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THE PREPARATION OF 2-(3-PYRIDYL)MALEIMIDE

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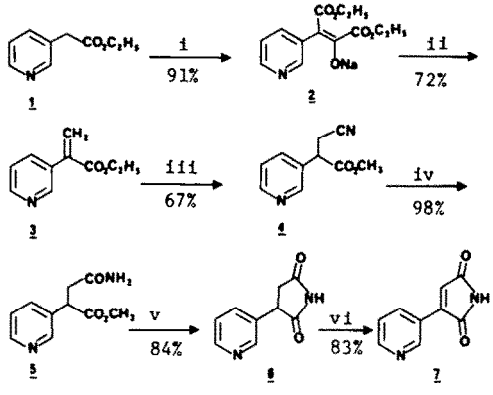
Abstract - The novel compound, 2-(3-pyridyl)maleimide, 7 was prepared by an efficient sequence involving the synthesis of ethyl 2-(3-pyridyl)-acrylate, 3, from ethyl 2-(3-pyridyl)acetate, 1, followed by Michael-addition of HCN (via acetone cyanohydrin-MeOH) to give cyanoester 4. Alternatively, 4 was prepared from the methyl ester 8 by alkylation with iodoacetonitrile. Acid hydrolysis gave amide-ester 5 which was then cyclized with NaOEt to 2-(3-pyridyl)succimide, 6. Oxidation of 6 to maleimide 7 was achieved with N-chlorosuccinimide in pyridine, to give an overall yield of 58%.

eports[1-3] from these laboratories have emonstrated the use of 2-arylmaleimides as eful synthons for various pericyclic eactions. In order to further extend our nthetic studies, we desired 2-(3-pyridyl)-leimide (7), a compound not previously scribed in the literature. We now wish to port an expeditious synthesis of 7 by a quence which might be applicable to other stems that are not amenable to the erwein reaction.[1,4]

Before embarking on a novel route to leimide 7, we attempted[5] the preparation its N-methyl derivative via the conven-onal Meerwein reaction involving the pper (II) catalyzed coupling of 3-pyridyl azonium cation with N-methylmaleimide, ich instead resulted in the formation of tractable tars. However, we were able to velop an efficient sequence (Scheme I) for e preparation of 7 starting from either hyl or methyl (3-pyridyl)acetate 1 and 8 spectively.

Condensation of 1 with diethyloxalate in luene and sodium ethoxide[6] gave the inter-diate diethyl 2-oxo-3-pyridylsuccinate (2) ich on subsequent reaction with 37% aqueous

Scheme I

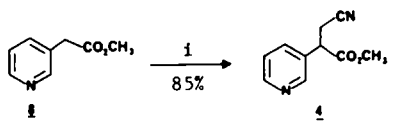


Reagents: (i) NaH/EtOH-$PhCH_3$/$(CO_2Et)_2$.
(ii) HCHO (37%)/K_2CO_3.
(iii) $Me_2CCN(OH)$/THF-MeOH/10% aq. Na_2CO_3(cat.), reflux.
(iv) Conc. H_2SO_4. (v) NaOEt/EtOH.
(vi) NCS/C_5H_5N.

formalin and potassium carbonate furnished ethyl-2-(3-pyridyl)-acrylate 3 in 83% yield. Compound 3 underwent a smooth HCN Michael-addition on refluxing with acetone cyanohydrin[7] in a THF-MeOH solvent mixture containing a catalytic amount of 10% aqueous sodium carbonate; transesterification of the starting ethyl ester

to methyl ester was observed in the product. Alternatively, a more direct route to 4 was the alkylation of 8 with iodoacetonitrile (Scheme II). This was realized in 85% yield

Scheme II.



8 4

Reagent: (i) LDA/ICH_2CN/THF, -78°C

by reacting 8 with LDA/THF/-78° C, followed by addition of iodoacetonitrile and warming the mixture to room temperature.

