Replacement of Methylthio Functions on Aromatic Heterocycles by Hydrogen, Alkyl, and Aryl Groups via Nickel-Induced Grignard Reactions

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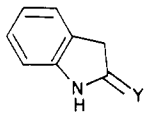
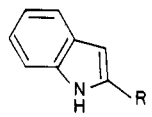
In continuation of studies of the new nickel-catalyzed, carbon–carbon bond-forming Grignard reaction inducing the replacement of alkylthio units from trigonal carbon sites[2] it became of interest to test the reaction in the field of heteroaromatic compounds.[3,4] The recent observation of the inertness of 2,6-diaryl-4-(methylthio)pyridines 1 toward Grignard reagents in attempts to prepare 4-alkyl-2,6-diarylpyridines[5] suggested the sulfides as interesting substrates for the same reaction under nickel catalysis.

As Table I indicates, the reactions of methylmagnesium bromide with all 4-(methylthio)pyridines under the influence of bis(triphenylphosphino)nickel dichloride led to γ-picolines.[6] Similar reactions of sulfide **1a** with phenylmagnesium and cyclohexylmagnesium bromides led to high yields of pyridines **2b** and **2e**, respectively. The latter reaction represents a good example of the recently introduced desulfurization process.[7] In accord with previous experience, the avoidance of sulfide reduction, such as the latter reaction, and the sulfide replacement by β-hydrogen-bearing alkyl groups required the use of [1,3-bis(diphenylphosphino)propane]nickel dichloride (dpppNiCl$_2$) in place of the above nickel species.[7] Under the influence of this nickel compound and *n*-butylmagnesium and cyclohexylmagnesium bromides, sulfide **1a** could be transformed in high yield into pyridines **2c** and **2d**, respectively.

2-(Methylthio)indole (**4a**),[8] prepared from oxindole (**3a**)



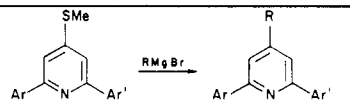
3a, Y = O
3b Y = S



4a, R = SMe
4b, R = C_6H_5
4c, R = Me
4d, R = *n*-Bu
4e, R = H

by treatment with Lawesson reagent[9] and S-methylation of the resultant thiooxindole (**3b**),[8] was chosen as the second type of heteroaromatic substrate for a study of the new nickel-catalyzed replacement reaction.

Table I. Nickel-Induced Grignard Reactions with 4-(Methylthio)pyridines[a]



			yield, %
Ar = Ar′ = C_6H_5	**1a**	**2a**, R = Me	89
Ar = Ar′ = C_6H_5	**1a**	**2b**, R = C_6H_5	87
Ar = Ar′ = C_6H_5	**1a**	**2c**, R = *n*-Bu	86[b]
Ar = Ar′ = C_6H_5	**1a**	**2d**, R = *c*-Hex	86[b]
Ar = Ar′ = C_6H_5	**1a**	**2e**, R = H	88[c]
Ar = Ar′ = C_6H_4OMe-*p*	**1b**	**2f**, R = Me	61[d]
Ar = Ar′ = 2-furyl	**1c**	**2g**, R = Me	44
Ar = Ar′ = 2-thienyl	**1d**	**2h**, R = Me	26[e]
Ar = C_6H_5, Ar′ = 2-thienyl	**1e**	**2i**, R = Me	23

[a] In dry benzene solution, at 80 °C, for 12 h, in the presence of [$(C_6H_5)_3P]_2NiCl_2$. [b] In the presence of dpppNiCl$_2$. [c] RMgBr = c-HexMgBr. [d] 76% of **2f** at 25 °C for 72 h. [e] At 25 °C for 48 h.

The Grignard reactions were carried out on the *N*-lithio or *N*-magnesio salts of indole **4a** in the presence of dpppNiCl$_2$. Reactions of phenylmagnesium and methylmagnesium bromides in benzene solution led to 2-substituted indoles **4b** (80%) and **4c** (72%), respectively. The reaction with *n*-butylmagnesium bromide gave **4d** (58%) and indole (**4e**) (30%). Reduction of the methylthio group with the use of isopropylmagnesium bromide and bis(triphenylphosphino)nickel dichloride[7,10] afforded indole (**4e**) (50%).

