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Short communication

The first attempt for the preparation of 2-(*tert*-butyl)-7-(trimethylsilyl)-3-((trimethylsilyl)oxy)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine-1-one

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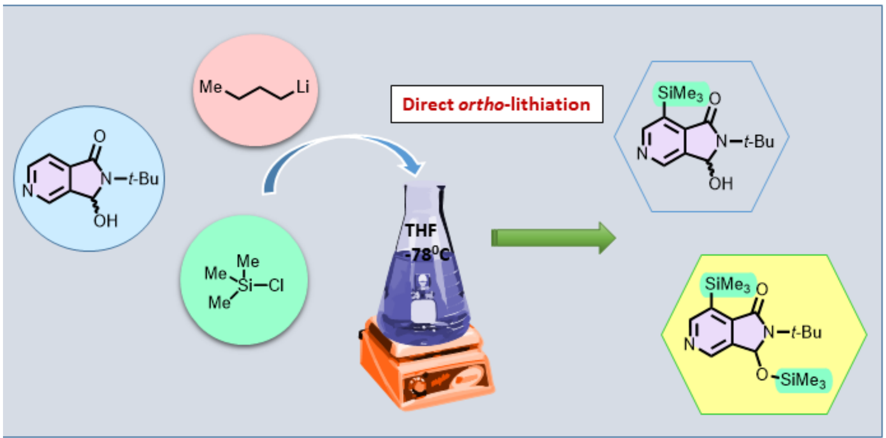
Abstract

2-(*tert*-butyl)-7-(trimethylsilyl)-3-((trimethylsilyl)oxy)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine-1-ones was synthesized based on a modification of the methodology described by us previously. The described protocol is simple and does not require the use of expensive and toxic catalysts. The method allows the desired products to be obtained in good yields. Moreover, the procedure is operationally simple and can be considered a more environmentally friendly alternative to conventional catalytic methods.



Keywords: pyrrolo[3,4-c]pyridine analogs, bioactivity, *ortho*-lithiation

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Five-membered heterocyclic compounds containing nitrogen are currently the subject of intensive research by many scientific teams [1-3]. This is due to the fact that structures of this type exhibit a range of biological activities. These types of heterocycles also play an important role in combating cancer, Alzheimer's, tuberculosis, inflammation, malaria, filariasis, and hypertension. They also exhibit antioxidant and antiviral [4-8] antibacterial activities [9-11]. Among the many possible molecular systems of this type, pyrrolo[3,4-c] pyridine analogs attract attention [12-13].

This work is a continuation of our work in this area. Previously, we described the lithiation of 2-(*tert*-butyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine-1-one **(1)** and the subsequent reaction of the resulting organolithium intermediate with various electrophilic agents (Scheme 1) [14].

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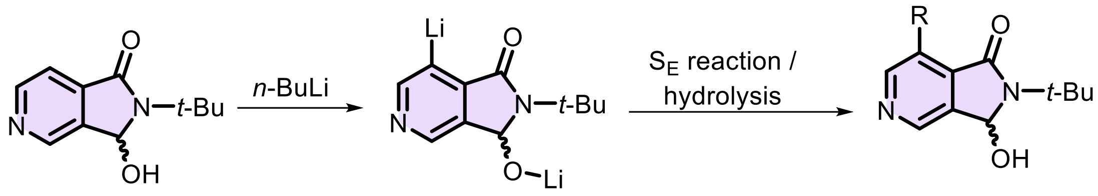
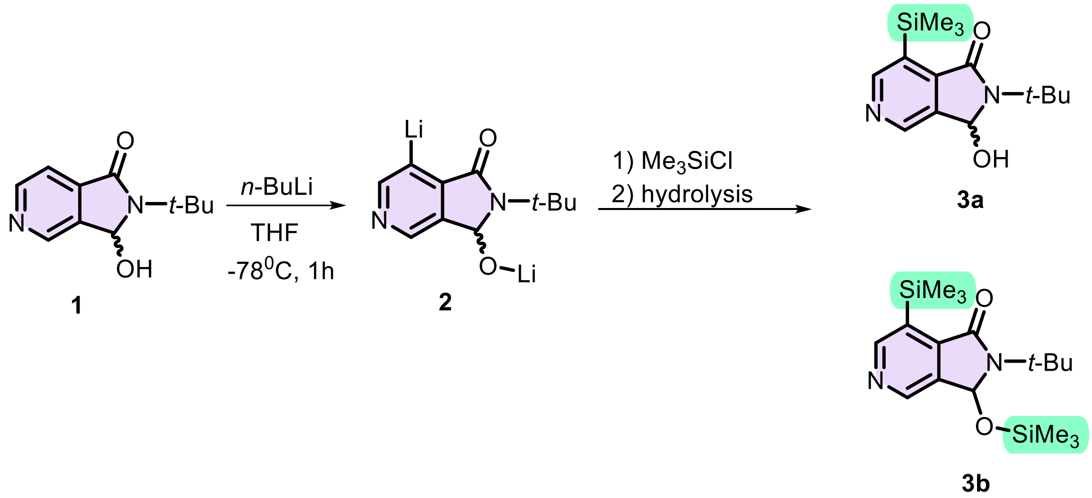


Scheme 1.

We now decided to investigate the possibility of modifying the reaction course leading to a product functionalized with a trimethylsilyl group. Our goal was to attempt to obtain a structure containing an additional trimethylsilyl molecular segment.

