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A significant substituent effect on the regioselectivity in addition of alkynes to 3-substituted pyridines

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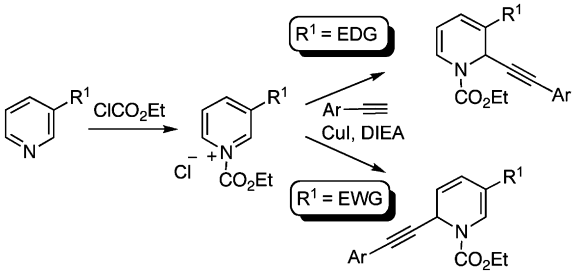
ABSTRACT

A substituent at the 3-position on a pyridine ring significantly affects the regioselectivity during the addition of alkynes to pyridinium salts. When the substituent is an electron-withdrawing group, 1,6-adducts are predominantly produced, whereas, 1,2-adducts become the major products when the substituent is an electron-donating group. The changes in the regioselectivity depending on the substituent can be explained by the difference in the product stabilities. The produced dihydropyridines are easily aromatized into disubstituted pyridines with chloranil in quantitative yields.

1. Introduction

The regioselective addition of nucleophiles to the pyridinium ring is a powerful method for the synthesis of substituted dihydropyridines.[1] In particular, the nucleophilic addition to 3-substituted pyridinium salts has received considerable attention because the produced dihydropyridines are key intermediates for the synthesis of disubstituted piperidines,[2,3] pyridines,[4,5] and various heterocyclic compounds.[6] In general, the regioselectivity significantly depends on both the properties of the nucleophiles and the substituent on the pyridine ring.[4b] Therefore, elucidation of substituent effects on the product distribution would provide insight into controlling the regioselectivity.

Continuing our research program on the regio- and stereoselective addition reaction to pyridinium salts,[7] we were interested in the addition of activated alkynes to 3-substituted pyridinium compounds because the produced ethynyldihydropyridines and corresponding pyridines are an important class of compounds as various synthetic intermediates[3,8] and biologically active compounds.[9] Among the reported alkynylation methods using various metallo alkynyl reagents,[3a,10] we focused on the copper-mediated addition reaction due to its potential applicability to organic synthesis.[3a,10a] We now report that the substituent at the 3-position of the pyridine ring significantly affects the preferred formation of the 1,2- and 1,6-adducts during the copper-mediated addition of alkynes to pyridinium salts (Scheme 1), and the product stabilities reflect the 1,2- and 1,6-selectivities. Moreover, the reported preference for the addition to methyl nicotinate[10a] was revised from the 1,2- to the 1,6-addition.



Scheme 1.

2. Results and discussion

We attempted to follow the reported 1,2-addition reaction of phenylacetylene to methyl nicotinate according to the literature;[10a] a mixture of the 1,2-, 1,4-, and 1,6-adducts were obtained in 42% yield with the ratio of 21:14:65 as shown in Table 1 (entry 1). The yield was significantly improved to 99% using 2 equiv of phenylacetylene and reagents (entry 2). A surprising feature in this reaction is that the 1,6-adduct **5a** was the major product, although it was assigned to the 1,2-dihydropyridine in the literature.[10a] The structure of the 1,6-adduct **5a** was confirmed after aromatization to the known methyl 6-phenylethynylnicotinate (**8a**)[9a] as described later. Various types of substituted terminal alkynes also served as nucleophiles. The addition of **2b** and **2c** gave **5ab** and **5ac** as the major products, respectively, similar to the case of **2a** (entries 3 and 4), suggesting the generality of the formation of the 1,6-adducts during the addition of alkynes to methyl nicotinate. On the other hand, the addition of **2d** required a longer reaction time for completion of the reaction, which resulted in a lower regioselectivity (entry 5). A remarkable feature is that the substituent at the

