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Synthesis of 4,4-dialkoxy-3-piperidinols. Application to the synthesis of γ-acetate dehydropipecolinonitrile

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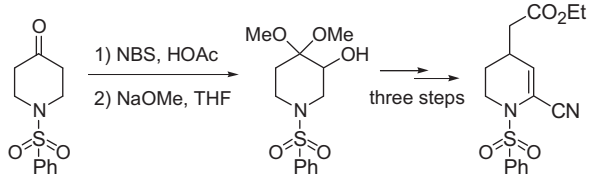
ABSTRACT

The synthesis of 4,4-dialkoxy-3-piperidinols **7** was carried out by the α-bromination of piperidin-4-one **5** with *N*-bromosuccinimide in acetic acid and alkoxide ion-mediated α,α-dialkoxyhydroxylation. Under acidic condition, trimethyl orthoformate-mediated reaction of compound **7a** yielded aminodienylester **8** in the presence of $Ph_3P{=}CHCO_2Et$. The γ-acetate dehydropipecolinonitrile **4** was also synthesized via boron trifluoride etherate-promoted addition of compound **8** with trimethylsilyl cyanide and *N*-bromosuccinimide and selective hydrogenation.

1. Introduction

Functionalized piperidines are prevalent scaffolds that serve as crucial building blocks for numerous syntheses of nitrogen heterocycles and have been previously reviewed.[1] In addition to their utility as synthetic precursors or targets, these functionalized piperidines are important intermediates present in a wide of natural products and pharmaceutically key compounds, such as hydroxypiperidine skeleton.[2,3] In the general preparation process of the substituted piperidinol skeleton, common synthetic methods include oxidation of tetrahydropyridine.[3] In this letter, we report a simple route for the synthesis of piperidin-3-ol with geminal dialkoxy groups, which consists in the α-bromination of piperidin-4-one with *N*-bromosuccinimide in acetic acid, followed by alkoxide ion-mediated α,α-dialkoxyhydroxylation. The methodology was employed to prepare the skeleton of γ-acetate dehydropipecolinonitrile (2-cyano-4-acetate-piperidine) with a pipecolinonitrile/glutamate combination. The synthetic approach is shown in Scheme 1.

The pipecolic acid and a related derivative (e.g., α-amino nitrile) with an important bioactive component are key ingredients in therapeutic agents for pharmaceutical research.[4] Most of these pipecolates are derived from natural or non-natural amino acids and offer a significant potential as peptidomimetics in which the torsion angle between the α carbon and the nitrogen of the amino acid is defined by the cyclic rigid ring and the position of the alkene. Some of these compounds are also important intermediates for the synthesis of azasugars and alkaloids. The molecular framework of pipecolic acid has been used as a core template to design various molecular targets. Cyclic α-amino nitriles are not only versatile intermediates in organic synthesis but also exhibit a valuable dual reactivity, which has been utilized in a broad range of synthetic applications (Fig. 1).



Scheme 1. Synthesis of 4,4-dimethoxy-3-piperidinol. Preparation of γ-acetate dehydropipecolinonitrile.

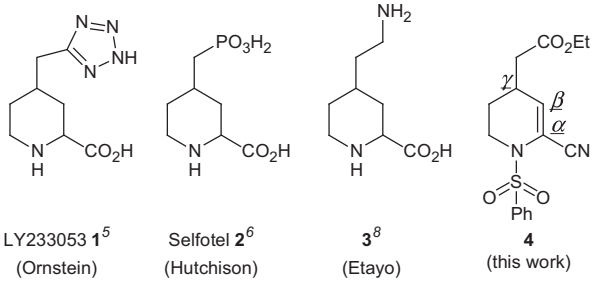


Fig. 1. Biological active substituted pipecolates.

