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Studies on the Synthesis of Pyridine Analogs of the Natural Product 3, 5, 4'-Trimethoxystilbene

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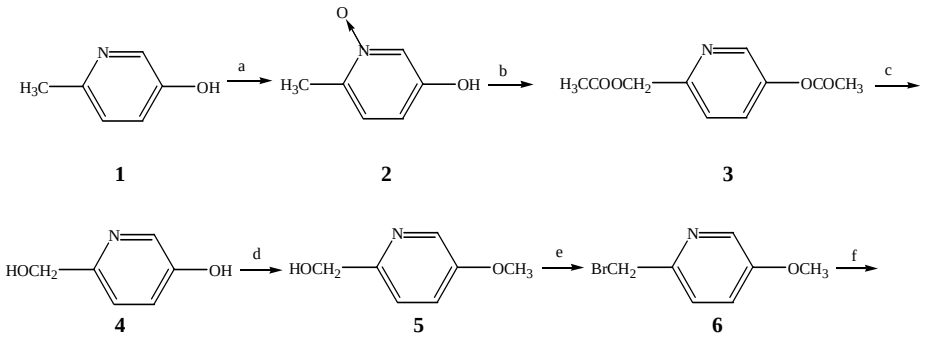
Abstract: Five pyridine analogs of the natural product, 3, 5, 4'-trimethoxystilbene, were synthesized. The final compounds were characterized by ^{1}H-NMR.

Keywords: Synthesis , pyridine analogs of 3, 5, 4'-trimethoxystilbene .

3,5,4'-Trimethoxystilbene is the methoxy precursor of a natural product 3,5,4'-trihydroxystilbene (resveratrol)[1] , which was reported to have many biological activities[2]. 3,5,4'-trimethoxystilbene itself is also a natural product[2]. We have synthesized 3,5,4'-trimethoxystilbene. In the screening of its anti-tumor activity using three different human cancer cell lines, 3,5,4'-trimethoxystilbene was found to have an IC_{50} 5.91 μmol/L for KB, 5.82 μmol/L for A2780, 7.08 μmol/L for HCT-8, respectively. So we designed and synthesized its analogs with a pyridine ring instead of the corresponding benzene ring for the purpose of comparison of their biological activities. We designed two synthetic approaches, one was similar to the method in our earlier published paper[3], using Wittig-Horner reaction as shown in **Scheme 1**.

Scheme 1 Synthetic route by Wittig-Horner reaction for compound **9**



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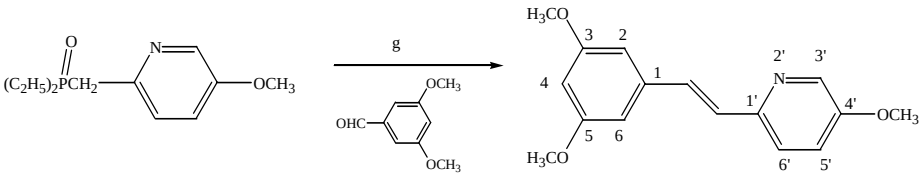


7 **8** **9**

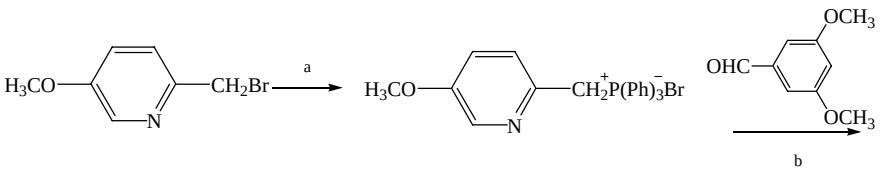
a) CH_3COOH/H_2O_2, 115℃, b) $(CH_3CO)_2O$,105℃, c)HCl, reflux 2hrs, d)K_2CO_3, CH_3COCH_3 / $(CH_3)_2SO_4$, reflux 3 hrs, e) CH_2Cl_2/PBr_3, f) $P(OC_2H_5)_3$, reflux, g) THF/NaH

Starting from 3-hydroxy-6-methyl pyridine **1** *via* a five-step reaction, the 3-methyl-6-bromomethylene pyridine **6** was obtained as pink solid (9.8%). When **6** was treated with triethylphosphite to prepare the Wittig-Horner reagent **7**, an oil complex was obtained, which was difficult to purify, either by prepared TLC or column chromatography.

