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A simple metal-free synthesis of 2-substituted pyridine-4,5-dicarboxylates and their *N*-oxides

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ABSTRACT

Herein a simple, metal-free synthesis of 2-alkyl-, 2-cycloalkyl-, 2-aryl-, and 2-heteroaryl-substituted pyridine 3,4-dicarboxylates and their *N*-oxides from the corresponding methyl ketones in good to excellent yield, demonstrated with 22 examples in each case, is described. The method complements the current coupling reactions of 2-heterocyclic organometallic reagents.

1. Introduction

Pyridines and their *N*-oxides with aromatic or heteroaromatic substituents are an important class of compounds, which have found applications in medicinal chemistry.[1] Among them are many biologically active compounds,[2] such as Streptonigrin,[3] Glyvec,[4] and Rosuvastatin,[5] and many natural products.[6] They are found also in MAP inhibitors,[7] and among P,N-ligands, used as catalysts in asymmetric reactions.[8,9]

There are many methods for the preparation of pyridines described in the literature.[10] Aryl–aryl bond formation is one of the most important tools of modern organic synthesis. These bonds are often found in natural products, such as alkaloids, as well as in numerous biologically active parts of pharmaceutical and agrochemical species, in polyaromatics used as organic conductors and semiconductors, and in ligands in asymmetric catalysis.[11] Palladium catalyzed reactions are powerful and useful tools for the synthesis of heterocycles, especially for the formation of C–C bonds in aryl and heteroaryl substituted heterocycles.[12–14] In this context, the Suzuki reaction has a special significance.[14] An attractive alternative is a mild Negishi cross-coupling of 2-heterocyclic organozinc reagents with aryl and heteroaryl chlorides,[15] which complements reactions with other 2-heteroarylorganometallic reagents.[16] Direct arylation and alkylation of nitropyridine *N*-oxides with Grignard reagents,[17a] and arylation of arene and *N*-heteroarenes with diaryliodonium salts without the use of transition metal catalysts[17b] have been reported recently. Furthermore, the down side of the use of organometallic reagents in pharmaceutical industry is their ever increasing cost, i.e., the progressive shortage of lithium, and the strict regulation regarding the residual traces of metals left in the final products.

In this communication we report a simple, metal-free synthesis of dimethyl 2-substituted pyridine-4,5-dicarboxylates and their *N*-oxides as an extension of the enaminone methodology recently developed in our laboratory. These have a broad applicability in the synthesis of numerous heterocyclic systems,[18] including natural products and their analogs,[19] in the regiospecific [2+2]cycloadditions with electron-poor acetylenes and further transformations of cycloadducts into highly substituted heterocyclic systems.[20]

2. Results and discussion

Polysubstituted butadienes, i.e., dimethyl 2-[(dimethylamino) methylene]-3-(2-substituted) succinates **3**, have been prepared from alkyl, aryl, and heteroaryl methyl ketones **1** by treatment with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) or *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) to give the corresponding 3-(dimethylamino)-1-substituted-prop-2-en-1-ones **2**, followed by microwave assisted [2+2]cycloaddition to dimethyl acetylenedicarboxylate (DMAD), as reported previously.[21] Polysubstituted aminobutadienes **3** prepared according to this procedure are isomeric to the aminobutadienes formed by the *Michael addition*. Consequently, they represent an alternative group of intermediates for the preparation of isomerically substituted pyridine derivatives, which cannot be obtained by the *Bohlmann–Rahtz*[22] synthesis. With this fact in mind, we decided to study the scope and limitations of this procedure. Compounds **3**, dissolved in MeOH, were treated with ammonium acetate (10-fold excess) at room temperature for 5–120 h to give dimethyl 2-substituted pyridine-4,5-dicarboxylates **4a**–**s** in 44–86% yield, while treatment with hydroxylamine hydrochloride (1.5 equiv) in MeOH for 2–120 h at room temperature gave the corresponding 2-substituted 4,5-bis(methoxycarbonyl)-pyridine *N*-oxides **5a**–**s** in 45–96% yield. In this manner, alkyl, alkenyl, cyclopentenyl, styryl, phenyl, substituted phenyl, ferrocenyl, pyrrol-2-yl, pyrrol-3-yl,

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furan-3-yl, thiophen-3-yl, substituted thiophen-3-yl, indol-3-yl, thiazol-2-yl, pyrid-2-yl, pyrazin-2-yl, and other substituents have been introduced at position 2 in pyridine or pyridine *N*-oxide (Scheme 1, Table 1).

Finally, the scope of this methodology was tested with di- and triacetyl-benzenes. Thus treatment of 1,3-(**6a**), 1,4-diacetyl-(**6b**) or 1,3,5-triacetylbenzene (**6c**) with DMFDMA furnished enaminones **7a**–**c**, respectively, followed by [2+2]cycloaddition of DMAD to give the corresponding succinates **8a**–**c**. Lastly, cyclization of **8a**–**c** with ammonium acetate yielded pyridine derivatives **9a**–**c**, respectively, whereas cyclization with hydroxylamine hydrochloride produced the expected pyridine *N*-oxides **10a**–**c**, both in moderate to good yields (61–87%) (Scheme 2). Compounds **9a**–**c** and **10a**–**c** could potentially be used in coordination and dendrimer chemistry.

The exclusive formation of pyridine and pyridine *N*-oxides upon cyclization of succinate derivatives **3** and **8** with ammonium acetate and hydroxylamine hydrochloride, respectively, could be attributed to the following facts: (i) under acidic conditions, the order of reactivity of the functional groups attached to the butadiene scaffolds **3** and **8** is the following: CH=CH–NMe_2 (masked formyl group)> ketone group>CO_2Me,[18d] thus first the protonated dimethylamino group is substituted by the nucleophile employed ('NH_3, NH_2OH'), followed by cyclocondensation with the ketone group, (ii) the succinate derivatives **3** and **8** in the solid state (see X-ray structures in Figs. 1–3 in Ref. 21b) are not planar (conjugated) but bent around the C(2)–C(3) single bond (torsion angles ranging from 50 to 62°) due to severe steric repulsion in the planar conformation, which conveniently puts the amino group of the C=C–NH_2 and C=C–NH–OH group, respectively, in a position suitable for attack on the carbonyl group (assuming a free rotation around the C(2)–C(3) single bond, for the fulfillment of the *Burgi–Dünitz* trajectory) (Scheme 3).

3. Structure determination

The structures of the new compounds were determined by ^1H and ^{13}C NMR spectroscopy, HRMS and microanalyses for C, H, and N. The structures of compounds **4h**–**j**,**l**,**m**, **5j**,**k**, **8b**, and **9b** were confirmed by X-ray analyses (Figs. 1–3).

4. Conclusion

In conclusion, we have described a simple, metal-free synthesis of 2-alkyl-, 2-cycloalkyl, 2-aryl-, and 2-heteroaryl-substituted pyridine 3,4-dicarboxylates and their *N*-oxides from the corresponding methyl ketones in good to excellent yield demonstrated with 22 examples with correct elemental analyses. This method complements the current reactions of the coupling of 2-heterocyclic organometallic reagents and tolerates a broad substituent scope in position 2 of the pyridine ring.

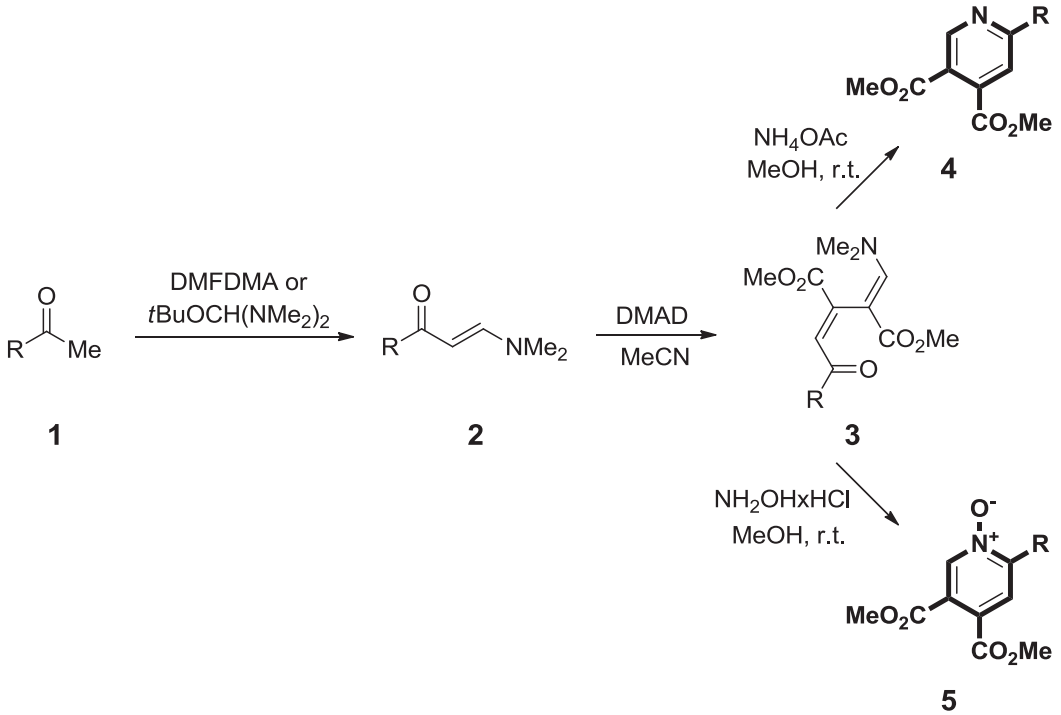
5. Experimental

5.1. General

Melting points were determined on a Kofler micro hot stage and on an SRS OptiMelt MPA100-Automated Melting Point System. NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^1H and 75.5 MHz for ^{13}C, and a Bruker UltraShield 500 plus at 500 MHz for ^1H and 126 MHz for ^{13}C, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer and Agilent 6224 Accurate Mass TOF LC/MS, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400 II. Column chromatography (CC) was performed on silica gel (Fluka, Silica gel 60, particle size: 0.035–0.070 mm).

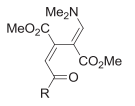
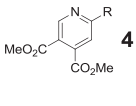
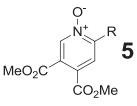
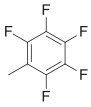
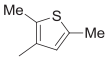
Methyl ketones **1a**–**s** and **6a**,**b**, *N*,*N*-dimethylformamide dimethyl acetal, *tert*-butoxy bis(dimethylamino)methane, are commercially available (Sigma–Aldrich). 1,1′,1″-(Benzene-1,3,5-triyl) triethanone (**6c**) was prepared following the literature procedure.[23]

Compounds **3d**,**f**,**j**–**o**,**q**–**s** have been described previously,[21] compound **4f** was prepared according to the procedure described in the literature.[24]



Scheme 1. Synthesis of 2-substituted pyridine-4,5-dicarboxylates **4** and the corresponding pyridine *N*-oxides **5** from methyl ketones **1**.

Table 1
The 2-substituted pyridine-4,5-dicarboxylates **4** and the corresponding pyridine *N*-oxides **5** prepared from methyl ketones **1**

Entry	R	 **3**	 **4**	 **5**
		Yield (%)		
a	Et	79	79	47
b	Pr	81	67	82
c	^{t}Bu	95	74	96
d		97[21a]	70	75
e		70	75	45
f		75[21a]	67[22]	71
g		76	76	72
h		32	86	67
i		83	55	47
j		69[21a]	48	46
k		91[21b]	45	75
l		16[21b]	44	80
m		70[21b]	78	78
n		70[21b]	83	81
o		86[21a]	54	93
p		67	46	54
q		75[21a]	80	65
r		67[21a]	47	56
s		46[21a]	72	74

5.2. General procedure for the synthesis of (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-substituated)succinates 3a–c,e,g–i,p and 8c

To a solution of (*E*)-3-(dimethylamino)-1-substituted-prop-2-en-1-one **2a**–**c**,**e**,**g**–**i**,**p** and **7c** (0.78–5.2 mmol) in MeCN (1–4 mL) was added excess dimethyl acetylenedicarboxylate (2.0 equiv) and the mixture was stirred in a closed vessel under microwave irradiation (300 W) at an automatically controlled constant temperature (CEM Corporation Discover microwave unit) or at room temperature. After cooling to room temperature, volatile compounds were evaporated in vacuo and the residue was purified with column chromatography using mixtures of EA/PE as a mobile phase. Fractions containing the product were combined and evaporated in vacuo.