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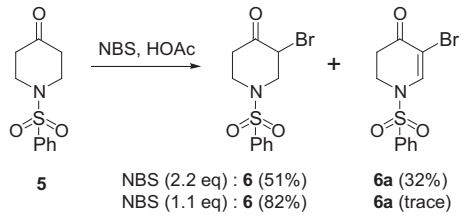
The synthesis of LY233053 **1**, a potent and selective NMDA receptor antagonist, was reported by Ornstein et al.[5] Hutchison et al. described Selfotel (CGS 19755) **2** as potent and selective NMDA receptor antagonist activity in biological testing.[6,7] Etayo et al. synthesized a conformationally constrained pipecolic acid/lysine chimera **3**[8,9]; however, there are few syntheses of dehydropipecolinate analogs **4**.[10]

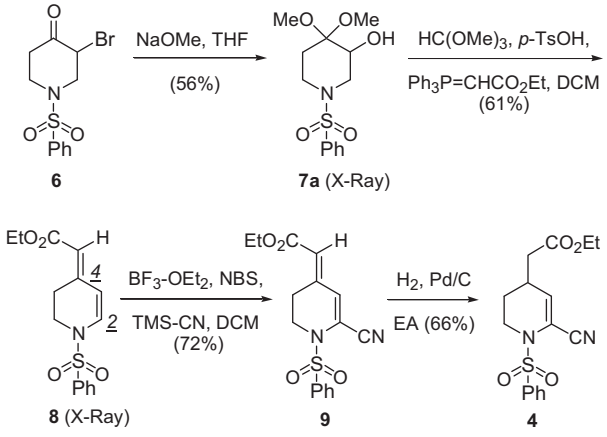
2. Results and discussion

To initiate our work, α-bromination of piperidin-4-one **5** (1.0 mmol) with *N*-bromosuccinimide (2.2 equiv) provided a mixture of 3-bromopiperidin-4-one **6** (51%) and 5-bromodihydropyridin-4-one **6a** (32%). It was confirmed that excess amounts of *N*-bromosuccinimide assisted the formation of enone **6a**. Furthermore, by adjusting the equivalent of *N*-bromosuccinimide (1.1 equiv), the yield of α-bromoketone **6** (82%) was increased (Equation 1).



Equation 1. NBS-mediated α-bromination of piperidin-4-one **5**.

Treatment of α-bromoketone **6** with sodium methoxide (4.0 equiv) in tetrahydrofuran (10 mL) yielded compound **7a** at a yield of 56% (Scheme 2). The Favorskii-type rearranged product was not observed under this reaction condition.[11] The structural framework of compound **7a** was determined using single-crystal X-ray analysis (Fig. 2).[12]



Scheme 2. Synthetic strategy toward compound **4**.

Furthermore, seven commercially available sodium alkoxides (R=**b**, ethyl; **c**, *n*-butyl; **d**, allyl; **e**, benzyl; **f**, phenyl; **g**, *i*-propyl; **h**, *tert*-butyl) were examined in the reaction. After changing the nucleophile, four 4,4-dialkoxypiperidin-3-ols **7b**–**e** were provided in 21–45% yields by the alkoxide ion-mediated rearrangement of bromide **6**, as shown in Scheme 3. But, attempts to extend this reaction to the three sodium alkoxides, including phenoxide, *i*-propoxide, and *tert*-butoxide were unsuccessful due to steric hindrance and the insufficient nucleophilic ability. During the process, the desired skeleton **7** was isolated in low or moderate yields among the complex product mixture. To the best of our knowledge, there are two literature reports on the alkoxide-mediated α,α-dialkoxyhydroxylation

