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NOVEL 3-AMINOTHIENO[2,3-*B*]PYRIDINE SYNTHESIS *VIA* A SILICON-DIRECTED ANIONIC CYCLIZATION

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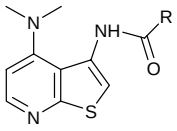
Abstract- A novel strategy yielding a 3-aminothiophene is described herein. This specifically relies upon an α-thiomethylsilane directing deprotonation, thereafter cyclization of the resultant anion into a pendant nitrile forms the necessary 3-aminothiophene ring.

During the course of one of our medicinal chemistry programs, the synthesis of **1** was required. Although there are few reports of thieno[2,3-*b*]pyridine syntheses in the literature, none allow for the substitution pattern we desired, as indicated in pyridine (**1**). Herein we report a novel thieno[2,3-*b*]pyridine synthesis, specifically *via* a silicon-directed anionic cyclization constructing the thiophene ring.



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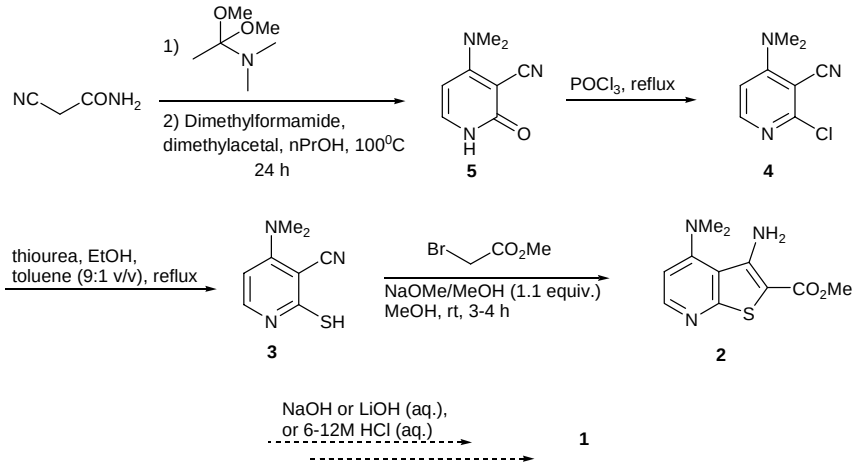
Our initial efforts to synthesize the desired thieno[2,3-*b*]pyridines followed the methods of Kadushkin and Granik (**Scheme 1**).[1-3] We attempted to access thienopyridine (**1**) *via* a decarboxylation of **2**, followed by acylation of the resultant amine. However, in our hands, attempts to hydrolyze ester (**2**) under both basic and acidic conditions resulted in decomposition of starting material (**2**).

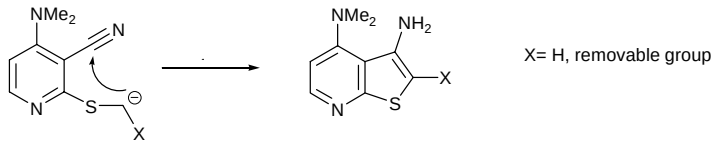
Scheme 1



Thus, a new method was required to synthesize thienopyridine (**1**). Hence, with insight gained from the previous route, we felt that an approach utilizing a stabilized methyl carbanion would serve to construct the desired thiophene ring (**Scheme 2**). Trialkylsilanes are known to stabilize adjacent carbanions in a variety of olefination reactions.[4-8] Therefore, we felt that a trimethylsilyl group would be ideally suited to

