silica gel, eluent: cyclohexane–EtOAc, 1:1) and recrystallization from *i*-PrOH, 24 mg (35%) of **4g** as yellow solid; mp 186 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.2 Hz, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 4.49 (q, *J* = 7.2 Hz, 2 H), 7.46–8.01 (m, 9 H), 8.50 (s, 1 H), 9.52 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.1, 61.8, 62.2, 117.8, 124.6, 125.4, 126.5, 127.0, 127.1, 127.9, 128.8, 129.2, 129.6, 131.1, 131.3, 133.7, 133.8, 134.2, 142.3, 144.1, 163.3, 165.7.

Anal. Calcd for $C_{25}H_{21}N_3O_6$: C, 65.35; H, 4.61; N, 9.15. Found: C, 65.37; H, 4.72; N, 9.05.

Reduction of the Nitro group and Cyclization of the Resulting Amino Derivatives; Ethyl 2-Oxo-8-phenyl-1,2-dihydrodipyrido[1,2-*a*;3′,2′-*d*]imidazole-3-carboxylate (5a)

In a two-necked flask equipped with a reflux condenser, **4a** (200 mg, 0.49 mmol) and glacial AcOH (10 mL) were stirred and heated at reflux. To this solution was added iron powder (766 mg, 13.72 mmol). The reflux was maintained for 24 h. After cooling, the solution was filtered through Celite and washed with glacial AcOH. The AcOH solution was evaporated on a rotary evaporator and the residue basified with aq sat. solution of Na_2CO_3. The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), and evaporated on a rotary evaporator to give, after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 4:1) and recrystallization from *i*-PrOH, 111 mg (68%) of **5a** as yellow solid; mp 218 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.50 (t, *J* = 7.1 Hz, 3 H), 4.53 (q, *J* = 7.1 Hz, 2 H), 7.41–7.78 (m, 7 H), 8.85 (s, 1 H), 11.88 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 62.5, 107.2, 118.3, 121.4, 125.8, 126.7, 128.3, 129.3, 131.6, 132.3, 136.3, 161.3, 169.8.

Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.29; H, 4.61; N, 12.54.

Ethyl 8-(2-Methylphenyl)-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3′,2′-*d*]imidazole-3-carboxylate (5b)

The reduction and cyclization of **4b** (600 mg, 1.42 mmol) in glacial AcOH (10 mL) with iron powder (2.22 g, 39.76 mmol) gave, after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 8:2) and recrystallization from *i*-PrOH, 150 mg (31%) of **5b** as yellow solid; mp 169 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 7.1 Hz, 3 H), 2.35 (s, 3 H), 4.53 (q, *J* = 7.1 Hz, 2 H), 7.27–7.34 (m, 4 H), 7.46 (dd, *J* = 0.8, 9.6 Hz, 1 H), 7.65 (dd, *J* = 0.7, 9.6 Hz, 1 H), 8.59 (s, 2 H), 8.81 (s, 2 H), 11.86 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.4, 62.5, 107.1, 117.4, 123.1, 126.1, 126.3, 128.5, 129.8, 130.8, 132.2, 133.7, 135.9, 136.5, 143.3, 148.3, 161.2, 169.8.

Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.16; H, 5.03; N, 12.14.

Ethyl 8-(4-Methoxyphenyl)-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3′,2′-*d*]imidazole-3-carboxylate (5c)

The reduction and cyclization of **4c** (250 mg, 0.57 mmol) in glacial AcOH (10 mL) with iron powder (891 mg, 15.96 mmol) (reaction time, 2 h) gave, after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 8:2) and recrystallization from *i*-PrOH, 95 mg (46%) of **5c** as green solid; mp 246 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 6.8 Hz, 3 H), 3.87 (s, 3 H), 4.53 (q, *J* = 6.8 Hz, 2 H), 7.02 (d, *J* = 7.9 Hz, 2 H), 7.54 (d, *J* = 7.9 Hz, 2 H), 7.67 (m, 2 H), 8.78 (m, 2 H), 11.87 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 55.4, 62.5, 107.1, 114.7, 118.2, 120.5, 125.4, 127.8, 128.7, 131.6, 132.2, 143.4, 148.4, 159.8, 161.1, 169.8.

Anal. Calcd for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56. Found: C, 65.77; H, 4.78; N, 11.47.