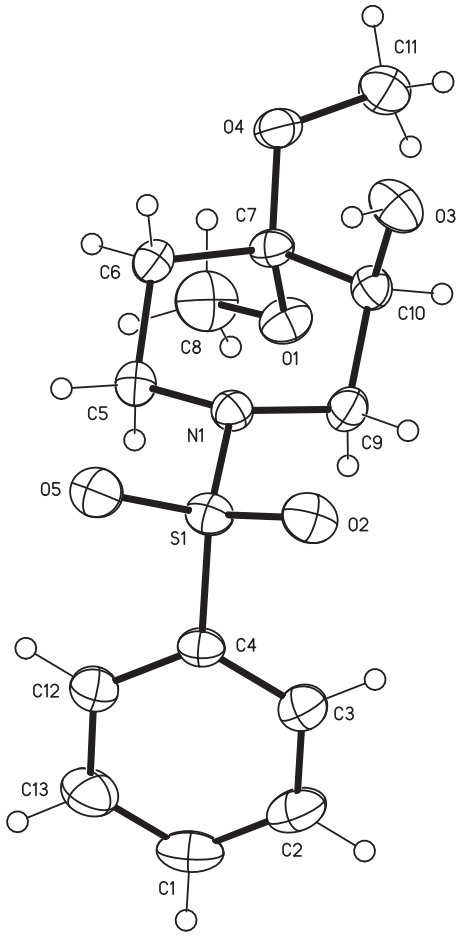
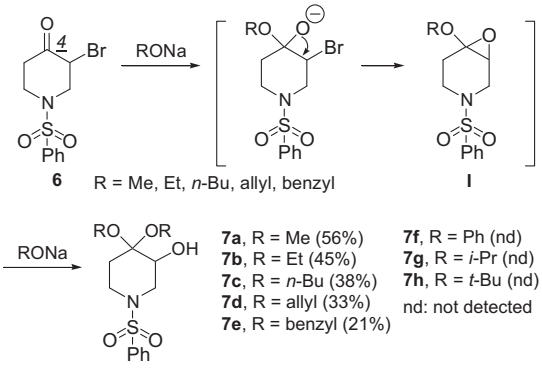


Fig. 2. X-ray structure of compound **7a**.



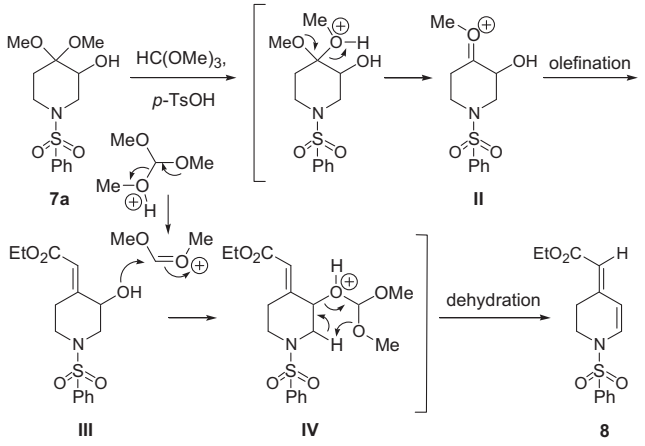
Scheme 3. A possible mechanism for synthesis of 4,4-dialkoxy-3-piperidinols **7**.

reaction with iodine or iodobenzene diacetate in the structural framework of piperidin-4-one.[3c,d] But, the use of bromine instead of iodine failed to afford any skeleton **7**.

A possible explanation for the transformation would be that sodium alkoxide might attack the carbonyl group at the C-4 position and generate the epoxide ring via an intramolecular debrominative ring-closure. In the next step, the ring-opening of intermediate **I** would occur to provide skeleton **7** by introducing the second equivalent of sodium alkoxide. Our pervious study attempted to increase the yield of skeleton **7** by the addition of some reagents (e.g., crown ether or hexamethylphosphoric triamide), failed under a number of conditions (prolonged reaction time, different solvents).

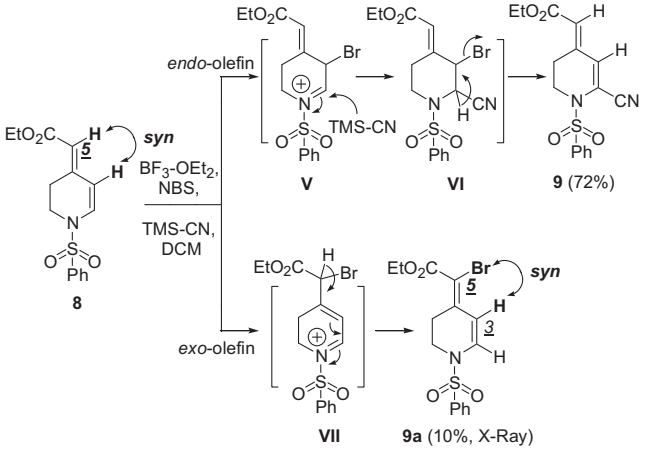
With the results in hand, compound **7a** was treated with ethyl triphenylphosphoranylidene acetate (2.0 equiv) and trimethyl

