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Domino Reaction of 3-(2-Formylphenoxy)propenoates and Amines: A Novel Synthesis of 1,4-Dihydropyridines from Salicaldehydes, Ethyl Propiolate, and Amines

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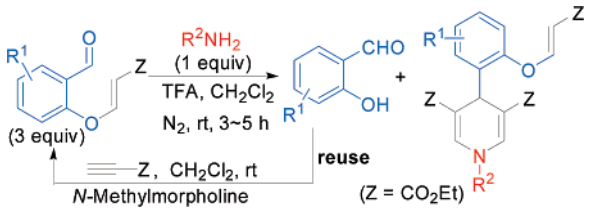

A novel synthesis of Hantzsch-type *N*-substituted 1,4-dihydropyridines from salicaldehydes, ethyl propiolate, and amines has been developed. Salicaldehydes were treated with ethyl propiolate in the presence of *N*-methylmorpholine to give ethyl 3-(2-formylphenoxy)propenoates. Three equivalents of ethyl 3-(2-formylphenoxy)propenoates reacted with 1 equiv of amines under trifluoroacetic acid (TFA) catalyst to furnish the corresponding *N*-substituted 1,4-dihydropyridines in good to excellent yields, recovering the starting material salicaldehydes. A possible mechanism for the domino process was proposed. Furthermore, the products can be easily derived via further transformations and three of them exhibited strong fluorescence ($\Phi_f = 0.36-0.63$).

1,4-Dihydropyridines (DHPs) have been extensively investigated due to their importance in medicinal chemistry and pharmacology.[1] 1,4-DHPs are potent blockers and activators of L-type calcium channels as well as antagonists at the DHP receptor.[2] They are also important reducing agents toward the application of the nicotinamide adenine dinucleotide coenzyme [NAD(P)H] models.[3] Sodium dithionite reduction has been largely applied to pyridinium salts bearing, in the 3- or 3,5-positions, electron-withdrawing groups such as −CN, −$CONH_2$, and −COOR, and chiefly affords the corresponding 1,4-dihydropyridines.[4] The reaction of 2-amino-5-formyl-4*H*-pyran with primary amines could also yield *N*-substituted 1,4-DHPs.[5] Hantzsch ester synthesis is a classical method for the construction of 1,4-DHP ring from aldehyde, and enamine or dicarbonyl compound as well as ammonia.[6] Additionally, a regioselective [4+2] cycloaddition of 1-aryl-4-phenyl-1-azadienes and allenic esters for the synthesis of *N*-aryl-1,4-DHPs[7] and a multicomponent reaction of alkyl amines, ethyl propiolate, and benzaldehydes for the construction of *N*-alkyl-1,4-DHPs have been reported.[8]

In recent years, the development of efficient synthetic strategies for the one-pot generation of multiple bonds is highly desirable. In this regard, domino reactions continue to attract much attention because of their considerable potential in this area.[9] As a part of our ongoing research into the discovery and development of a new domino process,[10] we herein report an acid-catalyzed domino reaction of 3-(2-formylphenoxy)propenoates and amines, which furnished a novel synthesis of both *N*-aryl- and *N*-alkyl-1,4-dihydropyridines.

In initial studies we treated *E*-3-(2-formylphenoxy)propenoate (**1a**) with an equivalent amount of aniline (**2a**) using TFA as a catalyst at room temperature, and obtained dihydropyridine **3a** (32% isolated yield), imine **4a** (45% isolated yield), and salicaldehyde (**5a**, 20% isolated yield), respectively (Scheme 1). Intrigued by this result, we performed the reaction using 3 equiv of **1a** and 1 equiv of **2a** under various conditions (see the Supporting Information, Table 1). The best yield of dihydropyridine **3a** was obtained with protonic acid TFA as the catalyst and CH_2Cl_2 as the solvent.

We then prepared several ethyl 3-(2-formylphenoxy)propenoates **1** from salicaldehydes **5** and ethyl propiolate by the published method,[11] and explored the scope employing these 3-(2-formylphenoxy)propenoates and a wide range of amines **2** (Scheme 2). As shown in Table 1, both aromatic (Table 1,

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(6) For reviews see: (a) Stout, D. M. *Chem. Rev.* **1982**, *82*, 223−243. (b) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1−42. (c) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141−1156.