In order to complete the synthesis of 7 at this stage, cyclization of 4 to succinimide 6 was required, followed by oxidation of 6 to maleimide 7. This transformation was accomplished in two steps. Hydration of the cyano group of 4 with conc. H_2SO_4[8] at room temperature gave amide 5 (98% yield) which on further cyclization with sodium ethoxide in ethanol at room temperature furnished the desired 2-pyridylsuccinimide 6. It is worth mentioning here that the one-step conversion of 4 to 6 was also tried by heating 4, at room temperature, with a 1:1:10 mixture of 2M Na_2CO_3, 30% H_2O_2 and acetone[9] which led to the formation of a complex mixture containing only a small amount of succinimide 6. Oxidation of 6 to 2-(3-pyridyl)maleimide 7 was achieved in 83% yield by stirring 6 with N-chlorosuccinimide[10] in dry pyridine at room temperature. The overall yield from 1 to 7 was 58%.

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Mel-Temp® apparatus and are uncorrected. IR samples were measured on a Perkin-Elmer 1310 spectrometer. FT-IR were measured on a Nicolet-7199 (50 scans). ^1H and ^{13}C-NMR spectra were recorded either on a Varian EM-360 spectrometer or on a Varian FT-80 using Me_4Si as the internal standard. Mass spectra were obtained on a Varian CH-7 spectrometer operating at 70 eV. UV spectra were run on a Varian Cary 219 spectrophotometer. All solvents were dried before use.

Ethyl α-methylene-3-pyridinylacetate (3). NaH (26.98 g, 0.51 mol) 50% dispersion in oil was added in 300 mL of dry toluene taken in a three necked round bottomed flask, equipped with a condenser, a dropping funnel and a mechanical stirrer. To this stirring mixture was slowly added 35 mL of absolute EtOH. The temperature of the resulting mixture was maintained below 30°C and to this gel-like mixture was added diethyloxalate (73.07 g, 0.5 mol) during 10 min. When hydrogen evolution had slowed, ethyl 3-pyridylacetate (82.59 g, 0.5 mol) was added during 1/2 h. The reaction mixture was further stirred at RT for 20 h under N_2 and then was filtered. The solid diethyl 2-oxo-3-pyridylsuccinate sodium salt, 2, 136.6g (95% yield) was suspended in 250 mL H_2O and to this stirring mixture was added 86 mL of 37% formalin, dropwise. The temperature was maintained below 25°C during the addition, and the mixture was stirred for an additional 1h. This was followed by the addition of anhydrous K_2CO_3 (65.5 g, 0.48 mol) in small portions. After stirring the resultant mixture vigorously for 1.5 h, it was diluted with 650 mL of water and the aq. solution was extracted with Et_2O (300 mL x 3), and the Et_2O extract was washed with water, brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated to give 72.45 g of the product which contained 3 and 1 in the ratio of 6:5. Yield based on ^1H NMR was 53% (72% based on recovered starting material). Compound 3 was easily separated from 1 in pure form by a Waters 500 A prep. LC system, using 1:1 EtOAc and hexane: bp (≃ 100°/0.2 mm, Kugelrohr); ^1H NMR (90MHz, $CDCl_3$) δ8.53 (d, J=1.5Hz, 1H, H-2 pyridyl), 8.4 (dd, J=5, 1.5Hz, 1H, H-6 pyridyl), 7.67 (dt, J=8, 1.5Hz, 1H, H-5 pyridyl), 7.17 (dd, J=8, 4.5Hz, 1H, H-4 pyridyl), 6.36 (s, 1H, vinyl H), 5.7 (s, 1H, vinyl H), 4.27 (q, J=6Hz, 2H,-CH_2-CH_3), 1.33 (t, J=7Hz, 3H,-CH_2-CH_3); IR (neat) 3420 (m), 1717 (s, ester), 1616(m), 1586 (m), 1566(m), 1206 (s) cm^{-1}; mass spectrum, m/z (rel intensity) 177(45,M+), 149(18), 133 (29), 104(100), 78(28), 77(30); UV max (MeOH) 230nM(ε5848), 262(ε3367). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 66.76; H, 6.64; N, 7.65.