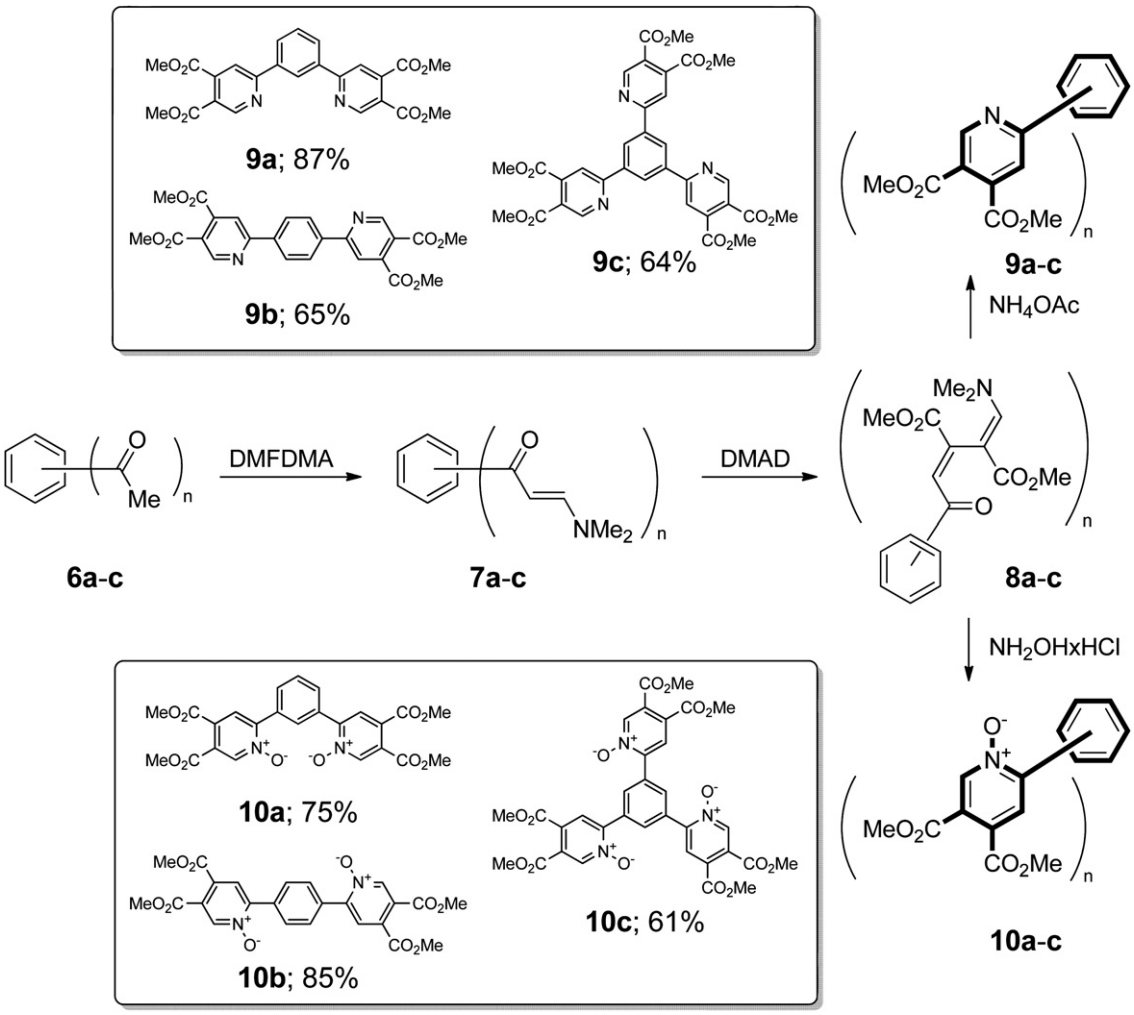
*5.2.1. (2E,3E)-Dimethyl 2-((dimethylamino)methylene)-3-(2-oxobutylidene)succinate (**3a**).* Prepared from (*E*)-1-(dimethylamino)pent-1-en-3-one (**2a**) (656 mg, 5.2 mmol), 80 °C, 5 min, chromatography (ethyl acetate/petroleum ether=1:1). Yield: 1.11 g (79%) of yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.05 (3H, t, J=7.3 Hz, C*H*$_3$); 2.58 (2H, q, J=7.3 Hz, C*H*$_2$); 2.87 (6H, s, N*Me*$_2$); 3.63 (3H, s, COO*Me*); 3.79 (3H, s, COO*Me*); 7.01 (1H, s, C*H*); 7.67 (1H, s, C*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 8.3, 37.2, 43.4, 51.5, 53.1, 91.4, 131.6, 137.3, 153.5, 169.0, 169.1, 201.5. EI-HRMS: m/z=270.1337 (MH^+); $C_{13}H_{20}NO_5$ requires: m/z=270.1341 (MH^+); ν_{max} (NaCl) 2976, 2950, 2904, 1720, 1692, 1686, 1603, 1432, 1284, 1241, 1217, 1122, 1088, 1029, 958, 871, 803, 778 cm^{-1}.

*5.2.2. (2E,3E)-Dimethyl 2-((dimethylamino)methylene)-3-(2-oxopentylidene)succinate (**3b**).* Prepared from (*E*)-1-(dimethylamino)hex-1-en-3-one (**2b**) (141 mg, 1.0 mmol), 80 °C, 5 min, chromatography (ethyl acetate/petroleum ether=1:1). Yield: 230 mg (81%) of yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (3H, t, J=7.4 Hz, C*H*$_3$); 1.62 (2H, s, J=7.4 Hz, C*H*$_2$); 2.43 (2H, m, C*H*$_2$); 2.92 (6H, s, N*Me*$_2$); 3.68 (3H, s, COO*Me*); 3.79 (3H, s, COO*Me*); 6.85 (1H, s, C*H*); 7.51 (1H, s, C*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 19.1, 39.7, 43.4, 51.7, 52.9, 104.4, 126.4, 143.0, 152.3, 165.6, 168.2, 196.8. EI-HRMS: m/z=284.1491 (MH^+); $C_{14}H_{22}NO_5$ requires: m/z=2784.1492 (MH^+); ν_{max} (NaCl) 2955, 1719, 1633, 1587, 1433, 1402, 1354, 1323, 1247, 1197, 1126, 1061, 1018, 969, 889, 806 cm^{-1}.

*5.2.3. (2E,3E)-Dimethyl 2-(3,3-dimethyl-2-oxobutylidene)-3-((dimethylamino)methylene)succinate (**3c**).* Prepared from (*E*)-1-(dimethylamino)-4,4-dimethylpent-1-en-3-one (**2c**) (155 mg, 1.0 mmol), 80 °C, 8 min, chromatography (ethyl acetate/petroleum ether=1:1). Yield: 282 mg (95%) of yellowish oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.17 (9H, s, ^{t}*Bu*); 2.87 (6H, s, N*Me*$_2$); 3.60 (3H, s, COO*Me*); 3.79 (3H, s, COO*Me*); 7.36 (1H, s, C*H*); 7.65 (1H, s, C*H*). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 26.4, 42.9, 44.4, 51.1, 52.8, 90.8, 129.0, 137.8, 152.7, 168.8, 168.9, 205.5. EI-HRMS: m/z=298.1648 (MH^+); $C_{15}H_{24}NO_5$ requires: m/z=298.1649 (MH^+); ν_{max} (NaCl) 2953, 1732, 1693, 1660, 1557, 1540, 1433, 1398, 1267, 1240, 1218, 1088, 1046, 975, 943, 887, 803, 772 cm^{-1}.

*5.2.4. (2E,3E)-Dimethyl 2-((dimethylamino)methylene)-3-((E)-2-oxo-4-phenylbut-3-en-1-ylidene)succinate (**3e**).* Prepared from (1*E*,4*E*)-1-(dimethylamino)-5-phenylpenta-1,4-dien-3-one (**2e**) (402 mg, 2.0 mmol), 60 °C, 2×5 min, chromatography (ethyl acetate/petroleum ether=1:1). Yield: 478 mg (70%) of red oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.87 (6H, s, N*Me*$_2$); 3.62 (3H, s, COO*Me*); 3.82 (3H, s, COO*Me*); 6.81 (1H, d, J=16.1 Hz, C*H*); 7.17 (1H, s, C*H*); 7.36–7.39 (3H, m, 3× *Ph*); 7.50–7.60 (4H, m, 2× C*H*+2*Ph*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 43.0, 51.2, 52.8, 91.8, 126.5, 128.3, 129.0, 130.5, 131.6, 134.6, 137.7, 143.6, 152.3, 168.5, 168.6, 190.3. EI-HRMS: m/z=344.1494 (MH^+); $C_{19}H_{22}NO_5$ requires: m/z=344.1498 (MH^+); ν_{max} (NaCl) 2982, 1731, 1645, 1584, 1565, 1470, 1433, 1424, 1387, 1328, 1222, 1174, 1127, 1087, 880, 827, 746, 702 cm^{-1}.

*5.2.5. (2E,3E)-Dimethyl 2-((dimethylamino)methylene)-3-(2-(2-fluorophenyl)-2-oxoethylidene)succinate (**3g**).* Prepared from (*E*)-3-(dimethylamino)-1-(2-fluorophenyl)prop-2-en-1-one (**2g**) (274 mg, 1.4 mmol), 100 °C, 15 min, chromatography (ethyl acetate/



Scheme 2. Synthesis of di- and trisubstituted benzenes with pyridine and pyridine *N*-Oxide derived substituents.

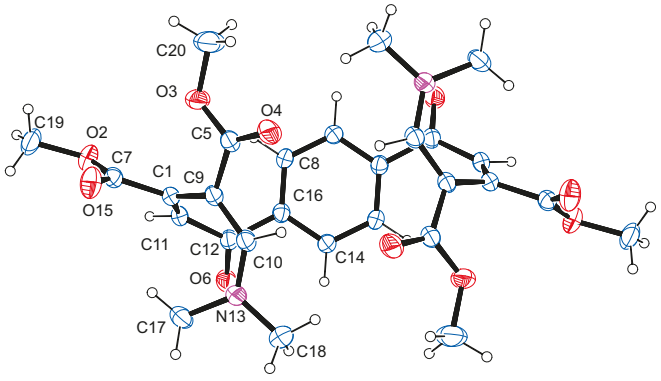


Fig. 1. ORTEP view of butadiene **8b**.

petroleum ether=1:1). Yield: 356 mg (76%) of red oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.88 (6H, s, N*Me*$_2$); 3.58 (3H, s, COO*Me*); 3.82 (3H, s, COO*Me*); 7.11 (1H, ddd, J_1=10.7 Hz, J_2=8.3 Hz, J_3=1.0 Hz, 1× *Ph*); 7.1 (1H, td, J_1=7.6 Hz, J_2=1.1 Hz, 1× *Ph*); 7.40 (1H, d, J=2.7 Hz, C*H*); 7.48 (1H, dddd, J_1=8.3 Hz, J_2=7.4 Hz, J_3=5.1 Hz, J_4=1.9 Hz, 1× *Ph*), 7.59 (1H, s, C*H*); 7.64 (1H, td, J_1=7.6 Hz, J_2=1.8 Hz, 1× *Ph*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 43.2, 51.1, 52.8, 92.1, 116.4 (d, J=22.7 Hz), 124.3 (d, J=3.6 Hz), 127.4 (d, J=12.3 Hz), 129.8 (d, J=4.5 Hz), 130.4 (d, J=2.3 Hz), 133.9 (d, J=8.9 Hz), 139.1 (d, J=1.2 Hz), 153.2, 160.9 (d, J=254.1 Hz), 168.4, 168.9, 188.3 (d, J=2.3 Hz). EI-HRMS: m/z=336.1245 (MH^+); $C_{17}H_{19}NO_5F$ requires: m/z=336.1247 (MH^+); ν_{max} (NaCl) 1722, 1694, 1610, 1547, 1482, 1450, 1434, 1401, 1273, 1246, 1217, 1089, 1043, 958, 866, 849, 802, 768 cm^{-1}.

*5.2.6. (2E,3E)-Dimethyl 2-((dimethylamino)methylene)-3-(2-oxo-2-(perfluorophenyl)ethylidene)succinate (**3h**).* Prepared from (*E*)-3-(dimethylamino)-1-(perfluorophenyl)prop-2-en-1-one (**2h**) (403 mg, 1.5 mmol), 100 °C, 30 min, chromatography (ethyl acetate/petroleum ether=1:2). Yield: 194 mg (32%) of red oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.89 (6H, s, N*Me*$_2$); 3.65 (3H, s, COO*Me*); 3.82 (3H, s, COO*Me*); 7.01 (1H, t, J=1.8 Hz, C*H*); 7.80 (1H, s, C*H*). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 43.9, 51.7, 53.2, 92.8, 116.2 (tm, J=17.0 Hz), 126.1, 137.7 (dm, J=254.9 Hz), 142.3, 142.6 (d, J=258.6 Hz), 144.2 (d, J=252.1 Hz), 155.5, 168.4, 168.8, 180.3. EI-HRMS: m/z=408.0847 (MH^+); $C_{17}H_{15}NO_5F_5$ requires: m/z=408.0865 (MH^+); ν_{max} (NaCl) 1728, 1692, 1651, 1606, 1519, 1497, 1435, 1400, 1323, 1247, 1218, 1155, 1093, 988, 898, 800, 764 cm^{-1}.

*5.2.7. (2E,3E)-Dimethyl 2-((dimethylamino)methylene)-3-(2-(2-nitrophenyl)-2-oxoethylidene)succinate (**3i**).* Prepared from (*E*)-3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one (**2i**) (440 mg, 2.0 mmol), 100 °C, 20 min, chromatography (ethyl acetate/petroleum ether=1:1). Yield: 631 mg (83%) of red oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.91 (6H, s, N*Me*$_2$); 3.57 (3H, s, COO*Me*); 3.79 (3H, s,

