SYNTHESIS OF SUBSTITUTED 3-PYRIDINECARBOXALDEHYDES

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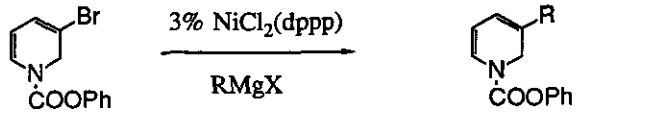
Abstract - Treatment of 3-substituted 1-(phenoxycarbonyl)-1,2-dihydropyridines with Vilsmeier reagent ($POCl_3$/DMF) gave 3-substituted 5-formyl-1-(phenoxycarbonyl)-1,2-dihydropyridines, which were aromatized with hot sulfur to provide 5-substituted 3-pyridinecarboxaldehydes. The formylation of 4-substituted 1-(phenoxycarbonyl)-1,4-dihydropyridines and subsequent aromatization gave 4-substituted 3-pyridinecarboxaldehydes.

Electrophilic substitution on the ring carbons of pyridine is difficult.[1] The Friedel-Crafts acylation and Vilsmeier formylation, which are important methods for the preparation of aryl ketones and aldehydes, fail in the pyridine series, making many 3-pyridyl ketones and 3-pyridinecarboxaldehydes difficult to prepare. Recently in our laboratories we have been developing syntheses of substituted pyridines via 1-acyldihydropyridine intermediates.[2,3] The β-position of a 1-acyldihydropyridine is electron rich and susceptible to electrophilic attack. We have reported the Friedel-Crafts acylation of several 1-acyldihydropyridines. The intermediate β-acylated 1-acyldihydropyridines could be aromatized with hot sulfur to provide substituted 3-acylpyridines.[3b] This synthetic sequence is tantamount to the regiospecific β-acylation of the pyridine ring system.

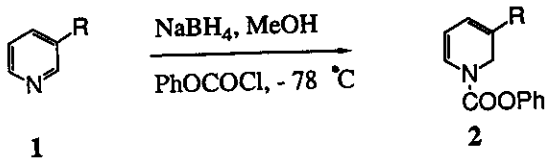
Shono[4] has described one example of a β-formylation of a 1-acyl-1,4-dihydropyridine, and we[5] recently reported the β-formylation of 1-(phenoxycarbonyl)-1,2-dihydropyridine via the Vilsmeier-Haack reaction. The regiospecific β-formylation of 1-acyldihydropyridines has considerable potential for the synthesis of substituted 3-pyridinecarboxaldehydes. We report here the preparation of several 5- and 4-substituted 3-pyridinecarboxaldehydes from 1-acyldihydropyridine intermediates.

Several 3-substituted pyridines were transformed into the 3-substituted 1-(phenoxycarbonyl)-1,2-dihydropyridines using Fowler's method (pyridine, phenyl chloroformate, $NaBH_4$, MeOH).[6] The hydride addition occurs regiospecifically[7] at the 2-position of the in situ formed 1-acylpyridinium salt to give the desired 1,2-dihydropyridines in moderate yields as shown in Table I.

Two additional 1,2-dihydropyridines, 3-phenyl-1-(phenoxycarbonyl)-1,2-dihydropyridine (2e) and 3-cyclohexyl-1-(phenoxycarbonyl)-1,2-dihydropyridine (2f), were prepared from 3-bromo-1-(phenoxycarbonyl)-1,2-dihydropyridine (2b) by utilizing a cross-coupling reaction.[8] Phenylmagnesium chloride was added to a solution of 2b in benzene containing a catalytic amount of bis(1,3-diphenylphosphino)propanenickel(II) chloride to provide dihydropyridine 2e in 67% yield. The analogous reaction using cyclohexylmagnesium chloride gave dihydropyridine 2f in 54% yield.



2e R = Ph
2f R = C_6H_{11}



1 2

Table I. Synthesis of 3-Substituted 1-(Phenoxycarbonyl)-1,2-dihydropyridines 2

Compound[a]	R	Yield, %[b]	mp, °C
2a	Br	35	92-94
2b	Cl	56	54-56
2c	OMe	50	c
2d	Me	49	35-36

[a]Reactions were performed following Fowler's procedure on a 20-mmol scale using 1.3 equiv of $NaBH_4$ and 1.0 equiv of PhOCOCl in methanol at -78°C. [b]Yields are for isolated, pure material obtained from preparative layer chromatography or recrystallization. [c]Dihydropyridine 2d was isolated as an unstable oil that was used immediately in the next step.

Formylation of 3-Substituted 1-Acyl-1,2-dihydropyridines. Shono's[4] method for the formylation of enecarbamates was followed with some variation in equivalents of reagents and temperature. Monoformylation occurred to give the 3-substituted 5-formyl-1,2-dihydropyridines 3 in good yields as shown in Table II.