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(11) (a) Ciganek, E. *Synthesis* **1995**, 1311−1314. (b) Yields of enoates **1** referring to salicaldehydes: **1a** (72%), **1b** (75%), **1c** (65%), **1d** (60%).

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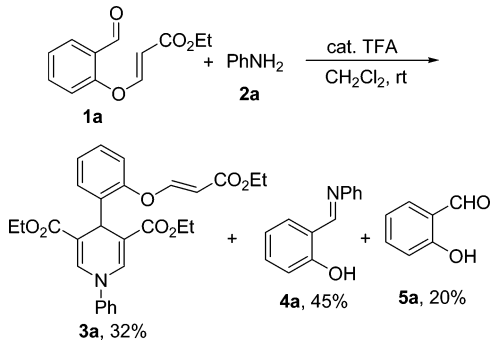
SCHEME 1. Reaction of Ethyl 3-(2-formylphenoxy)propenoate (1a) and Aniline (2a)



SCHEME 2. Synthesis of 1,4-Dihydropyridines 3 from Salicaldehydes 5, Ethyl Propiolate, and Amines 2

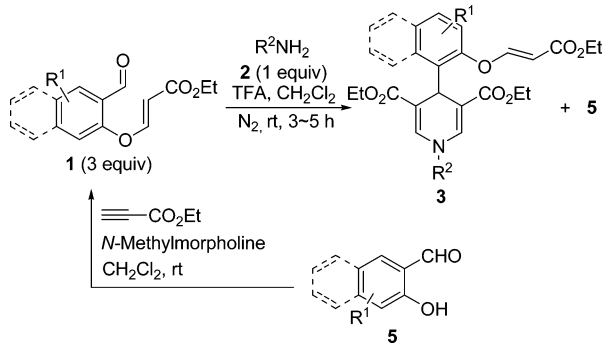
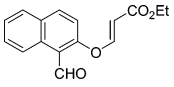


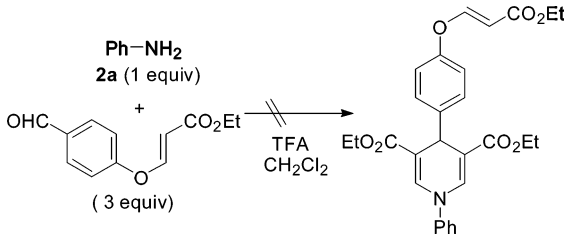
TABLE 1. Synthesis of 1,4-Dihydropyridines 3 from Ethyl 3-(2-Formylphenoxy)propenoates 1 and Amines 2

entry	R^1	R^2	product	yield (%)[a]
1	H (**1a**)	Ph (**2a**)	**3a**	98
2	**1a**	4-MePh (**2b**)	**3b**	98
3	**1a**	4-MeOPh (**2c**)	**3c**	95
4	**1a**	2,4-Me_2Ph (**2d**)	**3d**	98
5	**1a**	4-BrPh (**2e**)	**3e**	99
6	**1a**	4-MeCOPh (**2f**)	**3f**	85[b]
7	**1a**	4-NO_2Ph (**2g**)	**3g**	56[c]
8	4-MeO (**1b**)	**2b**	**3h**	95
9	**1b**	3-ClPh (**2h**)	**3i**	90
10	**1b**	4-Br-naphthen-1-yl (**2i**)	**3j**	95
11	5-Br (**1c**)	**2b**	**3k**	99
12	**1c**	4-HOPh (**2i**)	***3l***	75[d]
13	**1c**	4-EtO_2CPh (**2j**)	**3m**	50
14	**1c**	4-H_2NPh (**2k**)	**3n**	75[e]
15	**1c**	4-H_2NSO_2Ph (***2l***)	**3o**	75
16	 (**1d**)	**2a**	**3p**	89
17	**1d**	**2b**	**3q**	92
18	**1d**	**2e**	**3r**	90
19	**1a**	*i*-Pr (**2m**)	**3s**	92
20	**1b**	**2m**	**3t**	89
21	**1c**	**2m**	**3u**	90
22	**1a**	*n*-Bu (**2n**)	**3v**	85
23	**1a**	*n*-Oct (**2o**)	**3w**	88
24	**1a**	Bn (**2p**)	**3x**	93