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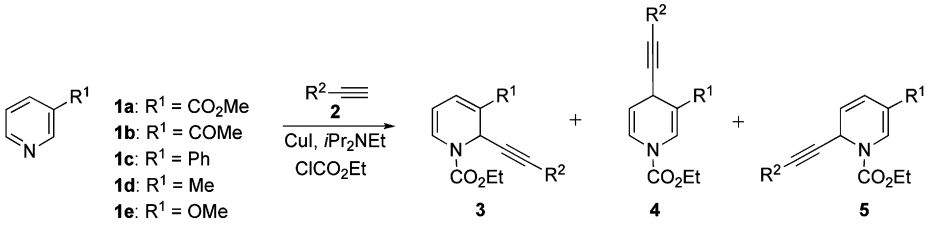
Table 1
Addition of terminal alkynes **2a**–**2d** to **1a**–**1e**[a]



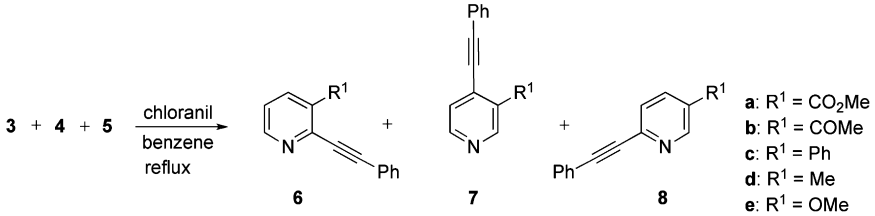
Entry	Compound	**2**(R^2)	Time/h	Product	Yield/%[b]	Ratio[c] **3**:**4**:**5**
1	**1a**	**2a**(Ph)[d]	5	**3a**–**5a**	42	21:14:65
2	**1a**	**2a**(Ph)	5	**3a**–**5a**	99	25:15:60
3	**1a**	**2b**(*p*-$MeOC_6H_4$)	5	**3ab**–**5ab**	82	28:17:55
4	**1a**	**2c**(*p*-MeC_6H_4)	5	**3ac**–**5ac**	75	25:17:58
5	**1a**	**2d**($C_6H_5(CH)_2CH_2$)	27	**3ad**–**5ad**	81	40:11:49
6	**1b**	**2a**(Ph)	25	**3b**–**5b**	99	32:18:50
7	**1c**	**2a**(Ph)	25	**3c**–**5c**	99	70:8:22
8	**1d**	**2a**(Ph)	24	**3d**–**5d**	99	56:16:28
9	**1e**	**2a**(Ph)	27	**3e**	97	100:0:0

[a] Two equiv of alkyne **2**, CuI, diisopropylethylamine (DIEA), and ethyl chloroformate were used unless otherwise noted.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectra.
[d] One equiv of **2a**, CuI, DIEA, and ethyl chloroformate were used.

3-position significantly influenced the regioselectivity (entries 1 and 6–9). The addition to acetylpyridine **1b** gave a 1,6-adduct **5b** as the major product similar to the case of **1a** (entry 6). On the other hand, 1,2-adducts **3c** and **3d** were the major products for the addition to **1c** and **1d** having a phenyl and a methyl group at the 3-position, respectively. Surprisingly, the addition to **1e** possessing a MeO group exclusively afforded the 1,2-adduct **3e**. These results suggest that the electronic properties of the substituents are significantly responsible for the preference during the 1,2- and 1,6-additions.

The structures of these dihydropyridines were determined after conversion to the corresponding pyridine derivatives due to the difficulty in the separation of the isomers by column chromatography. Among the various examined oxidizing agents, chloranil was the most effective for the aromatization of the dihydropyridines.[1b,1d,4b] The treatment of a mixture of the dihydropyridines **3a**–**5a** with 1 equiv of chloranil at rt provided only the methyl 4-phenylethynylnicotinate (**7a**) along with the recovery of **3a** and **5a** as shown in Table 2 (entry 1); the 1,4-dihydropyridine was much more reactive toward oxidation than the 1,2- and 1,6-dihydropyridines. The assignment of **7a** was based on the disappearance of the H4 peak of **4a** at δ 4.44 in the ^{1}H NMR spectrum. When the reaction was conducted at reflux temperature with 3 equiv of chloranil **6a**, **7a**, and **8a**[9a] were produced with recovery of the 1,2-dihydropyridine (**3a**) (entry 2). Comparison of the ^{1}H NMR data for the major product **8a** with that reported suggested that the structure of **8a** was methyl 6-phenylethynylnicotinate as described above. During the oxidation of a mixture of **3b**–**5b**, **4b** is also readily aromatized with chloranil even at rt (entry 3). The further oxidation at the reflux temperature resulted in **8b** with a small amount of **6b** (entry 4), the structures of which were determined by comparison of the ^{1}H NMR data with those already reported.[11] Aromatization of the other dihydropyridines was also performed under the same reaction conditions. The oxidation of a mixture of **3c**, **4c**, and **5c** gave **6c**, **7c**, and **8c**[12] in 52, 100, and 100% NMR yields, respectively (entry 5). An electron-donating substituent