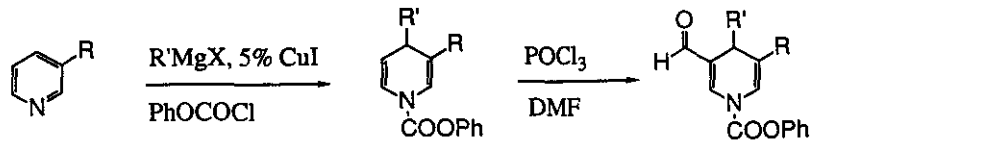
2 3

Table II. Synthesis of 3-Substituted 5-Formyl-1-(phenoxycarbonyl)-1,2-dihydropyridines 3 from 3-Substituted 1-(Phenoxycarbonyl)-1,2-dihydropyridines 2.

Dihydropyridine	R	Formylation Conditons[a]	Yield (%)[b] of 3	mp[c], °C
2a	Br	2.2 equiv. $POCl_3$/DMF; RT 20 h	57	118-120
2b	Cl	1.5 equiv. $POCl_3$/DMF; refluxed 40 min	64	113-114
2c	MeO	2.2 equiv. $POCl_3$/DMF; RT 24 h	59	107-109
2d	Me	1.1 equiv. $POCl_3$/DMF; refluxed 40 min	71	d
2e	Ph	2.2 equiv. $POCl_3$/DMF; RT 4.5 h	73	115-117
2f	C_6H_{11}	2.2 equiv. $POCl_3$/DMF; RT 18 h	65	113.5-115

[a]All reactions were run in methylene chloride and then hydrolyzed with excess KOAc in water. [b]Yields were obtained from radial preparative layer chromatography (EtOAc-hexanes). [c]Unless indicated, the products were recrystallized from ethyl acetate/hexane. [d]This product was isolated as a clear oil.

Formylation of 4-Substituted 1-Acyl-1,4-dihydropyridines. The copper-catalyzed regioselective addition of Grignard reagents to 1-acylpyridinium salts is a convenient method for the synthesis of 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines.[2] We prepared dihydropyridines 4 using this procedure and formylated them using the Vilsmeier reaction to give the aldehydes 5 as shown in Table III.



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5a R' = Ph, R = H
5b R' = Me, R = H
5c R' = Me, R = OMe

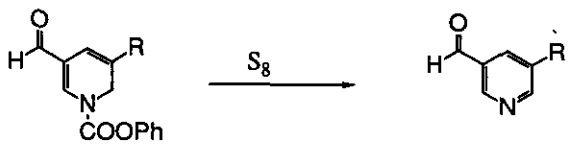
Table III. Synthesis of 4-Substituted 3-Formyl-1-(phenoxycarbonyl)-1,4-dihydropyridine[5] 5 from 4.

Dihydropyridine	R'	R	Formylation Conditions	Yield %[b] of 5	mp, °C
4a	Ph	H	2.2 equiv. $POCl_3$/DMF; RT 36 h	43	158-159.5
4b	CH_3	H	2.2 equiv. $POCl_3$/DMF; RT 20 h	60.5	c
4c	CH_3	CH_3O	2.2 equiv. $POCl_3$/DMF; RT 48 h	71	c

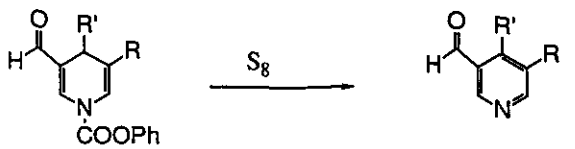
[a]All reactions were run in methylene chloride and then hydrolyzed with excess KOAc in water. Reactions were checked by TLC to determine when the reaction was complete. [b]Yields were obtained from Kugelrohr distillation. [c]Product was isolated as a light yellow oil.

Synthesis of Substituted 3-Pyridinecarboxaldehydes from 3 and 5. The 3-formyl-1,2-dihydropyridines 3 and 3-formyl-1,4-dihydropyridines 5 were aromatized using sulfur in refluxing decahydronaphthalene or naphthalene to provide the desired substituted 3-pyridinecarboxaldehydes as shown in Table IV.

This three-step synthesis is convenient and allows for the preparation of many substituted 3-pyridinecarboxaldehydes that would be difficult to prepare by other methods.



3 6



5 7

Table IV. Synthesis of Substituted 3-Pyridinecarboxaldehydes 6 and 7 from Dihydropyridines 3 and 5.