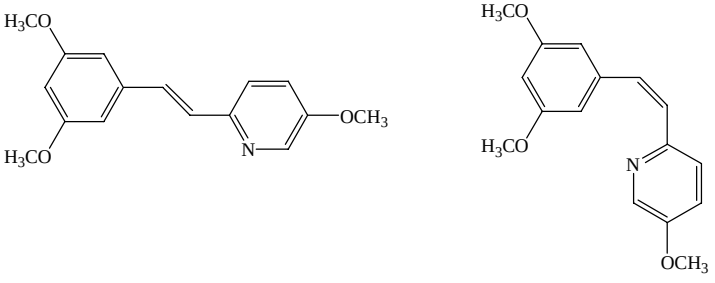
The other synthetic route was carried out, using Wittig reaction instead of Wittig-Horner reaction as shown in **Scheme 2**. We obtained a mixture of the target compound with *E* **9** and *Z* **11** configuration in ratio about 2:1. By careful silica column chromotography and recrylstallization, the pure2-[(*E*)-2-(3,5-dimethoxypheneyl)-1-ethenyl]-5-methoxy-pyridine **9** was obtained. The structure of compound **9** was characterized by MS and ^{1}H-NMR.

At the same time, several analogs of the compound **9** were designed and synthesized by the similar way of our earlier published paper as shown in **Scheme 3**.

Scheme 2 Synthetic route by Wittig reaction for compound **9**



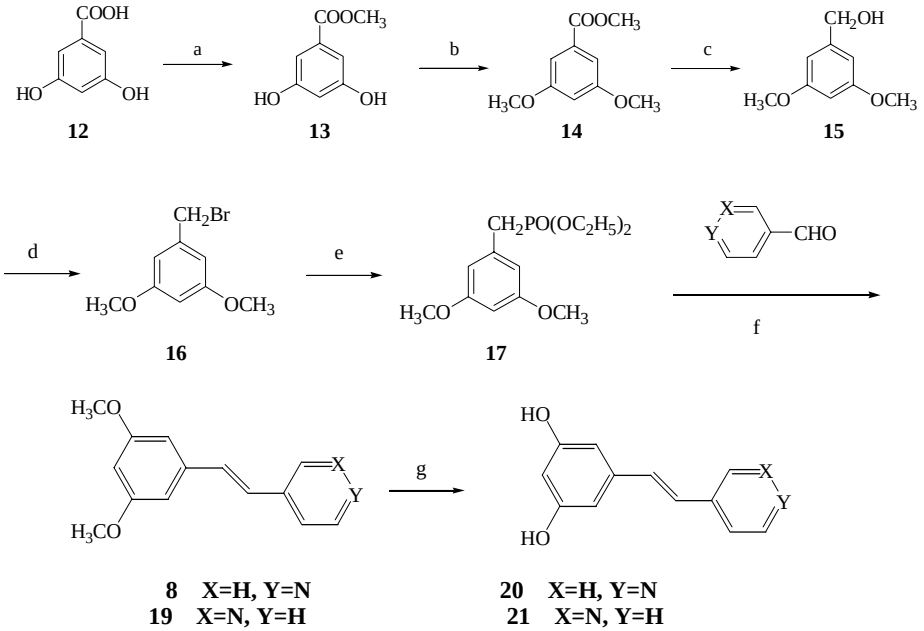
6 **10** **8**



9 **11**

a) toluene/$P(Ph)_3$, 120℃, 2 hrs, b) CH_2Cl_2/NaOH aq, r.t., 1 hr

Scheme 3 Synthetic route of analogs of compound **9**



a) HCl/CH_3OH, r.t. , b) $CH_3COCH_3/(CH_3)_2SO_4$, K_2CO_3, reflux 3 hrs, c) $C_2H_5OC_2H_5/LiAlH_4$, r.t. , d) CH_2Cl_2/PBr_3, e) $P(OC_2H_5)_3$ reflux 3 hrs, f) THF/NaH, g) CH_2Cl_2/BBr_3