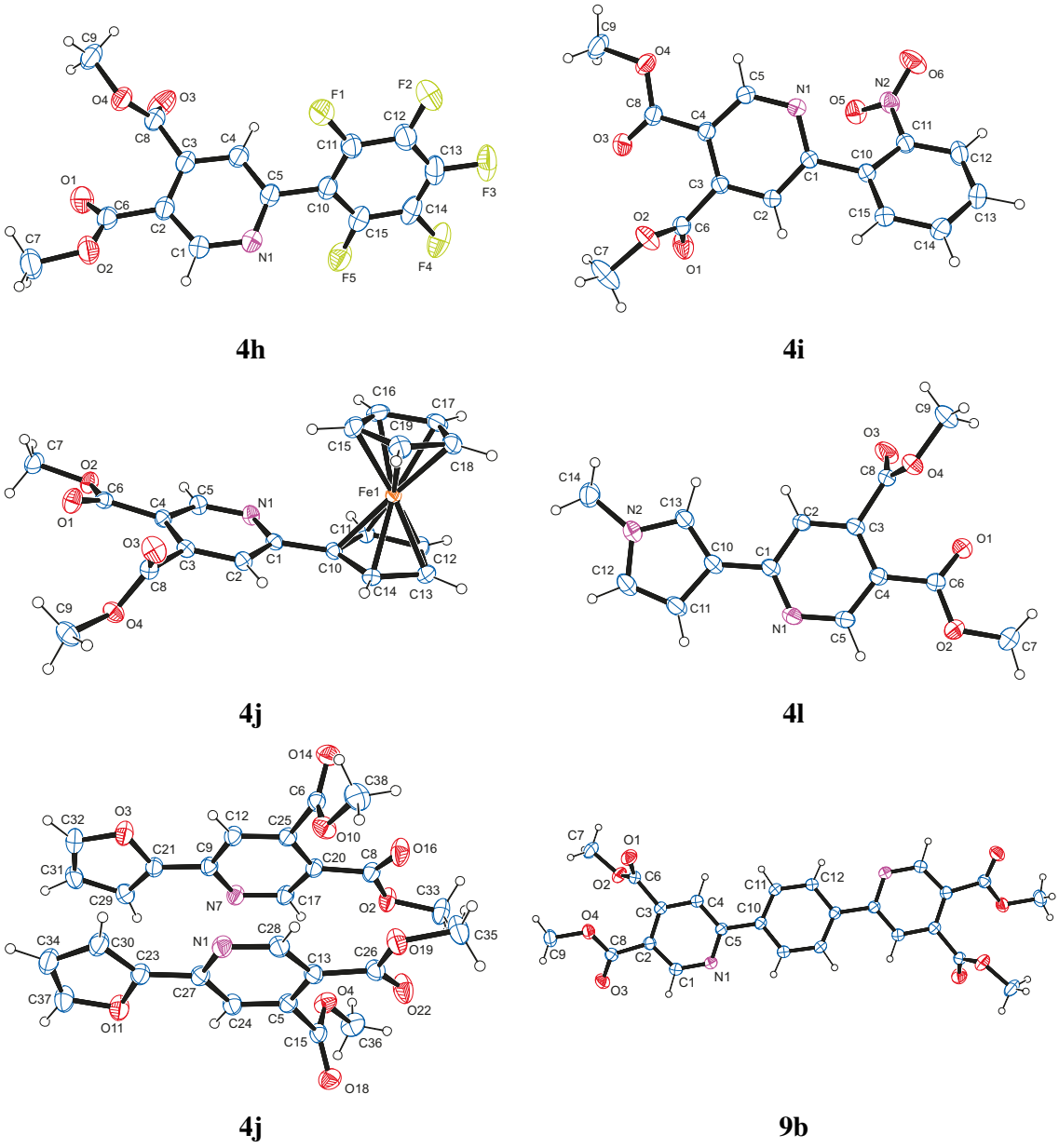


Fig. 2. ORTEP view of pyridines **4h**–**j**,**l**,**m**.

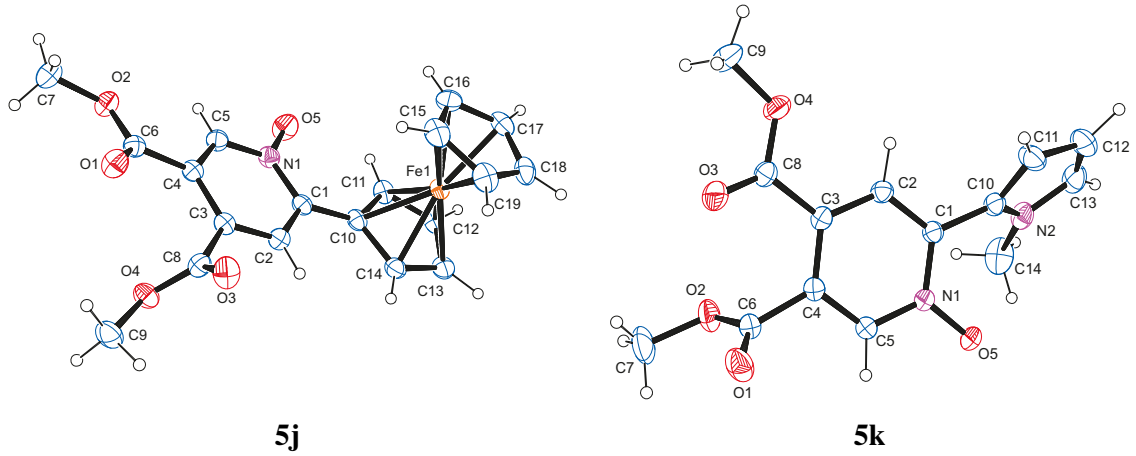
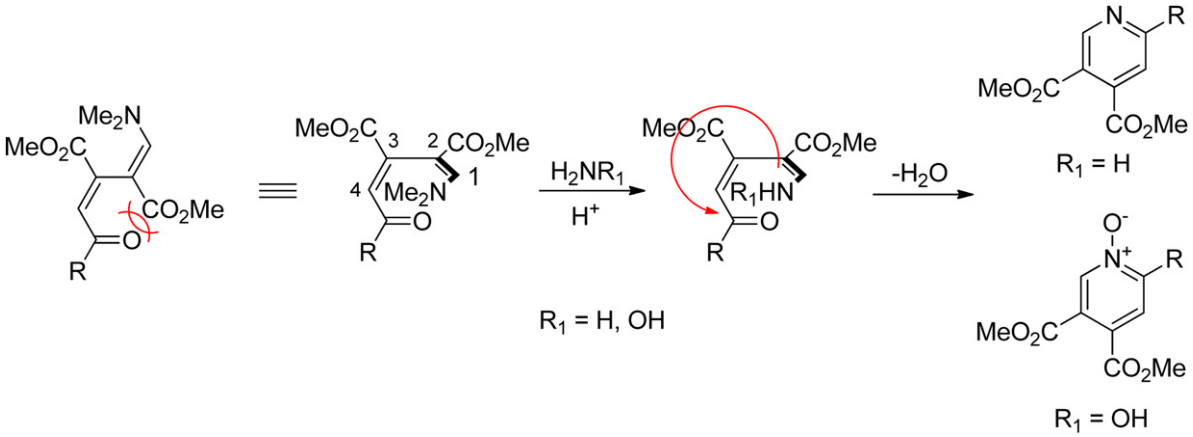


Fig. 3. ORTEP view of pyridine *N*-oxides **5j**,**k**.



Scheme 3. Proposed formation of pyridines and pyridine *N*-oxides.

COO*Me*); 7.16 (1H, s, C*H*); 7.44–7.47 (2H, m, C*H*+1× *Ph*), 7.58 (1H, td, J_1=7.7 Hz, J_2=1.6 Hz, 1× *Ph*); 7.67 (1H, td, J_1=7.5 Hz, J_2=1.3 Hz, 1× *Ph*); 8.03 (1H, dd, J_1=8.1 Hz, J_2=1.3 Hz, 1× *Ph*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 42.6, 50.7, 52.5, 90.8, 123.7, 128.8, 130.0, 130.8, 133.3, 136.1, 139.5, 146.4, 153.2, 167.6, 168.0, 190.6. EI-HRMS: *m*/*z*=363.1201 (MH^+); $C_{17}H_{19}N_2O_7$ requires: *m*/*z*=363.1192 (MH^+); ν_{max} (NaCl) 1723, 1695, 1684, 1654, 1617, 1603, 1527, 1435, 1399, 1346, 1261, 1088, 1044, 956, 856, 795 cm^{-1}.

*5.2.8. (2E,3E)-Dimethyl 2-(2-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-2-oxoethylidene)-3-((dimethylamino)methylene)succinate (**3p**).* Prepared from (*E*)-*tert*-butyl 3-(3-(dimethylamino)acryloyl)-1*H*-indole-1-carboxylate (**2p**) (354 mg, 1.1 mmol), 70 °C, 10 min, chromatography (ethyl acetate/petroleum ether=1:2). Yield: 348 mg (67%) of red oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.71 (9H, s, ^{t}*Bu*); 2.90 (6H, s, N*Me*$_2$); 3.62 (3H, s, COO*Me*); 3.85 (3H, s, COO*Me*); 7.33 (1H, td, J_1=7.5 Hz, J_2=1.2 Hz, indole); 7.35–7.41 (1H, m, indole); 7.46 (1H, s, C*H*); 7.55 (1H, s, C*H*), 8.11 (1H, d, *J*=8.2 Hz, indole); 8.29–8.37 (2H, m, 2× indole). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 28.3, 43.2, 51.4, 53.2, 85.7, 91.5, 115.2, 120.8, 122.7, 124.5, 125.8, 127.7, 131.4, 133.2, 135.8, 136.9, 149.3, 153.1, 169.0, 169.1, 187.3. EI-HRMS: *m*/*z*=457.1967 (MH^+); $C_{24}H_{29}N_2O_7$ requires: *m*/*z*=457.1969 (MH^+); ν_{max} (NaCl) 2982, 2949, 1744, 1693, 1643, 1603, 1584, 1540, 1450, 1435, 1372, 1309, 1271, 1242, 1191, 1144, 1087, 1044, 956, 882, 851, 767 cm^{-1}.

*5.2.9. (2E,2′E,2″E,3E,3′E,3″E)-Hexamethyl 3,3′,3″-(benzene-1,3,5-triyltris(2-oxoethan-2-yl-1-ylidene))tris(2-((dimethylamino)methylene)succinate) (**8c**).* Prepared from (2*E*,2′*E*,2″*E*)-1,1′,1″-(benzene-1,3,5-triyl)tris(3-(dimethylamino)prop-2-en-1-one) (**7c**) (290 mg, 0.78 mmol), 100 °C, 20 min, chromatography (ethyl acetate). Yield: 233 mg (38%) of red oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.90 (18H, s, 3× N*Me*$_2$); 3.57 (9H, s, 3× COO*Me*); 3.85 (9H, s, 3× COO*Me*); 7.53 (3H, s, C*H*); 7.57 (3H, s, C*H*); 8.52 (1H, s, C*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 43.3, 51.3, 53.0, 92.1, 127.2, 131.5, 138.8, 140.4, 153.4, 168.4, 168.6, 189.1. EI-HRMS: *m*/*z*=796.2929 (MH^+); $C_{39}H_{46}N_3O_{15}$ requires: *m*/*z*=796.2929 (MH^+); ν_{max} (NaCl) 1724, 1685, 1654, 1604, 1559, 1541, 1435, 1400, 1245, 1216, 1188, 1090, 1043, 953, 894, 837, 790 cm^{-1}.

5.3. General procedure for the synthesis of dimethyl 2-substituted pyridine-4,5-dicarboxylates

NH_4OAc (10-fold excess) was added to a solution of *(2E,3E)-dimethyl 2-[(dimethylamino)methylene]-3-(2-substituted)succinates* (0.29–3.70 mmol) in MeOH (10 mL). The reaction mixture was stirred from 5 h to 5 days at room temperature and after that volatile components were evaporated in vacuo and products were purified by column chromatography and crystallized from the appropriate solvents.

*5.3.1. Dimethyl 6-ethylpyridine-3,4-dicarboxylate (**4a**).* Prepared from (2*E*,3*E*)-dimethyl 2-[(dimethylamino)methylene]-3-[2-oxobutylidene]succinate (**3a**) (989 mg, 3.7 mmol) and NH_4OAc (2.83 g, 37 mmol), stirred for 24 h, chromatography (petroleum ether/ethyl acetate=1:1); yield: 655 mg (79%) of yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H, t, J_1=7.5 Hz, CH_3); 2.93 (2H, q, J_1=7.5 Hz, CH_2); 3.93 (3H, s, COOCH_3); 3.95 (3H, s, COOCH_3); 7.36 (1H, s, pyridine); 9.02 (1H, s, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.4, 31.3, 52.7, 53.1, 120.3, 122.2, 141.6, 150.1, 165.5, 167.3, 167.9. ESI-HRMS: *m*/*z*=224.0923 (MH^+); $C_{11}H_{14}NO_4$ requires: *m*/*z*=224.0929 (MH^+); ν_{max} (NaCl) 2971, 2953, 2883, 2842, 2359, 2330, 1734, 1595, 1553, 1457, 1435, 1384, 1297, 1205, 1137, 1075, 990, 963 cm^{-1}.

*5.3.2. Dimethyl 6-propylpyridine-3,4-dicarboxylate (**4b**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxopentylidene)succinate (**3b**) (230 mg, 0.85 mmol) and NH_4OAc (654 mg, 8.5 mmol), stirred for 5 days, chromatography (ethyl acetate/petroleum ether=1:2); yield: 135 mg (67%) of yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.98 (3H, t, *J*=7.4 Hz, CH_3); 1.79 (2H, sextet, *J*=7.2 Hz, CH_2); 2.86 (2H, t, *J*=7.5 Hz, CH_2); 3.93 (3H, s, COOCH_3); 3.95 (3H, s, COOCH_3); 7.32 (1H, s, pyridine); 9.00 (1H, d, *J*=0.5 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.8, 22.7, 40.4, 52.8, 53.1, 120.8, 122.1, 141.1, 150.3, 165.7, 166.9, 167.4. ESI-HRMS: *m*/*z*=238.1072 (MH^+); $C_{12}H_{16}NO_4$ requires: *m*/*z*=238.1079 (MH^+); ν_{max} (NaCl) 2959, 1733, 1596, 1555, 1436, 1380, 1297, 1207, 1139, 1075, 979, 895, 873, 824, 796, 769, 686 cm^{-1}.

*5.3.3. Dimethyl 6-(tert-butyl)pyridine-3,4-dicarboxylate (**4c**).* Prepared from (2*E*,3*E*)-dimethyl 2-(3,3-dimethyl-2-oxobutylidene)-3-((dimethylamino)methylene)succinate (**3c**) (298 mg, 1.0 mmol) and NH_4OAc (770 mg, 10.0 mmol), stirred for 5 days, chromatography (ethyl acetate/petroleum ether=1:5); yield: 187 mg (74%) of colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39 (9H, s, ^{t}Bu); 3.93 (3H, s, COOCH_3); 3.96 (3H, s, COOCH_3); 7.48 (1H, s, pyridine); 9.03 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 30.0, 52.9, 53.2, 97.9, 117.4, 121.7, 141.3, 149.9, 165.9, 167.9, 174.1. ESI-HRMS: *m*/*z*=252.1231 (MH^+); $C_{13}H_{18}NO_4$ requires: *m*/*z*=252.1230 (MH^+); ν_{max} (NaCl) 2957, 2869, 1734, 1592, 1559, 1435, 1364, 1295, 1257, 1194, 1138, 1068, 975, 880, 822, 801, 776 cm^{-1}.