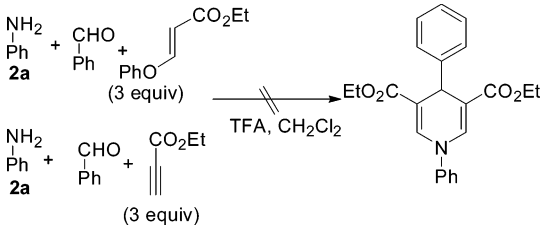
[a] Yield refers to aniline. [b] Reaction time: 12 h. [c] Reaction time: 12 h. [d] Solvent: acetone, 12 h. [e] Reaction time: 24 h.

entries 1−18) and aliphatic amines (Table 1, entries 19−24) afforded the corresponding dihydropyridines **3** in good to excellent yields (50−99%). The electron-rich anilines (Table 1, entries 1−4, 8, and 11) and halide-substituted aromatic amines

SCHEME 3. Reaction of Ethyl *E*-3-(4-Formylphenoxy)propenoate with Aniline



SCHEME 4. Three-Component Reactions of Aniline, Benzaldehyde, and Ethyl *E*-3-Phenoxypropenoates or Ethyl Propiolate



(Table 1, entries 5, 9, and 10) gave higher yields than the electron-deficient anilines (Table 1, entries 6, 7, 13, and 15), while 4-hydroxylaniline (Table 1, entry 12) and 4-aminoaniline (Table 1, entry 14) exhibited a decrease in yield as compared with other electron-rich anilines (Table 1, entries 1−4, 8, and 11). The products were characterized by ^{1}HNMR, ^{13}CNMR, MS and HRMS spectra and compound **3a** was further confirmed by an X-ray analysis (see the Supporting Information).

To view insight of the interesting discovery, we used 3 equiv of ethyl *E*-3-(4-formylphenoxy)propenoate[11a] instead of ethyl *E*-3-(2-formylphenoxy)propenoate (**1a**) to perform the process, and no products were detected (Scheme 3). We also investigated the possibility for three-component reactions of aniline (**2a**), benzaldehyde, and 3 equiv of ethyl *E*-3-phenoxypropenoates or ethyl propiolate (Scheme 4), but did not obtained the desired DHPs. These results suggest that the 3-(2-formylphenoxy)prop-2-enoate is a unique structure in the acid-catalyzed domino reaction.

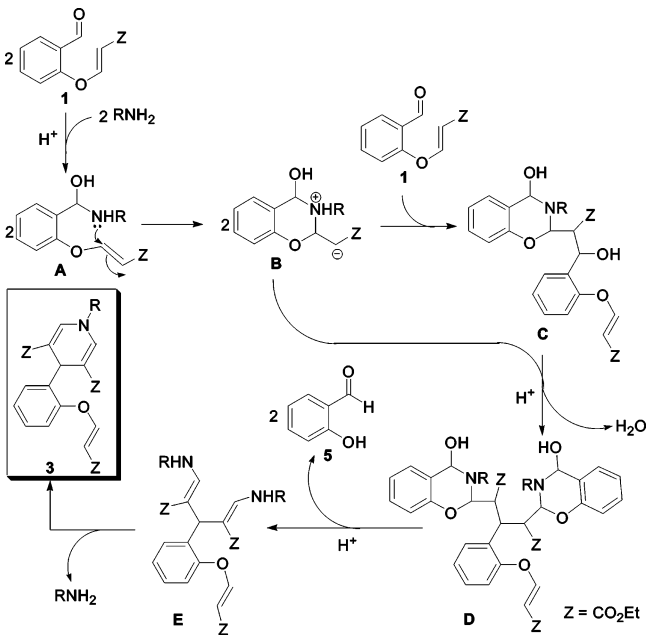
Consequently, a postulate for the formation of 1,4-dihydropyridines is outlined in Scheme 5. Amine as a nucleophile triggers the domino sequence by addition to the carbonyl group of aldehyde **1** to form **A**, which proceeds via an intramolecular addition to form the zwitterion **B**. **B** then attacks the carbonyl group of **1** to form **C**, followed by a domino protonation and substitution with **B** to give **D** and H_2O. **D** then decomposes to enamine **E** and salicaldehyde (**5**). Finally, **E** cyclizes to **3** and releases amine, which is similar to Carr's synthesis of pyrroles.[12] Thus, protonic acid can catalyze the reaction and amines are unable to trigger the domino sequence of ethyl *E*-3-(4-formylphenoxy)propenoate in Scheme 3.