Ethyl 8-(4-Fluorophenyl)-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3′,2′-*d*]imidazole-3-carboxylate (5d)

The reduction and cyclization of **4d** (320 mg, 0.75 mmol) in glacial AcOH (10 mL) with iron powder (1.17 g, 21.00 mmol) gave, after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 8:2) and recrystallization from *i*-PrOH, 110 mg (42%) of **5d** as yellow solid; mp 246 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 7.1 Hz, 3 H), 4.52 (q, *J* = 7.1 Hz, 2 H), 7.14–7.65 (m, 7 H), 8.78 (s, 1 H), 11.87 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 62.5, 107.2, 116.3, 118.4, 121.2, 124.7, 128.4, 131.3, 131.6, 132.3, 132.4, 132.5, 143.4, 161.2, 169.7, 162.9.

Anal. Calcd for $C_{19}H_{14}FN_3O_3$: C, 64.95; H, 4.02; N, 11.96. Found: C, 64.74; H, 4.08; N, 11.78.

Ethyl 8-(3-Trifluoromethylphenyl)-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3′,2′-*d*]imidazole-3-carboxylate (5e)

The reduction and cyclization of **4e** (250 mg, 0.52 mmol) in glacial AcOH (10 mL) with iron powder (813 mg, 14.56 mmol) gave, after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 9:1) and recrystallization from *i*-PrOH, 63 mg (30%) of **5e** as yellow solid; mp 239 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 7.1 Hz, 3 H), 4.53 (q, *J* = 7.1 Hz, 2 H), 7.58–7.88 (m, 6 H), 8.82 (s, 1 H), 8.89 (s, 1 H), 11.90 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 62.6, 107.5, 118.8, 122.0, 123.1, 123.5, 124.3, 125.0, 129.8, 130.8, 131.7, 131.9, 132.5, 137.2, 143.4, 148.2, 161.4, 169.7.

Anal. Calcd for $C_{20}H_{14}F_3N_3O_3$: C, 59.85; H, 3.52; N, 10.47. Found: C, 60.08; H, 3.41; N, 10.29.

Ethyl 8-Naphthalen-2-yl-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3′,2′-*d*]imidazole-3-carboxylate (5f)

The reduction and cyclization of **4f** (440 mg, 0.96 mmol) in glacial AcOH (10 mL) with iron powder (1.50 g, 26.88 mmol) gave, after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 8:2) and recrystallization from *i*-PrOH, 110 mg (30%) of **5f** as yellow solid; mp 253 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.50 (t, *J* = 7.1 Hz, 3 H), 4.54 (q, *J* = 7.1 Hz, 2 H), 7.52–8.10 (m, 9 H), 8.82 (s, 1 H), 8.98 (s, 1 H), 11.89 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 62.5, 107.3, 118.4, 121.6, 124.3, 125.6, 126.6, 126.8, 127.7, 128.2, 129.2, 131.5, 131.7, 132.4, 133.0, 133.5, 133.7, 153.6, 156.4, 161.3, 169.8.

MS (ESI-MS): *m*/*z* = 384 ([M + H]$^+$)

Ethyl 8-Naphthalen-1-yl-2-oxo-1,2-dihydrodipyrido[1,2-*a*;3′,2′-*d*]imidazole-3-carboxylate (5g)

The reduction and cyclization of **4g** (260 mg, 0.56 mmol) in glacial AcOH (10 mL) with iron powder (891 mg, 15.96 mmol) (reaction time, 4 h) gave, after purification by column chromatography (silica gel, eluent: $CHCl_3$–EtOAc, 8:2) and recrystallization from *i*-PrOH, 96 mg (44%) of **5g** as yellow solid; mp 199 °C.

^{1}H NMR ($CDCl_3$): δ = 1.50 (t, *J* = 7.1 Hz, 3 H), 4.54 (q, *J* = 7.1 Hz, 2 H), 7.48–7.96 (m, 9 H), 8.78 (s, 1 H), 8.84 (s, 1 H), 11.88 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.2, 62.5, 107.2, 117.5, 123.7, 125.0, 125.1, 125.4, 126.2, 126.7, 127.5, 128.7, 129.0, 131.5, 132.3, 133.9, 134.3, 134.6, 161.2, 169.8.

Anal. Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 71.93; H, 4.65; N, 10.96.

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