*5.3.4. Dimethyl 6-(cyclopent-1-en-1-yl)pyridine-3,4-dicarboxylate (**4d**).* Prepared from (2*E*,3*E*)-dimethyl 2-[2-(cyclopent-1-en-1-yl)-

2oxoethylidene]-3-[(dimethylamino)methylene]succinate (**3d**) (307 mg, 1 mmol) and NH_4OAc (771 mg, 10 mmol), stirred for 24 h, chromatography (petroleum ether/ethyl acetate=5:1), crystallized from and ethyl acetate/petroleum ether; yield: 183 mg (70%) of light brown solid. Mp 115.4–118.2 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.05 (2H, m, CH_2); 2.59 (2H, m, CH_2); 2.80 (2H, m, CH_2); 3.92 (3H, s, $COOCH_3$); 3.95 (3H, s, $COOCH_3$); 6.79 (1H, m, C*H*); 7.48 (1H, s, pyridine); 9.01 (1H, s, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.3, 32.3, 33.8, 52.7, 53.0, 118.1, 121.6, 135.8, 141.3, 142.6, 150.5, 158.5, 165.5, 167.5. ($C_{14}H_{15}NO_4$ requires: C, 64.36; H, 5.79; N, 5.36. Found C, 63.96; H, 5.74; N, 5.26); ESI-HRMS: m/z=262.1084 (MH^+); $C_{14}H_{16}NO_4$ requires: m/z=262.1079 (MH^+); ν_{max} (KBr) 2950, 2943, 2844, 2369, 1733, 1619, 1594, 1537, 1436, 1398, 1350, 1291, 1254, 1196, 1138, 1080, 959 cm^{-1}.

*5.3.5. (E)-Dimethyl 6-styrylpyridine-3,4-dicarboxylate (**4e**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-((*E*)-2-oxo-4-phenylbut-3-en-1-ylidene)succinate (**3e**) (230 mg, 0.67 mmol) and NH_4OAc (515 mg, 6.7 mmol), stirred for 2 days, chromatography (ethyl acetate/petroleum ether=1:1). Crystallized from ethyl acetate/petroleum ether; yield: 150 mg (75%) of yellow solid. Mp 73.4–75.7 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.90 (3H, s, $COOCH_3$); 3.95 (3H, s, $COOCH_3$); 7.15 (1H, d, J=16.2 Hz, C*H*); 7.28–7.39 (3H, m, Ph); 7.47 (1H, s, pyridine), 7.54–7.57 (2H, m, Ph); 7.74 (1H, d, J=16.2 Hz, C*H*); 9.03 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 52.7, 53.1, 119.7, 122.1, 126.2, 127.6, 128.9, 129.3, 135.9, 136.5, 141.7, 150.9, 159.3, 165.4, 167.3. ($C_{17}H_{15}NO_4$ requires: C, 68.68; H, 5.09; N, 4.71. Found C, 68.59; H, 4.88; N, 4.71); ESI-HRMS: m/z=298.1081 (MH^+); $C_{17}H_{16}NO_4$ requires: m/z=298.1079 (MH^+); ν_{max} (KBr) 3043, 3030, 3958, 1740, 1720, 1635, 1563, 1546, 1431, 1379, 1287, 1258, 1191, 1133, 1073, 967, 880, 825, 792, 756, 720, 691 cm^{-1}.

*5.3.6. Dimethyl 6-phenylpyridine-3,4-dicarboxylate (**4f**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxo-2-phenylethylidene)succinate (**3f**) (590 mg, 1.86 mmol) and NH_4OAc (1432 mg, 18.6 mmol), stirred for 2 days, chromatography (ethyl acetate/petroleum ether=1:3). Crystallized from ethyl acetate/petroleum ether; yield: 340 mg (67%) of white solid. Mp 73.9–76.9 °C (Ref. 22: mp 72–73 °C). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.95 (3H, s, $COOCH_3$); 3.97 (3H, s, $COOCH_3$); 7.45–7.52 (3H, m, Ph); 7.88 (1H, d, J=0.7 Hz, pyridine); 8.03–8.65 (2H, m, Ph); 9.13 (1H, d, J=0.7 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 52.9, 53.3, 118.5, 122.8, 127.5, 129.1, 130.5, 137.5, 141.8, 150.9, 160.9, 165.7, 167.4. ($C_{15}H_{13}NO_4$ requires: C, 66.41; H, 4.83; N, 5.16. Found C, 66.71; H, 4.71; N, 5.14); ESI-HRMS: m/z=272.0919 (MH^+); $C_{15}H_{14}NO_4$ requires: m/z=272.0923 (MH^+); ν_{max} (KBr) 3065, 3020, 2958, 1740, 1720, 1593, 1555, 1478, 1442, 1365, 1290, 1259, 1184, 1142, 1083, 949, 893, 827, 795, 772, 752, 689 cm^{-1}.

*5.3.7. Dimethyl 6-(2-fluorophenyl)pyridine-3,4-dicarboxylate (**4g**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-(2-fluorophenyl)-2-oxoethylidene)succinate (**3g**) (191 mg, 0.57 mmol) and NH_4OAc (438 mg, 5.7 mmol), stirred for 2 days, chromatography (ethyl acetate/petroleum ether=1:1). Crystallized from ethyl acetate/petroleum ether; yield: 125 mg (76%) of yellow solid. Mp 133.6–135.7 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.96 (3H, s, $COOCH_3$); 3.97 (3H, s, $COOCH_3$); 7.18 (1H, ddd, J_1=1.1 Hz, J_2=8.2 Hz, J_3=11.6 Hz, Ph); 7.28 (1H, td, J_1=1.2 Hz, J_2=7.6 Hz, Ph); 7.43 (1H, dddd, J_1=1.9 Hz, J_2=5.0 Hz, J_3=7.0 Hz, J_3=8.2 Hz, Ph); 8.00 (1H, dd, J_1=0.8 Hz, J_2=1.3 Hz, pyridine); 8.07 (1H, td, J_1=1.8 Hz, J_2=7.9 Hz, Ph); 9.16 (1H, d, J=0.7 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.0, 53.2, 116.6 (d, J=22.9 Hz), 122.4 (d, J=11.0 Hz), 123.2, 124.9 (d, J=3.6 Hz), 125.8 (d, J=10.9 Hz), 131.3 (d, J=2.4 Hz), 132.0 (d, J=8.8 Hz), 141.4 (d, J=0.4 Hz), 150.6, 160.9 (d, J=251.6 Hz), 165.5, 167.1. ^{19}F NMR ($CDCl_3$, 470.9 MHz): δ −112.0. ($C_{15}H_{12}FNO_4$ requires: C, 62.28; H, 4.18; N, 4.84. Found C, 62.29; H, 4.23; N, 4.74); ESI-HRMS: m/z=290.0820 (MH^+); $C_{15}H_{13}FNO_4$ requires: m/z=290.0829 (MH^+); ν_{max} (KBr) 2955, 1738, 1720, 1614, 1589, 1556, 1493, 1451, 1435, 1368, 1317, 1302, 1274, 1243, 1232, 1139, 1083, 1049, 963, 956, 912, 867, 821, 772, 755 cm^{-1}.

*5.3.8. Dimethyl 6-(perfluorophenyl)pyridine-3,4-dicarboxylate (**4h**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxo-2-(perfluorophenyl)ethylidene)succinate (**3h**) (92 mg, 0.23 mmol) and NH_4OAc (180 mg, 2.30 mmol), stirred for 4 h, chromatography (ethyl acetate/petroleum ether=1:8). Crystallized from ethyl acetate/petroleum ether; yield: 65 mg (86%) of white solid. Mp 86.7–88.5 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.98 (3H, s, $COOCH_3$); 3.99 (3H, s, $COOCH_3$); 7.71 (1H, s, pyridine); 9.18 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 53.4, 53.6, 106.5 (td, J_1=3.8 Hz, J_2=15.8 Hz), 124.3, 125.4, 138.1 (dm J=253.9 Hz), 141.2, 142.1 (dm, J=257.7 Hz), 144.9 (dm, J=252.9 Hz), 150.5, 151.0, 165.4, 166.1. ^{19}F NMR ($CDCl_3$, 470.9 MHz): −142.4, −151.4, −160.8. ($C_{15}H_8F_5NO_4$ requires: C, 49.88; H, 2.23; N, 3.88. Found C, 49.64; H, 2.23; N, 3.83); ESI-HRMS: m/z=362.0441 (MH^+); $C_{15}H_9F_5NO_4$ requires: m/z=361.0446 (MH^+); ν_{max} (KBr) 1740, 1724, 1654, 1636, 1552, 1529, 1500, 1443, 1365, 1303, 1274, 1195, 1140, 1087, 1065, 991, 979, 897, 829, 766, 717 cm^{-1}.

*5.3.9. Dimethyl 6-(2-nitrophenyl)pyridine-3,4-dicarboxylate (**4i**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-(2-nitrophenyl)-2-oxoethylidene)succinate (**3i**) (601 mg, 1.66 mmol) and NH_4OAc (1278 mg, 16.6 mmol), stirred for 1 day, precipitated from reaction mixture; yield: 289 mg (55%) of white solid. Mp 125.7–127.7 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.969 (3H, s, $COOCH_3$); 3.972 (3H, s, $COOCH_3$); 7.58–7.64 (2H, m, Ph); 7.67–7.73 (2H, m, pyridine+Ph); 7.96–7.99 (1H, m, Ph); 9.07 (1H, d, J=0.6 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.2, 53.5, 121.2, 124.2, 125.0, 130.4, 131.4, 132.9, 134.1, 141.6, 149.2, 150.6, 159.4, 165.5, 166.7. ($C_{15}H_{12}N_2O_6$ requires: C, 56.96; H, 3.82; N, 8.86. Found C, 57.07; H, 3.76; N, 8.81); ESI-HRMS: m/z=317.0789 (MH^+); $C_{15}H_{13}N_2O_6$ requires: m/z=317.0774 (MH^+); ν_{max} (KBr) 2955, 1738, 1726, 1593, 1551, 1532, 1435, 1362, 1297, 1260, 1195, 1137, 1104, 1078, 959, 910, 873, 849, 825, 782, 757, 709 cm^{-1}.

*5.3.10. Dimethyl 6-(ferrocenyl)pyridine-3,4-dicarboxylate (**4j**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-ferrocenyl-2-oxoethylidene)succinate (**3j**) (201 mg, 0.49 mmol) and NH_4OAc (377 mg, 4.9 mmol), stirred for 3 days, chromatography (ethyl acetate/petroleum ether=1:2). Crystallized from ethyl acetate/petroleum ether; yield: 89 mg (48%) of red solid. Mp 128.4–131.4 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.92 (3H, s, $COOCH_3$); 3.96 (3H, s, $COOCH_3$); 4.06 (5H, s, ferrocene); 4.51 (2H, t, J=1.8 Hz, ferrocene); 4.98 (2H, t, J=1.8 Hz, ferrocene); 7.44 (1H, d, J=0.7 Hz, pyridine); 8.96 (1H, d, J=0.7 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 52.7, 53.2, 68.2, 70.1, 71.4, 81.4, 117.6, 120.5, 141.2, 150.9, 164.8, 165.8, 167.8. ($C_{19}H_{17}NO_4Fe$ requires: C, 60.18; H, 4.52; N, 3.69. Found C, 59.85; H, 4.45; N, 3.56); ESI-HRMS: m/z=380.0601 (MH^+); $C_{19}H_{18}NO_4Fe$ requires: m/z=380.0585 (MH^+); ν_{max} (KBr) 3123, 3072, 3043, 3017, 2956, 1742, 1722, 1595, 1539, 1496, 1460, 1432, 1387, 1294, 1258, 1195, 1137, 1109, 1062, 1007, 957, 907, 888, 835, 824, 795, 769, 685 cm^{-1}.

*5.3.11. Dimethyl 6-(1-methyl-1H-pyrrol-2-yl)pyridine-3,4-dicarboxylate (**4k**).* Prepared from (2*E*,3*E*)-dimethyl 2-[(dimethylamino)methylene]-3-[2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethylidene] succinate (**3k**) (291 mg, 0.9 mmol) and NH_4OAc (694, 9 mmol), stirred for 24 h, chromatography (petroleum ether/ethyl acetate=5:1), crystallized from and ethyl acetate/petroleum ether; yield: 112 mg (45%) of white solid. Mp 105.8–107.8 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H, $COOCH_3$); 3.95 (s, 3H, $COOCH_3$); 4.02 (s, 3H, NCH_3); 6.18 (dd, 1H, J_1=2.7 Hz, J_2=3.9 Hz, pyrrole) 6.76 (m, 2H, pyrrole); 7.62 (d,

1H, J_1=0.6 Hz, pyridine); 8.99 (d, 1H, J_1=0.6 Hz, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 37.9, 52.6, 53.1, 108.6, 113.9, 118.3, 119.9, 129.1, 130.5, 141.5, 150.3, 155.8, 165.7, 167.7. ($C_{14}H_{14}N_2O_4$ requires: C, 61.31; H, 5.14; N, 10.21. Found C, 61.13; H, 5.15; N, 10.21); ESI-HRMS: *m*/*z*=275.1034 (MH^+); $C_{14}H_{15}N_2O_4$ requires: *m*/*z*=275.1032 (MH^+); ν_{max} (KBr) 3412, 2994, 2369, 2344, 1749, 1712, 1685, 1654, 1636, 1617, 1595, 1534, 1458, 1303, 1272, 1249, 1141, 1097, 958 cm^{-1}.