Methyl α-(cyanomethyl)-3-pyridinylacetate (4). Sodium carbonate (10% aq. solution), 12 mL) was added to a stirring mixture of 2-pyridylacrylate 3 (10 g, 0.056 mol) in a methanol-tetrahydrofuran (400:40 mL) mixture, and this was refluxed for 3½ h under N_2. After evaporation of the solvent in vacuo, the concentrate was diluted with 25 mL of water and the aqueous solution was extracted with CH_2Cl_2 (50 mL x 4), washed with brine and dried over anhyd. Na_2SO_4. Removal of the solvent furnished 7.2 g (67%) of 4 as a light-yellow, viscous liquid. This crude product was used without distillation for the next step. A small portion of the product was distilled for analytical data: bp (≃ 150°C/0.2 mm, Kugelrohr); ^1H NMR (90 MHz, $CDCl_3$)δ8.43 (d, J=1.5Hz, 1H, H-2 pyridyl), 8.43 (dd, J=6, 1.5Hz, 1H, H-6 pyridyl), 7.52 (dt, J=7, 1.5Hz, 1H, H-5 pyridyl), 7.18 (m, 1H, H-4 pyridyl), 3.94 (t, J=7Hz, 1H,-CH-CH_2-CN), 3.73 (s, 3H,-$COOCH_3$), 2.93 [heptet(7-lines), AB of ABX], 2H, -CH-CH_2-CN); IR (neat) 3360 (w, broad), 2240 (w, C≡N), 1740 (s, $COOCH_3$), 1540 (w, pyridyl H) cm^{-1}; mass spectrum, m/z (rel intensity) 190 (60, M+), 151 (24), 145 (25), 131 (67), 105 (100), 104 (43), 92 (40), 78 (38), 59 (44); ^{13}C NMR ($CDCl_3$) δ 170.8, 150, 149.3, 135, 131.6, 124, 117.1, 53.1, 45.1, 21.4. Anal. Calcd for $C_{10}H_{10}N_2O_2$:C, 63.15; H, 5.30; N, 14.73. Found: C, 62.57; H, 5.30; N, 14.46.

Methyl α-(cyanomethyl)-3-pyridinylacetate (4). Dry THF (5 mL) was cooled to -78° (acetone/dry-

:e bath) under an N_2 atmosphere. Diisopropyl- ıine (0.98 mL, 6.95 mmol) was added via ;ringe followed by a solution of n-butyl- ithium in hexane (7 mmol, 4.51 mL of 1.55 M ılution) which was injected over a period of min. After stirring for 0.5 h at -78°, ethylpyridylacetate 8 (1.0 g, 6.62 mmol) in mL of THF was added slowly. The solution ıs stirred for 0.5 h and iodoacetonitrile 1.17 g, 7 mmol) was added and again the ixture was stirred at - 78° C for 1 h. The y-ice bath was removed and the reaction ixture was stirred at room temperature for h. TLC of an aliquot showed no starting ıterial, and a spot which corresponded to the value of the authentic product. The eaction mixture was worked up by adding ıter (~ 20 mL), saturating it with salt, ex- :acting the aqueous solution with CH_2Cl_2 30 mL x 4), washing the extract with water, :ine, followed by drying over anhyd. Na_2SO_4. emoval of the solvent in vacuo gave 1.07 g the desired product (85% yield). This ıs identical with the previously characterized ımple of 4 (IR, ^1H NMR, TLC).

ethyl α-(2-amino-2-oxoethyl)-3-pyridinyl- :etate (5). To 801 mg (4.21 mmol) of β- anoester 3 was added 1 mL of conc. H_2SO_4 ıd the mixture was stirred under N_2 for 3 h, ıd then was diluted with 3 mL of water. The ueous solution was basified with concentra- ed NH_4OH solution. Excess MeOH was added this solution, and the precipitate which ormed was collected by filtration and washed ith 50 mL of 15% MeOH-$CHCl_3$ mixture. The lvent filtrate was removed under vacuum. To ıe concentrate was added 10 mL of MeOH. epetition of the above sequence gave 860 mg 8%) of 5 as a white solid which was ystallized from MeOH: mp 134.5-135.5° C. NMR (90MHz, DMSO-d_6) δ 8.46(d, J=1,5Hz, 1H, -2 pyridyl), 8.43 (ill-defined dd and partly ider 8.46 peak, 1H, H-6 pyridyl), 7.6(dt, J= 5, 1.5 Hz, 1H, H-5 pyridyl), 7.27 (dd, J=7, lz, 1H, H-4 pyridyl), 4.1 (t, J=6Hz, 1H, H-CH_2-$CONH_2$), 3.62 (s, 3H, -$COOCH_3$), 2.73 , AB^2 of ABX, 2H, -CH-CH_2-$CONH_2$); IR (Nujol) 80, 3090 (m, $CONH_2$), 1727 (s, $COOCH_3$), 67 (s, $CONH_2$), 1587 (m), 1575 (w), 1216 (s), 15 (s) cm^{-1}; mass spectrum, m/z (rel tensity) 208 (30,M+), 191 (43), 176 (88), 4 (48), 132 (52), 106 (94), 104 (94), 78 3); ^{13}C NMR (DMSO-d_6) δ 172.8, 171.4, 149.1, 8.4, 135.2, 134.1, 123.7, 52.0, 44.2, 37.9. al. calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 81; N, 13.45. Found: C, 57.54; H, 5.78; 13.23.

