An Effective, One-Pot Synthesis of Fully Substituted Pyridines under Microwave Irradiation in the Absence of Solvent

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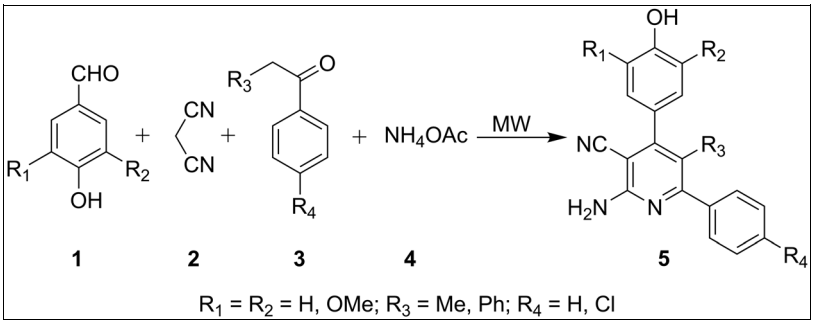

A convenient, rapid, and environmentally benign protocol is described for the preparation of fully substituted pyridine derivatives *via* four-component reactions between 2-substituted acetophenones, aromatic aldehydes, malononitrile, and ammonium acetate under microwave irradiation with good yield and without solvent.

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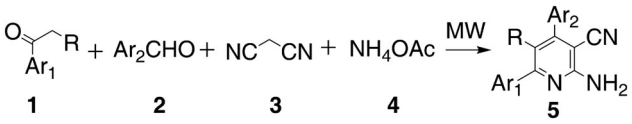
INTRODUCTION

The synthesis of 2-amino-3-cyanopyridine derivatives, a group of compounds containing the pyridine scaffold [1], has captured much attention of synthetic chemists due to their biological activities of antimicrobial [2], antihypertensive [3], cardiovascular [4], anti-inflammatory, analgesic, and antipyretic properties [5] as well as IKK-β inhibitory activity [6]. Additionally, a variety of heterocyclic compounds have been prepared with them as the important intermediates [7]. Although the highly substitute pyridines could be obtained widely in stepwise methods, for example, the preparation of 2-amino-6-aryl-4-methylsulfanylnicotinonitriles was carried out on ring transformation of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones by using cyanamide as a nucleophilic source [8], the multicomponent reactions (MCRs), a valuable approach widely applied to synthesis of pyridines [9], attracted our interest due to its exceptional synthetic efficiency, usually providing a robust protocol for constructing a chemically diverse range of molecules by the introduction of several functional groups in a single chemical event [10]. The preparation of fully substituted pyridines *via* a three-component reaction was first reported using triethylamine or 1,4-diazabicyclo[2.2.2]octane as a catalyst with unsatisfactory yields (20–48%) [11]. A basic ionic liquid 1-methyl-3-butylimidazolium hydroxide [12], piperidine/microwave [13], a Lewis acid, $ZnCl_2$ [14], and mesoporous silica [15] have been exploited as catalysts to improve the yields. These three components MCRs provided the fully substituted pyridines with two identical substitutions.

As part of our current ongoing medicinal chemistry project aiming to identify novel schistosome treatment, it is necessary to synthesize the substituted 2-amino-3-cyanopyridine compounds with five different substituents, using the aromatic aldehydes from lignin, one of the most abundant renewable natural resources richly found in wood pulp and papermaking waste. In that case, it will be easy to construct diversified pyridines and research their structure-activity relationships. The synthesis of such fully substituted pyridines was not reported, requiring the four-component MCRs, when we commenced our research programme. However, at around the same time as we prepared our manuscript, Kobayashi *et al*. reported the first synthesis of the substituted 2-amino-3-cyanopyridines with five different substituents but in rather low yields (11–37%) [7].

Although conductive heating is still the primary way for chemical transformations, the microwave technology as an alternative method accelerates reaction rate, shortens reaction time, and improves product yields. Because of transferring energy directly to the reactive species, the microwave synthesis attracts the interests of chemists to exploit new chemical reactions [16]. A synthesis of

Scheme 1



2,3,4,6-substituted pyridines with the microwave technology [7] was reported. This encourages us to continue our effort toward the synthesis of the fully substituted 2-amino-3-cyanopyridines under microwave irradiation.

Herein, we report the synthesis of fully substituted pyridines by the one-pot, four-component reaction of aromatic aldehydes obtained from lignin, 2-substituted acetophenones, malononitrile, and ammonium acetate under microwave irradiation (Scheme 1). The study on antischistosome activity of the synthesized compounds is currently under the way, and the results will be reported separately.

