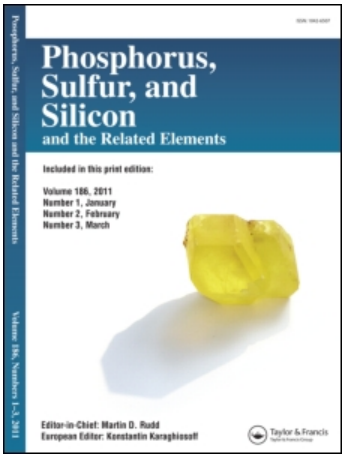

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Syntheses and Bioactivity of *o*- or *p*-Trifluoromethylphenyl Phosphates

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Syntheses and Bioactivity of *o*- or *p*-Trifluoromethylphenyl Phosphates

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o- *and* p-*Trifluoromethylphenyl phosphates designed as mechanism-based phosphotyrosine phosphatase inactivators have been prepared. Some of them show herbicidal activities.*

Keywords Herbicidal activities; phosphotyrosine phosphatase inactivator; trifluoromethylphenyl phosphates

INTRODUCTION

Protein phosphatases play important roles in the regulation of cell growth and metabolism. Recently,[1] Widlanski designed and synthesized 4-(fluoromethyl)phenyl phosphate, which is likely to function as a mechanism-based phosphotyrosine phosphatase inactivator. 4-(Fluoromethyl)phenyl phosphate undergoes a phosphatase-catalyzed hydrolytic reaction to give a reactive intermediate quinone methide that could irreversibly inactivate the phosphatase by forming a covalent bond to an active site residue (i.e., OH, SH, and NH_2 groups) shown in Scheme 1.

One can anticipate that trifluoromethylphenyl phosphates could exhibit bioactivity similar to 4-(fluoromethyl)phenyl phosphate. Some substituted trifluoromethylphenyl phosphates with insecticidal activity have been reported.[2] We are interested in the synthesis and

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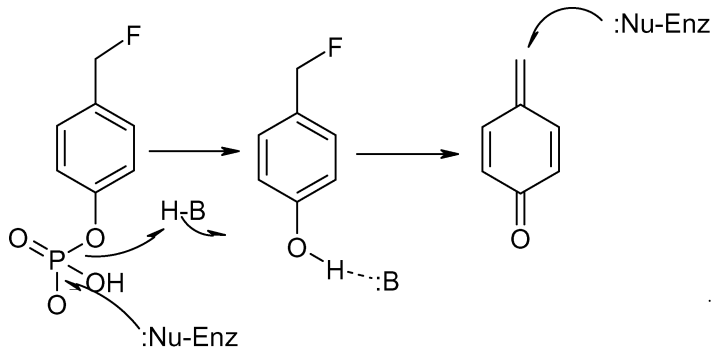
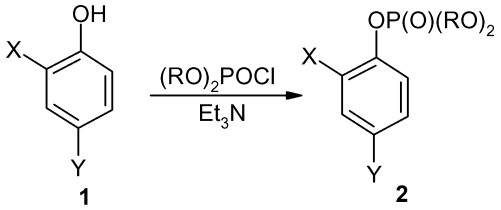


SCHEME 1

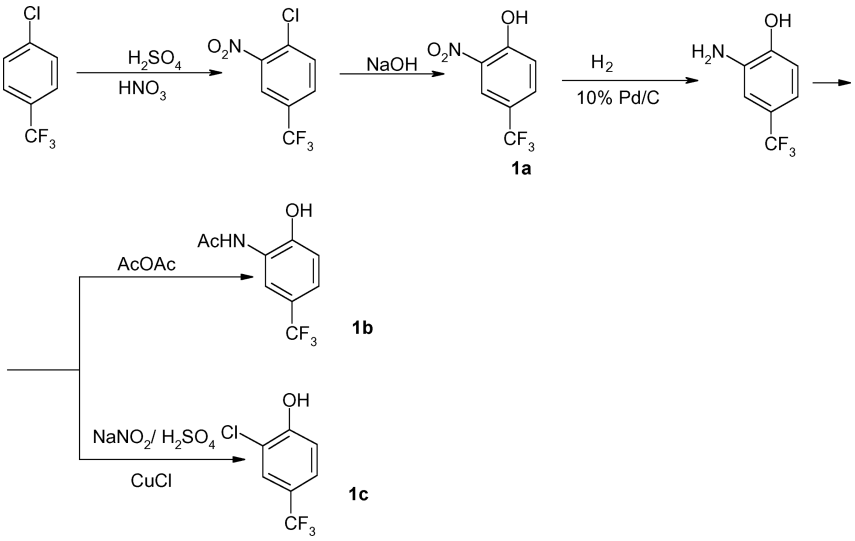
bioactivity of a series of substituted trifluoromethylphenyl phosphates, 2-X-4-Y-phenol phosphates (X or Y=CF_3).



