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A new efficient synthesis of 3-(4-pyridinyl)methylindoles

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Abstract—A new efficient method for the preparation of 3-(4-pyridinyl)methylindoles has been developed. The new method involves coupling of indoles with 4-pyridinecarboxaldehyde to give 3-indolyl 4-pyridinyl methanols, which upon treatment with triethylsilane in the presence of trifluoroacetic acid afford 3-(4-pyridinyl)methylindoles in 64–76% overall yield.

3-(4-Pyridinyl)methylindoles are important intermediates in organic synthesis especially in the synthesis of biologically active and medicinally useful agents. For example, they were used in the synthesis of potent and selective serotonin uptake inhibitors,[1–3] dual thromboxane synthase inhibitor/thromboxane receptor antagonists,[4] and compounds displaying anxiolytic activity.[5] In addition, 3-(4-pyridinyl)methylindoles were used in the synthesis of other nitrogen containing heterocycles such as indole alkaloids,[6] pyridocarbazoles,[7] and were involved in the synthesis of 4-skatylpiperidines.[8,9] Three methods have been previously reported for the preparation of 3-(4-pyridinyl)methylindoles. In the first method, indole was treated with a Grignard reagent and the resulting indolyl magnesium reagent was allowed to react with 4-(chloromethyl)pyridine hydrochloride, giving 3-(4-pyridinyl)methylindole.[6,9] Although straightforward, this method suffered from low overall yield (29%).[9] Theoretically, 1 equiv. of the indolyl magnesium reagent is consumed by HCl in 4-(chloromethyl)pyridine hydrochloride, which is usually used in the reaction due to the instability of its corresponding free base. This is not desirable especially for those difficult to obtain indole substrates. In the second method, the more readily available isonicotinyl chloride hydrochloride was used instead of 4-(chloromethyl)pyridine hydrochloride.[1] After reaction with the indolyl magnesium reagent, the resulting 3-indolyl 4-pyridinyl ketone was reduced to give 3-(4-pyridinyl)methylindole.[1] While the yield for the formation of 3-indolyl 4-pyridinyl ketone was satisfactory (>70%), the yield for the second step was rather disappointing, lowering the overall yields to 16–21%.[1] In the third method, 3-hydroxy-3-(4-pyridinyl)methyl-1*H*-indol-2-one was reduced to give 3-(4-pyridinyl)-methylindole in 44% yield, but substantial amount (12%) of the regioisomer, 2-(4-pyridinyl)methylindole was formed in the reaction.[10] In one of our drug discovery programs, we required an ease access to various 3-(4-pyridinyl)methylindoles. Herein, we describe an efficient method for the synthesis of the titled compounds.

Our synthesis of 3-(4-pyridinyl)methylindoles **4** entails the coupling[11] of indoles **1** with 4-pyridinecarboxaldehyde **2**, which is more stable and readily available than 4-(chloromethyl)pyridine hydrochloride and isonicotinyl chloride hydrochloride used in previous synthesis (Scheme 1). We envisioned that the hydroxyl group in the resulting 3-indolyl 4-pyridinyl methanols **3** could be selectively reduced in the presence of the reducible pyridine ring[12] by choice of an appropriate reducing agent. Thus, treatment of 5-fluoroindole **1b** with **2** using sodium hydroxide in methanol at room temperature for 4 hours afforded cleanly 3-(5-fluoroindolyl) 4-pyridinyl methanol **3b**. Quenching the reaction mixture with water and collecting the resulting precipitate by filtration gave **3b** in 97% yield.[13] Other 3-indolyl 4-pyridinyl methanols **3** were prepared similarly as shown in Table 1.