Table 2
Aromatization of dihydropyridines to disubstituted pyridines



Entry	Compounds[a]	Chloranil (equiv)	Temp	Time/h	Conv./%[b]		
					3→**6**	**4**→**7**	**5**→**8**
1	**3a**–**5a**	1	rt	1	0	100	0
2	**3a**–**5a**	3	Reflux	24	28	100	100
3	**3b**–**5b**	1	rt	1	0	100	0
4	**3b**–**5b**	3	Reflux	24	12	100	100
5	**3c**–**5c**	3	Reflux	24	52	100	100
6	**3d**–**5d**	3	Reflux	24	100	100	100
7	**3e**	3	Reflux	24	100	—	—

[a] A mixture of **3**–**5** was used except for **3e**.
[b] Determined by ^{1}H NMR spectra.

Table 3
The electrostatic charges and LUMO coefficients for **1a**–**1e**

Substrate	Charge[a]		LUMO coefficient[b]	
	2-Position	6-Position	2-Position	6-Position
1a	0.206	0.140	0.380	0.461
1b	0.177	0.131	0.396	0.485
1c	0.060	0.117	0.439	0.461
1d	0.001	0.108	0.359	0.370
1e	−0.152	0.022	0.486	0.424

[a] The electrostatic charges were obtained by AM1 calculations.
[b] The $2p_y$ component of the LUMO coefficients were indicated.

accelerated the aromatization; the 3-methyl and 3-methoxy substituted 1,2-dihydropyridines **3d** and **3e**, and 3-methyl 1,6-dihydropyridine **5d** were readily oxidized to give **6d**,[9b] **6e**, and **8d**[9b] in quantitative yields, respectively.

It is well documented that the regioselectivity for the nucleophilic addition to a pyridinium ion is often explained by the HSAB rule.[10c,13] In particular, it has been known that soft nucleophiles effectively attack the 4-position to give 1,4-dihydropyridines selectively. If the HSAB rule governs the selectivity in this reaction, the charge density or pyridinium LUMO coefficients has to affect the selectivity. Table 3 listed the electrostatic charges and the LUMO coefficients, in which only $2p_y$ components were listed because of the negligible values of $2p_x$ and $2p_z$. As can be seen from Table 3, neither the electron density nor the LUMO coefficient accounts for the substituent effects. Sundberg and his co-workers have suggested the importance of the product stabilities in determining the preference for 1,2-addition or 1,6-addition during the reduction of pyridinium into dihydropyridines with hydride reagents.[14] This hypothesis prompted us to study the relationship between the product energies and regioselectivities.

Table 4 lists the energies of the 1,2- and 1,6-adducts and their differences, ΔE, obtained by the DFT calculations at the B3LYP/6-31G* level. It is clear that ΔE is significantly dependent on the substituent. The 1,6-adducts **5a** and **5b** having an electron-withdrawing group are more stable than the corresponding 1,2-adducts **3a** and **3b**. In contrast, the 1,2-adducts **3d** and **3e** having an electron-donating group are more stable than the corresponding 1,6-adducts **5d** and **5e**. The opposite tendency for the phenyl-substituted **3c** would be due to a resonance effect; the conjugate system of **3c** is more effective for the resonance stabilization than cross-conjugate system of **5c**. The comparison of ΔE with the regioselectivity clearly showed a relationship between them. These results lead to the conclusion that the regioselectivity during the addition of alkynes to the pyridinium would be closely related to the product stabilities.

3. Conclusion

In summary, the regioselective addition of terminal alkynes to 3-substituted pyridines was performed. The substituents significantly affected the regioselectivity; when an electron-withdrawing group is attached to the pyridine ring, the 1,2-adducts were the major products, whereas, the 1,6-adducts became the major products when the substituent is an electron-donating group. The changes in the regioselectivity depending on the substituent can be explained by the difference in the product stabilities.