Further support for the proposed mechanism was obtained by an intermediate-capturing reaction, using 1 equiv of benzaldehyde, 1 equiv of **2b**, and 3 equiv of **1c** in the presence of 0.2 equiv of TFA. We observed that the reaction afforded 1,4-dihydropyridine **3y** in 40% yield and **3k** in 55% yield (Scheme 6). The results demonstrated that benzaldehyde could capture the intermediate **A** in the domino process to generate **3y**.

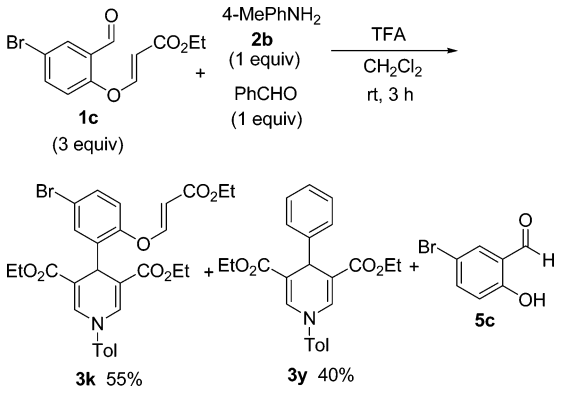
As the next step, we investigated the synthetic utility of **3** for their conversion to DHPs **6**. As shown in Scheme 7,

(12) Carr, R. M.; Norman, R. O. C.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 156−162.

SCHEME 5. Possible Mechanism for the Formation of DHPS



SCHEME 6. Capturing the Intermediate A by Benzaldehyde



treatment of **3** with pyrrolidine afforded **6** in almost quantitative yield. **6** could be easily converted into a range of alternative products, such as **8** and **9**, by further transformations of the phenolic hydroxyl group.

The correlation between optical properties (especially emission wavelengths and the fluorescence quantum yields) and the molecular structures can currently be described only empirically, since no detailed theoretical predictions are possible.[13] A large number of compounds should correlate with a better understanding of the inherent structure−property relationships from which specifically tailored materials can be produced. For this reason and as a part of our ongoing research project on development of new fluorescent molecules, we are interested in screening DHPs for their optical properties and testing the fluorescence properties of **3b**, **3h**, and **3k**. Maximum emission wavelengths (λ_{em} = 365.5−377 nm) were observed for these compounds in cyclohexane, CH_2Cl_2, MeOH, and THF, while

SCHEME 7. Conversions of DHPs 3

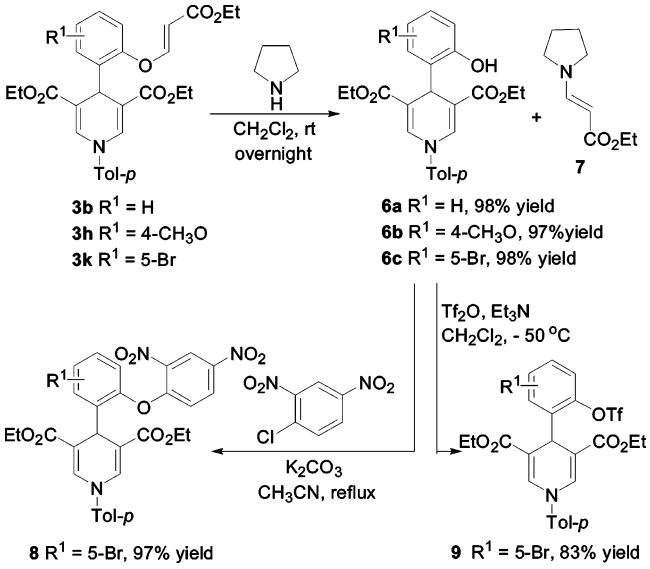


TABLE 2. Fluorescence Data for Compounds 3b, 3h, and 3k in Different Solvents

	in cyclohexane		in CH_2Cl_2		in THF		in MeOH	
compd	λ_{em}[a]	Φ_f	λ_{em}[a]	Φ_f	λ_{em}[a]	Φ_f	λ_{em}[a]	Φ_f
3b	365.5	0.39	370	0.63	373.5	0.47	368	0.46
3h	366	0.36	365.5	0.58	369.5	0.47	369.5	0.50
3k	366	0.39	375	0.55	370	0.52	377	0.57