*5.3.12. Dimethyl 6-(1-methyl-1H-pyrrol-3-yl)pyridine-3,4-dicarboxylate (**4l**).* Prepared from (2*E*,3*E*)-dimethyl 2-[(dimethylamino)methylene]-3-[2-(1-methyl-1*H*-pyrrol-3-yl)-2-oxoethylidene] succinate (**3l**) (352 mg, 1.1 mmol) and NH_4OAc (847 mg, 11 mmol), stirred for 5 days, chromatography (petroleum ether/ethyl acetate=7:1), crystallized from ethyl acetate; yield: 131 mg (44%) of light yellow solid. Mp 105.2–108.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 3H, NCH_3); 3.90 (s, 3H, COOCH_3); 3.94 (s, 3H, COOCH_3); 6.63 (m, 2H, pyrrole); 7.34 (t, 1H, J_1=1.9 Hz, pyrrole); 7.48 (d, 1H, J_1=0.6 Hz, pyridine); 8.97 (d, 1H, J_1=0.6 Hz, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 36.6, 52.5, 52.9, 107.6, 116.2, 119.6, 123.2, 123.7, 123.8, 141.8, 151.0, 158.4, 165.6, 167.9. ($C_{14}H_{14}N_2O_4$ requires: C, 61.31; H, 5.14; N, 10.21. Found C, 61.16; H, 5.22; N, 10.12); ESI-HRMS: *m*/*z*=275.1021 (MH^+); $C_{14}H_{15}N_2O_4$ requires: *m*/*z*=275.1032 (MH^+); ν_{max} (KBr) 3460, 2361, 2343, 1740, 1715, 1636, 1599, 1540, 1437, 1298, 1218, 1139, 973 cm^{-1}.

*5.3.13. Dimethyl 6-(furan-3-yl)pyridine-3,4-dicarboxylate (**4m**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-(furan-3-yl)-2-oxoethylidene)succinate (**3m**) (315 mg, 1.0 mmol) and NH_4OAc (770 mg, 10.0 mmol), stirred for 2 days, chromatography (ethyl acetate/petroleum ether=1:1). Crystallized from ethyl acetate/petroleum ether: yield: 203 mg (78%) of brownish solid. Mp 92.7–94.2 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (3H, s, COOCH_3); 3.97 (3H, s, COOCH_3); 6.57 (1H, dd, J_1=1.8 Hz, J_2=3.5 Hz, furan); 7.22 (1H, dd, J_1=0.7 Hz, J_2=3.5 Hz, furan); 7.59 (1H, dd, J_1=0.7 Hz, J_2=1.7 Hz, furan), 7.80 (1H, d, *J*=0.6 Hz, pyridine); 9.04 (1H, d, *J*=0.7 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 52.9, 53.2, 112.0, 112.8, 116.4, 122.0, 142.1, 145.1, 151.1, 152.3, 152.4, 165.4, 167.3. ($C_{13}H_{11}NO_5$ requires: C, 59.77; H, 4.24; N, 5.36. Found C, 60.05; H, 4.08; N, 5.34); ESI-HRMS: *m*/*z*=262.0715 (MH^+); $C_{13}H_{12}NO_5$ requires: *m*/*z*=262.0715 (MH^+); ν_{max} (KBr) 1739, 1718, 1604, 1577, 1548, 1490, 1438, 1352, 1299, 1282, 1257, 1193, 1138, 1093, 1011, 956, 919, 883, 851, 825, 796, 762, 733 cm^{-1}.

*5.3.14. Dimethyl 6-(thiophen-3-yl)pyridine-3,4-dicarboxylate (**4n**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxo-2-(thiophen-3-yl)ethylidene)succinate (**3n**) (162 mg, 0.5 mmol) and NH_4OAc (385 mg, 5.0 mmol), stirred for 3 days, chromatography (ethyl acetate/petroleum ether=1:1). Crystallized from ethyl acetate/petroleum ether; yield: 115 mg (83%) of yellow solid. Mp 101.3–104.6 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (3H, s, COOCH_3); 3.98 (3H, s, COOCH_3); 7.43 (1H, dd, J_1=3.0 Hz, J_2=5.1 Hz, thiophene); 7.70 (1H, dd, J_1=1.3 Hz, J_2=5.1 Hz, thiophene); 7.73 (1H, d, *J*=0.7 Hz, pyridine), 8.06 (1H, dd, J_1=1.3 Hz, J_2=3.0 Hz, thiophene); 9.08 (1H, d, *J*=0.7 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 52.9, 53.2, 118.1, 122.1, 126.3, 126.4, 127.0, 140.6, 141.9, 151.0, 156.7, 165.5, 167.4. ($C_{13}H_{11}NO_4S$ requires: C, 56.31; H, 4.00; N, 5.05. Found C, 56.25; H, 3.92; N, 5.00); ESI-HRMS: *m*/*z*=278.0489 (MH^+); $C_{13}H_{12}NO_4S$ requires: *m*/*z*=278.0487 (MH^+); ν_{max} (KBr) 3110, 2947, 2844, 1733, 1595, 1546, 1528, 1520, 1445, 1436, 1421, 1336, 1290, 1237, 1206, 1140, 1095, 1077, 955, 914, 898, 879, 849, 824, 809, 784, 727 cm^{-1}.

*5.3.15. Dimethyl 6-(2,5-dimethylthiophen-3-yl)pyridine-3,4-dicarboxylate (**4o**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-(2,5-dimethylthiophen-3-yl)-2-oxoethylidene)succinate (**3o**) (650 mg, 1.85 mmol) and NH_4OAc (1430 mg, 18.5 mmol), stirred for 2 days, chromatography (ethyl acetate/petroleum ether=1:3). Crystallized from ethyl acetate/petroleum ether; yield: 302 mg (54%) of yellow solid. Mp 94.7–97.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.43 (3H, s, CH_3); 2.65 (3H, s, CH_3); 3.94 (3H, s, COOCH_3); 3.96 (3H, s, COOCH_3); 7.02 (1H, d, *J*=1.1 Hz, thiophene); 7.57 (1H, d, *J*=0.7 Hz, pyridine), 9.09 (1H, d, *J*=0.7 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 15.4, 15.6, 53.1, 53.5, 120.2, 121.5, 126.6, 135.4, 136.5, 139.4, 141.7, 150.9, 159.0, 165.9, 167.8. ($C_{15}H_{15}NO_4S$ requires: C, 59.00; H, 4.95; N, 5.59. Found C, 59.03; H, 4.80; N, 4.57); ESI-HRMS: *m*/*z*=306.0806 (MH^+); $C_{15}H_{16}NO_4S$ requires: *m*/*z*=306.0800 (MH^+); ν_{max} (KBr) 3069, 3006, 2950, 2920, 1739, 1718, 1639, 1592, 1541, 1487, 1432, 1373, 1343, 1302, 1277, 1248, 1194, 1139, 1074, 1015, 959, 897, 878, 845, 824, 795, 768, 737 cm^{-1}.

*5.3.16. Dimethyl 6-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)pyridine-3,4-dicarboxylate (**4p**).* Prepared from (2*E*,3*E*)-dimethyl 2-(2-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-2-oxoethylidene)-3-((dimethylamino)methylene)succinate (**3p**) (348 mg, 0.67 mmol) and NH_4OAc (516 mg, 6.7 mmol), stirred for 2 day, chromatography (ethyl acetate/petroleum ether=1:10). Crystallized from ethyl acetate/petroleum ether; yield: 127 mg (46%) of yellow solid. Mp 135.4–138.1 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.70 (9H, s, Boc); 3.97 (3H, s, COOCH_3); 4.00 (3H, s, COOCH_3); 7.39 (2H, dqd, J_1=1.3 Hz, J_2=7.3 Hz, J_3=14.7 Hz, indole); 7.48 (1H, d, *J*=0.4 Hz, pyridine), 8.22–8.25 (2H, m, indole); 8.43–8.45 (1H, m, indole); 9.18 (1H, d, *J*=0.4 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 28.2, 52.8, 53.2, 84.8, 115.3, 118.6, 119.5, 121.3, 121.9, 123.8, 125.3, 126.9, 127.7, 136.2, 141.5, 149.3, 160.9, 157.5, 165.5, 167.5. ($C_{22}H_{22}N_2O_6$ requires: C, 64.38; H, 5.40; N, 6.83. Found C, 64.43; H, 5.19; N, 6.70); ESI-HRMS: *m*/*z*=411.1606 (MH^+); $C_{22}H_{23}N_2O_6$ requires: *m*/*z*=411.1551 (MH^+); ν_{max} (KBr) 1734, 1717, 1636, 1549, 1455, 1436, 1395, 1373, 1291, 1271, 1240, 1207, 1159, 1108, 1057, 1018, 989, 955, 879, 821, 766, 750 cm^{-1}.

*5.3.17. Dimethyl 6-(1,3-thiazol-2-yl)pyridine-3,4-dicarboxilate (**4q**).* Prepared from (2*E*,3*E*)-dimethyl 2-[(dimethylamino)methylene]-3-[2-oxo-2-(thiazol-2-yl)ethylidene]succinate (**3q**) (447 mg, 1.37 mmol) and NH_4OAc (1.056 g, 13.7 mmol), stirred for 24 h, chromatography (petroleum ether/ethyl acetate=4:1), crystallized from ethyl acetate; yield: 306 mg (80%) of light brown solid. Mp 128.0–130.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H, COOCH_3); 3.98 (s, 3H, COOCH_3); 7.54 (d, 1H, J_1=3.3 Hz, thiazole); 7.97 (d, 1H, J_1=3.3 Hz, thiazole); 8.36 (d, 1H, J_1=0.6 Hz, pyridine); 9.03 (d, 1H, J_1=0.6 Hz, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 53.0, 53.2, 117.9, 123.2, 124.9, 141.9, 144.8, 150.6, 154.3, 165.2, 166.5, 167.0. ($C_{12}H_{10}N_2O_4S$ requires: C, 51.79; H, 3.62; N, 10.07. Found C, 51.69; H, 3.55; N, 10.01); ESI-HRMS: *m*/*z*=279.0446 (MH^+); $C_{12}H_{11}N_2O_4S$ requires: *m*/*z*=279.0446 (MH^+); ν_{max} IR (KBr) 3462, 3103, 2994, 2359, 1740, 1720, 1636, 1589, 1551, 1437, 1414, 1374, 1298, 1275, 1242, 1134, 1084, 957, 921 cm^{-1}.

*5.3.18. Dimethyl 6-(pyridn-2-yl)pyridine-3,4-dicarboxylate (**4r**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxo-2-(pyridin-2-yl)ethylidene)succinate (**3r**) (126 mg, 0.4 mmol) and NH_4OAc (308 mg, 4.0 mmol), stirred for 3 days, chromatography (ethyl acetate/petroleum ether=1:1). Crystallized from ethyl acetate/petroleum ether; yield: 51 mg (47%) of white solid. Mp 109.7–111.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (3H, s, COOCH_3); 3.95 (3H, s, COOCH_3); 7.34 (1H, ddd, J_1=1.1 Hz, J_2=4.8 Hz, J_3=7.5 Hz, Py); 7.82 (1H, td, J_1=1.8 Hz, J_2=7.8 Hz, Py); 8.44 (1H, d, *J*=8.0 Hz, Py); 8.61 (1H, d, *J*=0.6 Hz, pyridine); 8.68 (1H, ddd, J_1=0.9 Hz, J_2=1.7 Hz, J_3=4.8 Hz, Py); 9.09 (1H, d, *J*=0.6 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.0, 53.2, 119.3, 122.0, 124.4, 125.0, 137.3, 141.9, 149.6, 150.4, 154.4, 159.5, 165.7, 167.2. ($C_{14}H_{12}N_2O_4$ requires: C, 61.76; H, 4.44; N, 10.29. Found C, 61.61; H, 4.33; N, 10.20); ESI-HRMS: *m*/*z*=273.0868 (MH^+); $C_{14}H_{13}N_2O_4$ requires: *m*/

z=273.0868 (MH^+); ν_{max} (KBr) 3065, 6007, 2951, 1736, 1719, 1585, 1549, 1460, 1440, 1370, 1298, 1282, 1227, 1196, 1133, 1097, 994, 966, 930, 870, 826, 785, 747, 685 cm^{-1}.

*5.3.19. Dimethyl 6-(pyrazin-3-yl)pyridine-3,4-dicarboxylate (**4s**).* Prepared from (2*E*,3*E*)-dimethyl 2-[(dimethylamino)methylene]-3-(2-oxo-2-(pyrazin-2-yl)ethylidene)succinate (**3s**) (159 mg, 0.5 mmol) and NH_4OAc (385 mg, 5 mmol), stirred for 3 days, chromatography (petroleum ether/ethyl acetate=5:1), crystallized from ethyl acetate; yield: 98.5 mg (72%) of white solid. Mp 150.2–152.8 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.98 (s, 3H, $COOCH_3$); 3.99 (s, 3H, $COOCH_3$); 8.58 (s, 1H, pyridine); 8.66 (m, 2H, pyrazine); 9.15 (s, 1H, pyridine); 9.70 (d, 1H, J_1=1.5 Hz, pyrazine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 53.1, 53.3, 119.6, 125.2, 141.9, 144.1, 144.2, 146.7, 149.4, 150.5, 157.6, 166.8, 168.7. ($C_{13}H_{11}N_3O_4$ requires: C, 57.14; H, 4.06; N, 15.38. Found C, 57.01; H, 4.00; N, 15.36); ESI-HRMS: m/z=274.0824 (MH^+); $C_{13}H_{12}N_3O_4$ requires: m/z=274.0828 (MH^+); ν_{max} IR (KBr) 2961, 1745, 1718, 1654, 1559, 1436, 1268, 1294, 1100, 1017, 794 cm^{-1}.