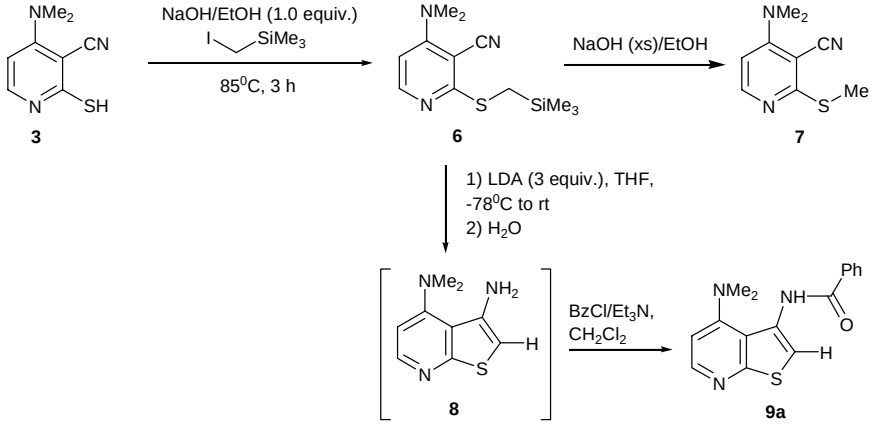
direct and concomitantly stabilize the anion generated from deprotonation on the methylene adjacent to the sulfur atom. To our knowledge, an α-silyl-stabilized carbanion has not been employed in an intramolecular reaction to synthesize a thiophene ring. Our hope was that once the thiophene had been formed, the resulting arylsilane would then be desilylated easily under mildly basic or acidic conditions.

Scheme 2



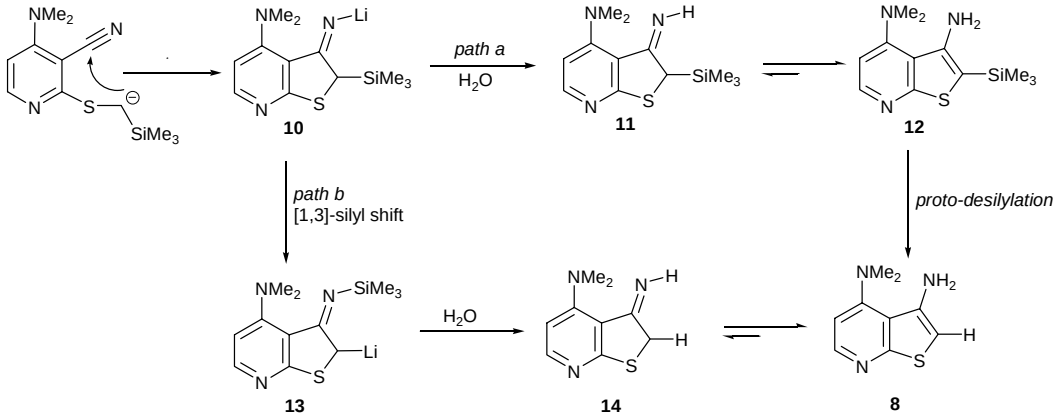
In an effort to deprotonate silane (**6**) (itself synthesized *via* alkylation of mercaptan (**3**) with iodomethyltrimethylsilane)[9,10] (**Scheme 4**) under mild conditions, a one-pot deprotonation/cyclization was attempted by using excess NaOH (aq.) in ethanol. Unfortunately, this only caused proto-desilylation to afford methyl thioether (**7**). Thus anhydrous conditions were employed to generate the α-silicon-stabilized carbanion. When silane (**6**) was treated with LDA (3 equiv.) at -78^0C under anhydrous conditions and then warmed to room temperature, aminothienopyridine (**8**) was synthesized in 77% yield. Interestingly, it was found that three equivalents of LDA were required for complete conversion of silane (**6**) to thienopyridine (**8**). Although thienopyridine (**8**) was characterized by ^{1}H NMR spectrometry, it is not an indefinitely stable compound and as such was acylated directly with benzoyl chloride to afford thienopyridine (**9a**).