Table 4
The energies for **3** and **5**, and their differences ΔE with the isomer ratio[a]

Isomers	Substituent	E[a] (kcal/mol)	ΔE (kcal/mol)	Ratio (**3**:**5**)
3a	CO_2Me	−659 981.64	−0.34	24:76
5a		−659 981.98		
3b	COMe	−612 772.38	−0.91	39:61
5b		−612 773.29		
3c	Ph	−661 974.18	0.43	76:24
5c		−661 973.75		
3d	Me	−541 656.85	1.43	67:33
5d		−541 655.42		
3e	OMe	−588 848.52	3.93	100:0
5e		−588 844.59		

[a] The energies were obtained by DFT calculations at the B3LYP/6-31G* level.

4. Experimental section

4.1. General information

Column chromatography and TLC were carried out using silica gel. IR spectra were taken on a Fourier transform infrared spectrophotometer as neat films between NaCl plates or as KBr pellets. ^{1}H NMR spectra were obtained at 400 MHz as dilute solutions in $CDCl_3$, C_6D_6 or DMSO-d_6 and the chemical shifts were reported relative to internal TMS. High- and low-resolution mass spectra were recorded at an ionizing voltage of 70 eV by electron impact. Semi-empirical and ab initio calculations were conducted with SPARTAN PC Pro '06.

4.2. General procedure for the addition of alkynes 2 to 3-substituted pyridines 1

To a solution of a pyridine derivative (1.0 mmol) in dry dichloromethane (6.0 ml) was added dropwise ethyl chloroformate (286 μl, 3.0 mmol) at 0 °C under nitrogen atmosphere. After the solution was stirred for about 20 min at 0 °C, phenylacetylene (220 μl, 2.0 mmol) and copper(I) iodide (0.382 g, 2.0 mmol) were added to the solution, and then diisopropylethylamine (340 μl, 2.0 mmol) was added dropwise to the solution. The mixture was stirred at rt for 5 h. The reaction was quenched with water and the precipitate was filtered. The filtrate was extracted with CH_2Cl_2 at pH 8–9. The organic layer was washed with water and brine, and was dried over anhydrous magnesium sulfate. The evaporation of the solvent gave a crude product, which was purified by column chromatography on silica gel with a 1:2 mixture of AcOEt and hexane to afford a mixture of the isomeric dihydropyridines **3**, **4**, and **5** (75–99%).

*4.2.1. A mixture of **3a**–**5a***

The product ratio of a mixture of **3a**–**5a** is determined to be 24:14:56 by ^{1}H NMR spectrum. ^{1}H NMR for **3a** (400 MHz, $CDCl_3$, 50 °C) δ 7.38–7.35 (2H, m), 7.33–7.23 (3H, m), 7.12 (2H, d, J=5.9 Hz), 6.28 (1H, br), 5.57–5.28 (1H, m), 4.41–4.28 (2H, m), 3.82 (1H, s), 1.38–1.34 (3H, m). ^{1}H NMR for **4a** (400 MHz, $CDCl_3$, 50 °C) δ 7.98 (1H, s), 7.38–7.35 (2H, m), 7.27–7.10 (3H, m), 6.87 (1H, d, J=7.8 Hz), 5.23 (1H, dd, J=8.3, 4.4 Hz), 4.44 (1H, d, J=4.4 Hz), 4.41–4.30 (2H, m), 3.81 (1H, s), 1.39–1.33 (3H, m). ^{1}H NMR for **5a** (400 MHz, $CDCl_3$, 50 °C) δ 7.90 (1H, s), 7.38–7.35 (2H, m), 7.27–7.10 (3H, m), 6.50 (1H, d, J=9.8 Hz), 5.78 (1H, d, J=5.4 Hz), 5.66 (1H, dd, J=9.8, 5.9 Hz), 4.41–4.30 (2H, m), 3.78 (3H, s), 1.39–1.33 (3H, m).

