COMMUNICATIONS

LETTERS

Oxygen-Directed Functionalization of Thiophene

Jahyo Kang† and Keun Jo Lim

Department of Chemistry, Sogang University, Seoul 121, Korea

Wan-Ju Kim† and Chul Hae Lee

Korea Advanced Institute of Science and Technology, P.O. Box 131, Dong Dae Mun, Seoul 131, Korea

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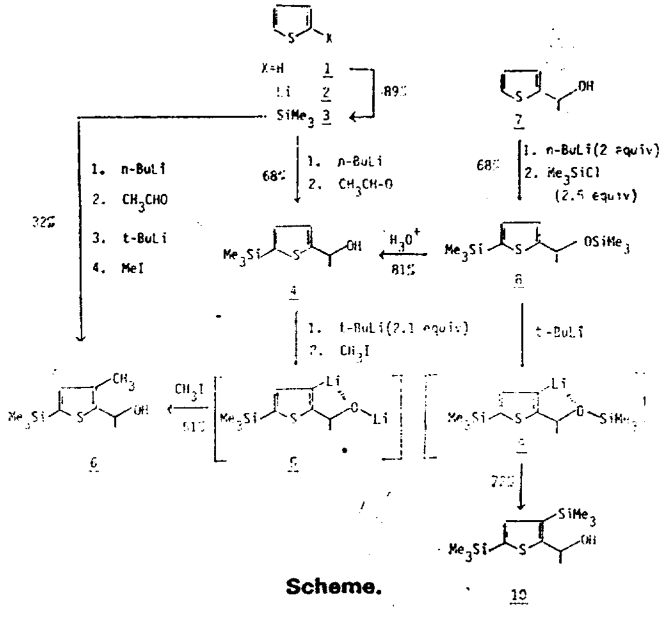
In connection with a synthetic program for biologically active compounds, were needed a series of vicinally 2, 3-disubstituted thiophenes. Survey of existing literature indicates that functionalization at carbons at 2- or 5-position (designated as C-2 and C-5, hereafter) presents no difficulties, which is normally possible with electrophilic reagents or by metalation with organo lithiums[1,2]. However, C-3 functionalization, especially with unsubstituted carbons at 2 or 5-position, is difficult for the same reason. Herein is reported a solution for this problem.

α-Lithiation of thiophene **1** with *n*-butyllithium (0.95 equiv. THF) at −78°C generated the thienyl organometallic **2**[2], which was quenched with 1.1 equiv Me_3SiCl in Et_3N(1:1) (−78 °C→rt) to give the corresponding silane **3** (bp 123-8°) in 89 % yield[4]. Subsequent metalation (*n*-BuLi, THF, −78 →0°C (1h) at C-5, followed by the reaction with 1.5 equiv acetaldehyde (78°C→0°) afforded the carbinol **4** in 68% yield[4]; TLC R_f 0.50 (50 % ether/hexane).

The crucial oxygen-directed metalation[3] could be executed eventlessly; treatment of the alcohol **4** with 2.1 equiv *tert*-butyllithium in ether at −78°C for 1hr and at 0°C for 3 hr generated alkoxy dianion **5**, which was subsequently alkylated with methyl iodide to yield the trisubstituted thiophene **6** in 51 %[4] after aqueous work-up and silica gel-chromatography; TLC R_f 0.54 (50 % ether/hexane). More significantly, the metallated species **5** did not undergo the well-documented fragmentation processes[5] even under refluxing HMPA-ether. Presumably, the internally chelated structure of **5** would well account for this stability. Alternatively, the transannular difunctionalization to form the alcohol **6** could be achieved, albeit in mere 32 % yield[4], using one-pot procedure; metalation (*n*-BuLi, ether, −78°C) of silane **3**, acetaldehyde quenching (1.1 equiv, −78 °C), second metalation (1.2 equiv *t*-BuLi, −78 →0°C), and subsequent reaction with 1.1 equiv methyl iodide (0 °C).

Also, α-thienyl methyl carbinol (bp 76-7°/8mm, TLC R_f 0.51 (50 % ether/hexane), prepared from α-thienyllithium **2**, could be cleanly 5-lithiated with 2 equiv *n*-BuLi in THF at −78°C[6] and the resulting dianion was *bis*-silylated with 2.5 equiv trimethylsilyl chloride (THF-Et_3N, 0°C) to afford a unusually TLC-stable silyl ether **8** in 68 % yield after aqueous work-up and chromatography[4]; TLC R_f 0.78 (50 % ether/hexane). Its chemical identity was further confirmed by correlation of the corresponding *o*-desilylated product [HOAc (cat.), MeOH, rt] to the previously prepared thienylethanol **4**(vide supra). Quite surprisingly, even the silyl ether functionality in the ether **8** was shown to direct the metalation with 1.2 equiv *t*-BuLi (ether, −78 →0°C) and the incipient anion **9**, in turn, underwent rapid rearrangement to a more stable alkoxide. Thus, after aqueous work-up and stripping-off



Scheme.

of solvents, the *bis*–silyl alcohol 10 (with purity $>$ 95 % by TLC and NMR) was obtained in 72 % yield[4]; TLC R_f 0.44 (50 % ether/hexane) (Scheme).