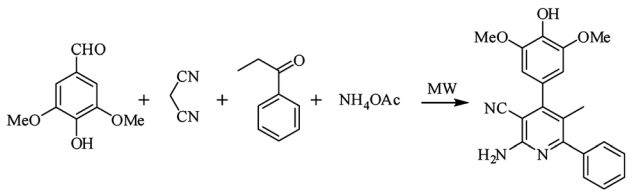
RESULTS AND DISCUSSION

Our study started with exploration and optimization for the synthesis of fully substituted pyridine derivatives under different reaction parameters and conditions using propiophenone (1 mmol), syringaldehyde (1 mmol), ammonium acetate (2 mmol), and malononitrile (1 mmol) (Table 1) as a model reaction. The transformation was first performed in EtOH considering the possible generation of ethoxide ion in the presence of NH_4OAc that might facilitate the intermediate formation. Such expectation was not realized as trace of the desired product was observed and no product could be isolated (Table 1, entry 1). Once the solvent was changed to 1,4-dioxane, more product was obtained but the yield was still poor (20%, Table 1, entry 2). Interestingly, when the reaction was carried out without any solvent, we isolated the desired fully substituted pyridine **5a** in a yield of 49% (Table 1, entry 3). Next, the microwave technology was applied for the reaction either with or without solvent. Not surprisingly, the yield was improved under microwave irradiation (Table 1, entries 4–6). Again, it was also noticed that more product was formed in neat instead of in the solvents. The microwave technology application not only increased the yield but also shorten the reaction time—even after 2-min reaction time, 67% of the product was afforded (Table 1, entry 6) and longer irradiation could increase the yield from 67–71% to 75% (Table 1, entries 7 and 8).

After establishment of a general experimental protocol, we applied the optimized conditions for the four components MCRs with different 4-hydroxy-benzyladehydes and ethylphenylketones (Table 2). The different substituents on 4-hydroxy-benzyladehydes showed no impact on the yield (Table 2, entries 1–3). A Cl-substituent on the ethylphenylketone gave the corresponding pyridine derivates in similar yields as well (Table 2, entries 4–6), while the reaction with benzylphenylketone provided the products in slightly lower yield (Table 2, entries 7–9) as expected because of the steric hindrance of the phenyl group.

Table 1

Optimization of reaction conditions for the synthesis of highly substituted pyridines.[a]

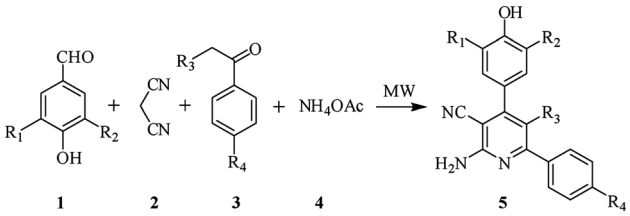


Entries	Solvents	Temperature	MW	Time	Yield (%)[b]
1	Ethanol	Reflux	No	Overnight	–[c]
2	1,4-Dioxane	Reflux	No	Overnight	20
3	No solvent	110°C	No	Overnight	49
4	Ethanol	110°C	Yes	10 min	13
5	1,4-Dioxane	110°C	Yes	10 min	37
6	No solvent	110°C	Yes	2 min	67
7	No solvent	110°C	Yes	5 min	71
8	No solvent	110°C	Yes	10 min	75

[a]Propiophenone (1 mmol), syringaldehyde (1 mmol), malononitrile (1 mmol) and ammonium acetate (2 mmol).
[b]Isolated yield.
[c]No product isolated.

Table 2

One-pot synthesis of highly substituted pyridine derivatives **5a–i**.



Entries	Products	R_1	R_2	R_3	R_4	Yield (%)[a]
1	**5a**	OMe	OMe	Me	H	75
2	**5b**	OMe	H	Me	H	72
3	**5c**	H	H	Me	H	73
4	**5d**	OMe	OMe	Me	Cl	76
5	**5e**	OMe	H	Me	Cl	71
6	**5f**	H	H	Me	Cl	72
7	**5g**	OMe	OMe	Ph	H	64
8	**5h**	OMe	H	Ph	H	66
9	**5i**	H	H	Ph	H	63

[a]Isolated yield.

