6658 J. Org. Chem. 1995, 60, 6658−6659

Preparation of 3-Thienylzinc and -magnesium Halide via Oxidative Addition of Active Zinc and Magnesium to 3-Iodothiophene

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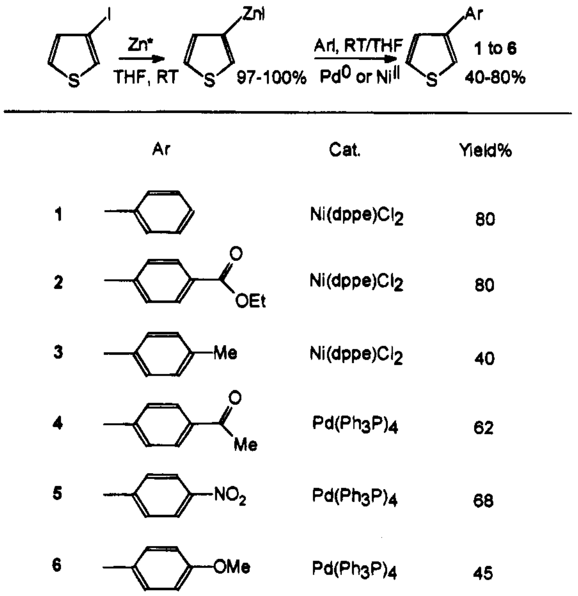
Received July 18, 1995

β-Substituted thiophenes are very useful chemical compounds which have application in both materials and pharmaceutical science. For instance, poly(3-substituted thiophenes) with long side chains are soluble, processable conducting polymers, and the properties of these polymers are strongly dependent on the properties of the functional groups.[1] Recently, β-substituted thiophene and furan derivatives have been found to be topical carbonic anhydrase inhibitors.[2] Consequently, the synthesis of 3-substituted functionalized thiophenes becomes important. Many 3-substituted thiophenes have been prepared by a variety of methods of which the reaction of 3-thienyl organometallics with electrophiles is the most popular.

A few 3-thienyl organometallics have been prepared. The procedures for the metalation of thiophene at the 3-position include the metal−halogen exchange reaction of 3-bromothiophene with *n*-butyllithium[3] and the metathesis of the 3-lithiothiophene with different metal halides.[4,6] The reaction of electrophiles with 3-thienyl organometallics leads to 3-substituted thiophenes, and the method has been widely used since it was introduced by Gronowitz. 3-Lithiothiophene was demonstrated to have a temperature-dependent stability in polar ethereal solvents and slowly underwent 2- and 3-regioexchange as well as decomposition at temperatures higher than −25 °C.[3b,5] However, 3-bromothiophene is rather unreactive toward magnesium.[4d,6] No reports about the preparation of 3-thienyl organometallics *via* oxidative addition of metals to 3-halothiophenes were presented, and Gronowitz's method became the only methodology for synthesis of 3-thienyl organometallics.

The formation of novel organometallic compounds by the reaction of organic substrates with finely divided metal powders (active metals) represents a powerful tool for the synthetic chemist.[7] Rieke metals (M*),[8] generated from the reduction of metal salts with lithium using naphthalene or biphenyl as an electron carrier in THF, are frequently the most active metal powder. Not only commercial Mg but also Zn* and Mg* are unreactive toward 3-bromothiophene. Our first attempt at synthesizing either 3-thienylzinc or the magnesium bromide by the oxidative addition of Zn* and Mg* to 3-bromothiophene failed, even though Mg* and Zn* can readily undergo oxidative addition to 2-bromothiophene or other aromatic heterocyclic halides.[9] In this paper, we would like to report the preparation of the 3-thienylzinc and magnesium iodides through the oxidative addition of active metals Mg* and Zn* to 3-iodothiophene[10] and the further transformations of these organometallic reagents.

Scheme 1. Preparation of 3-Thienylzinc Iodide via Oxidative Addition of Zn* to 3-Iodothiophene and Catalyzed Coupling Reactions of the Organozinc with Aryl Halides



The Rieke metals, Zn* and Mg*, are generally prepared through the reduction of ZnCl$_2$ and MgCl$_2$ by Li using naphthalene as an electron carrier in THF as mentioned above.[7] The active metals can be washed using THF to remove both the electron carrier and the lithium chloride. These Rieke metals readily undergo oxidative addition to 3-iodothiophene to form 3-thienyl organometallic reagents which react with electrophiles in THF at room temperature. The preparation of the active metals and the reactions of the organometallics are conducted under an inert argon atmosphere.