[a] Units: nm.

the corresponding fluorescent quantum yields (Φ_f = 0.36−0.63) were calculated based on 9,10-diphenylanthrance (Table 2).[14]

In conclusion, we have demonstrated a novel synthesis of *N*-substituted 1,4-dihydropyridines from salicaldehydes, ethyl propiolate, and amines. Thus, salicaldehydes were treated with ethyl propiolate in the presence of *N*-methylmorpholine to give ethyl 3-(2-formylphenoxy)propenoates. Three equivalents of ethyl 3-(2-formylphenoxy)propenoates reacted with 1 equiv of amines under TFA catalyst to furnish the corresponding *N*-substituted 1,4-dihydropyridines in good to excellent yields. The resulting byproduct salicaldehydes could be recovered and reused as the starting materials. Three of the synthesized 1,4-dihydropyridines exhibited strong fluorescence (Φ_f = 0.36−0.63). Further studies on the optical properties and biological activities of this type of 1,4-DHPs are in progress.

Experiment Section

General Procedure for Synthesis of 1,4-Dihydropyridines 3. A solution of *E*-3-(2-formylphenoxy)propenoates **1** (3 mmol), amines **2** (1 mmol), and TFA (0.2 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature under N_2 for 3−5 h. The reaction mixture was then diluted with CH_2Cl_2 (15 mL), washed with saturated sodium carbonate, water, and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue was chromatographed on silica gel column with ethyl acetate/hexane (1:4) as

(13) Schiedel, M.-S.; Briehn, C. A.; Bäuerle, P. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4677−4680.

(14) Optically dilute measurements with refractive-index corrections, maximal absorption of solutions ≤0.04. Measurements referenced to 9,10-diphenylanthrance (Φ_f = 0.90 ± 0.02): (a) Lakowicz, J. R., Ed. *Principles of Fluorescence Spectroscopy*, 2nd ed.; Kluwer Academic/Plenum Publishers: New York, 1999. (b) Demas, J. N.; Grosby, G. A. *J. Phys. Chem.* **1971**, *75*, 991−1024.

eluent to give products **3** and salicaldehydes **5**, respectively. **5** could be reused as the starting material. The products were further recrystallized from ethyl acetate/hexane.

1,4-Dihydropyridine 3a: colorless crystals; mp 124−125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, J = 12.6 Hz, 1H), 7.67 (s, 2H), 7.45 (m, 3H), 7.30 (m, 3H), 7.22 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 5.51 (d, J = 12.6 Hz, 1H), 5.23 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.09 (q, J = 7.2 Hz, 4H), 1.27 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3, 166.7, 160.1, 154.1, 143.0, 136.2, 136.0, 131.8, 129.9, 128.3, 126.2, 124.8, 120.4, 118.0, 109.8, 101.8, 60.2, 59.9, 33.5, 14.3, 14.2 ppm; IR (KBr) υ 2980, 1705, 1647, 1598, 1582, 1486, 1280, 1228, 1126, 754, 691 cm^{-1}; MS (ESI) m/z 514.2 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{28}H_{29}NO_7$ ([M + Na]$^+$) 514.1842, found 514.1838.

1,4-Dihydropyridine 3s: pale green crystals; mp 96−97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, J = 12.0 Hz, 1H), 7.29 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 7.27 (s, 2H), 7.16 (m, 1H), 7.09 (m, 1H), 6.90 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 5.58 (d, J = 11.6 Hz, 1H), 5.20 (s, 1H), 4.18 (q, J = 7.6 Hz, 2H), 4.04 (m, 4H), 3.69 (m, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3, 166.8, 160.4, 153.1, 137.6, 136.0, 131.3, 127.8, 124.9, 117.6, 107.9, 101.4, 59.8, 59.7, 55.5, 32.6, 21.9, 14.2, 14.1 ppm; IR (KBr) υ 2980, 1712, 1646, 1581, 1480, 1439, 1320, 1117, 1031 948, 780 cm^{-1}; MS (ESI) m/z 480.2 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{25}H_{31}NO_7$ ([M + Na]$^+$) 480.1985, found 480.1980.