*4.2.2. A mixture of **3ab**–**5ab***

The product ratio of a mixture of **3ab**–**5ab** is determined to be 28:17:55 by ^{1}H NMR spectrum. ^{1}H NMR for **3ab** (400 MHz, $CDCl_3$, 50 °C) δ 7.32–7.29 (2H, m), 7.11 (2H, d, J=5.9 Hz), 6.80–6.76 (3H, m), 6.25 (1H, br), 5.56–5.52 (1H, m), 4.41–4.29 (2H, m), 3.77 (3H, s), 1.39–1.34 (3H, m). ^{1}H NMR for **4ab** (400 MHz, $CDCl_3$, 50 °C) δ 7.97 (1H, s), 7.32–7.29 (2H, m), 6.87 (1H, d, J=7.8 Hz), 6.80–6.76 (3H, m), 5.23 (1H, dd, J=8.3, 4.4 Hz), 4.42 (1H, d, J=4.9 Hz), 4.41–4.29 (2H, m), 3.81 (3H, s), 1.39–1.34 (3H, m). ^{1}H NMR for **5ab** (400 MHz, $CDCl_3$, 50 °C) δ 7.90 (1H, s), 7.32–7.29 (2H, m), 6.80–6.76 (3H, m), 6.49 (1H, d, J=9.8 Hz), 5.76 (1H, d, J=5.9 Hz), 5.65 (1H, dd, J=9.3, 5.4 Hz), 4.41–4.29 (2H, m), 3.78 (3H, s), 1.39–1.34 (3H, m).

*4.2.3. A mixture of **3ac–5ac***

The product ratio of a mixture of **3ac–5ac** is determined to be 25:17:58 by ^{1}H NMR spectrum. ^{1}H NMR for **3ac** (400 MHz, $CDCl_3$, 50 °C) δ 7.28–7.24 (2H, m), 7.11 (1H, d, J=5.9 Hz), 7.08–7.04 (3H, m), 6.26 (1H, br), 5.56–5.52 (1H, m), 4.41–4.27 (2H, m), 3.81 (3H, s), 1.94 (6H, s), 1.39–1.34 (3H, m). ^{1}H NMR for **4ac** (400 MHz, $CDCl_3$, 50 °C) δ 7.97 (1H, s), 7.28–7.24 (2H, m), 7.08–7.04 (2H, m), 6.87 (1H, d, J=7.8 Hz), 6.23 (1H, dd, J=7.8, 4.4 Hz), 4.42 (1H, d, J=4.4 Hz), 4.41–4.27 (2H, m), 3.80 (6H, s), 1.39–1.34 (3H, m). ^{1}H NMR for **5ac** (400 MHz, $CDCl_3$, 50 °C) δ 7.90 (1H, s), 7.28–7.24 (2H, m), 7.08–7.04 (2H, m), 6.49 (1H, d, J=9.8 Hz), 5.76 (1H, d, J=5.9 Hz), 5.65 (1H, dd, J=9.8, 4.9 Hz), 4.41–4.27 (2H, m), 3.78 (6H, s), 1.39–1.34 (3H, m).

*4.2.4. A mixture of **3ad–5ad***

The product ratio of a mixture of **3ad–5ad** is determined to be 40:11:49 by ^{1}H NMR spectrum. ^{1}H NMR for **3ad** (400 MHz, $CDCl_3$, 50 °C) δ 7.26–7.18 (2H, m), 7.17–7.11 (3H, m), 7.06 (2H, d, J=6.9 Hz), 6.05 (1H, br), 5.52–5.49 (1H, m), 4.37–4.32 (2H, m), 3.79 (3H, s), 2.65–2.62 (2H, m), 2.17–2.11 (2H, m), 1.81–1.71 (2H, m), 1.36–1.32 (3H, m). ^{1}H NMR for **4ad** (400 MHz, $CDCl_3$, 50 °C) δ 7.92 (1H, s), 7.26–7.18 (2H, m), 7.17–7.11 (3H, m), 6.86 (1H, d, J=7.8 Hz), 5.15 (1H, dd, J=7.8, 4.4 Hz), 4.37–4.32 (2H, m), 4.30 (1H, d, J=4.4 Hz), 3.78 (3H, s), 2.65–2.62 (2H, m), 2.17–2.11 (2H, m), 1.81–1.71 (2H, m), 1.36–1.32 (3H, m). ^{1}H NMR for **5ad** (400 MHz, $CDCl_3$, 50 °C) δ 7.87 (1H, s), 7.26–7.18 (2H, m), 7.17–7.11 (3H, m), 6.44 (1H, d, J=9.8 Hz), 5.58 (1H, dd, J=9.8, 5.9 Hz), 5.53 (1H, d, J=6.3 Hz), 4.37–4.32 (2H, m), 2.65–2.62 (2H, m), 2.17–2.11 (2H, m), 1.81–1.71 (2H, m), 1.36–1.32 (3H, m).

