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Room Temperature Stable 3-Lithiothiophene: a Facile Synthesis of 3-Functional Thiophenes

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Abstract: 3-Functionalized thiophenes were readily prepared by reacting electrophiles with 3-lithiothiophene at room temperature. 3-Lithiothiophene was found to be stable in hexane at room temperature.

Poly(3-substituted thiophenes) are highly conducting polymers with good solubility, stability, and processability.[1] The precursors, especially 3-functionalized thiophenes, are fascinatingly attractive. Although few approaches to 3-functionalized thiophenes exist, the reaction of 3-lithiothiophene with different electrophiles at low temperature is a useful approach. A general method for the preparation of 3-lithiothiophene was introduced by S. Gronowitz.[2] Following his method, Noftle and Arnswald recently synthesized 3-lithiothiophene and 3-substituted thiophenes of the group IV elements at -78°C in good yields.[3]

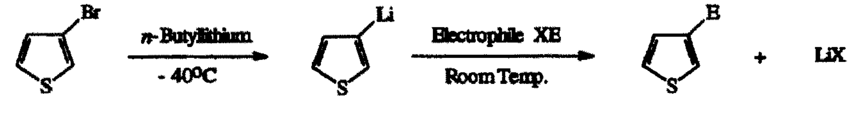
As shown by Gronowitz's procedure, 3-lithiothiophene was formed through the metal-halogen exchange reaction of 3-bromothiophene with *n*-butyllithium in polar solvents, such as ethers, at -70°C. The 3-lithiothiophene was only stable at this temperature and was converted into 2-lithiothiophene when the system was warmed up to room temperature.[3a, 4] This places a severe limitation on choice of electrophiles as many react with 3-lithiothiophene only at room temperature to form the desired 3-substituted thiophenes.

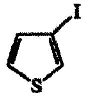
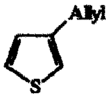
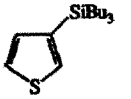
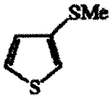
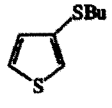
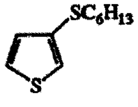
Recently, we found that 3-lithiothiophene was stable in hexane even at room temperature. The preparation is quite simple and straightforward. 3-Bromothiophene was dissolved in pure hexane and mixed with one equivalent of *n*-butyllithium at -40°C, no reaction was observed even when the reaction system was warmed up to room temperature, since metal-halogen exchange is very slow in hydrocarbon solvents.[5] Surprisingly however, a white solid (presumably 3-lithiothiophene) precipitated from the solution when a small amount of THF (:hexane = 1:10) was added to the flask *via* syringe at -40°C. Aryl-lithium compounds have previously been shown to have poor solubility in hydrocarbon solvents.[5] In order to prove that the 3-lithiothiophene didn't convert into 2-lithiothiophene in hexane at room temperature, we warmed up the system to room temperature and trapped the lithiothiophene with different electrophiles with excellent regioselectivity (3-position isomer > 99.5% compared to 2-position isomer) and good yields as shown in Table 1.

The following is a typical procedure for the preparation of 3-lithiothiophene and its derivatives: 3-bromothiophene (0.02 mol) was dissolved in hexane (30 mL), then mixed with *n*-butyllithium (0.021 mol) at -40°C under argon. THF (3 mL) was transferred into the flask. When the 3-bromothiophene had been completely consumed (15 min), more hexane (10mL) was added and it was warmed to room temperature. The

3-lithiothiophene was then allowed to react with various electrophiles at room temperature. The reaction mixture was worked up and products were isolated by vacuum-distillation or chromatography.

Table 1. Reactions of 3-Lithiothiophene with Different Electrophiles at R. T. in Hexane : THF = 10:1 System.



Entry	Electrophile	Product^a	Yield %^{b}	Entry	Electrophile	Product^a	Yield %^{b}
1	ICH_2CH_2I		63	2	$BrCH_2CH=CH_2$		40
3	n-Bu_3SiCl		58	4	MeSSMe		71
5	(n-BuS-)$_2$		55	6	$(C_6H_{13}S\text{-})_2$		52

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a) Elemental analysis, ^{1}H NMR, ^{13}C NMR, and FTIR were all consistent with the indicated formulation. b) Isolated yields: entries 1-4 were isolated by distillation, entries 5-6 were isolated by chromatography on silicon gel.

Room temperature stable 3-lithiothiophene has two obvious advantages: 1) it can react with different electrophiles over a wide temperature range; 2) the insoluble 3-lithiothiophene solid can be purified by removing the reaction solvent along with the byproducts. It also can be treated with other metal salts to obtain new 3-metalated thiophenes for further transformation.

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