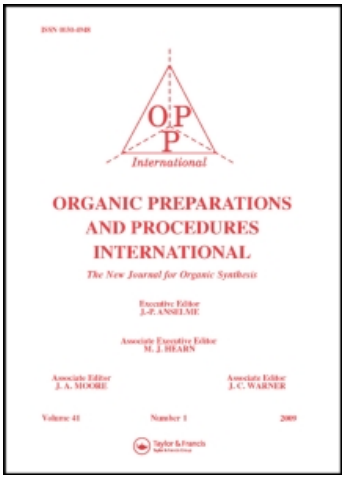

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A DIELS-ALDER SYNTHESIS OF PYRIDINES

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A DIELS-ALDER SYNTHESIS OF PYRIDINES

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(07/30/03)

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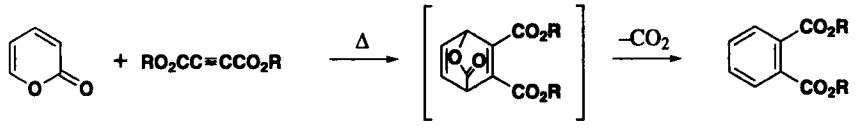
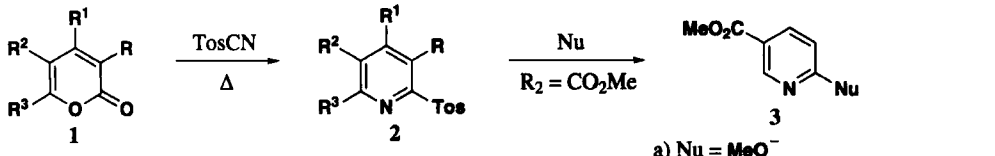
Benzene rings may be obtained by the reaction of α-pyrones with acetylenic dienophiles followed by aromatization with pericyclic loss of carbon dioxide (*Eq. 1*).[1] The aromatization step is commonly too rapid to allow isolation of the bicyclic intermediate. We surmised



(1)

that a similar reaction, using a nitrile as the dienophile bearing an electron-withdrawing group (as in toluenesulfonyl cyanide), could achieve a parallel synthesis of substituted pyridines (*Eq. 2*).[2,3]



1 2 3

a) R, R¹, R³ = H, R² = CO_2Me
b) R = H, R¹, R³ = Me, R² = CO_2Me
c) R = Br, R¹, R³ = H, R² = CO_2Me
d) R, R² = H, R¹ = OH, R³ = Me
e) R, R² = H, R¹ = OMe, R³ = Me
f) R, R² = H, R¹, R³ = Me

a) Nu = MeO^-
b) Nu =
c) Nu =

(2)

In the event, when tosyl cyanide was heated neat with methyl coumalate (**1a**) at 165°C and the reaction product chromatographed, the tosyl nicotinate (**2a**) was formed in 54% yield.[5] Several other available pyrones were also subjected to these conditions at temperatures of 125-180°C with mixed results as summarized in *Table 1*[5]. Trials with more stable[6] activated nitrile dienophiles such as cyanoformates afforded no cycloaddition products even at 210°C (*Eq. 2*).

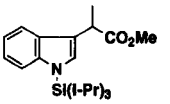
Table 1. Reaction of α-Pyrones with Tosyl Cyanide

Product	Yield (%)	mp (°C)	Time (hrs)	Temp (°C)	Catalysis
2a	54	189-190	2	165	none
2a	82	189-190	1	65	$TiCl_4$
2b	0	----	2	180	none
2c	0	----	2	180	none
2d	49	167-168	2	125	none
2e	60	155-156	2	165	none
2f	0	-----	2	120	none

Catalysis of the reaction with several Lewis acids was more successful. With methyl coumalate (**2a**, *Table 1*), the best results were obtained with $TiCl_4$ in dichloroethane, which afforded an 82% yield in one hour at 65°C. Other Lewis acids tried on **2a** ($AlCl_3$, BF_3, $ZnCl_2$) gave lower yields and required longer times. However, attempts with $TiCl_4$ on the unsuccessful direct reactions (**2b,c,f**) still delivered no pyridine products.[5]

The tosyl group on the α-position of the pyridines obtained serves as a good leaving group which is easily displaced by nucleophiles such as methoxide, amines or enolates,[5] as shown in *Table 2*. This substantially expands the scope of this synthesis for the acquisition of variously substituted pyridines such as compound **3c** for example.