*5.3.20. Tetramethyl 6,6′-(1,3-phenylene)bis(pyridine-3,4-dicarboxylate) (**9a**).* Prepared from (2*E*,2′*E*,3*E*,3′*E*)-tetramethyl 3,3′-(1,3-phenylenebis(2-oxoethan-2-yl-1-ylidene))bis(2-((dimethylamino)methylene)succinate)) (**8a**) 834 mg, 1.5 mmol) and NH_4OAc (2310 mg, 30.0 mmol), stirred for 3 days, chromatography (ethyl acetate). Crystallized from ethyl acetate/petroleum ether; yield: 604 mg (87%) of brownish solid. Mp 147.1–150.3 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.98 (6H, s, $COOCH_3$); 4.00 (6H, s, $COOCH_3$); 7.64 (1H, t, J=7.8 Hz, Ph); 8.00 (2H, d, J=0.7 Hz, pyridine), 8.18 (2H, dd, J_1=1.8 Hz, J_2=7.8 Hz, Ph); 8.77 (1H, t, J=1.6 Hz, Ph); 9.18 (2H, d, J=0.7 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.1, 53.4, 118.7, 123.2, 126.4, 129.4, 129.9, 138.4, 142.0, 151.0, 160.2, 165.6, 167.4. ($C_{24}H_{20}N_2O_8$ requires: C, 62.07; H, 4.34; N, 6.03. Found C, 61.99; H, 4.17; N, 5.99); ESI-HRMS: m/z=465.1299 (MH^+); $C_{24}H_{21}N_2O_8$ requires: m/z=465.1298 (MH^+); ν_{max} (KBr) 3007, 2955, 1744, 1724, 1594, 1557, 1436, 1369, 1305, 1291, 1266, 1195, 1139, 1085, 963, 882, 859, 824, 795, 777, 690 cm^{-1}.

*5.3.21. Tetramethyl 6,6′-(1,4-phenylene)bis(pyridine-3,4-dicarboxylate) (**9b**).* Prepared from (2*E*,2′*E*,3*E*,3′*E*)-tetramethyl 3,3′-(1,4-phenylenebis(2-oxoethan-2-yl-1-ylidene))bis(2-((dimethylamino)methylene)succinate) (**8b**) (439 mg, 0.79 mmol) and NH_4OAc (1217 mg, 15.8 mmol), stirred for 3 days, precipitated from reaction mixture; Crystallized from ethyl acetate; yield: 239 mg (65%) of brownish solid. Mp 184.7–186.9 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.98 (6H, s, $COOCH_3$); 4.00 (6H, s, $COOCH_3$); 7.97 (2H, d, J=0.6 Hz, pyridine), 8.22 (4H, s, Ph); 9.17 (2H, d, J=0.6 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 53.1, 53.4, 118.7, 123.3, 128.1, 139.3, 142.0, 151.1, 159.9, 165.7, 167.4. ($C_{24}H_{20}N_2O_8$ requires: C, 62.07; H, 4.34; N, 6.03. Found C, 61.87; H, 4.18; N, 5.94); ESI-HRMS: m/z=465.1317 (MH^+); $C_{24}H_{21}N_2O_8$ requires: m/z=465.1298 (MH^+); ν_{max} (KBr) 3008, 2959, 1728, 1713, 1591, 1551, 1479, 1435, 1325, 1307, 1270, 1248, 1198, 1146, 1126, 1086, 962, 899, 852, 785, 748, 687 cm^{-1}.

*5.3.22. Hexamethyl 6,6′,6″-(benzene-1,3,5-triyl)tris(pyridine-3,4-dicarboxylate) (**9c**).* Prepared from (2*E*,2′*E*,2″*E*,3*E*,3′*E*,3″*E*)-hexamethyl 3,3′,3″-(benzene-1,3,5-triyltris(2-oxoethan-2-yl-1-ylidene)) tris(2-((dimethylamino)methylene)succinate) (**8c**) (230 mg, 0.29 mmol) and NH_4OAc (670 mg, 8.7 mmol), stirred for 1 day, precipitated from reaction mixture; Crystallized from ethyl acetate/petroleum ether; yield: 122 mg (64%) of brownish solid. Mp 215.3–217.4 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.99 (9H, s, $COOCH_3$); 4.02 (9H, s, $COOCH_3$); 8.10 (3H, d, J=0.7 Hz, pyridine), 8.89 (3H, s, Ph); 9.20 (3H, d, J=0.7 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.1, 53.5, 118.8, 123.6, 128.0, 139.2, 142.2, 151.1, 159.5, 165.6, 167.3. ($C_{33}H_{27}N_3O_{12}\times H_2O$ requires: C, 58.67; H, 4.33; N, 6.22. Found C, 58.80; H, 4.03; N, 6.16); ESI-HRMS: m/z=658.1649 (MH^+); $C_{33}H_{28}N_3O_{12}$ requires: m/z=658.1673 (MH^+); ν_{max} (KBr) 3009, 2956, 1730, 1638, 1617, 1590, 1556, 1436, 1367, 1351, 1303, 1243, 1196, 1141, 1092, 1068, 975, 882, 826, 795, 770, 697 cm^{-1}.

5.4. General procedure for the synthesis of 2-substittued 4,5-bis(methoxycarbonyl)-pyridine 1-oxides

$NH_2OH\times HCl$ (1.5-fold excess) was added to a solution of *(2E,3E)-dimethyl 2-[(dimethylamino)methylene]-3-(2-substituted)succinates* (0.23–3.07 mmol) in MeOH (10 mL). The reaction mixture was stirred from 2 h to 5 days at room temperature and after that volatile components were evaporated in vacuo and products were purified by column chromatography and crystallized from appropriate solvents.

*5.4.1. 2-Ethyl-4,5-bis(methoxycarbonyl)pyridine 1-oxide (**5a**).* Prepared from (2*E*,3*E*)-dimethyl 2-[(dimethylamino)methylene]-3-(2-oxobutylidene)succinate (**3a**) (311 mg, 1.2 mmol) and $NH_2OH\times HCl$ (125 mg, 1.8 mmol), stirred for 2 h, chromatography (petroleum ether/ethyl acetate=1:1); yield: 123 mg (47%) of yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3H, J_1=7.5 Hz, CH_3); 2.95 (q, 2H, J_1=7.5 Hz, CH_2); 3.98 (s, 3H, $COOCH_3$); 3.99 (s, 3H, $COOCH_3$); 7.63 (s, 1H, pyridine); 8.46 (s, 1H, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 10.2, 23.5, 53.2, 53.4, 124.5, 126.3, 128.5, 139.3, 156.1, 164.3, 164.9. ESI-HRMS: m/z=240.0876 (MH^+); $C_{11}H_{14}NO_5$ requires: m/z=240.0872 (MH^+); ν_{max} IR (NaCl): 3416, 2953, 2842, 2364, 2330, 1734, 1723, 1617, 1537, 1431, 1307, 1294, 1274, 1241, 1186, 1131, 1060, 963 cm^{-1}.

*5.4.2. 4,5-Bis(methoxycarbonyl)-2-propylpyridine 1-oxide (**5b**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxopentylidene)succinate (**3b**) (868 mg, 3.07 mmol) and $NH_2OH\times HCl$ (320 mg, 4.6 mmol), stirred for 2 h, chromatography (ethyl acetate/petroleum ether=1:1); yield: 640 mg (82%) of yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.04 (3H, t, J=7.4 Hz, CH_3); 1.78 (2H, sextet, J=7.5 Hz, CH_2); 2.90 (2H, t, J=7.5 Hz, CH_2); 3.93 (3H, s, $COOCH_3$); 3.94 (3H, s, $COOCH_3$); 7.63 (1H, s, pyridine); 8.46 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.8, 19.1, 32.2, 53.1, 53.3, 125.4, 126.1, 128.6, 139.3, 154.7, 164.3, 164.7. ESI-HRMS: m/z=254.1030 (MH^+); $C_{12}H_{16}NO_5$ requires: m/z=254.1028 (MH^+); ν_{max} (NaCl) 3123, 3040,2958, 2875, 1734, 1616, 1534, 1435, 1402, 1296, 1241, 1049, 970, 913, 867, 804, 769, 671 cm^{-1}.

*5.4.3. 2-(tert-Butyl)-4,5-bis(methoxycarbonyl)pyridine 1-oxide (**5c**).* Prepared from (2*E*,3*E*)-dimethyl 2-(3,3-dimethyl-2-oxobutylidene)-3-((dimethylamino)methylene)succinate (**3c**) (282 mg, 0.95 mmol) and $NH_2OH\times HCl$ (99 mg, 1.4 mmol), stirred for 24 h, chromatography (ethyl acetate/petroleum ether=1:1); yield: 245 mg (96%) of yellowish oil. ^1H NMR ($CDCl_3$, 500 MHz): δ 1.51 (9H, s, ^tBu); 3.93 (3H, s, $COOCH_3$); 3.94 (3H, s, $COOCH_3$); 7.72 (1H, s, pyridine); 8.34 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 26.7, 36.6, 53.3, 53.5, 124.3, 125.9, 128.8, 141.4, 160.3, 164.6, 165.2. ESI-HRMS: m/z=268.1182 (MH^+); $C_{13}H_{18}NO_5$ requires: m/z=268.1179 (MH^+); ν_{max} (NaCl) 2957, 1732, 1610, 1537, 1489, 1436, 1306, 1277, 1240, 1200, 1136, 1116, 1037, 970, 912, 804, 776, 665 cm^{-1}.

*5.4.4. 2-(Cyclopent-1-en-1-yl)-4,5-bis(methoxycarbonyl)pyridine 1-oxide (**5d**).* Prepared from (2*E*,3*E*)-dimethyl 2-[2-(cyclopent-1-en-1-yl)-2-oxoethylidene]-3-[(dimethylamino)methylene]succinate (**3d**) (432 mg, 1.4 mmol) and $NH_2OH\times HCl$ (146 mg, 2.1 mmol), stirred for 24 h, chromatography (petroleum ether/ethyl acetate=1:1), crystallized from ethyl acetate/petroleum ether; yield: 291 mg (75%) of yellow solid. Mp 124.0–126.2 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.00 (pent, 2H, J_1=7.8 Hz, cyclopentene); 2.67–2.72 (m, 2H, cyclopentene); 2.78–2.84 (m, 2H, cyclopentene);

3.93 (s, 3H, COOCH_3); 3.94 (s, 3H, COOCH_3); 7.63 (s, 1H, pyridine); 7.91–7.94 (m, 1H, cyclopentene); 8.49 (s, 1H, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.2, 34.5, 35.0, 53.2, 53.4, 125.2, 126.3, 126.6, 132.3, 140.9, 142.6, 146.8, 164.3, 165.1. ($C_{14}H_{15}NO_5$ requires: C, 60.64; H, 5.45; N, 5.05. Found C, 60.51; H, 5.45; N, 5.03); ESI-HRMS: m/z=278.1021 (MH^+); $C_{14}H_{16}NO_5$ requires: m/z=278.1028 (MH^+); ν_{max} IR (KBr) (cm^{-1}): 3550, 3472, 3276, 3051, 2950, 2358, 1742, 1723, 1635, 1609, 1533, 14,734, 1426, 1295, 1233, 1138, 1066, 965 cm^{-1}.

*5.4.5. (E)-4,5-Bis(methoxycarbonyl)-2-styrylpyridine 1-oxide (**5e**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-((*E*)-2-oxo-4-phenylbut-3-en-1-ylidene)succinate (**3e**) (478 mg, 1.4 mmol) and $NH_2OH\times HCl$ (146 mg, 2.1 mmol), stirred for 3 h, precipitated from reaction mixture; yield: 198 mg (45%) of white solid. Mp 157.2–158.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (3H, s, COOCH_3); 3.95 (3H, s, COOCH_3); 7.35–7.42 (3H, m, Ph); 7.55–7.62 (3H, m, Ph+C*H*); 7.73 (1H, d, J=16.7 Hz, C*H*); 7.97 (1H, s, pyridine), 8.46 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.3, 53.4, 117.3, 123.0, 126.7, 127.7, 128.2, 129.1, 130.0, 135.7, 138.2, 140.1, 149.7, 164.2, 165.0. ($C_{17}H_{15}NO_5$ requires: C, 65.17; H, 4.83; N, 4.47. Found C, 65.29; H, 4.89; N, 4.45); ESI-HRMS: m/z=314.1019 (MH^+); $C_{17}H_{16}NO_5$ requires: m/z=314.1028 (MH^+); ν_{max} (KBr) 1734, 1726, 1653, 1625, 1576, 1525, 1432, 1406, 1293, 1269, 1261, 1235, 1151, 1126, 1056, 687, 960, 904, 884, 799, 761, 715, 691 cm^{-1}.

*5.4.6. 4,5-Bis(methoxycarbonyl)-2-phenylpyridine 1-oxide (**5f**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxo-2-phenylethylidene)succinate (**3f**) (419 mg, 1.32 mmol) and $NH_2OH\times HCl$ (139 mg, 2.0 mmol), stirred for 4 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallized from ethyl acetate/petroleum ether; yield: 268 mg (71%) of white solid. Mp 120.5–121.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (3H, s, COOCH_3); 3.89 (3H, s, COOCH_3); 7.39–7.44 (3H, m, Ph); 7.74–7.77 (2H, m, Ph); 7.78 (1H, s, pyridine); 8.44 (1H, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.1, 53.4, 126.1, 127.4, 128.5, 129.2, 129.4, 130.5, 131.0, 140.4, 150.7, 164.2, 164.4. ($C_{15}H_{13}NO_5$ requires: C, 62.72; H, 4.56; N, 4.88. Found C, 62.81; H, 4.42; N, 4.85); ESI-HRMS: m/z=286.0718 ($M-H^-$); $C_{15}H_{12}NO_5$ requires: m/z=286.0721 ($M-H^-$); ν_{max} (KBr) 1740, 1723, 1610, 1533, 1452, 1434, 1397, 1306, 1277, 1231, 1126, 1070, 1029, 954, 911, 877, 801, 783, 763, 718, 690 cm^{-1}.