Starting from 3,5-dihydroxybenzoic acid *via* five steps, we obtained **17**, which was condensed with 3- and 4-pyridine carboxaldehyde to give **18** or **19**, respectively. The protective groups were then removed by boron tribromide in CH_2Cl_2 at room temperature under nitrogen atmosphere to give the corresponding hydroxy analogs **20** and **21**, which were purified by silica column chromatography.

The biological evaluation of the target compounds **9**,**18**,**19**,**20**,**21** is under going.

Acknowledgments

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References and Notes

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5. For compound **9**, colorless crystal mp 60-62℃; ^{1}H-NMR (500MHz, $CDCl_3$) δ ppm: 8.294 (d, 2H, J=3.0Hz, H-3') ; 7.434 (d,1H, J=9.0Hz, H-6') ; 7.280 (dd, 1H, J=9.0,3.0Hz, H-5') ; 6.724 (d, 2H, J=2.5Hz, H-2,6) ; 6.420 (t,1H, J=2.5Hz, H-4) ; 7.433,7.180(d, each 1H, J=16.5Hz, H-α , β) ; 3.897 (s,3H, OCH_3-4') ; 3.824 (s, 6H, OCH_3-3,5)
   MS: 270 (M-1)$^+$, 256 , 240
   For compound **18**, mp 67-70℃; ^{1}H-NMR (300MHz, $CDCl_3$) δ ppm: 7.574 (d, 2H, J=4.8Hz,

H-3 ',5') ; 7.360 (d,2H, J=4.8Hz, H-2',6') ; 6.685 (d, 2H, J=2.1Hz, H-2,6); 6.450 (t, 1H, J=2.1Hz, H-4); 7.229,6.982(d, each 1H, J=16.5Hz, H-α , β) ; 3.835 (s,6H, OCH_3-3,5)
For compound **19**, mp 63-65℃; ^{1}H-NMR (300MHz, $CDCl_3$) δ ppm:8.711(d, 1H, J=1.8Hz, H-2') ; 8.491 (dd,1H,J=4.8,1.8Hz, H-6'); 7.832 (dt,1H, J=7.5,1.8Hz, H-4'); 7.292(dd,1H,J=7.5, 4.8Hz, H-5'); 6.680(d,2H,J=2.4Hz,H-2,6); 6.431(t,1H,J=2.4Hz,H-4) 7.107,7.034(d, each 1H, J=16.2Hz, H-α , β); 3.840(s,6H, OCH_3-3,5)
For compound **20** mp >300℃; ^{1}H-NMR (300MHz, DMSO-d_6) δ ppm: 8.760 (d, 2H, J=6.3Hz, H-3',5') ; 8.110(d,2H,J=6.3Hz, H-2',6'); 6.568(d,2H,J=2.1Hz, H-2,6); 6.301(t,1H,J=2.1Hz, H-4) ; 7.738,7.278(d, each 1H, J=16.5Hz, H-α , β) ; 9.433(s,D_2O exchangeable, OH-3,5)
For compound **21**, mp >300℃; ^{1}H-NMR (500MHz, DMSO-d_6) δ ppm: 9.104(br,1H, H-2'); 8.671(br,1H, H-6'); 8.611(br,1H, H-4'); 7.876(br,1H, H-5'); 6.578 (d,2H,J=2.4Hz, H-2,6); 6.315 (t,1H,J-2.4Hz, H-4); 7.405,7.176 (d, each 1H, J=16.5Hz, H-α , β) ; 9.359 (s, D_2O exchangeable, OH-3,5)

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