orthoformate (4.0 equiv) in the presence of *p*-toluenesulfonic acid (1.0 equiv) to give compound **8** at a yield of 61%.[13] The resulting structural framework of cyclic aminodienylester **8** exhibited a conformationally restricted character of an enaminic and *s-trans* (2*Z*,4*E*)-diene conformer with the electronic 'push–pull' nature.[14] The reaction mechanism was proposed as follows (Scheme 4): (i) intermediate **II** was first generated by hydrolysis of compound **7a** under acidic condition, (ii) stereoselective olefination of α-hydroxyketone generated (*E*)-intermediate **III**, and then (iii) diene **8** was isolated by trimethyl orthoformate-promoted dehydration of intermediate **IV**. In the absence of trimethyl orthoformate, the complex product mixture was isolated. We envisioned that the function of trimethyl orthoformate might enhance the dehydration condition for constructing this carbon framework. While poring over recent literature,[15] we found that aspergilone A, containing similar rigid structure to a push–pull functional group, not only possessed in vitro selective cytotoxicity but also showed potent antifouling activity.



Scheme 4. A possible mechanism for the formation of compound **8**.

Next, boron trifluoride etherate promoted the efficient addition of enamine **8** with trimethylsilyl cyanide and *N*-bromosuccinimide (1.2 equiv) resulted in α-amino nitrile **9** (72%) and α-bromo ester **9a** (10%), as shown in Scheme 5. The structures of compounds **8** and **9a** were determined using single-crystal X-ray analysis (Fig. 3).[12] Between C-3 hydrogen and C-5 hydrogen or C-5 bromo group, this *syn*-geometric conformation was shown on the push-pull skeleton.



Scheme 5. Reaction of compound **8**.

The transformation from compound **8** to **9** and **9a** was a regioselective bromination, followed by debromocyanation reaction. The initial event might be considered as the formation of the bromnium ion from *endo*- or *exo*-olefin. For the *endo*-olefin motif of diene **8**, the lone-pair of nitrogen atoms promoted the ring-opening of the brominium ion to form intermediate **V**. Cyanide can trap the iminium ion and lead the reaction to produce intermediate **VI**, which could eliminate bromide by α-hydrogen abstraction to form compound **9**. In another way, bromination of the *exo*-olefin motif was converted to intermediate **VII**, which could stabilize the iminium ion by α-hydrogen abstraction to form compound **9a**. In comparison with the yield ratios both *endo*- and *exo*-olefin on the skeleton of *s-trans* diene **8**, we found that the *endo*-olefin motif performed a better bromination priority. Furthermore, by treating compound **8** with an excess *N*-bromosuccinimide (2.2 equiv) under the abovementioned conditions, a complex mixture was observed. Finally, selective hydrogenation was accomplished by treatment of compound **9** with hydrogen on 10% Pd-activated carbon in ethyl acetate to yield compound **4** at a yield of 66%.[16] In particular, fully hydrogenated piperidine **4a** could also be provided at a yield of 9% under these conditions.

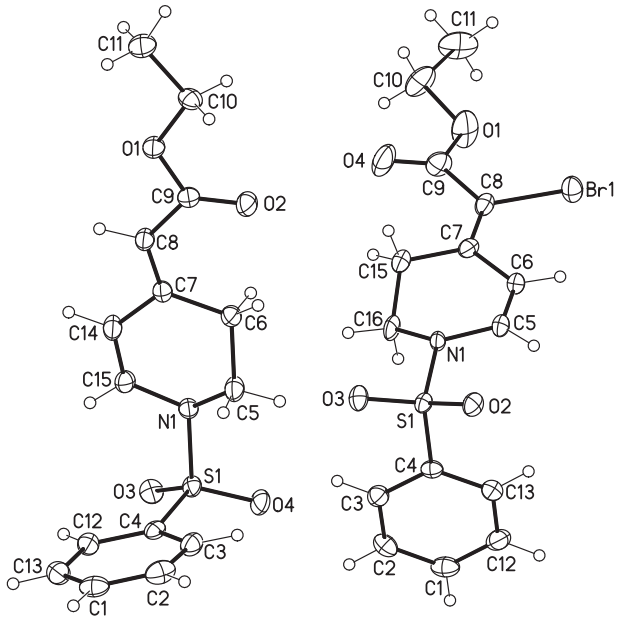


Fig. 3. X-ray structures of compounds **8** and **9a**.