Scheme 4



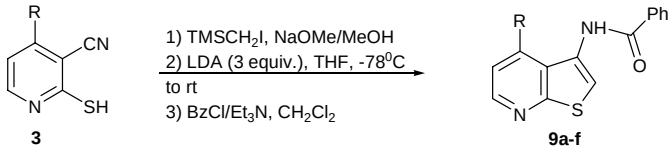
A plausible mechanism can be envisaged in which the methylene between the sulfur and silicon atoms is deprotonated, followed by nucleophilic addition to the nitrile to form metallo-imine species (**10**) (**Scheme 5**). What is unclear is whether tautomerization of the imine occurs upon aqueous treatment to form amino-thiophene (**12**) *via* imine (**11**) (*path a*), or whether a [1,3]-silyl shift[11,12] occurs under the reaction conditions to afford intermediate (**13**) (*path b*). In the latter case, the TMS group would be hydrolyzed rapidly once subjected to aqueous workup, making isolation of iminosilane (**13**) difficult (if not impossible). In practice, we have not been able to observe an intermediate such as vinylsilane (**12**) in the analysis of crude reaction mixtures (^{1}H NMR, LRMS spectrum). While we believe this provides some evidence for the reaction proceeding *via path b*, we recognize further studies need to be conducted (perhaps with a bulkier silane) to elucidate the mechanism.

Scheme 5



Analogs of thienopyridine (**9**) were synthesized to explore the scope of this reaction. Results of the cyclization reaction are reported in the table below.[13] (Yields are non-optimized.) Each compound was acylated with benzoyl chloride for characterization purposes.

In conclusion, a novel silicon-directed thieno[2,3-*b*]pyridine synthesis has been discovered. We believe this method may also be applied toward the synthesis of a variety of arene-fused thiophenes.



Compound	R	Yield of cyclization
9a	NMe_2	77%
9b	H	28%
9c	*i*-Pr	42%
9d	Ph	42%
9e	4-OMe-Ph	43%
9f	OMe	70%

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13. A representative procedure is illustrated by the synthesis of thienopyridine (**9a**). Mercaptopyridine (**3**)[1] (2.0 g, 11.2 mmol) was suspended in EtOH/H_2O (20 mL, 1:1 v/v). NaOH (s) (0.47 g, 11.8 mmol) was added to the mixture, followed by addition of iodomethyltrimethysilane (1.83 mL, 12.3 mmol). The mixture was heated to 80^0C for 12 h. The reaction mixture was then cooled to rt and diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was dried (Na_2SO_4), filtered, and then concentrated. The residue was then purified *via* silica gel chromatography (9:1 hexanes/EtOAc). Concentration of the desired fractions afforded silane (**6**), which was taken directly into the next reaction. Silane (**6**) (2.25 g, 8.5 mmol) was dissolved in THF (30 mL) and then cooled to -78^0C. To this solution was added LDA (14 mL, 1.8 M in THF, Aldrich, 25.2 mmol). The deep brown mixture was stirred at -78^0C for 30 min and then warmed to rt. The reaction mixture was poured into a separatory funnel and diluted with ether (100 mL) and H_2O (200 mL). The ethereal layer was dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to silica gel chromatography (3:1 hexanes/EtOAc) to afford aminothiophene (**8**) as a light brown oil (1.27 g, 77%, 60% from mercaptopyridine (**3**)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, 1H, J=5.4 Hz), 6.94 (d, 1H, J=5.1 Hz), 6.22 (s, 1H), 4.2-4.5 (br s, 2H), 2.96 (s, 6H). LRMS calcd: 193.2; found: 194.3 (M+H). A small sample of aminothiophene (**8**) was acylated with benzoyl chloride in CH_2Cl_2 and Et_3N. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.28 (br s, 1H), 8.52 (d, 1H, J=5.1 Hz), 8.20 (s, 1H), 7.93 (m, 2H), 7.56 (m, 3H), 7.12 (d, 1H, J=5.1 Hz), 2.90 (s, 6H). LRMS Calcd: 297.2; Found: 298.3 (M+H). mp 154-155^0C. Anal. Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.32; H, 5.26; N, 13.99.