Experimental Section

Melting points were determined on Reichert, Mel-Temp, and Thomas-Hoover capillary melting point apparatuses and are uncorrected. Ultraviolet spectra of cyclohexane solutions and infrared spectra of KBr pellets were recorded on Perkin-Elmer 550 and Perkin-Elmer 1330 spectrophotometers, respectively. ^{1}H NMR spectra of $CDCl_3$ or CCl_4 solutions with Me_4Si as internal standard were obtained on Perkin-Elmer R600, Varian T-60, and Varian EM-390 spectrometers and a 360-MHz instrument with a highly modified Varian HR-220 console, an Oxford magnet, and a Nicolet 1180-E computer system.

General Procedure for the Reactions of Grignard Reagents with 4-(Methylthio)pyridines. A 2.85 M ethereal solution of methylmagnesium bromide, 35 μL (0.10 mmol), was added dropwise to a stirring suspension of 32.5 mg (0.05 mmol) of [$(C_6H_5)_3P]_2NiCl_2$ in 15 mL of dry benzene under argon and the mixture refluxed for 15 min. After this catalyst reduction, 0.55 mmol of the required Grignard reagent and a solution of 0.50 mmol of the appropriate thioether in 10 mL of dry benzene were added and the mixture was heated at 80 °C for 12 h. It then was cooled, poured into 50 mL of saturated ammonium chloride solution, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated. The residue was crystallized or chromatographed on silica gel (elution with hexane or 20:1 hexane–ethyl acetate).

2,6-Diphenyl-4-methylpyridine (2a) was prepared from a 2.85 M ethereal solution of methylmagnesium bromide and **1a**: mp 72–73 °C (EtOH) (lit.[11] mp 73–74 °C); UV λ_{max} 245 nm (log ε 4.47); IR 1595 (m, C=C), 1580 (m), 1550 (m) cm^{-1}; ^{1}H NMR δ (CCl_4) 2.40 (s, 3, Me), 7.2–7.5 (m, 8, aryl Hs), 8.0–8.2 (m, 4, aryl Hs); exact mass, *m/e* 245.1204 (calcd for $C_{18}H_{15}N$, *m/e* 245.1204).

2,4,6-Triphenylpyridine (2b) was prepared from a 3.00 M ethereal solution of phenylmagnesium bromide and **1a**: mp 133–134 °C (EtOH) (lit.[12] mp 139 °C); UV λ_{max} 251 nm (log ε 4.55); IR 1600 (m, C=C), 1580 (m), 1550 (m) cm^{-1}; ^{1}H NMR δ (CCl_4)

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7.3–7.8 (m, 13, Ar Hs), 8.1–8.3 (m, 4, Ar Hs); exact mass, *m/e* 307.1361 (calcd for $C_{23}H_{17}N$, *m/e* 307.1361).

2,6-Diphenyl-4-*n*-butylpyridine (2c) was prepared from a 2.00 M ethereal solution of *n*-butylmagnesium bromide, **1a**, and 27.1 mg (0.050 mmol) of dpppNiCl$_2$: liquid; UV λ_{max} 246 nm (log ϵ 4.43); IR 1595 (m, C=C), 1580 (m), 1540 (m) cm^{-1}; ^{1}H NMR δ (CCl_4) 0.95 (t, 3, J = 7 Hz, Me), 1.2–1.9 (m, 4, methylenes), 2.68 (t, 2, J = 7 Hz, benzyl Hs), 7.3–7.5 (m, 8, Ar Hs), 8.0–8.2 (m, 4, Ar Hs); exact mass, *m/e* 287.1674 (calcd for $C_{21}H_{21}N$, *m/e* 287.1674).