*4.2.5. A mixture of **3b–5b***

The product ratio of a mixture of **3b–5b** is determined to be 32:18:50 by ^{1}H NMR spectrum. ^{1}H NMR for **3b** (400 MHz, $CDCl_3$, 50 °C) δ 7.40–7.33 (2H, m), 7.31–7.20 (3H, m), 7.00 (2H, d, J=5.9 Hz), 6.41 (1H, br), 5.60–5.56 (1H, br), 4.46–4.27 (2H, m), 2.35 (3H, s), 1.41–1.34 (3H, m). ^{1}H NMR for **4b** (400 MHz, $CDCl_3$, 50 °C) δ 7.93 (1H, s), 7.40–7.33 (2H, m), 7.31–7.20 (3H, m), 6.89 (1H, d, J=8.3 Hz), 5.29 (1H, dd, J=8.3, 4.4 Hz), 4.51 (1H, d, J=4.4 Hz), 4.46–4.27 (2H, m), 2.37 (3H, s), 1.41–1.34 (3H, m). ^{1}H NMR for **5b** (400 MHz, $CDCl_3$, 50 °C) δ 7.85 (1H, s), 7.40–7.33 (2H, m), 7.31–7.20 (3H, m), 6.64 (1H, d, J=9.8 Hz), 5.77 (1H, d, J=5.4 Hz), 5.70 (1H, dd, J=9.8, 5.4 Hz), 4.46–4.27 (2H, m), 2.31 (3H, s), 1.41–1.34 (3H, m).

*4.2.6. A mixture of **3c–5c***

The product ratio of a mixture of **3c–5c** is determined to be 70:8:22 by ^{1}H NMR spectrum. ^{1}H NMR for **3c** (400 MHz, $CDCl_3$) δ 7.61 (2H, d, J=7.8 Hz), 7.38–7.25 (3H, m), 6.96 (1H, d, J=7.3 Hz), 6.85 (1H, d, J=7.3 Hz), 6.48 (1H, J=5.9 Hz), 6.31 (1H, s), 6.14 (1H, s), 5.69–5.61 (1H, m), 4.42–4.29 (2H, m), 1.44–1.33 (3H, m). ^{1}H NMR for **4c** (400 MHz, $CDCl_3$) δ 7.61 (2H, d, J=7.8 Hz), 7.51–7.20 (9H, m), 7.01 (1H, s), 6.30–5.10 (1H, m), 4.57 (1H, d, J=4.4 Hz), 4.32–4.24 (2H, m), 1.35–1.18 (3H, m). ^{1}H NMR for **5c** (400 MHz, $CDCl_3$) δ 7.61 (2H, d, J=7.8 Hz), 7.51–7.20 (9H, m), 6.46 (1H, d, J=6.3 Hz), 5.90–5.76 (2H, m), 4.32–4.24 (2H, m), 1.35–1.18 (3H, m).

*4.2.7. A mixture of **3d–5d***

The product ratio of a mixture of **3d–5d** is determined to be 56:16:28 by ^{1}H NMR spectrum. ^{1}H NMR for **3d** (400 MHz, $CDCl_3$) δ 7.56–7.39 (2H, m), 7.34–7.26 (3H, m), 6.76 (1H, d, J=6.8 Hz), 6.64 (1H, d, J=7.3 Hz), 6.73 (1H, d, J=5.4 Hz), 5.61 (1H, s), 5.48 (1H, s), 5.34–6.28 (1H, m), 4.34–4.24 (2H, m), 1.94 (3H, s), 1.37–1.14 (3H, m). ^{1}H NMR for **4d** (400 MHz, $CDCl_3$) δ 7.56–7.39 (3H, m), 7.34–7.26 (3H, m), 6.51 (1H, s), 5.83–5.79 (1H, m), 4.97 (1H, br), 4.34–4.24 (2H, m), 1.86 (3H, s), 1.37–1.14 (3H, m). ^{1}H NMR for **5d** (400 MHz, $CDCl_3$) δ 7.56–7.39 (3H, m), 7.34–7.26 (3H, m), 5.91 (1H, d, J=9.3 Hz), 5.73–5.61 (2H, m), 4.34–4.24 (2H, m), 1.81 (3H, s), 1.37–1.14 (3H, m).