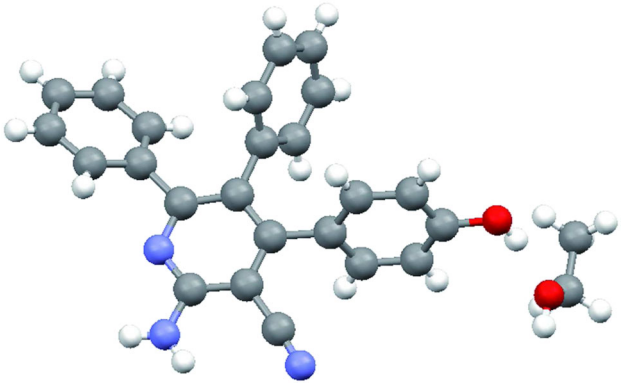


Figure 1. Structure of **5i**-ethanol.

All the products were characterized with IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry (MS), and elemental analysis (EA). Furthermore, the structure of **5i**·ethanol was established by the X-ray crystallographic analysis (Fig. 1, CCDC 804795) [17].

The mechanism of the formation of fully substituted pyridines was discussed by Magedov *et al.* [11], Beining Chen [13], and Banerjee *et al.* [15]. According to our results, we believe that the oxidation with atmospheric oxygen contributed to some more content than the Knoevenagel adduct hydrogen-transfer as the yields in our hands were much higher (up to 75%) under microwave irradiation in a sealed system but without removal of air.

CONCLUSIONS

A microwave irradiated four-component MCR was described for the rapid solvent-free synthesis of fully substituted pyridine derivatives with five different substituents in good yields. The HO-group and/or MeO-group on the aromatic aldehydes at 3, 4, and 5 positions showed no impact for the pyridine derivates formation, while the steric hindrance of the phenyl group of the ketones was observed providing lower yield. Such transformation provided additional information for the mechanism study. The preliminary bioactivity test against schistosome of the synthesized compounds showed some promising results and more systematical studies are underway, and the results will be published separately.

EXPERIMENTAL

Vanillin, syringaldehyde, and *p*-hydroxybenzaldehyde were synthesized according to previously reported methods [18]. Other reagents were obtained from Sinopharm Chemical Reagent. All reactions were conducted in CEM Discover. All synthesized compounds were characterized by infrared (IR), ^{1}H-NMR, ^{13}C-NMR, MS, and EA. IR spectra were recorded with a Nicolet Magna-IR 550 spectrometer. Mass spectra were recorded on WATERS Q-TOF Premier mass spectrometer using electrospray ionization (ESI). ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz, respectively. Elemental analyses (C, H, N, and S) were conducted using a PE-2400(II) elemental analyser, and results were found to be in good agreement (±0.2%) with the calculated values.

Typical procedure for the preparation of highly substituted pyridines. A grinded mixture of the 2-substituted acetophenone (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol), and ammonium acetate (2 mmol) was put in a 20-mL reactor without removal of air and irradiated in a microwave oven at 110° C for 10 min. The reaction mixture was cooled to room temperature. The crude product was purified by recrystallization or column chromatography.

4-(4-Hydroxy-3,5-dimethoxyphenyl)-5-methyl-6-phenyl-2-amino-3-cyanopyridine 5a (0.27 g, 75%). IR (KBr) ν (cm^{-1}): 3483, 3366, 3222, 2970, 2938, 1626, 1604, 1556, 1518, 1448, 1245, 1114, 723, 706; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 7.40–7.54 (m, 5H, ArH), 6.67 (s, 2H, ArH), 3.80 (s, 6H, 2×OCH_3), 1.92 (s, 3H, CH_3); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ (ppm): 161.7, 158.4, 156.1, 148.3, 140.5, 136.2, 129.2, 128.8, 128.4, 127.3, 117.7, 117.4, 106.7, 90.0, 56.7, 17.4; MS (ESI) *m/z*: 362.1 $[M+H]^+$, 384.1 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; found: C, 69.71; H, 5.35; N, 11.74.

4-(4-Hydroxy-3-methoxyphenyl)-5-methyl-6-phenyl-2-amino-3-cyanopyridine 5b (0.24 g, 72%). IR (KBr) ν (cm^{-1}): 3477, 3349, 3226, 2222, 1631, 1558, 1515, 1448, 1271, 1244, 1216, 1121, 776; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 7.42–7.52 (m, 5H, ArH), 6.96 (d, 1H, ArH, J = 1.8 Hz), 6.91 (d, 1H, ArH, J = 7.8 Hz), 6.91 (dd, 1H, ArH, J = 1.8, 7.8 Hz), 3.80 (s, 3H, OCH_3), 1.89 (s, 3H, CH_3); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ (ppm): 161.7, 158.4, 155.9, 147.9, 147.3, 140.5, 129.2, 128.8, 128.4, 128.3, 121.7, 117.7, 117.4, 115.8, 113.2, 90.0, 56.3, 17.3; MS (ESI) *m/z*: 332.0 $[M+H]^+$, 354.0 $[M+Na]^+$, 370.0 $[M+K]^+$; Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68; found: C, 72.41; H, 5.29; N, 12.60.