Table 2. Reactions of 2-Tosylpyridines (2) with Nucleophiles

Cmpd	Nu	Yield (%)	mp (°C)	Time (hrs)	Temp (°C)
3a	NaOMe	98	oil	0.5	25
3b	$(CH_2)_4NH$	85	122.6-123.6	4	25
3c		76	oil	0.5	-78

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 400 MHz instrument at ambient temperature using TMS as internal standard and $CDCl_3$ as solvent. Mass spectrometry was recorded on the Micromass QUATTRO II instrument. The solvents and reagents were purified by the following methods: diethyl ether, glyme and THF were distilled from sodium with benzophenone as an indicator. DMF, CH_2Cl_2 and xylene were distilled from calcium hydride. Benzene and toluene were distilled from P_4O_{10}. Methanol and ethanol were dried over magnesium.

6-Toluenesulfonylnicotinic Acid Methyl Ester (2a). Typical Procedure.- Methyl coumalate (0.77 g, 5.0 mmol) and tosyl cyanide (1.09 g, 6.0 mmol) were placed in a 50 mL flask equipped with a condenser. The mixture was heated at 165°C in an oil bath with vigorous stirring under N_2 for two hours. The mixture was partitioned between CH_2Cl_2 (30 mL) and aq. $NaHCO_3$ (sat. 20 mL). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude material was purified by chromatography on silica gel using hexane:ethyl acetate (3:1) to give a white crystalline product (0.786 g, 54%), mp. 189.1-190.2°C. ^1H NMR ($CDCl_3$): δ 9.10 (s, 1H), 8.48 (d, 1H, J = 8.0Hz), 8.22 (d, 2H, J = 8.0Hz), 7.92 (d, 1H, J = 8.0Hz), 7.34 (d, 2H, J = 8.0Hz), 3.94 (s, 3H), 2.40 (s, 3H) ^{13}C NMR (pyridine-d_5): d 164.2, 162.1, 151.4, 145.3, 139.4, 135.1, 129.9, 129.2, 128.4, 121.5, 52.9, 21.7.

Mass spectrum (ES^+): Expected for $C_{14}H_{13}NO_4S$: 291.06. Found: 292.06

Anal. Calcd. for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81. Found: C, 57.59; H, 4.43; N, 4.73

The same method was used to prepare the following two compounds:

2-Methyl-6-(toluenesulfonyl)pyridin-4-ol (2d), white solid (49%), mp. 167-168°C.
^{1}H NMR ($CDCl_3$): δ 7.84 (d, 2H, J = 8.0Hz), 7.36 (s, 1H), 7.26 (d, 2H, J = 8.0Hz), 6.76 (s, 1H), 5.2 (bs, 1H), 2.54 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (pyridine-d_5): δ 164.7, 160.8, 160.4, 143.9, 135.1, 129.8, 129.2, 114.3, 104.6, 22.9, 21.5.
Mass spectrum (ES^+): Expected for $C_{13}H_{13}NO_3S$: 263.06. Found: 264.06
Anal. Calcd. for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.17; H, 4.99; N, 5.20
4-Methoxy-2-methyl-6-(toluenesulfonyl)pyridine (2e). white solid (60%), mp 155-156°C
^{1}H NMR ($CDCl_3$): δ 7.88 (d, 2H, J = 8.0Hz), 7.56 (s, 1H), 7.29 (d, 2H, J = 8.0Hz), 6.98 (s, 1H), 5.2 (bs, 1H), 3.70 (s, 3H), 2.59 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (pyridine-d_5): δ 165.1, 161.3, 160.4, 144.2, 135.9, 131.8, 129.0, 113.2, 105.7, 55.6, 22.6, 21.3.
Mass spectrum (ES^+): Expected for $C_{14}H_{15}NO_3S$: 277.08. Found: 278.08
Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.76; H, 5.33; N, 5.15
6-Methoxynicotinic Acid Methyl Ester (3a).- To a solution of 6-(toluenesulfonyl)-nicotinic acid methyl ester (146 mg, 0.5 mmol) in methanol (5 mL) was added a NaOMe/MeOH solution (0.5 M, 2.0 mL, 1.0 mmol) at r.t. The mixture was stirred at r.t. under N_2. After the reaction was complete (30 min as indicated by TLC), the solvent was removed *in vacuo* and the crude product was partitioned between CH_2Cl_2 (10 mL) and H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (10 mL x 2). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was passed through a short plug of silica gel and a colorless oil was obtained (78.5 mg, 97.5%). ^{1}H NMR ($CDCl_3$): δ 8.90 (d, 1H, J = 2.0Hz), 8.15 (dd, 1H, J = 8.0, 2.0Hz), 6.77 (d, 1H, J = 8.0Hz), 4.00 (s, 3H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.2, 150.2, 139.7, 125.9, 119.8, 110.9, 54.2.
Mass Spectrum (ES^+): Expected for $C_8H_9NO_3$: 167.06. Found: 168.06
Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.65; H, 5.30; N, 8.50
6-(N-Pyrrolidinyl)nicotinic Acid Methyl Ester (3b).- To a solution of 6-tolue-nesulfonylnicotinic acid methyl ester (146 mg, 0.5 mmol) in CH_3CN/DMF (5 mL, v/v 1:1) was added pyrrolidine (106.7 mg, 125 µl, 1.5 mmol) *via* a syringe and a spatulaful of K_2CO_3. The mixture was stirred at r.t for 4 hours. Water (10 mL) was then added and the mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by chromatography on silica gel using CH_2Cl_2-MeOH (98:2) to afford 87.7 mg (85%) of a white solid mp.122.6-123.6°C.
^{1}H NMR ($CDCl_3$): δ 9.11 (d, 1H, J = 2.0Hz), 7.82 (dd, 1H, J = 8.0, 2.0Hz), 6.82 (d, 1H, J = 8.0Hz), 3.91 (s, 3H), 2.82 (t, 4H, J = 7.2Hz), 1.62 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 165.3, 148.5, 138.2, 124.6, 117.5, 106.8, 53.5, 52.1, 22.5.
Mass spectrum (ES^+): Expected for $C_{11}H_{14}N_2O_2$: 206.11. Found: 207.11
Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.17; H, 6.99; N, 13.43
C-Substituted Nicotinic Acid Methyl Ester 3c.- To a solution of 6-toluenesulfonyl-nicotinic acid methyl ester (146 mg, 0.5 mmol) in anhydrous THF was added N-*tris*(isopropylsilyl)-3-