*5.4.7. 2-(2-Fluorophenyl)-4,5-bis(methoxycarbonyl)pyridine 1-oxide (**5g**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-(2-fluorophenyl)-2-oxoethylidene)succinate (**3g**) (191 mg, 0.57 mmol) and $NH_2OH\times HCl$ (59 mg, 0.86 mmol), stirred for 4 h, chromatography (ethyl acetate/petroleum ether=1:1). Crystallized from ethyl acetate/petroleum ether; yield: 126 mg (72%) of yellow solid. Mp 132.0–134.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.92 (3H, s, COOCH_3); 3.97 (3H, s, COOCH_3); 7.18–7.24 (1H, m, Ph); 7.24–7.30 (1H, m, Ph); 7.46–7.53 (1H, m, Ph); 7.58 (1H, td, J_1=1.7 Hz, J_2=7.4 Hz, Ph); 7.85 (1H, s, pyridine); 8.50 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.2, 53.5, 116.2 (d, J=21.3 Hz), 119.3 (d, J=14.2 Hz), 124.3 (d, J=3.6 Hz), 125.4, 128.6 (d, J=2.1 Hz), 130.6, 131.0 (d, J=2.3 Hz), 132.5 (d, J=8.6 Hz), 139.9, 146.9, 160.1 (d, J=252.1 Hz), 164.1, 164.2. ^{19}F NMR ($CDCl_3$, 470.9 MHz): −116.9. ($C_{15}H_{12}FNO_5$ requires: C, 59.02; H, 3.96; N, 4.59. Found C, 59.22; H, 4.07; N, 4.35); ESI-HRMS: m/z=306.0774 (MH^+); $C_{15}H_{13}FNO_5$ requires: m/z=306.0778 (MH^+); ν_{max} (KBr) 3045, 2959, 1746, 1719, 1623, 1608, 1581, 1529, 1484, 1453, 1425, 1314, 1288, 1256, 1239, 1134, 1073, 965, 926, 818, 773, 755, 745, 664 cm^{-1}.

*5.4.8. 4,5-Bis(methoxycarbonyl)-2-(perfluorophenyl)pyridine 1-oxide (**5h**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino) methylene)-3-(2-oxo-2-(perfluorophenyl)ethylidene)succinate (**3h**) (95 mg, 0.23 mmol) and $NH_2OH\times HCl$ (25 mg, 0.35 mmol), stirred for 2 days, chromatography (ethyl acetate/petroleum ether=1:2). Crystallized from ethyl acetate/petroleum ether; yield: 43 mg (67%) of white solid. Mp 120.8–122.8 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.95 (3H, s, COOCH_3); 4.00 (3H, s, COOCH_3); 7.89 (1H, s, pyridine); 8.50 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 53.6, 53.9, 106.5 (td, J_1=4.2 Hz, J_2=17.4 Hz), 125.0, 129.8, 132.7, 138.1 (dm J=251.0 Hz), 139.2, 139.9, 143.5 (dm, J=234.6 Hz), 145.0 (dm, J=249.7 Hz), 163.6, 164.1. ^{19}F NMR ($CDCl_3$, 470.9 MHz): −137.4, −150.3, −161.3. ($C_{15}H_8F_5NO_5$ requires: C, 47.76; H, 2.14; N, 3.37. Found C, 47.72; H, 2.06; N, 3.70); ESI-HRMS: m/z=378.0388 (MH^+); $C_{15}H_9F_5NO_5$ requires: m/z=378.0395 (MH^+); ν_{max} (KBr) 1737, 1657, 1529, 1500, 1437, 1398, 1319, 1307, 1273, 1247, 1205, 1136, 1038, 992, 968, 913, 866, 821, 804, 735, 695, 670 cm^{-1}.

*5.4.9. 4,5-Bis(methoxycarbonyl)-2-(2-nitrophenyl)pyridine 1-oxide (**5i**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-(2-nitrophenyl)-2-oxoethylidene)succinate (**3i**) (440 mg, 1.2 mmol) and $NH_2OH\times HCl$ (125 mg, 1.8 mmol), stirred for 12 h, precipitated from reaction mixture; yield: 187 mg (47%) of white solid. Mp 170.9–172.3 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (3H, s, COOCH_3); 3.98 (3H, s, COOCH_3); 7.45 (1H, dd, J_1=1.4 Hz, J_2=7.5 Hz, Ar); 7.70 (1H, dd, J_1=1.6 Hz, J_2=7.8 Hz, Ar); 7.78 (1H, dd, J_1=1.4 Hz, J_2=7.5 Hz, Ar); 7.87 (1H, d, J=0.6 Hz, pyridine); 8.20 (1H, dd, J_1=1.2 Hz, J_2=8.1 Hz, Ar); 8.42 (1H, d, J=0.6 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.4, 53.7, 124.8, 126.3, 126.4, 126.6, 131.0, 131.6, 132.0, 139.4, 148.8, 149.7, 164.2, 164.3. ($C_{15}H_{12}N_2O_7$ requires: C, 54.22; H, 3.64; N, 8.43. Found C, 54.26; H, 3.48; N, 8.38); ESI-HRMS: m/z=665.1353 (2 MH^+); $C_{30}H_{25}N_4O_{14}$ requires: m/z=665.1362 (2 MH^+); ν_{max} (KBr) 1736, 1717, 1653, 1624, 1531, 1430, 1398, 1356, 1319, 1298, 1282, 1250, 1134, 1071, 958, 917, 859, 802, 777, 731, 698 cm^{-1}.

*5.4.10. 2-(Ferrocenyl)-4,5-bis(methoxycarbonyl)pyridine 1-oxide (**5j**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-ferrocenyl-2-oxoethylidene)succinate (**3j**) (340 mg, 0.82 mmol) and $NH_2OH\times HCl$ (85 mg, 1.23 mmol), stirred for 1 day, chromatography (ethyl acetate/petroleum ether=1:2). Crystallized from ethyl acetate/petroleum ether; yield: 149 mg (46%) of red solid. Mp 148.6–151.2 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.95 (3H, s, COOCH_3); 3.96 (3H, s, COOCH_3); 4.18 (5H, s, ferrocene); 4.57 (2H, t, J=1.5 Hz, ferrocene); 5.23 (2H, t, J=1.5 Hz, ferrocene); 7.81 (1H, s, pyridine); 8.46 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 126.0 MHz): δ 53.4, 53.5, 70.2, 70.3, 71.6, 74.3, 124.6, 125.9, 126.6, 141.93, 153.2, 164.6, 165.4. ($C_{19}H_{17}NO_5Fe$ requires: C, 57.75; H, 4.34; N, 3.54. Found C, 57.86; H, 4.07; N, 3.58); ESI-HRMS: m/z=396.0536 (MH^+); $C_{19}H_{18}NO_5Fe$ requires: m/z=396.0534 (MH^+); ν_{max} (KBr) 3085, 2953, 1733, 1609, 1533, 1506, 1456, 1435, 1399, 1372, 1300, 1225, 1212, 1134, 1098, 1036, 1001, 962, 880, 825, 800, 774,668 cm^{-1}.

*5.4.11. 4,5-Bis(methoxycarbonyl)-2-(1-methyl-1H-pyrrol-2-yl)pyridine 1-oxide (**5k**).* Prepared from (2*E*,3*E*)-dimethyl 2-[(dimethylamino)methylene]-3-[2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethylidene] succinate (**3k**) (512 mg, 1.6 mmol) and $NH_2OH\times HCl$ (167 mg, 2.4 mmol), stirred for 24 h, chromatography (petroleum ether/ethyl acetate=1:1), crystallized from petroleum ethyl acetate/ether; yield: 342 mg (75%) of dark brown solid. Mp 110.7–116.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H, NCH_3); 3.91 (s, 3H, COOCH_3); 3.95 (s, 3H, COOCH_3); 6.22 (dd, 1H, J_1=2.6 Hz, J_2=3.8 Hz, pyrrole); 6.47 (dd, 1H J_1=1.8 Hz, J_2=3.8 Hz, pyrrole); 6.84–6.86 (m, 1H, pyrrole); 7.77 (d, 1H, J_1=0.3 Hz, pyridine); 8.47 (d, 1H, J_1=0.3 Hz, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 36.1, 53.1, 53.4, 108.9, 114.4, 123.9, 125.9, 126.7, 128.5, 129.0, 140.0, 145.0, 164.2, 164.4. ($C_{14}H_{14}N_2O_5$ requires: C, 57.93; H, 4.86; N, 9.65. Found C, 57.72; H, 4.87; N, 9.61); ESI-HRMS: m/z=291.0985 (MH^+); $C_{14}H_{15}N_2O_5$ requires: m/z=291.0981 (MH^+); ν_{max}

IR (KBr) 3545, 3483, 3420, 3092, 2945, 2366, 2344, 1739, 1725, 1617, 1560,1522, 1438, 1322, 1301, 1233, 1130, 1082, 991 cm^{-1}.

*5.4.12. 4,5-Bis(methoxycarbonyl)-2-(1-methyl-1H-pyrrol-3-yl)pyridine 1-oxide (**5l**).* Prepared from (2*E*,3*E*)-dimethyl 2-[(dimethylamino)methylene]-3-[2-(1-methyl-1*H*-pyrrol-3-yl)-2-oxoethylidene] succinate (**3l**) (736 mg, 2.3 mmol) and $NH_2OH\times HCl$ (237 mg, 3.5 mmol), stirred for 3 days, chromatography (ethyl acetate), crystallized from ethyl acetate/petroleum ether; yield: 539 mg, (80%) of white-yellow solid. Mp 146.5–148.8 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H, NCH_3); 3.92 (s, 3H, COOCH_3); 3.93 (s, 3H, COOCH_3); 6.63 (dd, 1H, J_1=1.8 Hz, J_2=3.0 Hz, pyrrole); 6.68–6.70 (m, 1H, pyrrole); 7.90 (s, 1H, pyridine); 8.44 (t, 1H, J_1=1.8 Hz, pyrrole); 8.54 (s, 1H, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 36.6, 53.0, 53.1, 108.1, 113.9, 122.5, 123.1, 123.7, 127.5, 128.1, 140.9, 146.7, 164.3, 165.7. ($C_{14}H_{14}N_2O_5$ requires: C, 57.93; H, 4.86; N, 9.65. Found C, 57.78; H, 4.86; N, 9.61); ESI-HRMS: m/z=291.0983 (MH^+); $C_{14}H_{15}N_2O_5$ requires: m/z=291.0981 (MH^+); ν_{max} IR (KBr) 3555, 3493, 3415, 3235, 3105, 2961, 2362, 2342, 1740, 1719, 1608, 1539, 1473, 1442, 1372, 1303, 1280, 1216, 1172, 1133, 1069, 941 cm^{-1}.

*5.4.13. 2-(Furan-3-yl)-4,5-bis(methoxycarbonyl)pyridine 1-oxide (**5m**).* Prepared from (2*E*,3i)-dimethyl 2-((dimethylamino)methylene)-3-(2-(furan-3-yl)-2-oxoethylidene)succinate (**3m**) (315 mg, 1.0 mmol) and $NH_2OH\times HCl$ (104 mg, 1.5 mmol), stirred for 4 h, chromatography (ethyl acetate/petroleum ether=1:1). Crystallized from ethyl acetate/petroleum ether; yield: 216 mg (78%) of grayish solid. Mp 128.4–129.7 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.95 (3H, s, COOCH_3); 3.96 (3H, s, COOCH_3); 6.64 (1H, dd, J_1=1.8 Hz, J_2=3.5 Hz, furan); 7.65 (1H, dd, J_1=0.6 Hz, J_2=1.8 Hz, furan); 8.07 (1H, dd, J_1=0.6 Hz, J_2=3.5 Hz, furan), 8.25 (1H, s, pyridine); 8.52 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.3, 53.4, 113.0, 118.4, 122.5, 126.6, 127.0, 140.7, 141.5, 144.3, 145.3, 164.1, 165.0. ($C_{13}H_{11}NO_6$ requires: C, 56.32; H, 4.00; N, 5.05. Found C, 56.35; H, 3.84; N, 4.99); ESI-HRMS: m/z=278.0663 (MH^+); $C_{13}H_{12}NO_6$ requires: m/z=278.0665 (MH^+); ν_{max} (KBr) 3126, 2953, 1722, 1613, 1536, 1502, 1458, 1435, 1388, 1308, 1291, 1267, 1242, 1192, 1158, 1131, 1083, 998, 962, 935, 903, 892, 834, 805, 777, 769, 720, 670 cm^{-1}.

*5.4.14. 4,5-Bis(methoxycarbonyl)-2-(thiophen-3-yl)pyridine 1-oxide (**5n**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxo-2-(thiophen-3-yl)ethylidene)succinate (**3n**) (79 mg, 0.24 mmol) and $NH_2OH\times HCl$ (25.5 mg, 0.37 mmol), stirred for 4 h, chromatography (ethyl acetate/petroleum ether=1:1); yield: 57 mg (81%) of red solid. Mp 121.5–123.5 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.95 (3H, s, COOCH_3); 3.96 (3H, s, COOCH_3); 7.43 (1H, dd, J_1=3.1 Hz, J_2=5.2 Hz, thiophene); 7.65 (1H, dd, J_1=1.3 Hz, J_2=5.2 Hz, thiophene); 8.06 (1H, s, pyridine), 8.54 (1H, s, pyridine); 8.99 (1H, dd, J_1=1.3 Hz, J_2=3.1 Hz, thiophene). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.3, 53.5, 125.5, 125.8, 126.7, 127.0, 127.5, 130.5, 131.1, 141.2, 145.7, 164.2, 164.9. ($C_{13}H_{11}NO_5S$ requires: C, 53.24; H, 3.78; N, 4.78. Found C, 53.25; H, 3.82; N, 4.73); ESI-HRMS: m/z=294.0429 (MH^+); $C_{13}H_{12}NO_5S$ requires: m/z=294.0436 (MH^+); ν_{max} (KBr) 3122, 3097, 2950, 1721, 1612, 1525, 1437, 1384, 1309, 1239, 1208, 1184, 1134, 1070, 1012, 966, 910, 872, 813, 803, 775, 726, 699, 666 cm^{-1}.