4-(4-Hydroxyphenyl)-5-methyl-6-phenyl-2-amino-3-cyanopyridine 5c (0.22 g, 73%). IR (KBr) ν (cm^{-1}): 3447, 3330, 3224, 2212, 1644, 1557, 1486, 1408, 1301, 770, 712; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 7.67–7.71 (m, 2H, ArH), 7.42–7.58 (m, 3H, ArH), 7.38 (d, 2H, ArH, J = 8.1 Hz), 7.16 (d, 2H, ArH, J = 8.1 Hz), 1.90 (s, 3H, CH_3); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ (ppm): 165.4, 161.9, 159.4, 151.0, 138.2, 130.5, 129.0, 128.9, 128.6, 128.5, 117.2, 115.5, 115.4, 81.5, 16.9; MS (ESI) *m/z*: 302.1 $[M+H]^+$, 324.0 $[M+Na]^+$, 340.0 $[M+K]^+$; Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94; found: C, 75.79; H, 5.21; N, 14.00.

4-(4-Hydroxy-3,5-dimethoxyphenyl)-5-methyl-6-(4-chlorophenyl)-2-amino-3-cyanopyridine 5d (0.30 g, 76%). IR (KBr) ν (cm^{-1}): 3463, 3364, 3239, 2203, 1642, 1611, 1551, 1520, 1415, 1332, 1125, 831; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 8.69 (s, 1H, OH), 7.51–7.59 (m, 4H, ArH), 6.66–6.70 (m, 4H, ArH, NH_2), 3.80 (s, 6H, 2×OCH_3), 1.91 (s, 3H, CH_3); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ (ppm): 159.8, 158.0, 155.8, 147.9, 138.9, 136.0, 133.1, 130.7, 128.0, 126.7, 117.1, 116.8, 106.3, 89.8, 56.2, 16.9; MS (ESI) *m/z*: 396.1 $[M+H]^+$, 418.1 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{18}ClN_3O_3$: C, 63.72; H, 4.58; N, 10.62; found: C, 63.83; H, 4.50; N, 10.51.

4-(4-Hydroxy-3-methoxyphenyl)-5-methyl-6-(4-chlorophenyl)-2-amino-3-cyanopyridine 5e (0.26 g, 71%). IR (KBr) ν (cm^{-1}): 3462, 3338, 3211, 2228, 1634, 1556, 1516, 1276, 1242, 1092,

1032, 824; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 9.32 (s, 1H, OH), 7.50–7.58 (m, 4H, ArH), 6.95 (d, 1H, ArH, J = 1.8 Hz), 6.90 (d, 1H, ArH, J = 8.1 Hz), 6.78 (dd, 1H, ArH, J = 1.8, 8.1 Hz), 6.67 (s, 2H, NH_2), 3.79 (s, 3H, OCH_3), 1.88 (s, 3H, CH_3); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ (ppm): 160.3, 158.5, 156.2, 147.9, 147.5, 139.4, 133.6, 131.2, 128.4, 128.2, 121.7, 117.6, 117.3, 116.0, 113.3. 90.3, 56.3, 17.3; MS (ESI) *m/z*: 366.0 [M +H]$^+$; Anal. Calcd. for $C_{20}H_{16}ClN_3O_2$: C, 65.67; H, 4.41; N, 11.49; found: C, 65.76; H, 4.55; N, 11.40.

4-(4-Hydroxyphenyl)-5-methyl-6-(4-chlorophenyl)-2-amino-3-cyanopyridine 5f (0.24 g, 72%). IR (KBr) ν (cm^{-1}): 3457, 3360, 3241, 2217, 1634, 1550, 1516, 1249, 1167, 1092, 842; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 9.75 (s, 1H, OH), 7.48–7.55 (m, 4H, ArH), 7.19 (d, 2H, ArH, J = 7.5 Hz), 6.89 (d, 2H, ArH, J = 7.5 Hz), 6.67 (s, 2H, NH_2), 1.85 (s, 3H, CH_3); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ (ppm): 159.8, 158.0, 157.8, 155.4, 133.1, 130.9, 130.7, 129.8, 127.9, 127.2, 117.1, 116.8, 115.3, 89.9, 16.7; MS (ESI) *m/z*: 336.1 [M+H]$^+$, 358.1 [M +Na]$^+$; Anal. Calcd. for $C_{19}H_{14}ClN_3O$: C, 67.96; H, 4.20; N, 12.51; found: C, 67.85; H, 4.29; N, 12.44.