As shown in Scheme 1, 3-thienylzinc iodide was generated by the reaction of 3-iodothiophene with Rieke zinc (Zn*). Iodothiophene reacted slightly exothermically with Zn* (2 equiv) immediately upon addition. The conversion of 3-iodothiophene to 3-thienylzinc iodide was

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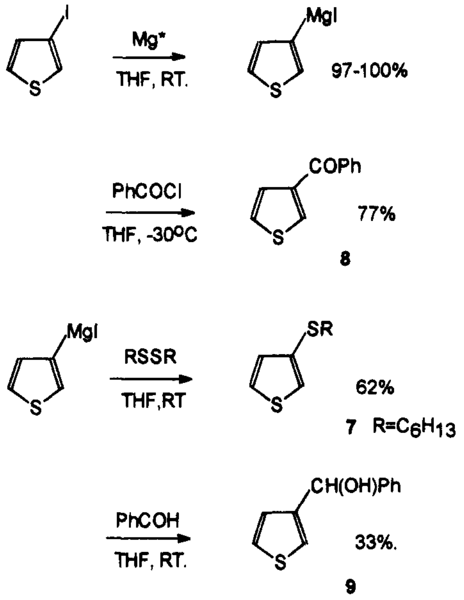
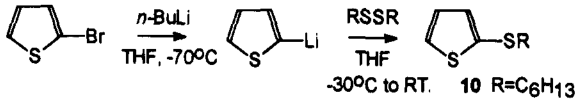
Scheme 2. Preparation of 3-Thienylmagnesium Iodide and Its Cross-Coupling Reactions with Different Electrophiles



Scheme 3. NMR Data



^{13}C NMR Chemical Shift and the Assignment for 7 and 10 Thiophene Ring

	C_2	C_3	C_4	C_5
7	122.6	132.3	129.6	126.0
10	135.0	133.1	127.4	128.8

^{1}H NMR Chemical Shift and the Assignment for 7 and 10 Thiophene Ring

	H_2	H_3	H_4	H_5
7	7.11(dd)	-	7.02(dd)	7.31(dd)
10	-	7.11(dd)	6.97(dd)	7.32(dd)

completed in 8–10 h according to GC analysis. The resulting 3-thienylzinc iodide underwent cross-coupling reactions with different aromatic halides using either Ni(dppe)Cl_2 or Pd(Ph_3P)$_4$ as catalyst. These reactions provided differentially functionalized and nonfunctionalized 3-arylthiophenes in good yields. The reactivity of the organozinc species was found to be substrate dependent, and the halides with an electron-withdrawing group in the *para* position were more active than the halides with an electron-donating group in the *para* position.

3-Thienylmagnesium iodide was also readily prepared from the oxidative addition of Mg* to 3-iodothiophene. Generally, 97–100% of 3-iodothiophene transformed to 3-thienylmagnesium iodide in 5–7 h using 1.5 equiv of Mg*. The 3-thienyl Grignard reagent reacted with different electrophiles such as aldehydes, acid chlorides, as well as alkyl disulfides and afforded 3-substituted thiophenes (Scheme 2).

3-Lithiothiophene in THF is temperature sensitive and converts to 2-lithiothiophene at temperatures above −25 °C. Therefore, the regiostability of the 3-thienylzinc iodide and magnesium iodide, prepared by exothermic oxidative addition in THF at room temperature, was also questionable. In order to clarify the room temperature regiostability of 3-thienylmagnesium iodide, we compared the NMR data of the products of $C_6H_{13}SSC_6H_{13}$ addition with 3-thienyl magnesium iodide at ambient temperature and 2-lithiothiophene at −30 °C to room temperature. The NMR data of the products obtanied in these transformations are summarized in Scheme 3.

According to the comparative analysis of the ^{1}H and ^{13}C NMR data of 3-(hexylthio)thiophene (**7**), prepared from 3-thienylmagnesium iodide, and 2-(hexylthio)thiophene (**10**), prepared from 2-lithiothiophene, it is easy to distinguish the structures of these two compounds. No detectable amount of **10** was found in the NMR spectra of compound **7** and in the GC spectra of crude and chromatographically purified **7**. This information leads to the conclusion that 3-thienylmagnesium iodide is regiostable in THF at room temperature[11] and maintains regiostability during coupling. Similarly, 3-thienylzinc iodide was also regiostable in THF at ambient temperature as shown by comparison of product **1** and 3-phenylthiophene prepared via phenylmagnesium bromide and 3-bromothiophene. The identical chemical shifts in the NMR data of these two compounds are indicative of the same molecular structure.[12]

In this report, we present a simple but efficient procedure of preparing 3-thienylzinc and -magnesium iodide reagents via oxidative addition of Rieke zinc and Rieke magnesium. These organometallics are regiostable in THF at room temperature as indicated by NMR studies. These organometallics are precursors to 3-substituted thiophenes, and the preparation of other thiophene derivatives mediated by 3-thienylzinc and -magnesium iodide are currently in progress.

Acknowledgment. We are very grateful to Dr. Richard Shoemaker for his help in performing the NMR experiments and data analysis. The financial support provided by the National Institutes of Health (GM35153) is also gratefully appreciated.

Supporting Information Available: Compound characterization data and HETCOR NMR spectra of compound **7** and **10** (7 pages).

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(11) Although 3-thienylmagnesium bromide was prepared via metathesis of 3-lithiothiophene with magnesium bromide in ethyl ether as described in refs 4d,e and 6, the room temperature regiostability of the Grignard reagent was not discussed.

(12) Compound 1: ^{13}C NMR δ 142.4, 135.9, 128.8, 127.1, 126.4, 126.3, 126.2, 120.3. The 3-phenylthiophene prepared from 3-bromothiophene: ^{13}C NMR 142.3, 135.8, 128.8, 127.1, 126.4, 126.3, 126.2, 120.2. See Chen, T.-A. Ph.D. dissertation, University of Nebraska—Lincoln, 1994, p 52.