*5.4.15. 2-(2,5-Dimethylthiophen-3-yl)-4,5-bis(methoxycarbonyl)pyridine 1-oxide (**5o**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-(2,5-dimethylthiophen-3-yl)-2-oxoethylidene)succinate (**3o**) (521 mg, 1.45 mmol) and $NH_2OH\times HCl$ (152.0 mg, 2.18 mmol), stirred for 2 h, chromatography (ethyl acetate/petroleum ether=1:1); yield: 434 mg (93%) of yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ 2.41 (3H, s, CH_3); 2.44 (3H, s, CH_3); 3.93 (3H, s, COOCH_3); 3.97 (3H, s, COOCH_3); 6.88 (1H, d, J=1.0 Hz, thiophene); 7.70 (1H, s, pyridine), 8.51 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 14.9, 15.3, 53.3, 53.6, 125.7, 126.1, 127.5, 129.3, 136.9, 139.9, 140.4, 147.9, 164.4, 164.6. ESI-HRMS: m/z=322.0743 (MH^+); $C_{15}H_{16}NO_5S$ requires: m/z=322.0749 (MH^+); ν_{max} (KBr) 2954, 2921, 1731, 1612, 1528, 1507, 1435, 1338, 1301, 1239, 1129, 1058, 962, 916, 849, 802, 775, 736, 708 cm^{-1}.

*5.4.16. 2-(1-(tert-Butoxycarbonyl)-1H-indol-3-yl)-4,5-bis(methoxycarbonyl)pyridine 1-oxide (**5p**).* Prepared from (2*E*,3*E*)-dimethyl 2-(2-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-2-oxoethylidene)-3-((dimethylamino)methylene)succinate (**3p**) (116 mg, 0.26 mmol) and $NH_2OH\times HCl$ (27.0 mg, 0.33 mmol), stirred for 3 days, precipitated from reaction mixture; yield: 60 mg (54%) of white solid. Mp 155.5–158.4 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 1.70 (9H, s, Boc); 3.97 (3H, s, COOCH_3); 3.98 (3H, s, COOCH_3); 7.38 (1H, td, J_1=1.0 Hz, J_2=8.0 Hz, indole); 7.43 (1H, td, J_1=1.0 Hz, J_2=8.5 Hz, indole); 7.82 (1H, d, J=7.8 Hz, indole); 8.27 (1H, s, pyridine), 8.34 (1H, d, J=8.2 Hz, indole); 8.61 (1H, s, pyridine); 9.05 (1H, s, indole). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 28.3, 53.5, 53.6, 85.2, 109.9, 116.1, 119.8, 124.0, 125.4, 125.7, 126.6, 127.2, 127.6, 131.1, 135.5, 140.7, 145.6, 149.2, 164.4, 165.1. ($C_{22}H_{22}N_2O_7$ requires: C, 61.97; H, 5.20; N, 6.57. Found C, 62.23; H, 5.16; N, 6.58); ESI-HRMS: m/z=427.1489 (MH^+); $C_{22}H_{23}N_2O_7$ requires: m/z=427.1500 (MH^+); ν_{max} (KBr) 3071, 2957, 1743, 1732, 1612, 1533, 1454, 1399, 1344, 1310, 1296, 1242, 1147, 1126, 1064, 1028, 960, 854, 835, 781, 762, 748 cm^{-1}.

*5.4.17. 4,5-Bis(methoxycarbonyl)-2-(thiazol-2-yl)pyridine 1-oxide (**5q**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxo-2-(thiazol-2-yl)ethylidene)succinate (**3q**) (162 mg, 0.5 mmol) and $NH_2OH\times HCl$ (52.0 mg, 0.75 mmol), stirred for 4 h, chromatography (ethyl acetate/petroleum ether=1:1); yield: 95 mg (65%) of brown solid. Mp 148.8–156.0 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.97 (3H, s, COOCH_3); 3.98 (3H, s, COOCH_3); 7.67 (1H, d, J=3.1 Hz, thiazole); 8.18 (1H, d, J=3.1 Hz, thiazole); 8.61 (1H, s, pyridine), 8.97 (1H, s, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.5, 53.7, 124.2, 124.8, 127.8, 128.7, 139.6, 143.6, 144.2, 153.9, 164.0, 164.6. ($C_{12}H_{10}N_2O_5S$ requires: C, 48.98; H, 3.43; N, 9.52. Found C, 49.04; H, 3.46; N, 9.44); ESI-HRMS: m/z=295.0385 (MH^+); $C_{12}H_{11}N_2O_5S$ requires: m/z=295.0389 (MH^+); ν_{max} (KBr) 2708, 1719, 1618, 1535, 1506, 1465, 1431, 1395, 1315, 1281, 1233, 1193, 1130, 1080, 1059, 1002, 960, 915, 881, 804, 774 cm^{-1}.

*5.4.18. 4,5-Bis(methoxycarbonyl)-[2,2′-bipyridine] 1-oxide (**5r**).* Prepared from (2*E*,3*E*)-dimethyl 2-((dimethylamino)methylene)-3-(2-oxo-2-(pyridin-2-yl)ethylidene)succinate (**3r**) (126 mg, 0.4 mmol) and $NH_2OH\times HCl$ (42 mg, 0.6 mmol), stirred for 3 h, chromatography (ethyl acetate/petroleum ether=1:1); yield: 64 mg (56%) of brown oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.95 (3H, s, COOCH_3); 3.97 (3H, s, COOCH_3); 7.40 (1H, ddd, J_1=0.9 Hz, J_2=4.8 Hz, J_3=7.5 Hz, Py); 7.85 (1H, td, J_1=1.8 Hz, J_2=7.9 Hz, Py); 8.51 (1H, s, pyridine); 8.70 (1H, s, pyridine); 8.76 (1H, d, J=4.7 Hz, Py); 8.94 (1H, d, J=8.1 Hz, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.2, 53.5, 125.2, 125.5, 126.5, 128.3, 129.9, 136.7, 141.0, 148.1, 148.6, 149.8, 164.3, 164.6. ESI-HRMS: m/z=289.0814 (MH^+); $C_{14}H_{13}N_2O_5$ requires: m/z=289.0824 (MH^+); ν_{max} (KBr) 3127, 3047, 3002, 2955, 1731, 1615, 1584, 1458, 1430, 1308, 1269, 1225, 1130, 1099, 1080, 1011, 989, 956, 905, 874, 795, 781, 742, 714, 664 cm^{-1}.

*5.4.19. 4,5-Bis(methoxycarbonyl)-2-(pyrazin-2-yl)pyridine 1-oxide (**5s**).* Prepared from (2*E*,3*E*)-dimethyl 2-[(dimethylamino)methylene]-3-[2-oxo-2-(pyrazin-2-yl)ethylidene]succinate (**3s**) (462 mg, 1.5 mmol) and $NH_2OH\times HCl$ (156 mg, 2.25 mmol), stirred for 24 h, chromatography (ethyl acetate), crystallized from ethyl acetate; yield: 322 mg (74%) of white-yellow solid. Mp 130.8–132.6 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H, COOCH_3); 3.99 (s, 3H, COOCH_3); 8.52 (s, 1H, pyridine); 8.70 (d, 2H, J_1=0.9 Hz, pyrazine); 8.74 (dd, 1H, J_1=1.5 Hz, J_2=2.4 Hz, pyrazine); 10.19 (s, 1H, pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 53.3, 53.6, 126.4, 128.2, 130.8, 140.8, 144.2, 144.3, 145.8, 146.3, 146.7, 164.0, 164.2. ($C_{13}H_{11}N_3O_5$ requires:

C, 53.98; H, 3.83; N, 14.53. Found C, 53.83; H, 3.78; N, 14.45); ESI-HRMS: m/z=290.0785 (MH^+); $C_{13}H_{12}N_3O_5$ requires: m/z=290.0777 (MH^+); ν_{max} IR (KBr) 3545, 3116, 2950, 2366, 1739, 1717, 1610, 1488, 1458, 1384, 1314, 1288, 1249, 1202, 1143, 1096, 971 cm^{-1}.

*5.4.20. 6,6′-(1,3-Phenylene)bis(3,4-bis(methoxycarbonyl)pyridine 1-oxide) (**10a**).* Prepared from (2*E*,2′*E*,3*E*,3′*E*)-tetramethyl 3,3′-(1,3-phenylenebis(2-oxoethan-2-yl-1-ylidene))bis(2-((dimethylamino) methylene)succinate) (**8a**) (518 mg, 0.9 mmol) and $NH_2OH\times HCl$ (188 mg, 2.7 mmol), stirred for 2 h, precipitated from reaction mixture; Crystallized from ethyl acetate/petroleum ether; yield: 337 mg (75%) of white solid. Mp 196.5–198.9 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.94 (6H, s, $COOCH_3$); 3.98 (6H, s, $COOCH_3$); 7.66 (1H, t, J=7.8 Hz, Ph); 7.90 (2H, s, pyridine), 7.97 (2H, d, J=7.8 Hz, Ph); 8.31 (1H, s, Ph); 8.53 (2H, s, pyridine). ^{13}C NMR ($CDCl_3$, 1265 MHz): δ 53.4, 53.7, 126.6, 127.6, 128.9, 130.0, 130.2, 131.4, 131.5, 140.5, 150.0, 164.2, 164.4. ($C_{24}H_{20}N_2O_{10}$ requires: C, 58.07; H, 4.06; N, 5.64. Found C, 58.13; H, 3.89; N, 5.58); ESI-HRMS: m/z=497.1184 (MH^+); $C_{24}H_{21}N_2O_{10}$ requires: m/z=497.1196 (MH^+); ν_{max} (KBr) 3039, 2955, 1734, 1716, 1636, 1614, 1536, 1439, 1396, 1371, 1310, 1278, 1239, 1194, 1140, 1077, 1031, 979, 960, 907, 859, 826, 802, 774, 725, 699 cm^{-1}.

*5.4.21. 6,6′-(1,4-Phenylene)bis(3,4-bis(methoxycarbonyl)pyridine 1-oxide) (**10b**).* Prepared from (2*E*,2′*E*,3*E*,3′*E*)-tetramethyl 3,3′-(1,4-phenylenebis(2-oxoethan-2-yl-1-ylidene))bis(2-((dimethylamino) methylene)succinate) (**8b**) (472 mg, 0.85 mmol) and $NH_2OH\times HCl$ (177 mg, 2.55 mmol), stirred for 2 h, precipitated from reaction mixture; Crystallized from DMF/H_2O; yield: 359 mg (85%) of yellowish solid. Mp 242.8–245.7 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.96 (6H, s, $COOCH_3$); 3.99 (6H, s, $COOCH_3$); 7.91 (2H, s, pyridine), 8.00 (4H, s, Ph); 8.53 (2H, s, pyridine). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 53.5, 53.7, 126.5, 127.6, 129.5, 130.1, 133.0, 140.7, 150.0, 164.2, 164.4. ($C_{24}H_{20}N_2O_{10}$ requires: C, 58.07; H, 4.06; N, 5.64. Found C, 58.19; H, 4.17; N, 5.70); ESI-HRMS: m/z=497.1176 (MH^+); $C_{24}H_{21}N_2O_{10}$ requires: m/z=497.1196 (MH^+); ν_{max} (KBr) 3108, 3053, 1732, 1719, 1637, 1612, 1526, 1453, 1433, 1307, 1289, 1242, 1202, 1135, 1078, 962, 930, 884, 849, 807, 771, 710, 690 cm^{-1}.

*5.4.22. 6,6′,6″-(Benzene-1,3,5-triyl)tris(3,4-bis(methoxycarbonyl) pyridine 1-oxide) (**10c**).* Prepared from (2*E*,2′*E*,2″*E*,3*E*,3′*E*,3″*E*)-hexamethyl 3,3′,3″-(benzene-1,3,5-triyltris(2-oxoethan-2-yl-1-ylidene)) tris(2-((dimethylamino)methylene)succinate) (**8c**) (190 mg, 0.24 mmol) and $NH_2OH\times HCl$ (75.0 mg, 1.1 mmol), stirred for 12 h, precipitated from reaction mixture; yield: 104 mg (61%) of brownish solid. Mp 230.1–233.2 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.95 (9H, s, $COOCH_3$); 4.97 (9H, s, $COOCH_3$); 7.96 (3H, s, pyridine), 8.47 (3H, s, Ph); 8.53 (3H, s, pyridine). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 53.5, 53.8, 126.9, 127.7, 130.4, 131.8, 132.1, 140.6, 149.1, 164.1, 164.3. ($C_{33}H_{27}N_3O_{15}\times H_2O$ requires: C, 54.78; H, 4.04; N, 5.81. Found C, 54.88; H, 3.77; N, 5.76); ESI-HRMS: m/z=706.1508 (MH^+); $C_{33}H_{28}N_3O_{12}$ requires: m/z=706.1515 (MH^+); ν_{max} (KBr) 1755, 1720, 1701, 1623, 1527, 1468, 1393, 1374, 3950, 1236, 1193, 1092, 1068, 1024, 901, 793, 769 cm^{-1}.

5.5. X-ray structure analysis for compounds 4h–j,l,m, 5j–k, 8b, and 9b

For X-ray structure determination, the crystals of the aforementioned compounds were mounted on the tip of glass fibers and transferred to the goniometer head. Data were collected on a Nonius Kappa CCD diffractometer using monochromated Mo Kα radiation at room temperature by using Nonius Collect software.[25] Data reduction and integration were performed with the software package DENZO-SMN.[26] The coordinates of all of the non-hydrogen atoms were found via direct methods using the SIR97 structure solution program.[27] A full-matrix least-squares refinement on F^2 magnitudes with anisotropic displacement parameters for all non-hydrogen atoms using SHELXL-97 was employed.[28] All H atoms were initially located in difference Fourier maps. Methyl H atoms were subsequently treated as riding atoms in geometrically idealized positions with bond lengths C–H 0.96 Å and Uiso(H)= 1.5Ueq(C). Rotations of the methyl groups were allowed whereas their tilting was not permitted. The coordinates and Uiso's of other non-methyl hydrogen atoms were refined independently.

Figures depicting the structures were prepared by ORTEP3.[29]

CCDC 859534–859542 contain the supplementary crystallographic data for structures **4h**–**j**,**l**,**m**, **5j**–**k**, **8b**, and **9b**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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