3. Conclusion

In summary, we present a simple synthesis of γ-acetate dehydropipecolinonitrile via the key alkoxide ion-mediated α,α-dialkoxyhydroxylation reaction. This method started from inexpensive starting material and reagents, installed the carboxylic equivalent functional groups through a short sequence, thus provided a potential intermediate for chemical biology research. Further investigation is required regarding their structure–activity of the desulfonated compounds of **4**, **8**, and **9**.

4. Experimental section

4.1. General

Tetrahydrofuran (THF) was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried over anhydrous magnesium sulfate before concentration in vacuo. Melting points were

determined with a SMP3 melting apparatus. Infrared spectra were recorded with a Perkin–Elmer 100 series FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 200/400 and at 50/100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf–Nonius FR-590 diffractometer (CAD4, Kappa CCD). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN–OS–Rapid Analyzer or Elementar Vario EL III.

4.2. 1-Benzenesulfonyl-3-bromopiperidin-4-one (6) and 1-benzenesulfonyl-5-bromo-2,3-dihydro-1*H*-pyridin-4-one (6a)

N-Bromosuccinimide (400 mg, 2.2 mmol) was added to a solution of compound **5** (240 mg, 1.0 mmol) in acetic acid (5 mL) at rt. The reaction mixture was stirred at 60 °C for 2 h. Saturated sodium bicarbonate solution (2 mL) and dichloromethane (10 mL) were added to the reaction mixture and the solvent was concentrated. The residue was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt=6/1–4/1) afforded compounds **6** (162 mg, 51%) and **6a** (100 mg, 32%). For compound **6**: white solid; mp=86–88 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3288, 2940, 1767, 1132 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{11}H_{13}BrNO_3S$ 317.9800, found 317.9803; ^{1}H NMR (200 MHz): δ 7.81–7.76 (m, 2H), 7.63–7.53 (m, 3H), 4.58–4.55 (m, 1H), 3.98–3.89 (m, 1H), 3.62–3.55 (m, 1H), 3.42–3.22 (m, 2H), 2.98–2.84 (m, 1H), 2.59–2.66 (m, 1H). For compound **6a**: viscous gum; IR ($CHCl_3$) 3240, 2934, 1756, 1120 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{11}H_{11}BrNO_3S$ 315.9643, found 315.9644; ^{1}H NMR (400 MHz): δ 8.10 (s, 1H), 7.86–7.84 (m, 2H), 7.72–7.70 (m, 1H), 7.64–7.60 (m, 2H), 3.79 (t, J=7.2 Hz, 2H), 2.69 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz): δ 184.46, 143.40, 137.66, 134.50, 129.95 (2×), 127.36, 127.28, 102.02, 44.06, 35.18.

4.3. A representative procedure of skeleton 7 is as follows

Sodium alkoxide (RONa, 2.0 mmol) was added to a stirring solution of 3-bromopiperidin-4-one **6** (160 mg, 0.5 mmol) in the co-solvent of different alcohol (ROH, 1 mL) and tetrahydrofuran (10 mL) at rt. The reaction mixture was stirred at reflux temperature for 12 h. The total procedure was monitored by TLC until the reaction was completed. Water (1 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=4/1 to 1/1) afforded compounds **7**.