Triethylsilane was selected for our reduction of 3-indolyl 4-pyridinyl methanols **3** to 3-(4-pyridinyl)methylindoles **4**. The choice of triethylsilane was based on two considerations. First, although the reduction of **3** with hydrosilane has not been reported, we expected that the hydroxyl group in **3** would behave like a benzylic alcohol, which could be reduced by hydrosilane giving the corresponding methylene product. Second, triethylsilane is a mild and readily

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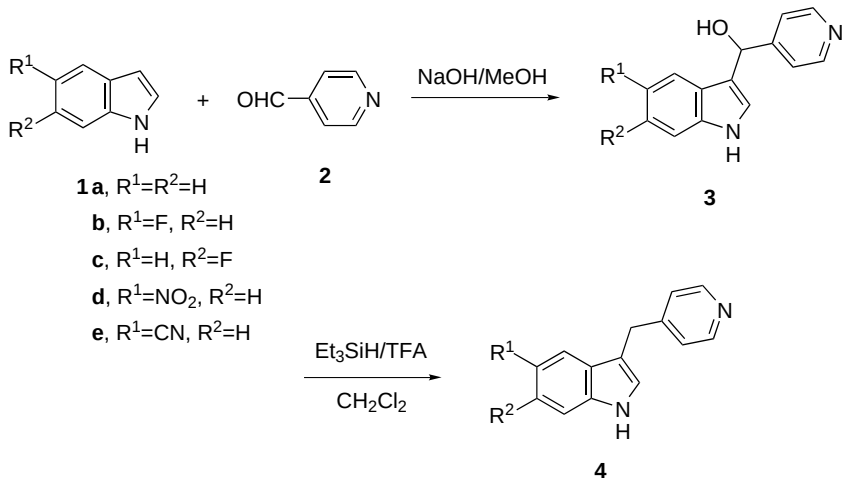


Scheme 1.

Table 1. Preparation of 3-(4-pyridinyl)methylindoles

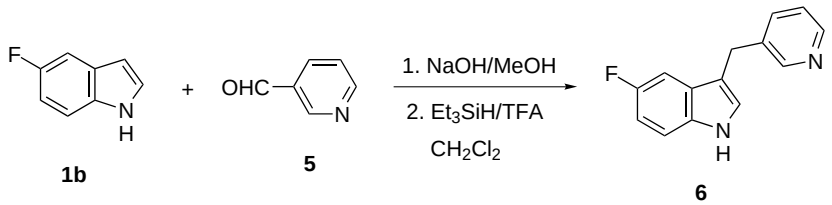
Entry	R^1	R^2	Conditions for **3**		Yield (%)[a] for **3**	Conditions for **4**		Yield (%)[b] for **4**
			Temp. (°C)	Time (h)		Temp. (°C)	Time (h)	
1	H	H	0–rt	18	97	25	16	66
2	F	H	0–rt	14	95	25	18	80
3	H	F	0–rt	18	98	25	18	68
4	NO_2	H	0–rt	18	90	25	2	78
5	CN	H	0–rt	17	89	25	4	73

[a] Isolated yield by filtration.
[b] Isolated yield by chromatography.

available reducing agent and is not expected to react with the pyridine ring in **3**, nor the other reducible functional groups such as NO_2 and CN in **3d** and **3e**. Thus, treatment of **3b** with triethylsilane[14] in methylene chloride in the presence of trifluoroacetic acid at room temperature overnight gave the compound **4b** as a single product, which was isolated in 80% yield. Under similar conditions, other 3-(4-pyridinyl)-methylindoles **4** were prepared in 66–78% yields (Table 1).[15]

As can be seen from Table 1, the present method for the preparation of 3-(4-pyridinyl)methylindoles is more advantageous compared with those reported previously. Using the known approaches via indolyl magnesium intermediates, it would be difficult to prepare 3-(4-pyridinyl)methylindoles such as **4d** and **4e**, as the functional groups such as nitro and cyano groups in these substrates will interfere with the Grignard reagents and reducing reagents used in these methods. As an extension to the new method, 3-(3-pyridinyl)methylindole **6** was prepared in 50% overall yield using 3-pyridinecarboxaldehyde **5** (Scheme 2).

In summary, a new efficient method for the preparation of 3-(4-pyridinyl)methylindoles has been developed. The new method involves coupling of indoles with 4-pyridinecarboxaldehyde to give 3-indolyl 4-pyridinyl methanols, which upon reaction with triethylsilane in the presence of trifluoroacetic acid afford 3-(4-pyridinyl)methylindoles in 64–76% overall yield. The new method is more advantageous than known approaches and can be used to prepare other pyridinylmethylindole isomers.