General Procedure for Transformation of Dihydropyridines 3 to 6. To a solution of **3** (1 mmol) in CH_2Cl_2 (15 mL) was added pyrrolidine (5 mmol), and the mixture was stirred overnight at room temperature. After completion, the mixture was diluted with CH_2Cl_2 (15 mL), washed with dilute hydrochloric acid (1 N, 5 mL) and then brine (15 mL), dried over anhydrous Na_2SO_4, and filtrated through diatomite. After the filtrate was concentrated in vacuum, the product was crystallized from ethyl acetate.

1,4-Dihydropyridine 6a: pale yellow crystals; mp 150−151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (b, 1H), 7.68 (s, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.10 (m, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 5.13 (s, 1H), 4.13 (m, 4H), 2.39 (s, 3H), 1.16 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 152.9, 140.7, 136.8, 133.6, 130.5, 128.8, 128.1, 121.1, 118.2, 109.7, 60.8, 30.3, 20.9, 14.1 ppm; IR (KBr) υ 3449, 2983, 1698, 1679, 1594, 1578, 1514, 1474, 1429, 1305, 1282, 1209, 1083, 1064, 823 cm^{-1}; MS (ESI) m/z 430.1 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{24}H_{25}NO_5$ ([M + Na]$^+$) 430.1625, found 430.1620.

Procedure for the Synthesis of 1,4-Dihydropyridine 8. A mixture of **6c** (1 mmol), 2,4-dinitrochlorobenzene (1 mmol), and K_2CO_3 (2 mmol) in CH_3CN (15 mL) was refluxed for 2 h. After being concentrated, the residue was diluted with ethyl acetate (20 mL), then washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtrated through diatomite. The filtrate was concentrated to achieve **8** as pale yellow solids. Mp 169−172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (d, J = 2.0 Hz, 1H), 8.31 (dd, J_1 = 2.4 Hz, J_2 = 9.6 Hz, 1H), 7.64 (d, J = 1.6 Hz, 1H), 7.54 (s, 2H), 7.35 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 9.6 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.8 Hz, 1H), 5.27 (s, 1H), 4.09 (m, 4H), 2.37(s, 3H), 1.18 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.2, 156.0, 151.1, 141.4, 140.38, 140.35, 139.7, 136.9, 136.5, 135.3, 131.5, 130.4, 128.3, 121.6, 121.4, 120.2, 119.0, 108.8, 60.3, 33.8, 20.8, 14.2 ppm; IR (KBr) υ 2918, 1699, 1608, 1578, 1536, 1516, 1473, 1344, 1268, 1234, 1209 cm^{-1}; MS (ESI) m/z 674.1 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{30}H_{26}BrN_3O_9$ ([M + Na]$^+$) 674.0743, found 674.0740.

Procedure for the Synthesis of 1,4-Dihydropyridine 9. To a solution of **6c** (1 mmol) and Et_3N (3 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of trifluomethyl sulfinic anhydride (1.5 mmol) in CH_2Cl_2 (5 mL) at −50 °C for 30 min. The mixture was stirred for 2 h and then treated with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/hexane, 1:10) and then recrystallized from ethyl acetate/hexane to give pure product as colorless crystals. Mp 117−120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (s, 2H), 7.55 (d, J = 2.4 Hz, 1H), 7.36 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.8 Hz, 1H), 5.29 (s, 1H), 4.12 (m, 4H), 2.39 (s, 3H), 1.16 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 146.2, 141.0, 140.6, 137.4, 136.8, 135.0, 131.3, 130.5, 121.2, 121.0, 118.5 (q, J_{C-F} = 317.3 Hz), 108.8, 60.5, 33.0, 20.9, 14.1 ppm; IR (KBr) υ 2983, 1714, 1696, 1595, 1575, 1522, 1473, 1425, 1241, 1199, 1140, 1077, 611 cm^{-1}; MS (ESI) m/z 640.0 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{25}H_{23}BrF_3NO_7S$ ([M + Na]$^+$) 640.0223, found 640.0212.

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Supporting Information Available: Detailed experimental procedures, characterizaton data, copies of ^{1}H and ^{13}C NMR spectra for all products, and crystallographic information files (CIF) for compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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