We began our studies by modifying the reaction procedure previously described in [14]. To achieve this, we increased the amount of trimethylsilyl chloride introduced and extended the reaction time. Chromatographic analysis of the reaction mixture showed that in this case, in addition to the previously isolated product **3a**, a second organic compound was also formed (Scheme 2). This compound **3b** was successfully isolated using chromatographic methods and identified based on elemental analysis and spectral data.



Scheme 2.

In particular, it turned out that analysis of the elemental composition indicates the incorporation of a second trimethylsilyl segment and corresponds to the gross formula $C_{17}H_{30}N_2O_2Si_2$. A characteristic band from the bond from the carbonyl group can be easily detected in the IR spectrum of the analyzed compound. The ^{1}H NMR spectrum provides the most information. In the strongest field of this spectrum, two large singlets originating from the methyl groups of the $SiMe_3$ segments are found. In the slightly stronger field, a singlet from the protons of the *t*-butyl group is found. In the moderately weak field, there is a signal from proton at the 5-membered heterocyclic ring, while in the weakest field, signals from the protons of the pyridine ring are found. This analysis is perfectly complemented by the ^{13}C NMR spectrum. In the most intense region of the ^{13}C NMR spectrum, two characteristic singlets corresponding to the methyl carbons bound to silicon atoms. The *t*-butyl substituent is identified by a quaternary carbon signal accompanied by three equivalent methyl carbon signals. The dihydropyrrole fragment gives rise to aliphatic signals associated with its sp^3-hybridized carbon atoms. Signals attributable to the aromatic carbons of the pyrrolo[3,4-c]pyridine system are observed in the typical aromatic region. In the moderately weak field, there is a signal from the carbonyl carbon, as expected for an amide-type carbonyl group.

Experimental

All reagents and commercially available materials were used without additional purification unless otherwise stated. *n*-Butyllithium (2.5 M solution in hexane) were purchased from Aldrich and were analyzed immediately before use by applying the double titration procedure [15] with 1,2-dibromoethane in heptane solution (second step). *N,N,N′,N′*-Tetramethyl-1,2-ethylendiamine (TMEDA; Aldrich, 99.5%) was distilled prior

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to use and stored over KOH pellets. Chlorotrimethylsilane (purity 99%) was obtained from Fluka. Tetrahydrofuran (POCH, pure) was distilled from sodium benzophenone ketyl prior to use.

Reagents and solvents were handled by using standard syringe techniques. All of the air- and moisture-sensitive reactions were carried out under an argon atmosphere. Analytical thin layer chromatography (TLC) was conducted on Merck silica gel plates (Kieselgel 60 F254, layer thickness 0.2 mm) with UV detection at 254 and/or 365 nm. Gravitational column chromatography (GCC) separations and purifications were performed on silica gel 60 (0.063-0.100 mm) from Merck. ^{1}H and ^{13}C{1H} NMR spectra were obtained at ~ 294 K for solutions in $CDCl_3$ with a Bruker Avance III spectrometer at a frequency of 600.3 MHz (^{1}H) and 150.9 MHz (^{13}C), respectively, by using standard pulse sequences. The ^{1}H signal of residual $CHCl_3$ and ^{13}C signal of the solvent were used as internal references (δ = 7.26 ppm and δ = 77.00, respectively) [16-17]. All NMR spectra were processed with the TopSpin 4.0.5 program; [18] the spectra are included in the SI. Infrared (IR) spectra was taken in KBr disks on a Thermo Nicolet Nexus FT-IR spectrometer; absorption frequencies are given in cm^{-1}. Melting points was determined on a Boëtius microscope hot stage and are uncorrected.

Preparation of 2-(*tert*-butyl)-3-hydroxy-7-(trimethylsilyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine-1-one (**3a**) and 2-(*tert*-butyl)-7-(trimethylsilyl)-3-((trimethylsilyl)oxy)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine-1-one (**3b**)

To a stirred solution of 2-(*tert*-butyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine-1-one **(1)** (1 mmol) and TMEDA (2 mmol) in THF (30 ml) *n*-butyllithium (2.5 M in hexane, 2 mmol) was added at - 78^{0}C. The solution was kept at - 78^{0}C for 1 h and an Me_3SiCl (3 mmol) was added. Stirring at - 78^{0}C was continued for 3 h, and then the reaction mixture was warmed to RT, followed by the addition of a saturated aqueous solution of ammonium chloride (5 mL). The post-reaction mixture were extracted with dichloromethane, and the extracts were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The individual products were purified by column chromatography (silica gel, methanol : petroleum ether 1:1). Two detected products were obtained. Products **3a** was identified by chromatographic techniques based on samples prepared earlier [14].

2-(*tert*-butyl)-7-(trimethylsilyl)-3-((trimethylsilyl)oxy)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine-1-one (**3b**)

White powder (0.080 g, 30% yield). R_f = 0.21 (methanol : petroleum ether 1:1). Mp: 130-133^{0}C. IR (KBr, cm^{-1}): 1686 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$): 8.80 (1H, s, 6-H), 8.75 (1H, s, 4-H), 6.25 (1H, s, 3-H), 1.59 (9H, s, *t*-Bu), 0.42 (9H, s, 7-$SiMe_3$), 0.05 (9H, s, O-$SiMe_3$).
^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): 167.1 (1), 155.1 (1), 146.3 (1), 144.8 (1), 137.5 (1), 131.8 (1), 81.9 (1), 55.0 (1), 28.2 (3), 1.2 (3), -1.0 (3). Anal. Calcd. For $C_{17}H_{30}N_2O_2Si_2$: C, 58.24; H, 8.62; N, 7.99 Found C, 58.45; H, 8.78; N, 7.82.

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