RESULTS AND DISCUSSION

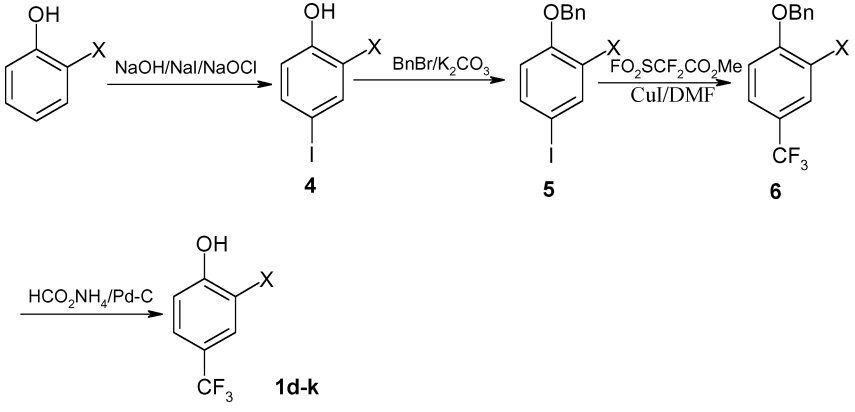
Trifluoromethylation of phenol with trifluoromethyl bromide is not a satisfactory method for the synthesis of trifluoromethylphenol,[3] because of the low yield and poor regioselectivity. We prepared the *p*-substituted trifluoromethylphenols **1a–c**, starting from p-chlorotrifluoromethylbenzenes via nitration, hydrolysis, reduction, and diazotisation according to the literature,[4] as shown in Scheme 2. The *p*-substituted trifluoromethylphenols **1d–f** were synthesizied from *o*-substituted phenols via iodination[4] with high regioselectivity followed by trifluoromethylation[5] as shown in Scheme 3. The *o*-substituted-trifluoromethylphenols **1h–m** were prepared by the same route from *p*-substituted phenols. The results are summarized in Table I.

We have determined the herbicidal activities of the compounds **2** with respect to the growth inhibition of the rape roots under the condition of darkness. The results of the test proved that some of the compounds exhibited herbicidal activities. At a concentration of 10



SCHEME 2 Method A.

μg/ml, the rape roots growth inhibition rates (%) of compounds **2a**, **2e**, **2i**, **2n**, and **2o** were respectively 63.6, 67.8, 73.6, 73.6, and 45.4. Other compounds were inactive or exhibited low activity. Under the same experimental conditions, the commercial herbicide methsulfuron-methyl DPX-T6376 is 77.5% and Miekuotin DUS-06 is 19.5%. The comparison of 2c with 2e indicated that the hydrolysis of the phosphate would affect the herbicidal activity. The activity of the isopropyl phosphate



SCHEME 3 Method B.

TABLE I Synthesis of Trifluoromethylphenyl Phosphates 2

No.	R	X	Y	Method	Phosphorylation Yield
2a	i-Pr	NO_2	CF_3	A	70
2b	i-Pr	NHAc	CF_3	A	65
2c	i-Pr	Cl	CF_3	A	76
2d	Me	CH_3	CF_3	B	45
2e	Me	Cl	CF_3	B	35
2f	Me	Ph	CF_3	B	77
2g*	Me	H	CF_3	B	57
2h	Me	CF_3	CH_3	B	73
2i	Me	CF_3	Cl	B	87
2j	Me	CF_3	Ph	B	90
2k	Me	CF_3	F	B	43
2l	Me	CF_3	t-Bu	B	62
2m**	Me	CF_3		B	56
2n*	Me	CF_3	H	B	50
2o*	Me	CF_3	Naphthol-2	B	77

*Commercial material.
**Pyrimidine compound.