*4.2.8. Ethyl 3-methoxy-2-(phenylethynyl)pyridine-1(2H)-carboxylate (**3e**)*

Yellow oil; IR (neat) 2980, 2220, 1714, 1662, 1601, 1409, 1377, 1324, 1264, 1223, 1111, 1024, 893, 758, 732, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.40 (2H, m), 7.34–7.25 (3H, m), 6.60 (1H, d, J=7.8 Hz), 6.48 (1H, d, J=7.3 Hz), 5.72 (1H, s), 5.59 (1H, s), 5.44–5.37 (1H, m), 5.07 (1H, d, J=4.4 Hz), 4.34–4.17 (2H, m), 3.67 (3H, s), 1.35–1.29 (3H, m); MS (EI) m/z: 283 (M^+, 100%), 252 (38), 210 (63), 195 (77), 180 (55), 167 (49), 139 (41); HRMS calcd for $C_{15}H_{12}O_2N$: 283.1208, found: 283.1181.

4.3. General procedure for the oxidation of a mixture of the isomeric dihydropyridines 3–5

A mixture of the isomeric dihydropyridines **3**, **4**, and **5** (0.209 mmol) and chloranil (0.628 mmol) in dry benzene (3 ml) was refluxed for 24 h under nitrogen atmosphere. The reaction mixture was cooled at rt and the precipitate was filtered. The filtrate was extracted with ether and the extract was washed with 5% $NaHCO_3$. The ether solution was dried over anhydrous magnesium sulfate and was evaporated in vacuo to give an oily product, which was purified by column chromatography on silica gel and TLC with a 1:2 mixture of AcOEt and hexane to afford a mixture of **6**, **7**, and **8**.

*4.3.1. Methyl 2-phenylethynylnicotinate (**6a**)*

Yellow crystal; mp 97.5–99.0 °C (recrystallization from ether–hexane); IR (KBr) 1729, 1593, 1434, 1281, 1112, 1023, 914, 860, 768, 738, 715, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (1H, d, J=1.6 Hz), 7.95 (1H, dd, J=8.4, 2.4 Hz), 7.42–7.32 (5H, m), 6.83 (1H, d, J=8.0 Hz), 3.91 (3H, s); MS (EI) m/z: 274 (36, M^++2), 272 (M^+, 100%), 238 (14), 212 (13), 178 (13), 152 (9), 151 (8), 102 (6); HRMS calcd for $C_{15}H_{12}O_2N$: 238.0868, found: 238.0852.

*4.3.2. 3-Phenyl-2-phenylethynylpyridine (**6c**)*

Yellow oil; IR (neat) 3056, 2221, 1954, 1887, 1598, 1579, 1558, 1490, 1443, 1415, 1242, 1213, 1114, 1006, 916, 776, 755, 700, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (1H, dd, J=4.9, 1.5 Hz), 7.72 (1H, dd, J=7.8, 2.0 Hz), 7.66 (2H, d, J=6.8 Hz), 7.51–7.25 (9H, m); (400 MHz, benzene) δ 8.45 (1H, dd, J=4.3, 1.5 Hz), 7.50–7.48 (2H, m), 7.31–7.28 (2H, m), 7.21–7.12 (4H, m), 6.88–6.86 (3H, m), 6.61 (1H, dd, J=7.8, 4.4 Hz); ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 148.54, 141.23, 139.80, 138.12, 136.72, 131.75, 129.22, 128.74, 128.18, 128.08, 128.07, 122.71, 122.33, 91.81, 88.61; MS (EI) m/z: 255 (M^+, 100%), 254 (83), 226 (16), 200 (9), 150 (15), 127 (30), 102 (24), 878 (15), 77 (25), 63 (30), 51 (43); HRMS calcd for $C_{19}H_{12}N$: 254.0970, found: 254.1031.

