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CONVENIENT SYNTHESES OF 6-ARYLMETHYL- AND 6-(1-E-PROPENYL)-3-PYRIDINOLS

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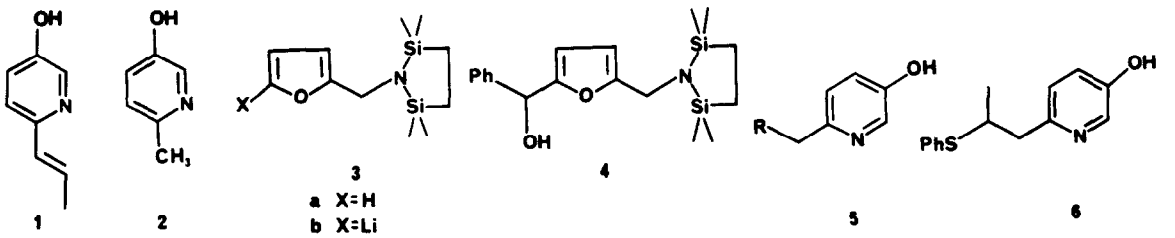
ABSTRACT: 1-(2-Furylmethyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane 3a was reacted sequentially with t-butyllithium, an aldehyde and hydrochloric acid to produce the corresponding 6-substituted 3-pyridinol.

Recently we needed a convenient, simple, large scale synthesis of 6-substituted 3-pyridinol derivatives including 6-(1-E-propenyl)-3-pyridinol 1[1]. This molecule is important since it is an intermediate in the synthesis of the N-terminal amino acid of the nikkomycins, a group of potent antifungal agents. The related compound 6-methyl-3-pyridinol 2 is readily available from the acid mediated reaction of formaldehyde with 2-aminomethylfuran.[2] Additionally such ring expansion methodology can be used to prepare 2-alkyl and 2-aryl substituted 3-pyridinols from 2-furyl alkyl or aryl ketones and ammonia.[3] In spite of all these studies the process is limited by the availability of the starting 2,5-disubstituted furans. Herein we report a simple procedure for converting 2-aminomethylfuran into the corresponding pyridine derivatives via C-5 lithiation.[4]

2-Aminomethylfuran was protected by reaction with 1,2-bis-(chlorodimethylsilyl)ethane[5] and triethylamine in anhydrous dichloromethane solution to produce 3a[6] (83%). This material was cleanly metallated by reaction with t-butyllithium in THF and the resultant C-5 anion 3b condensed with benzaldehyde. The adduct 4 was not isolated but was directly rearranged in situ by reaction with hydrochloric acid to produce 6-benzyl-3-pyridinol 5(R=Ph)[7] (37%).



1 2 3 a X=H b X=Li 4 5 6

The procedure was extended to the additional aromatic aldehydes 5(R=4-MeC$_6$H$_4$; 42%), 5(R=3-MeC$_6$H$_4$; 57%) and 5(R=2-naphthyl; 36%). In an attempt to prepare 1, propenal was reacted with 3b but acidification gave only an intractable polymer. In contrast, 3b reacted cleanly with 2-phenylthiopropanal[8] followed by hydrochloric acid to produce 6 together with the desired olefin 1. Oxidation of the mixture using oxone[9] followed by reflux in toluene solution cleanly gave 1[10] (14%). Although the yields of 6-substituted 3-pyridinols by this chemistry are only modest the procedure is both concise and experimentally straightforward to effect.

Experimental

1-(2-Furylmethyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane. A solution of 1,2-bis-(chlorodimethylsilyl)ethane (6.36g) in anhydrous CH_2Cl_2 (11mL) was added to a stirred mixture of freshly distilled 2-aminomethylfuran (2.61mL) and dry triethylamine (10.28mL) in anhydrous CH_2Cl_2 (19mL) at 0°C under nitrogen. After the addition was complete, the mixture was warmed to room temperature and stirred for 2h. The triethylammonium chloride was filtered off, the residue evaporated and distilled to give 3a (5.87g, 83%): bp 48°C at 200mm Hg.

3-Hydroxy-6-(4-methylbenzyl)pyridine (general procedure). To a stirred solution of 3a (50.4mg) in anhydrous THF (5mL) at -78°C under nitrogen was slowly added t-butyllithium in hexane (1.7M; 1.37mL). The mixture was warmed to -42°C and stirring continued for 2h. 4-Methylbenzaldehyde (0.373mL) was added and the mixture stirred at room temperature for 1h. The solution was recooled to -78°C, quenched with hydrochloric acid (1M; 12.7mL) and refluxed (18h). The residue was cooled, diluted with ether and extracted with hydrochloric acid (3x25mL). The combined acidic extracts were washed with diethyl ether (50mL) and neutralized to pH7 with aqueous sodium hydroxide (1M). The solution was extracted with diethyl ether (3x50mL), the combined extracts were dried ($MgSO_4$) and evaporated to yield pure crystalline 3-hydroxy-6-(4-methylbenzyl)pyridine (0.175g, 42%).

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10. The product 1 was identical with material that was prepared from 2 via sequential reaction with n-butyllithium, acetaldehyde, toluene-4-sulfonyl chloride, DBU, and potassium hydroxide.

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