2c, which was inactive, was obviously lower compared with the methyl phosphate **2e**. The possible reason is that isopropyl phosphate is more difficult to hydrolyze to form the electrophilic quinone methide intermediates. When an electron-withdrawing group, such as Cl, NO_2, is present in the benzene ring of the phenol, the herbicidal activity is higher. The same effect was observed for 4-(fluoromethyl) phenyl phosphate, which required an electron-withdrawing group as a better phosphatase inactivator.[6]

In order to test the inhibition activity against phosphatases, dimethyl *p*-trifluoromethylphenyl phosphates were hydrolyzed to the corresponding *o*- or *p*-trifluoromethylphenyl phosphoric acid monoesters by the $TMSBr/H_2O$ sequence according to the reference methods.[7] We have preliminarily tested their inhibition rates against protein tyrosine phoshatase 1B (PTP1B). At a concentration of 500 μM, inhibition rates (%) of compounds **2g**, **2i**, **2k**, and **2l** are respectively 54.0, 57.2, 63.2, and 89.1. Further biochemical evaluation of these compounds is underway.

EXPERIMENTAL

All melting points are uncorrected. ^{1}HNMR spectra were recorded on a Bruker AM-300 spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Mass and HRMS spectra were taken on a Finnigan GC-MS-4021 spectrometer. Elemental analyses were done by the

Elemental Analyses Group of the Shanghai Institute of Organic Chemistry (SIOC). The known compounds were identified in agreement with the literature data, and only the NMR data are reported here. The starting materials **1g**, **1n**, and **1o** are commercially available from J&K Chemical Co.

Typical Procedure for the Preparation of Substituted Trifluoromethylphenols: Method A (Scheme 1)

2-Nitro-4-(trifluoromethyl)phenol (1a)[8]

Compound **1a** was prepared from 4-trifluoromethyl-chlorobenzene via nitration followed by hydrolysis. The nitration yield was 73.2%, and the hydrolysis yield was 85.7%.

2-Acetamino-4-(trifluoromethyl)phenol (1b)[9]

2-Nitro-4-(trifluoromethyl)phenol (**1**) was reduced by catalytic hydrogenation in anhydrous methanol with 10%Pd/C as catalyst at 1 atm H_2 to give 2-amino-4-(trifluoromethyl)phenol in 93% yield. To a solution of 2-amino-4-(trifluoromethyl)phenol (1.0 g) in absolute ethyl acetate (20 mL), acetic anhydride (1.2 mL) was added dropwise at 0–5°C, and white crystals formed slowly. After 10 min, the solvent was evaporated in vacuum. Recrystallization from a mixture of petroleum ether (60–90°C) and ethyl acetate gave pure 2-acetoamino-4-(trifluoromethyl)phenol (**1b**), yield 81%.

2-Chloro-4-(trifluoromethyl)phenol (1c)

2-Chloro-4-(trifluoromethyl)phenol (**1c**) was prepared via diazotation of 2-amino-4-(trifluoromethyl)phenol according to the reference methods.[8]

Method B (Scheme 2)

Typical Procedure of Iodination[4]

2-Methylphenol (50 mmol) was dissolved in 100 mL of methanol. Sodium iodide (7.5 g, 50 mmol) and sodium hydroxide (2.0 g, 50mmol) were added, and the solution was cooled to 0°C. Aqueous sodium hypochlorite (61.5mL, 5.2% NaOCl) was added dropwise over 90 min at 0–3°C. The resulting slurry was stirred for 2h at 0–2°C and then was treated with 20 mL of 10% aqueous sodium thiosulfate. The mixture was neutralized using 5% aqueous HCl. Then ether (75 mL) was added. The organic layer was washed with brine (70 mL) and dried over Na_2SO_4. Filtration and rotary evaporation at 40°C afforded 10.63 g of

2-iodo-4-methylphenol (**4h**), colorless liquid, yield 91%. ^{1}H-NMR δ 7.46 (d, 1H, $J = 2$ Hz, H-3), 7.02 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 2$ Hz, H-5), 6.86 (d, 1H, $J = 8$ Hz, H-6), 5.28 (s, 1H, OH), 2.23 (s, 3H, CH_3); MS (m/e, %): 235 (M^++1, 11.70), 234 (M^+, 100.00), 108 (12.52), 107 (47.49), 79 (11.84), 78 (18.01), 77 (39.40), 51 (17.37).