*4.3.3. 3-Methoxy-2-phenylethynylpyridine (**6e**)*

Yellow crystal; mp 57.0–59.0 °C (recrystallization from ether–hexane); IR (KBr) 2217, 1575, 1494, 1464, 1440, 1430, 1275, 1251, 1212, 1117, 1012, 798, 756, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (1H, dd, J=3.9, 2.0 Hz), 7.64–7.61 (2H, m), 7.36–7.35 (3H, m), 7.26–7.20 (2H, m), 3.93 (3H, s); (400 MHz, DMSO-d_6) δ 8.18 (1H, d, J=4.4 Hz), 7.59–7.56 (3H, m), 7.47–7.40 (4H, m), 3.90 (3H, s); (400 MHz, C_6D_6) δ 8.18 (1H, dd, J=4.9, 1.6 Hz), 7.55–7.53 (2H, m), 6.92–6.89 (3H, m), 6.58–6.54 (1H, m), 6.34 (1H, dd, J=8.3, 1.5 Hz), 3.12 (3H, s); MS (EI) m/z: 209 (M^+, 100%), 208 (57), 180 (76), 166 (46), 139 (26), 127 (27), 69 (25); HRMS calcd for $C_{14}H_{11}ON$: 209.0841, found: 209.0883.

*4.3.4. Methyl 4-phenylethynylnicotinate (**7a**)*

Yellow crystal; mp 64–66 °C; IR (KBr) 1720, 1591, 1296, 1280, 1134, 1124, 1021, 779, 762, 696, 689 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 9.18 (1H, s), 8.69 (1H, d, J=4.8 Hz), 7.62–7.59 (2H, m), 7.49 (1H, d, J=5.2 Hz), 7.41–7.39 (3H, m), 4.00 (3H, s); MS (EI) m/z: 237 (M^+, 76%), 212 (35), 206 (57), 178 (63), 151 (100), 126 (36), 102 (43), 77 (42); HRMS calcd for $C_{15}H_{11}O_2N$: 237.0790, found: 237.0728.

*4.3.5. 3-Acetyl-4-phenylethynylpyridine (**7b**)*

Yellow oil; IR (neat) 2218, 1684, 1576, 1528, 1496, 1358, 1264, 962, 840, 758, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (1H, s), 8.68 (1H, d, J=4.8 Hz), 7.60–7.57 (2H, m), 7.48 (1H, d, J=5.2 Hz), 7.45–7.38 (3H, m), 2.80 (3H, s); MS (EI) m/z: 221 (M^+, 100%), 206 (87), 178 (33), 151 (50), 150 (45); HRMS calcd for $C_{15}H_{11}ON$: 221.0840, found: 221.0800.

*4.3.6. 3-Phenyl-4-phenylethynylpyridine (**7c**)*

Yellow oil; IR (neat) 2218, 1955, 1891, 1717, 1623, 1579, 1492, 1446, 1415, 1007, 932, 756, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (1H, dd, J=4.4, 1.2 Hz), 7.72 (1H, dd, J=1.6, 8.0 Hz), 7.59–7.56 (2H, m), 7.43–7.33 (9H, m), 7.03 (1H, s); MS (EI) m/z: 256 ($(M+1)^+$, 97%), 254 ($(M-1)^+$, 81), 226 (29), 102 (62), 77 (100); HRMS calcd for $C_{19}H_{14}N$: 256.1127, found: 256.1082.

*4.3.7. 3-Methyl-4-phenylethynylpyridine (**7d**)*

Yellow oil; IR (neat) 2215, 1623, 1582, 1445, 1244, 1166, 1108, 930, 859, 767, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (1H, s), 7.60–7.58 (2H, m), 7.48 (1H, d, J=8.0 Hz), 7.43 (1H, d, J=8.0 Hz), 7.37–7.26 (3H, m), 2.08 (3H, s); MS (EI) m/z: 193 (M^+, 80%), 165 (41), 139 (29), 102 (51), 63 (66); HRMS calcd for $C_{14}H_{12}N$: 194.0970, found: 194.0966.

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