Dihydropyridine	Equiv of S_8	Solvent	Time of Reflux	Pyridine	Yield %	mp, °C
3a	1.0	naphthalene	2 hr	6a	54[a]	95-96
3b	1.0	naphthalene	2 hr	6b	55[a]	69-70(69-70)[9]
3c	1.2	decalin	6 hr	6c	69[a]	33-34
3d	1.0	naphthalene	2 hr	6d	71[a]	38-39 (37)[10]
3e	1.0	decalin	2 hr	6e	51[a]	c
3f	1.2	decalin	2 hr	6f	36[a]	c
5a	1.1	naphthalene	2.5 hr	7a	69[a]	c
5b	1.5	decalin	5.5 hr	7b	53[b]	c
5c	1.5	decalin	6 hr	7c	67[b]	70.5-71.5

[a]Yields obtained from radial preparative layer chromatography. [b]Yields obtained from Kugelrohr distillation. [c]Product was isolated as a clear oil.

EXPERIMENTAL

Reactions involving organometallic reagents were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. Cuprous iodide (CuI), ultrapure, was obtained from Alfa Products. Other solvents and reagents from commercial sources were generally used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H nmr spectra were recorded on a Varian EM-360 or JEOL FX-90-Q spectrometer. Ir spectra were recorded on a Perkin-Elmer 710B spectrophotometer. Radial preparative layer chromatography was carried out by using a Chromatotron (Harrison Assoc., Palo Alto, CA). Combustion analyses were performed by M. H. W. Laboratories, Phoenix, AZ.

Preparation of 3-Phenyl-1-(phenoxycarbonyl)-1,2-dihydropyridine (2e). A stirred solution of 1.00 g (3.57 mmol) of 3-bromo-1-(phenoxycarbonyl)-1,2-dihydropyridine (2a) and 0.096 g (0.17 mmol) of bis(1,3-diphenylphosphino)propanenickel(II) chloride in 8 ml of dry benzene was cooled to 0°C. Phenylmagnesium chloride in THF (2.20 ml, 4.2 mmol) was added dropwise and the reaction was stirred for 2 h at RT. An aqueous solution (20 ml) of 20% NH_4Cl was added at 0°C and the mixture was warmed to RT. The aqueous layer was extracted with Et_2O (2 x 20 ml). The combined organic layer was washed with 20-ml portions of water and brine, and dried over $MgSO_4$. The solution was filtered and concentrated to yield 1.28 g of crude product. This material was purified by radial preparative layer chromatography (silica gel, hexanes-CH_2Cl_2, 50:50) to yield 0.652 g (67%) of 2e as a clear viscous oil: ^1H nmr ($CDCl_3$) δ 6.91-7.74 (m, 11 H), 6.50 (d, 1 H), 5.58 (t, 1 H) 4.95 (br d, 2 H); ir (neat) 3065, 1725, 1490, 1365, 1205, 1080 cm^{-1}.

3-Cyclohexyl-1-(phenoxycarbonyl)-1,2-dihydropyridine (2f). Dihydropyridine 2f was prepared from 2a and cyclohexylmagnesium chloride by using the procedure described above for the preparation of 2e. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc-hexanes, 20:80) to give 0.431 g (55%) of 2f as a clear oil: ^1H nmr (CCl_4) δ 6.95-7.65 (m, 5 H), 6.80 (d, 1 H), 5.63 (d, 1 H), 5.25 (t, 1 H), 4.41 (br d, 2 H), 0.85 - 2.30 (br m, 11 H); ir (neat) 2915, 1850, 1727, 1595, 1495, 1358, 1200, 1075, 750, 685 cm^{-1}.

4-Methyl-1-(phenoxycarbonyl)-1,4-dihydropyridine (4b). General Procedure for the Preparation of 1,4-Dihydropyridines 4. In a 300 ml three neck flask, a solution of cuprous iodide (0.28 g, 1.5 mmol) and methyl sulfide (8 ml) in 15 ml of THF was stirred at RT for 10 min. THF (140 ml) and 2.43 ml (30 mmol) of pyridine were added to the reaction and the solution was cooled to -23°C (dry ice/CCl_4). Phenyl chloroformate (3.86 ml, 30 mmol) was added slowly. A thick white ppt. formed upon addition, and the mixture was stirred for 10 min. Methylmagnesium chloride in THF (10.0 ml, 30 mmol) was added to the heterogeneous mixture, which turned homogeneous upon complete addition of the Grignard reagent. The reaction was stirred for 20 min at -23°C, then at RT for an additional 20 min, followed by addition of aqueous 20% NH_4Cl (70 ml). To this solution was added 150 ml of ether, and the organic layer was washed with 40-ml portions of 20% NH_4Cl/NH_4OH (50:50), water, 10% HCl, water and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to give 6.13 g (95%) of the crude product as a yellow oil. Kugelrohr distillation (bp 110-160°C/1.8 mm Hg) gave 5.87 g (91%) of 4b as a colorless oil: ^1H nmr ($CDCl_3$) δ 7.1-7.5 (m, 5 H), 6.85 (d, 2 H), 4.85-5.05 (m, 2 H), 3.0-3.1 (m, 1 H), 1.18 (d, 3 H), ^{13}C nmr ($CDCl_3$) 150.5, 129.4, 125.7, 121.8, 121.4, 113.0, 112.4, 27.5, 24.3; ir (neat) 2960, 1720, 1330, 1190, 730 cm^{-1}. A small sample of this material was purified for combustion analysis by radial preparative layer chromatography (silica gel, EtOAc-hexanes, 10:90). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.10; N, 6.51. Found: C, 72.33; H, 6.06; N, 6.27.