*4.3.1. 1-Benzenesulfonyl-4,4-dimethoxy-piperidin-3-ol (**7a**).* White solid; mp=113–114 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3623, 2936, 1141 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{13}H_{20}NO_5S$ 302.1062, found 302.1066; ^{1}H NMR (400 MHz): δ 7.80–7.76 (m, 2H), 7.62–7.51 (m, 3H), 3.80–3.78 (m, 1H), 3.65 (ddd, J=2.0, 3.6, 12.4 Hz, 1H), 3.57–3.48 (m, 1H), 3.22 (s, 3H), 3.13 (s, 3H), 2.83 (dd, J=2.0, 12.4 Hz, 1H), 2.56 (dt, J=3.2, 12.4 Hz, 1H), 2.10 (br s, 1H), 1.96–1.89 (m, 1H), 1.85–1.79 (m, 1H); ^{13}C NMR (100 MHz): δ 136.85, 132.81, 129.08 (2×), 127.51 (2×), 98.25, 66.46, 48.92, 48.10, 47.82, 42.89, 27.40. Anal. Calcd for $C_{13}H_{19}NO_5S$: C, 51.81; H, 6.35; N, 4.65. Found: C, 52.08; H, 6.71; N, 4.92. Single-crystal X-ray diagram: crystal of compound **7a** was grown by slow diffusion of ethyl acetate into a solution of compound **7a** in dichloromethane to yield colorless prism. The compound crystallizes in the triclinic crystal system, space group P–1, a=6.7112 (2) Å, b=10.0918 (2) Å, c=11.1626 (3) Å, V=720.59 (3) Å^3, Z=2, D_{calcd}=1.389 g/cm^3, F(000)=320, 2θ range 1.85–26.38°, R indices (all data) R1=0.0539, wR2=0.1470.

*4.3.2. 1-Benzenesulfonyl-4,4-diethoxy-piperidin-3-ol (**7b**).* White solid; mp=79–80 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3629, 2937, 1149 cm^{-1}; rms (ESI, M^++1) calcd for $C_{15}H_{24}NO_5S$ 330.1375, found 330.1378; ^{1}H NMR (400 MHz): δ 7.79–7.76 (m, 2H), 7.61–7.50 (m, 3H), 3.76 (br s, 1H), 3.62 (ddd, J=2.0, 4.0, 12.4 Hz, 1H), 3.56–3.34 (m, 5H), 2.86 (dd, J=2.0, 12.0 Hz, 1H), 2.60 (dt, J=2.8, 12.4 Hz, 1H), 2.40 (br s, 1H), 1.97–1.89 (m, 1H), 1.82–1.76 (m, 1H), 1.15 (t, J=7.2 Hz, 3H), 1.05 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 136.95, 132.71, 128.99 (2×), 127.47 (2×), 98.11, 67.07, 55.84, 55.46, 48.75, 42.96, 28.37, 15.23, 15.10. Anal. Calcd for $C_{15}H_{23}NO_5S$: C, 54.69; H, 7.04; N, 4.25. Found: C, 54.88; H, 4.54; N, 4.43.

*4.3.3. 1-Benzenesulfonyl-4,4-di-n-butoxy-piperidin-3-ol (**7c**).* Viscous oil; IR ($CHCl_3$) 3638, 2949, 1152 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{19}H_{32}NO_5S$ 386.2001, found 386.2003; ^{1}H NMR (400 MHz): δ 7.80–7.77 (m, 2H), 7.62–7.57 (m, 1H), 7.55–7.51 (m, 2H), 3.77 (br s, 1H), 3.65–3.59 (m, 1H), 3.56–3.25 (m, 5H), 2.86 (dd, J=2.4, 12.0 Hz, 1H), 2.59 (dt, J=3.2, 12.0 Hz, 1H), 1.98–1.89 (m, 1H), 1.83–1.75 (m, 1H), 1.66 (br s, 1H), 1.59–1.47 (m, 2H), 1.44–1.28 (m, 2H), 1.22–1.12 (m, 2H), 1.05–0.95 (m, 2H), 0.89 (t, J=7.2 Hz, 3H), 0.81 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 136.81, 132.69, 128.96 (2×), 127.58 (2×), 97.88, 67.14, 60.07, 59.81, 48.80, 43.00, 31.81, 31.77, 28.22, 19.42, 19.38, 13.87, 13.78.

*4.3.4. 1-Benzenesulfonyl-4,4-diallyloxy-piperidin-3-ol (**7d**).* Viscous oil; IR ($CHCl_3$) 3634, 2924, 1143 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{17}H_{24}NO_5S$ 354.1375, found 354.1382; ^{1}H NMR (400 MHz): δ 7.79–7.77 (m, 2H), 7.60–7.51 (m, 3H), 5.99–5.73 (m, 2H), 5.32–5.06 (m, 4H), 4.67 (d, J=16.4 Hz, 1H), 4.50 (d, J=16.4 Hz, 1H), 4.06–3.86 (m, 3H), 3.82–3.79 (m, 1H), 3.65–3.60 (m, 1H), 3.58–3.46 (m, 1H), 2.93 (dd, J=2.4, 12.0 Hz, 1H), 2.67 (dt, J=3.2, 12.0 Hz, 1H), 2.09–1.97 (m, 1H), 1.86–1.81 (m, 1H); ^{13}C NMR (100 MHz): δ 136.99, 134.05, 134.01, 132.77, 129.03 (2×), 127.50 (2×), 116.87, 116.33, 98.78, 67.27, 61.73, 61.46, 48.84, 42.92, 28.58.