Typical Procedure of Benzyl Protection

A mixture of **4h** (10 mmol), benzyl bromide (15 mmol), K_2CO_3(15 mmol), and DMF (20 mL) was stirred at 40–50°C for 12 h under an anhydrous atmosphere. The mixture was cooled, neutralized using 5% HCl, then diluted with 100 mL of water and extracted with ether. The organic layer was washed with water and brine, dried over Na_2SO_4, and filtrated. Evaporation of the solvent gave a crude product that was purified by flash column chromatography to afford benzyl 2-iodo-4-methylphenyl ether (**5h**), yield 88%. ^{1}H-NMR δ 7.58 (d, 1H, $J = 1.5$ Hz), 7.45 (d, 2H, $J = 7.3$ Hz), 7.34 (t, 2H, $J = 7.3$ Hz), 7.28 (t, 1H, $J = 7.3$ Hz), 7.01 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 1.5$ Hz), 6.70 (d, 1H, $J = 8$ Hz), 5.07 (s, 2H), 2.20 (s, 3H); MS (m/e, %): 324 (M^+, 34.35), 288 (17.60), 197 (8.03), 180 (6.70), 91 (100.00), 78 (5.65), 65 (9.63), 51 (6.21).

Typical Procedure of Trifluoromethylation[5]

5h (8 mmol) was treated with FO_2SCF_2COOMe (32 mmol) in dimethylformamide (DMF) in the presence of catalytic amounts of CuI (24 mmol) at 80°C for 24 h. The solution was washed with saturated aqueous NH_4Cl, filtered, and extracted with ether. The organic layer was washed with water and brine, dried over Na_2SO_4, and filtrated. Evaporation of the solvent gave a crude product that was purified by flash column chromatographyto obtain benzyl 4-methyl-2-trifluroromethylphenyl ether (**6h**), yield 74%. ^{1}H-NMR δ 7.72∼7.50 (m, 7H), 7.19 (d, 1H, $J = 8.4$ Hz), 5.42 (s, 2H), 2.58 (s, 3H); MS (m/e, %): 266(M^+, 14.39), 265 (M^+-1, 8.13), 181 (6.64), 127 (8.80), 92 (4.55), 91 (100.00), 65 (9.31), 63 (3.13).

Typical Procedure for the Hydrogenolytic Debenzylation

A solution of **6h** (6 mmol) and $HCOONH_4$(90 mmol) in methanol (7 mL) with 10% (mol) Pd/C as catalyst was refluxed for 1.5 h, filtrated, and evaporated. The product was used directly in the next reaction without purification.

Typical Procedure of Phosphorylation

4.8 mmol of $ClPO(OCH_3)_2$ was added dropwise to a mixture of the trifluoromethylphenol (4 mmol), MeCN (8 mL), and Et_3N (4.8 mmol) at room temperature, followed by TLC. After the reaction was finished and

the solvent was evaporated, the residue was purified by flash column chromatography to give the phosphate **2**.

Diisopropyl 2-Nitro-4-(trifluoromethyl)phenyl phosphate (2a)

^{1}H-NMR δ: 7.8–8.2 (m, 3H, PhH), 4.7–4.85 (m, 2H, CH), 1.35 (dd, 12H, J = 8.4Hz, J = 11Hz, CH_3); MS (m/e, %): 352 (M-F, 0.5), 312 (3.86), 288 (10.19), 270 (47.2), 241 (100), 207 (15.99), 190 (18.26); Anal. Calcd. for $C_{13}H_{17}F_3NO_6P$: C, 42.06; H, 4.62. Found: C, 41.84; H, 4.45.