3-Formyl-4-methyl-1-(phenoxycarbonyl)-1,4-dihydropyridine (5b). General Procedure for the -Formylation of Dihydropyridines 2 and 4. Phosphorus oxychloride (5.40 ml, 57.9 mmol) was added slowly to a stirred solution of 8.9 ml (116 mmol) of DMF in 10 ml of CH_2Cl_2 at 0°C. The solution was stirred at RT for 25 min, then transferred via a double tipped needle into a solution of 5.67 g (26.3 mmol) of 1,4-dihydropyridine 4b in 35 ml of dry CH_2Cl_2 at 0°C. The ice bath was removed and stirring was continued at RT for 20 h, during which time the reaction turned bright yellow. After cooling to 0°C, an aqueous solution of KOAc (15 g) in H_2O (50 ml) was added slowly. The mixture was refluxed for 20 min, separated, and extracted with CH_2Cl_2 (50 ml). The organic phase was washed with 40-ml portions of water, saturated $NaHCO_3$, water and brine, and then dried over $MgSO_4$. The solution was filtered and concentrated to yield 6.4 g of the crude product. Kugelrohr distillation (bp 120-180°C/2 mm Hg); provided 3.86 g (60.5%) of aldehyde 5b as a light yellow viscous oil: ^1H nmr ($CDCl_3$) δ 9.42 (s, 1 H), 7.75 (s, 1 H), 7.15-7.50 (m, 5 H), 6.88 (d, 1 H), 5.08-5.30 (m, 1 H), 4.35-4.45 (m, 1 H), 1.22 (d, 3 H). ^{13}C nmr ($CDCl_3$) 190.6, 150.0, 140.4, 140.3, 129.5, 126.4, 121.0, 120.6, 115.5, 115.4, 25.7, 22.6; ir (neat) 1750, 1680, 1625, 1355, 1325, 1180 cm^{-1}. A small sample of this material was purified for combustion analysis by radial preparative layer chromatography (silica gel, EtOAc-hexanes, 10:90). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.11; H, 5.40; N, 5.76. Found C, 69.22; H, 5.23; N, 5.74.

5-Bromo-3-pyridinecarboxaldehyde (6a). General Procedure for the Aromatization of Dihydropyridines 3 and 5. In a 50 ml round bottom flask was placed 0.271 g (0.88 mmol) of dihydropyridine 3a, *0.029 g (0.90 mmol) of sublimed sulfur* and 6 g of naphthalene. The reaction mixture was refluxed for 2 h under a N_2 atmosphere using an air condenser, during which time the solution turned black. The reaction mixture was cooled to RT, dissolved in 30 ml of Et_2O, and extracted with 10% HCl (3 x 20 ml). The combined acid extracts were washed with 20 ml of Et_2O and cooled to 0°C. Methylene chloride (30 ml) was added and the mixture was made basic with 25% NaOH, and extracted with CH_2Cl_2 (2 x 20 ml). The combined organic phase was washed with brine, dried (K_2CO_3), filtered, and concentrated *to give 0.132 g of a brown*

oil. This material was purified by radial preparative layer chromatography (silica gel, EtOAc-hexanes, 30:70) to give 0.089 g (54%) of 6a as a white solid: ^{1}H nmr ($CDCl_3$) 10.25 (s, 1 H), 8.99-9.21 (m, 2 H), 8.46 (s, 1 H); ir (KBr) 3050, 1680, 1575, 1390, 1220, 1015 cm^{-1}. This compound was prepared for elemental analysis by recrystallization from hexanes: mp 95-96°C. The white crystals were then sublimed (1.2 mm Hg) using a cold finger apparatus: mp 95-96°C. Anal. Calcd for C_6H_4BrNO: C, 38.74; H, 2.17; N, 7.53. Found: C, 38.80; H, 2.30; N, 7.66.

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