In summary, herein is reported a methodology by which C–3 functionalization on thiophene rings is cleanly achieved by means of C–5 protection with a silyl group (which is a super proton equivalent)[7,8] and of *ortho*–metalation utilizing an existing anchoring group at C–2. In view of recent brillant progress in organosilane chemistry[7,8], one should be able to transform the silicon–bearing carbons into nucleophiles or electrophiles, as well as its parent methine carbons. Extension of this concept and data refinement are under vigovous progress.

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(4) All thin layer chromatography utilized silicagel plates (Baker-flex) witha 1:1 (v/v) mixture of ether and hexane. The yields herein are not optimized, and the nmr spectral data for some selected compounds are summarized (CCl_4, $CHCl_3$ reference):
3, 7.0~7.4(m, 3H), 0.30 (s, 9H); **4,** 6.9 (m, 2H), 4.9(q, 1H), 1.46(d, 3H), 0.23(s, 9H); **6,** 6.83(s, 1H), 4.96(q, 1H), 2.13(s, 3H), 1.43(d, 3H), 0.23(s, 9H); **7,** 6.8–7.2(m, 3H), 4.9 (q, 1H), 1.43(d, 3H); **8,** 6.8(m, 2H), 4.96 (g, 1H), 1.41(d, 3H), 0.60(s, 9H), 0.26(s, 9H); 4.96(q, 1H), 1.41(d, 3H), 0.60(s, 9H), 0.26(s, 9H); **10,** 6.96(s, 1H), 5.1(q, 1H), 1.4(d, 3H), 1.4(d, 3H), 0.16(s, 18H).

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A Simple Proton NMR Spectrum of Coordinated Acrylonitrile

Myoung Kie Lee, Taehyun Kwon and Chong Shik Chin†

Department of Chemistry, Sogang University, CPO Box 1142, Seoul 121, Korea (*Received January 18, 1984*)

We wish to report a simple 8–line proton NMR spectrum for coordinated acrylonitrile in $[Rh(CH_2{=}CHCN)(CO)(P(C_6H_5)_3)_2]ClO_4$[1] where $CH_2{=}CHCN$ is coordinated through nitrogen[2] (free acrylonitrile gives rise to a complex 13–line ABC pattern). There have been two reports giving detailed proton NMR spectral data for coordinated acrylonitrile through nitrogen to transition metals.[4,5] It was found that the proton NMR spectra of coordinated acrylonitrile (in $[Ru(NH_3)_5(CH_2{=}CHCN)]^{2+}$ and $[Rh(NH_3)_5(CH_2{=}CHCN)]^{3+}$,[4] and $W(CO)_4(CH_2{=}CHCN)_2$[5]) are essentially identical with that of free acrylonitrile except that the chemical shifts are slightly shifted and the coupling constants show small changes. Accordingly, computer refinements were necessary to obtain the spectral parameters in both studies.[4,5]

Figure 1 is proton NMR spectrum of $[Rh(CH_2{=}CHCN)(CO)(P(C_6H_5)_3)_2]ClO_4$ which we recently prepared.[1] There are only 8 peaks attributable to the coordinated acrylonitrile in the region of 5.0~7.0 ppm (relative to TMS) in Figure 1, whereas free acrylonitrile shows a complex ABC pattern centered at *ca.* 6.0 ppm.[6] It is easily seen in Figure 1 that the doublet of doublet at 6.05 ppm is due to H(A) coupled by H(B) and H(C). The coupling constants, *J*(AB) and *J*(AC) are clearly confirmed by the two doublets at 5.35 ppm due to H(C) and at 5.47 ppm due to H(B), respectively, whereas the coupling between the geminal protons, H(B) and H(C) is not observed. No evidence is obtained for the coupling due to ^{103}Rh or ^{31}P.

Table 1 summarizes the spectral data for free $CH_2{=}CHCN$ and $CH_2{=}CHCN$ in $[Rh(CH_2{=}CHCN)(CO)(P(C_6H_5)_3)_2]ClO_4$. The small downfield shift (+0.31 ppm) for H(A) observed in this study lies within the range of the downfield shifts (+0.13~0.40 ppm) reported for the acrylonitrile coordinated through nitrogen in the previous studies.[4,5] The changes in the chemical shifts of H(B) and H(C) due to the coordination through nitrogen have been reported to be either way (upfield shift: −0.27 ppm for H(B) and −0.16 ppm for H(C) in Ru(II) complex,[4] and downfield shift: +0.37 ppm for H(B) and +0.43 ppm for H(C) in Rh (III)