Diisopropyl 2-(N-Acetylamino)-4-(trifluoromethyl)phenyl phosphate (2b)

^{1}H-NMR δ: 8.63 (s, 1H, PhH), 8.56 (s, 1H, NH), 7.3 (s, 2H, PhH), 4.75 (m, 2H, OCH2), 2.23 (s, 3H, $COCH_3$), 1.34 (dd, 12H, J = 7.5 Hz, J = 32 Hz, CH_3); MS (m/e, %): 383 (M+1), 341 (8.17), 299 (11.74), 282 (17.38), 257 (100), 239 (34.93), 177 (26.84); Anal. Calcd. for $C_{15}H_{21}F_3NO_5P$: C, 47.00; H, 5.52. Found: C, 47.13; H, 5.27.

Diisopropyl 2-Chloro-4-(trifluoromethyl)phenyl phosphate (2c)

^{1}H-NMR δ: 7.49–7.70 (m, 3H, PhH), 4.8 (m, 2H, OCH_2), 1.35 (dd, J = 8.2 Hz, J = 13Hz, 12H, CH_3), MS (m/e, %): 360 (M, 1.01), 325 (9.4), 283 (13.52), 277 (12.5), 241 (100), 223 (2.07), 196 (15.30); Anal. Calcd. for $C_{13}H_{17}ClF_3O_4P$: C, 43.29; H, 4.75. Found: C, 43.13; H, 4.47.

Dimethyl 2-Methyl-4-(trifluoromethyl)phenyl phosphate (2d)

^{1}H-NMR δ 7.47–7.35 (m, 3H), 3.88 (d, 6H, J = 11 Hz), 2.34 (s, 3H); MS (m/e, %): 284 (M^+, 29.72), 269 (59.88), 175 (19.02), 172 (100), 127 (22.41), 110 (16.61), 109 (44.80), 79 (23.94); Anal. Calcd. for $C_{10}H_{12}F_3O_4P$: C, 42.27; H, 4.26. Found: C, 42.37; H, 4.38.

Dimethyl 2-Chloro-4-(trifluoromethyl)phenyl ester (2e)

^{1}H-NMR δ 7.74–7.52 (m 3H), 3.95 (d, 6H, J = 11.4 Hz); MS (m/e, %): 307 (M^++2, 9.49), 305 (M^+, 27.02), 285 (14.90), 270 (13.45), 269 (100.00); Anal. Calcd. for $C_9H_9ClF_3O_4P$: C, 35.49; H, 2.98. Found: C, 35.67; H, 3.11.

Dimethyl 5-(Trifluoromethyl)[1,1′-biphenyl]-2-yl ester (2f)

^{1}H-NMR δ 7.66∼7.38 (m, 8H), 3.62 (d, 6H, J = 11.5Hz); MS (m/e, %): 346 (M^+, 100.00), 327 (17.12), 234 (17.21), 233 (17.30), 217 (22.44), 165 (82.92), 109 (35.56); Anal. Calcd. for $C_{15}H_{14}F_3O_4P$: C, 52.03; H, 4.08. Found: C, 51.86; H, 4.00.

Dimethyl 4-(Trifluoromethyl)phenyl phosphate (2g)

^{1}H-NMR δ 7.65–7.28(m 4H), 3.87(d, 6H, $J = 11.4$); MS (m/e, %): 270 (M^+, 73.63), 251 (53.47), 172 (32.31), 162 (46.88), 158 (100.00), 109 (79.91), 96 (51.00), 79 (27.01); Anal. Calcd. for $C_9H_{10}F_3O_4P$: C, 40.01; H, 3.73. Found: C, 40.38; H, 3.92.

Dimethyl 4-Methyl-2-(trifluoromethyl)phenyl phosphate (2h)

^{1}H-NMR δ 7.48–7.26 (m, 3H), 3.88 (d, 6H, $J = 11$ Hz), 2.34 (s, 3H); MS (m/e, %): 284 (M+, 25.19), 244 (19.91), 191(12.91), 109 (46.19), 127 (28.46), 149 (23.95), 97 (50.70), 71 (57.23), 69 (70.76), 57 (92.85), 55 (65.63), 44(51.79), 43(100.00); Anal. Calcd. for $C_{10}H_{12}F_3O_4P$: C, 42.27; H, 4.26. Found: C, 42.59; H, 4.21.