*4.3.5. 1-Benzenesulfonyl-4,4-dibenzyloxy-piperidin-3-ol (**7e**).* Viscous oil; IR ($CHCl_3$) 3630, 2938, 1132 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{25}H_{28}NO_5S$ 454.1688, found 454.1670; ^{1}H NMR (200 MHz): δ 8.01–7.42 (m, 15H), 4.88–4.62 (m, 3H), 3.98–3.72 (m, 2H), 3.88–3.66 (m, 1H), 3.52–3.46 (m, 1H), 3.44–3.38 (m, 1H), 2.88 (dd, J=2.8, 12.4 Hz, 1H), 2.70 (dt, J=2.8, 12.4 Hz, 1H), 1.99–1.94 (m, 1H), 1.80–1.77 (m, 1H).

4.4. (1-Benzenesulfonyl-2,3-dihydro-1*H*-pyridin-4-ylidene) acetic acid ethyl ester (8)

Trimethyl orthoformate (215 mg, 2.0 mmol) was added to a stirring solution of compound **7a** (150 mg, 0.5 mmol) in the dichloromethane (10 mL) at rt. *p*-Toluenesulfonic acid (TsOH, 86 mg, 0.5 mmol) was added to the reaction mixture. The reaction mixture was stirred at rt for 20 min. Furthermore, ethyl triphenylphosphoranylidene acetate (Ph_3P=$CHCO_2Et$, 348 mg, 1.0 mmol) was added to the reaction mixture. The reaction mixture was stirred at reflux temperature for 22 h. The total procedure was monitored by TLC until the reaction was completed. Water (1 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=4/1 to 1/1) afforded compound **8** (94 mg, 61%) as a white solid. Mp=99–100 °C (recrystallized from hexane and ethyl

acetate); IR ($CHCl_3$) 3418, 2940, 1768, 1133 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{15}H_{18}NO_4S$ 308.0957, found 308.0961; ^1H NMR (400 MHz): δ 7.78–7.74 (m, 2H), 7.62–7.48 (m, 3H), 6.98 (dd, J=1.2, 8.4 Hz, 1H), 6.81 (dd, J=0.4, 8.4 Hz, 1H), 5.29 (t, J=0.4 Hz, 1H), 4.08 (q, J=7.2 Hz, 2H), 3.39 (t, J=6.4 Hz, 2H), 2.48 (dt, J=1.2, 6.8 Hz, 2H), 1.19 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 166.55, 146.56, 136.89, 133.38, 129.32 (2×), 126.88 (2×), 112.58, 110.44, 105.88, 59.59, 42.66, 24.71, 14.07. Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.57; N, 4.56. Found: C, 58.88; H, 5.90; N, 4.89. Single-crystal X-ray diagram: crystal of compound **8** was grown by slow diffusion of ethyl acetate into a solution of compound **8** in dichloromethane to yield colorless prism. The compound crystallizes in the triclinic crystal system, space group P–1, a=8.1105 (3) Å, b=8.1143 (3) Å, c=12.6883 (4) Å, V=730.14 (4) Å^3, Z=2, D_{calcd}=1.398 g/cm^3, F(000)=324, 2θ range 1.65–26.40°, R indices (all data) $R1$=0.0348, $wR2$=0.0930.