4-(4-Hydroxy-3,5-dimethoxyphenyl)-5,6-diphenyl-2-amino-3-cyanopyridine 5g (0.27 g, 64%). IR (KBr) ν (cm^{-1}): 3480, 3406, 3282, 3136, 2211, 1627, 1548, 1516, 1453, 1414, 1227, 1118, 717, 705; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H, OH), 6.36–7.17 (m, 14H, ArH, NH_2), 3.53 (s, 6H, 2×OCH_3); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ (ppm): 160.0, 159.0, 154.8, 147.2, 140.0, 137.4, 135.4, 131.4, 129.3, 127.7, 127.4, 127.3, 126.1, 124.1, 116.8, 107.4, 84.8, 55.8; MS (ESI) *m/z*: 424.1 [M+H]$^+$, 446.2 [M+Na]$^+$; Anal. Calcd. for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92; found: C, 73.86; H, 5.15; N, 9.80.

4-(4-Hydroxy-3-methoxyphenyl)-5,6-diphenyl-2-amino-3-cyanopyridine 5h (0.26 g, 66%). IR (KBr) ν (cm^{-1}): 3471, 3382, 3290, 3124, 2216, 1633, 1547, 1518, 1460, 1279, 1234, 1028, 707; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 9.12 (s, 1H, OH), 6.54–7.17 (m, 15H, ArH, NH_2), 3.56 (s, 3H, OCH_3), 1.89 (s, 3H, CH_3); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ (ppm): 160.5, 159.5, 155.3, 147.1, 146.9, 140.5, 137.8, 132.0, 129.8, 128.2, 127.9, 127.8, 126.6, 124.7, 122.5, 117.2, 115.4, 114.2, 89.9, 55.8; MS (ESI) *m/z*: 394.1 [M+H]$^+$, 416.1 [M +Na]$^+$; Anal. Calcd. for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68; found: C, 76.41; H, 4.80; N, 10.63.

4-(4-Hydroxyphenyl)-5,6-diphenyl-2-amino-3-cyanopyridine 5i (0.23 g, 63%). IR (KBr) ν (cm^{-1}): 3475, 3360, 3206, 2212, 1611, 1550, 1513, 1450, 1273, 1230, 1110, 865, 703; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 9.51 (s, 1H, OH), 6.80–7.22 (m, 14H, ArH, NH_2), 6.60 (d, 2H, ArH, J = 8.4 Hz); ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ (ppm): 160.0, 158.9, 157.1, 155.0, 140.0, 137.2, 131.5, 130.3, 129.3, 127.7, 127.3, 127.2, 127.1, 126.1, 124.4, 116.6, 114.6, 89.5; MS (ESI) *m/z*: 364.3 [M+H]$^+$; Anal. Calcd. for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72; N, 11.56; found: C, 79.21; H, 4.79; N, 11.50.

X-Ray structure determination of 5i. Colorless blocks, $C_{26}H_{23}N_3O_2$, M_r = 409.47, Orthorhombic, space group P_{cab}, a = 9.3681(12) Å, b = 9.9916(14) Å, c = 46.994(10) Å, β = 90.00°, V = 4398.8(12) Å^3, Z = 8, D_{calc} = 1.237 g cm^{-3}, F(000) = 1728, μ (MoKα) = 0.080 mm^{-1}, crystal dimensions 0.30 × 0.20 × 0.20 mm^3. Intensity data were collected using a Bruker Smart APEX CCD-based diffractometer at 293(2) K, graphite monochromator Mo Kα radiation (λ = 0.071073 nm) using a φ-ω can mode. Four thousand nine hundred ninety-two reflections [3946 unique (R_{int} = 0.0237)] were collected in the range of 1.73 < θ < 25.37 ($0 \le h \le 11$, $0 \le k \le 12$, $-10 \le l \le 56$), of which 2312 reflections were observed with $I > 2\sigma(I)$. The final R and wR values were 0.0665 and 0.1504, s = 1.005, (δ/σ) max = 0.044. The maximum peak and minimum peak in the final difference map is 0.418 and –0.202 e Å^{-3}, respectively. CCDC number for compound **5i** is CCDC 804795.

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[17] CCDC 804795 contains the supplementary crystallographic data recorded for the 2-amino-3-cyano-4,5,6-triarylpyridine **5i**·ethanol reported in this Letter. 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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