2,6-Diphenyl-4-cyclohexylpyridine (2d) was prepared from a 2.00 M ethereal solution of cyclohexylmagnesium bromide, **1a**, and 27.1 mg (0.050 mmol) of dpppNiCl$_2$: liquid; UV λ_{max} 246 nm (log ϵ 4.47); IR 1600 (m, C=C), 1580 (m), 1550 (m) cm^{-1}; ^{1}H NMR δ (CCl_4) 1.2–2.1 (m, 10, methylenes), 2.3–2.7 (m, 1, methine), 7.3–7.5 (m, 8, Ar Hs), 8.1–8.3 (m, 4, Ar Hs); exact mass, *m/e* 313.1830 (calcd for $C_{23}H_{23}N$, *m/e* 313.1830).

2,6-Diphenylpyridine (2e) was prepared from a 2.00 M ethereal solution of cyclohexylmagnesium bromide and **1a**: mp 80–81 °C (EtOH) (lit.[13] mp 81–82 °C); UV λ_{max} 246 nm (log ϵ 4.42); IR 1590 (m, C=C), 1560 (m), 1540 (m) cm^{-1}; ^{1}H NMR δ (CCl_4) 7.3–7.6 (m, 9, Ar Hs), 8.0–8.2 (m, 4, Ar Hs); exact mass, *m/e* 231.1048 (calcd for $C_{17}H_{13}N$, *m/e* 231.1048).

2,6-Bis(*p*-methoxyphenyl)-4-methylpyridine (2f) was prepared from a 2.85 M ethereal solution of methylmagnesium bromide and **1b**: mp 121 °C (hexane); ^{1}H NMR δ ($CDCl_3$) 2.43 (s, 3, Me), 3.89 (s, 6, 2 OMe), 7.04, 8.12 (d, 2 each, J = 9 Hz, Ar Hs), 7.41 (s, 2, pyridine β-Hs).

Anal. Calcd for $C_{20}H_{19}O_2N$: C, 78.65; H, 6.28; N, 4.59. Found: C, 78.73; H, 6.30; N, 4.56.

2,6-Di-2-furyl-4-methylpyridine (2g) was prepared from a 2.85 M ethereal solution of methylmagnesium bromide and **1c**: mp 64 °C (hexane); ^{1}H NMR δ ($CDCl_3$) 2.45 (s, 3, Me), 6.5–6.7 (m, 2, furan 2 H-4), 7.15 (d, 2, J = 5 Hz, 2 H-3), 7.44 (s, 2, pyridine β-Hs), 7.59 (d, 2, J = 1 Hz, 2 H-5).

Anal. Calcd for $C_{14}H_{11}O_2N$: C, 74.64; H, 4.93; N, 6.22. Found: C, 74.57; H, 4.97; N, 6.20.

2,6-Di-2-thienyl-4-methylpyridine (2h) was prepared from a 2.85 M ethereal solution of methylmagnesium bromide and **1d**: mp 81 °C (hexane); ^{1}H NMR δ ($CDCl_3$) 2.42 (s, 3, Me), 7.1–7.7 (m, 6, thiophene Hs), 7.36 (s, 2, pyridine β-Hs).

Anal. Calcd for $C_{14}H_{11}NS_2$: C, 65.32; H, 4.32; N, 5.44. Found: C, 65.21; H, 4.36; N, 5.40.

4-Methyl-2-phenyl-6-(2-thienyl)pyridine (2i) was prepared from a 2.85 M ethereal solution of methylmagnesium bromide and **1e**: mp 102–104 °C (Et_2O); ^{1}H NMR δ ($CDCl_3$) 2.43 (s, 3, Me), 7.1–7.7 (m, 3, thiophene Hs), 7.49 (s, 5, benzene Hs), 8.1–8.3 (m, 2, pyridine β-Hs).

Anal. Calcd for $C_{16}H_{13}NS$: C, 76.45; H, 5.22; N, 5.57. Found: C, 76.26; H, 5.29; N, 5.52.

α-(Methylthio)indole (4a) was prepared from thiooxindole (**3b**) by a published procedure.[8] The latter, in turn, was produced in the following manner.

A solution of 2.60 g (20.0 mmol) of oxindole (**3a**) in 20 mL of dry hexamethylphosphoramide was flushed with argon, and 4.00 g (10.0 mmol) of 2,4-bis(*p*-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide[9] was added portionwise. The mixture was heated at 110 °C under argon for 1 h, and the orange solution was cooled and poured into 100 mL of water. It was extracted exhaustively with ether, and the extract was dried (Na_2SO_4) and evaporated. Chromatography of the residual oil on a short silica column and elution with 2:1 hexane–ethyl acetate gave 2.70 g (90%) of yellow, crystalline **3b**: mp 147–149 °C (lit.[8] mp 147–149 °C).