indoleacetic acid methyl ester (207 mg, 0.6 mmol), itself prepared from indoleacetic acid ester and *tris*(isopropyl)silyl chloride and base. The mixture was cooled in an acetone-Dry Ice bath (-78°C). To this mixture was cannulated a solution of LDA (1.5 M, 0.5 mL, 0.75 mmol) in THF (5 mL) at -78°C. The mixture was stirred at -78°C for 30min, removed from the acetone-dry ice bath and allowed to warm to r.t. with stirring at r.t. for an additional 1 hour. The reaction mixture was concentrated and the crude product was partitioned between CH_2Cl_2 (20 mL) and aq. NH_4Cl (sat. 15 mL). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (15 mL x 2). The combined organic layers were dried over Na_2SO_4 and the product was purified by chroma-tography on silica gel using hexane-ethyl acetate (3:1) to give 182 mg (76%) of a colorless oil. ^1H NMR ($CDCl_3$): δ 9.18 (d, 1H, J = 1.6Hz), 8.16 (dd, 1H, J = 8.4, 1.6Hz), 7.50 (d, 1H, J = 8.4Hz), 7.44 (d, 1H, J = 8.0Hz), 7.39 (s, 1H), 7.30 (d, 1H, J = 8.0Hz), 7.16 (t, 1H, J = 8.0Hz), 7.06 (t, 1H, J = 8.0Hz), 5.55 (s, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 1.71 (m, 3H), 1.10 (s, 18H).

Mass spectrum (ES^+): Expected for $C_{27}H_{36}N_2O_4Si$: 480.24. Found: 481.24

Anal. Calcd. for $C_{27}H_{36}N_2O_4Si$: C, 67.47; H, 7.55; N, 5.83. Found: C, 67.51; H, 7.67; N, 5.97

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2. An earlier report in Polish [T. Jaworski and S. Kwiatkowski, *Rocz. Chem.*, **44**, 555 (1970); *Chem Abst.*, **73**, 130845 (1970)] claimed this reaction with an unactivated nitrile (benzonitrile) and isodehydracetate (**1b**) for 250 hours at 215°C in 20% yield. However, no examples of this reaction with activated nitriles, nor any later citations of this work could be found.[3] Much has been done instead with activated *N*-tosylaldimines and dienes to afford pyridine derivatives at lower oxidation states.[4]

3. We later discovered an analogous synthesis of isoquinolines *via* tosyl cyanide on an unstable fused α-pyrone intermediate [P. van Broek, P. van Doren, and G. Hoornaert, *Synthesis*, 473 (**1992**)].

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6. Tosyl cyanide decomposes extensively above 160°C.

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