(3-Pyridinyl)-2,5-pyrrolidinedione (6). To a irring solution of NaOEt [prepared from Na 0 mg, 1.73 mmol) in 30 mL of EtOH], a solu- on of pyridyl amide 6 (208 mg, 1 mmol, ssolved in 3 mL of dry EtOH) was slowly ded. The reaction mixture was stirred at om temperature for 1.5 h. Excess NaOEt was stroyed by a few drops of water, followed by lvent removal under vacuum to give the crude oduct (white solid) which was filtered ough a small column of SiO_2-gel (6 g), using MeOH in $CHCl_3$ as the eluent. This furnished mg (83%) of 6 as a colorless solid which crystallized from MeOH:mp 178-179°C; ^1H NMR MHz, DMSO-d_6) δ 11.05 (s broad, 1H, OC-NH- , 8.4 (s broad, 2H, H-2 and H-6 pyridyl), 3 (dt, J=6, 1.5 Hz, 1H, H-5 pyridyl), 7.26 , J=8, 4Hz, 1H, H-4 pyridyl), 4.21 (dd, , 6Hz, 1H, -CH-CH_2-CO), 3 (o, AB of ABX, 2H, -CH-CH_2-CO); IR (Nujol) 3222 (s, $CONH_2$), 3082 (w, $CONH_2$), 1775, 1714 (s, succinimide, CO), 1591 (w), 1578 (m), 1196 (s), 1181 (s) cm^{-1}; mass spectrum m/z (rel intensity), 176 (25, M+), 133 (10), 105 (100), 104 (37), 78 (20),52 (19), 51 (20); ^{13}C NMR (DMSO-d_6) δ 179, 177.4, 149.4, 148.4, 135.3, 134.0 (b), 124.0 (b), 44.5, 37.2. Anal. calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.20; H, 4.43; N, 15.99.

3-(3-Pyridinyl)-1H-pyrrole-2,5-dione (7). To a stirring solution of pyridyl succimide 6 (200 mg, 1.36 mmol) in 1.5 mL of dry pyridine was added a solution of N-chlorosuccinimide (167 mg, 1.25 mmole in 1.5 mL of dry pyridine) and this was stirred at RT for 24 h under N_2. The solid which formed was filtered and washed with 2 mL of pyridine to give 45.4 mg of the product. Since the filtrate still contained the desired product (TLC:5% MeOH-$CHCl_3$), it was concentrated in vacuo and subjected to flash chromatography[11] on SiO_2-gel (25 g), eluant:5% MeOH in $CHCl_3$, to give 125 mg of the product 7 (combined yield: 83%), and this was crystallized from a MeOH-CH_2Cl_2 mixture: mp 203-205°C; ^1H NMR (80 MHz, DMSO-d_6) δ 11.5 (s broad, 1H, OC-NH-CO), 9.32 (d, J=2Hz, 1H, C-2 pyridyl), 8.85 (dd, J=5, 2Hz, 1H, H-6 pyridyl), 8.52 (dt, J=8, 2Hz, 1H, H-5 pyridyl), 7.69 (dd, J=8, 4 Hz, 1H, H-4 pyridyl), 7.5 (s, 1H, = CH); IR (Nujol) 3096 (m, imide NH), 1755 (m), 1721 (s, imide CO), 1608 (w), 1588 (m), 1559 (w), 1142 (m) cm^{-1}; mass spectrum, m/z (rel intensity) 174 (51, M+), 131 (10), 103 (100), 76 (30), UVmax (MeOH) 218 nM (ε 5568), 228 (5916), 244 (5394), 310 (1740); ^{13}C NMR (DMSO-d_6) δ 171.7, 171.3, 150.9, 148.9, 140.7, 135.7, 127.2, 125.0, 123.6. Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 16.08. Found: C, 61.59; H, 3.47; N, 15.78.

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