General Procedure for the Reactions of Grignard Reagents with α-(Methylthio)indole (4a). A 1.6 M hexane solution of *n*-butyllithium, 0.75 mL (1.20 mmol), was added to a solution of 200 mg (1.20 mmol) of α-(methylthio)indole (**4a**) in 10 mL of dry benzene, and the mixture was stirred under argon at room temperature for 15 min.

A 2.90 M ethereal solution of methylmagnesium bromide, 86 μL (0.25 mmol), was added dropwise to a stirring suspension of 70 mg (0.12 mmol) of dpppNiCl$_2$ in 5 mL of dry benzene under argon, and the mixture refluxed was for 15 min. It then was added to the above suspension of the lithio salt of **4a**. Immediately thereafter there was added 1.40 mmol of required Grignard reagent, and the mixture was heated at 80 °C for the time cited below. It then was cooled and poured into 50 mL of 1 N hydrochloride acid solution, and the water solution was extracted with ether. The combined organic solutions were washed with saturated brine solution, dried (K_2CO_3), and evaporated. The residue was crystallized or chromatographed on silica gel (elution with 20:1 hexane–ethyl acetate).

For the reactions utilizing the magnesio salt of **4a**, whose product yields are quoted in the Discussion section, the above *n*-butyllithium solution was replaced by 0.42 mL (1.20 mmol) of a 2.90 M ethereal solution of methylmagnesium bromide. The product yields of the reactions utilizing the lithio salt of **4a** were slightly lower from those of the reactions of the magnesio salt.

α-Phenylindole (4b) was prepared from a 2.80 M ethereal solution of phenylmagnesium bromide (3.5 h): mp 187–188 °C (lit.[14] mp 188–189 °C), spectrally identical with an authentic sample.

α-Methylindole (4c) was prepared from a 2.90 M ethereal solution of methylmagnesium bromide (6 h): mp 56–58 °C (lit.[15] mp 58–60 °C), spectrally the same as an authentic sample.

α-*n*-Butylindole (4d) and indole (4e) were prepared from a 2.80 M ethereal solution of *n*-butylmagnesium bromide (3.5 h). **4d**: IR 3400 (m, NH), 1620 (w), 1590 (w), 1550 (m, C=C); ^{1}H NMR δ (CCl_4) 0.86 (t, 3, J = 7 Hz, Me), 1.1–1.8 (m, 4, methylenes), 2.51 (t, 2, J = 7 Hz, benzyl CH_2), 6.09 (br s, 1, indole β-H), 6.6–7.6 (m, 5, Ar Hs, NH); spectrally identical with literature data.[16] **4e**: spectrally the same as an authetic specimen.

Indole (4e) was prepared from a 1.90 M ethereal solution of isopropylmagnesium bromide and 81 mg (0.12 mmol) of [(C_6H_5)$_3$P]$_2$NiCl$_2$ (replacing the above dpppNiCl$_2$) (45 h): **4e** spectrally identical with sample above.

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The Direct Cyclization of α-Acylamino-Substituted Hydroxamates to β-Lactams

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With the discovery of biologically active monocyclic β-lactam antibiotics such as the nocardicins **1**, monobactams **2**[1] (monosulfactams **3**), and, most recently, the oxamazins **4**,[2] considerable importance has been placed on the synthesis of such key intermediates as **5a** and **5b**. Prior routes to these molecules have utilized expensive reagents or resulted in competitive side-product formation, or both. Herein is provided a straightforward and efficient route to these versatile β-lactams (Scheme I).

By taking advantage of the low pK of the hydroxamate N–H bond (pK 6–10), we previously developed a synthetic route which relied on a Mitsunobu reaction[3] to promote the key cyclization step (eq 1, X = OH).[4] This proved effective when the nitrogen was protected as a carbamate (i.e., **6b**, **6c**). However, when R was a simple acyl derivative

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