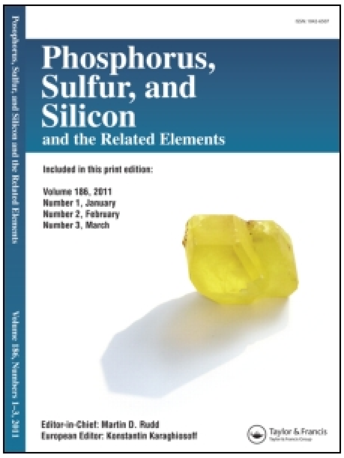

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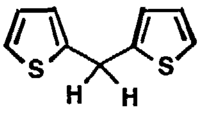
On the Acidity and Lithiation-Functionalization of Thiophenes: Revisited for their Use in the Synthesis of Thiophene-Based Novel π-Systems

MASAJI ODA,* TETSUYA ENOMOTO, TAKESHI KAWASE,
and HIROYUKI KURATA,
Department of Chemistry, Graduate School of Science, Osaka University,
Toyonaka, Osaka 560, Japan

When lithium diisopropylamide is used for lithiation and functionalization of thiophenes, whose acidity is here measured to be pKa = 35-36 in THF-Hex (5:3), the equilibrated nature of lithiation is to be taken into consideration.

Although lithiation of thiophenes are long known and applied to organic syntheses, some fundamental problems associated with the acidity of proton(s) at C-2(5) position, equilibrium in lithiation when bases other than alkyllithium are used, and regioslectivity of lithiation in rather complex thiophene derivatives seem to remain to be further clarified. In the course of our synthetic studies on thiophene-based novel π-systems of structural and physicochemical interest, it became desirable to get deeper insight in these problems.

We have recently reported doubly regioselective lithiation and functionalization of bis(2-thienyl)methane **1** and tris(2-thienyl)methane **3**.[1,2] Compound **1** is regioselectively lithiated either at the C-5 postion of the theinyl groups or methylene carbon (Cα) by choice of bases, solvents, and additives, where kinetic and thermodynamic control are important factors. The same is true for **2**. Compound **3** is, however, almost exclusively lithiated at Cα under any conditions because of high thermodynamic stability of Cα anion, but introduction of equilibrium in lithiation and taking advantage of large reactivity difference between Cα and C-5 anion made it possible clean triple functionalization at C-5 of the thienyl groups. LDA played key roles in changing the selectivity.



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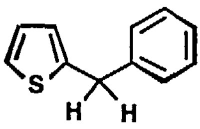

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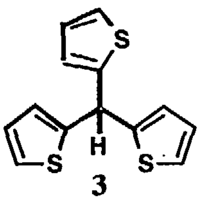
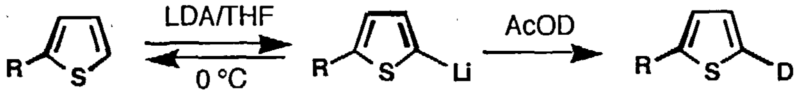


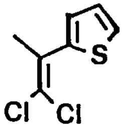
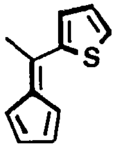
3

Varied values of pKa (30-38) have been reported for thiophene. The value, pKa = 33.0 in THF[3], is the most recent. In our lithiation of thiophenes using LDA, however, we felt the acidity of thiophene is somewhat weaker. Solvent effect is conceivable for the weakening because we usually use commercially available hexane solution of n-BuLi for the preparation of LDA in THF. The acidity data in THF-Hex would be thus of most practical use. Therefore, pKa of thiophenes in THF-hexane (5:3) were measured as follows: a thiophene and LDA (1:1) are equilibrated at 0 °C for 1 h in THF-Hex (5:3; 0.63 M), the mixture rapidly added with excess AcOD under efficient stirring (Scheme 1), and % deuterium incorporation at C-2 or C-5 measured by ^{1}H NMR. The results are summarized in Table 1. The value pKa = 35.9±0.1 is calculated for thiophene on the basis of pKa = 35.7[4] for i-Pr$_2$NH. The effect of substituents at C-2 for C-5H is observable but not so significant. The % deuterations, namely pKa's, are in good correaltion with the relevant ^{13}C chemical shifts (Fig. 1).



Scheme 1

Table 1. pKa of thiophenes

R	%D (±3)	pKa (±0.1)	^{13}C/ppm
H	43	35.9	125.0
n-Hep	41	36.1	122.7
p-BrC$_6$H$_4$	48	35.8	125.2
Br	54	35.6	126.9
	55	35.5	127.4
	60	35.3	130.0

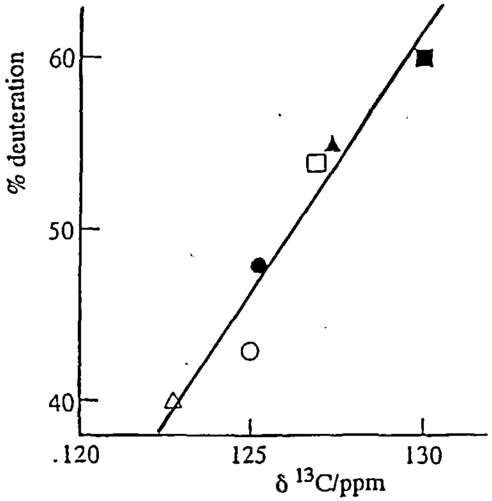


Fig. 1 Correlation of %D with ^{13}C chemical shift

Thus, when LDA is used in lithiation of thiophenes, choice of electrophile is important for good results of subsequent functionalization.

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