Dimethyl 4-Chloro-2-(trifluoromethyl)phenyl phosphate (2i)

^{1}H-NMR δ 7.61–47 (m, 3H), 3.88 (d, 6H, $J = 11$ Hz); MS(m/e, %): 306 (M^++2, 19.06), 304 (M^+, 55.55), 264 (49.66), 178 (20.21), 176 (60.42), 148 (28.89), 109 (100.00), 79 (25.45); Anal. Calcd. for $C_9H_9ClF_3O_4P$: C, 35.49; H, 2.98. Found: C, 35.50; H, 3.12.

Dimethyl 3-(trifluoromethyl)[1,1′-biphenyl]-4-yl ester (2j)

^{1}H-NMR δ 7.84∼7.39 (m, 8H), 3.92 (d, 6H, $J = 11.5$ Hz); MS (m/e, %): 347 (M^++1, 16.62), 346 (M+, 100.00), 218 (29.02), 205 (10.68), 190 (14.83), 188 (9.35), 109 (21.40), 43 (9.80); Anal. Calcd. for $C_{15}H_{14}F_3O_4P$: C, 52.03; H, 4.08. Found: C, 52.04; H, 4.29.

Dimethyl 4-Fluoro-2-(trifluoromethyl)phenyl phosphate (2k)

^{1}H-NMR δ 7.60–7.16 (m, 3H), 3.88 (d, 6H, $J = 12$ Hz); MS (m/e, %): 288 (M^+, 84.96), 248 (96.60), 219 (18.51), 205 (23.46), 160 (76.91), 132 (45.56), 109 (100.00), 79 (23.61); Anal. Calcd. for:$C_9H_9F_4O_4P$ C, 37.52; H, 3.15. Found: C, 37.56; H, 3.49.

Dimethyl 4-Tert-butyl-2-(trifluoromethyl)phenyl ester (2l)

^{1}H-NMR δ 7.62∼7.47 (m, 3H), 3.89 (d, 6H, $J = 11.42$ Hz), 1.32 (s, 9H); MS (m/e, %): 326 (M^+, 6.14), 311 (100.00), 183 (7.92), 155 (4.00), 131 (9.89), 109 (7.36), 41 (3.66); Anal. Calcd. for $C_{13}H_{18}F_3O_4P$: C, 47.86; H, 5.56. Found: C, 47.61; H, 5.38.

Dimethyl 6-Methyl-2-phenyl-5-(trifluoromethyl)-4-pyrimidinyl ester (2m)

^{1}H-NMR δ 8.60–8.51 (m, 2H), 7.62–7.53 (m, 3H), 4.08 (d, 6H, $J =$ 11.7 Hz), 2.85 (q, 3H); MS (m/e, %): 362 (M^+, 21.11), 293 (7.77), 267 (14.54) 254 (100.00), 221 (43.17), 151 (10.95), 104 (84.05), 77 (28.59);

Anal. Calcd. for $C_{14}H_{14}F_3N_2O_4P$: C, 46.42; H, 3.90. Found: C, 46.05; H, 4.25.

Dimethyl 2-(Trifluoromethyl)phenyl phosphate (2n)

^{1}H-NMR δ 7.64–7.22(m, 4H), 3.90(d, 6H, $J = 11.4$ Hz); MS (m/e, %): 270 (M^+, 50.49), 251 (78.42), 230 (100.00), 187 (15.94), 158 (16.78), 142 (30.06), 114 (57.63), 109 (22.37); Anal. Calcd. for $C_9H_{10}F_3O_4P$: C, 40.02; H, 3.73. Found: C, 40.19; H, 3.85.

Dimethyl 1-(Trifluoromethyl)-2-naphthalenyl ester (2o)

^{1}H-NMR δ 8.32–7.50(m, 4H), 3.83(d, 6H, $J = 11.5$ Hz); MS (m/e, %): 321 (M^++1, 14.05), 320 (M^+, 100.00), 251 (14.39), 208 (7.14), 192 (14.60), 164 (31.23), 133 (13.02), 109 (16.85); Anal. Calcd. for $C_{13}H_{12}F_3O_4P$: C, 48.76; H, 3.78. Found C, 48.68; H, 3.84.

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