Scheme 2.

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12. Direct reductive alkylation of indoles with 4-pyridinecarboxaldehyde has previously been reported, however, the product was the over-reduced compound, 3-(4-piperidinyl)methylindole.[8]
13. Physical and spectroscopic data for compounds: **3a**, mp 190–193°C; lit.[11e] 151–152°C; **3b**, mp 171–173°C; ^{1}H NMR (DMSO-d_6) δ 5.84 (s, 1H), 5.93 (s, 1H), 6.86–6.90 (m, 1H), 7.16–7.19 (m, 1H), 7.24 (s, 1H), 7.31–7.33 (m, 1H), 7.42–7.43 (m, 2H), 8.47–8.48 (m, 2H), 11.06 (s, 1H); **3c**, mp 178–179°C; ^{1}H NMR (DMSO-d_6) δ 5.84 (d, J=4.1 Hz, 1H), 5.93 (d, J=3.8 Hz, 1H), 6.75–6.79 (m, 1H), 7.08–7.11 (m, 1H), 7.16 (d, J=2.0 Hz, 1H), 7.42 (d, J=7.3 Hz, 2H), 7.44–7.45 (m, 1H), 8.46–8.47 (m, 2H), 11.01 (s, 1H); **3d**, mp 265°C (dec.); ^{1}H NMR (DMSO-d_6) δ 6.06 (s, 1H), 6.11 (s, 1H), 7.42 (s, 1H), 7.44–7.46 (m, 2H), 7.52 (d, J=9.0 Hz, 1H), 7.96 (dd, J=9.0, 2.2 Hz, 1H), 8.49 (d, J=2.2 Hz, 1H), 8.50–8.52 (m, 2H), 11.72 (s, 1H); **3e**, mp 197–199°C; ^{1}H NMR (DMSO-d_6) δ 5.99 (s, 1H), 6.00 (s, 1H), 7.39 (s, 1H), 7.41 (dd, J=8.5, 1.5 Hz, 1H), 7.44–7.46 (m, 2H), 7.51 (d, J=8.5 Hz, 1H), 7.98–7.99 (m, 1H), 8.48–8.50 (m, 2H), 11.56 (s, 1H).
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15. Physical and spectroscopic data for compounds: **4a**, mp 110°C, lit.[9] 108–110°C; ^{1}H NMR (DMSO-d_6) δ 4.05 (s, 2H), 6.91–6.94 (m, 1H), 7.03–7.07 (m, 1H), 7.22 (d, J=2.4 Hz, 1H), 7.25–7.27 (m, 2H), 7.34 (d, J=8.2 Hz, 1H), 7.39 (d, J=7.9 Hz, 1H), 8.40–8.42 (m, 2H), 10.91 (s, 1H); **4b**, mp 141–142°C, lit.[1] mp 149°C; **4c**, mp 131°C; ^{1}H NMR (DMSO-d_6) δ 4.03 (s, 2H), 6.77–6.81 (m, 1H), 7.11 (dd, J=10.2, 2.3 Hz, 1H), 7.21 (d, J=2.3 Hz, 1H), 7.26 (d, J=6.0 Hz, 2H), 7.38 (dd, J=8.7, 5.5 Hz, 1H), 8.40–8.42 (m, 2H), 10.98 (s, 1H); **4d**, mp 196–197°C; ^{1}H NMR (DMSO-d_6) δ 4.16 (s, 2H), 7.28–7.30 (m, 2H), 7.50 (s, 1H), 7.52 (d, J=9.0 Hz, 1H), 7.97 (dd, J=8.8, 2.2 Hz, 1H), 8.41–8.42 (d, J=2.0 Hz, 1H), 8.43–8.45 (m, 2H), 11.71 (s, 1H); **4e**, mp 185–187°C; ^{1}H NMR (DMSO-d_6) δ 4.09 (s, 2H), 7.28–7.30 (m, 2H), 7.40 (dd, J=8.5, 1.7 Hz, 1H), 7.44 (s, 1H), 7.49 (d, J=1.7 Hz, 1H), 8.00–8.01 (m, 1H), 8.42–8.44 (m, 2H), 11.53 (s, 1H).