4.5. (1-Benzenesulfonyl-6-cyano-2,3-dihydro-1*H*-pyridin-4-ylidene)acetic acid ethyl ester (9) and (1-benzenesulfonyl-2,3-dihydro-1*H*-pyridin-4-ylidene)-bromo-acetic acid ethyl ester (9a)

N-Bromosuccinimide (90 mg, 0.5 mmol) was added to a solution of compound **8** (123 mg, 0.4 mmol) with trimethylsilyl cyanide (3 mL) in dichloromethane (10 mL) at rt. The reaction mixture was stirred at rt for 5 min. Boron trifluoride etherate (~0.1 mL) was added to the reaction mixture. The reaction mixture was stirred at rt for 3 h. Saturated sodium bicarbonate solution (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=6/1 to 3/1) afforded compounds **9** (96 mg, 72%) and **9a** (16 mg, 10%). For compound **9**: white solid; mp=64–65 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3424, 2948, 2134, 1771, 1138 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{16}H_{17}N_2O_4S$ 333.0909, found 333.0912; ^1H NMR (400 MHz): δ 7.96–7.93 (m, 2H), 7.69–7.65 (m, 1H), 7.60–7.56 (m, 2H), 6.32 (s, 1H), 5.74 (s, 1H), 4.14 (q, J=7.2 Hz, 2H), 3.70 (t, J=6.0 Hz, 2H), 2.93–2.90 (m, 2H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 165.36, 143.54, 137.92, 134.05, 129.68 (2×), 128.67, 127.42 (2×), 119.71, 115.86, 114.06, 60.51, 44.83, 24.97, 14.12. Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43. Found: C, 58.01; H, 5.10; N, 8.78. For compound **9a**: white solid; mp=107–108 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3432, 2931, 1760, 1122 cm^{-1}; ^1H NMR (200 MHz): δ 7.81–7.78 (m, 2H), 7.60–7.53 (m, 3H), 7.11 (d, J=8.0 Hz, 1H), 6.01 (d, J=8.0 Hz, 1H), 4.21 (q, J=7.2 Hz, 2H), 3.40 (t, J=6.6 Hz, 2H), 3.04 (t, J=6.6 Hz, 2H), 1.28 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{15}H_{16}BrNO_4S$: C, 46.64; H, 4.18; N, 3.63. Found: C, 46.82; H, 4.49; N, 3.79. Single-crystal X-ray diagram: crystal of compound **9a** was grown by slow diffusion of ethyl acetate into a solution of compound **9a** in dichloromethane to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group P 1 21/c 1, a=10.0231 (10) Å, b=5.4646 (6) Å, c=28.654 (3) Å, V=1568.7 (3) Å^3, Z=4, D_{calcd}=1.636 g/cm^3, F(000)=784, 2θ range 1.42–26.44°, R indices (all data) $R1$=0.0603, $wR2$=0.1562.

4.6. (1-Benzenesulfonyl-6-cyano-1,2,3,4-tetrahydropyridin-4-yl) acetic acid ethyl ester (4)

Palladium on activated carbon (10%, 5 mg) was added to a solution of compound **9** (100 mg, 0.3 mmol) in ethyl acetate (10 mL). Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 20 h. The reaction mixture was filtered and evaporated to yield crude product. Purification on silica gel (hexane/ethyl acetate=4/1 to 2/1) afforded compound **4** (65 mg, 66%). Viscous oil; IR ($CHCl_3$) 3434, 2938, 2158, 1777, 1145 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{16}H_{19}N_2O_4S$ 335.1066, found 335.1068; ^1H NMR (400 MHz): δ 7.92–7.89 (m, 2H), 7.68–7.63 (m, 1H), 7.59–7.52 (m, 2H), 6.06 (d, J=3.6 Hz, 1H), 4.11 (q, J=7.2 Hz, 2H), 3.72 (ddd, J=3.6, 6.4, 14.0 Hz, 1H), 3.43 (ddd, J=2.8, 9.6, 14.0 Hz, 1H), 2.74–2.66 (m, 1H), 2.23 (dd, J=6.4, 16.0 Hz, 1H), 2.15 (dd, J=8.0, 16.0 Hz, 1H), 1.75 (ddt, J=2.8, 6.4, 13.2 Hz, 1H), 1.23 (t, J=7.2 Hz, 3H), 1.19–1.16 (m, 1H); ^{13}C NMR (100 MHz): δ 170.65, 162.82, 137.77, 133.71, 129.45 (2×), 127.51 (2×), 114.51, 113.57, 60.93, 44.18, 38.36, 30.35, 25.94, 14.11.

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