Pergamon

PII: S0040-4039(96)02507-5

Tetrahedron Letters, Vol. 38, No. 6, pp. 993-996, 1997
Copyright © 1997 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/97 $17.00 + 0.00

Preparation and Coupling Reaction of Thienylmanganese Bromides

Seung-Hoi Kim, and Reuben D. Rieke*

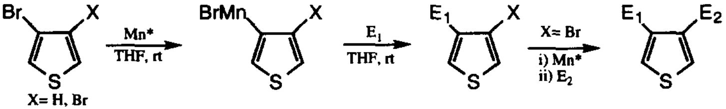
Department of Chemistry, University of Nebraska-Lincoln, Lincoln, Nebraska 68588-0304

Abstract : 3-Thienylmanganese bromide, 3-bromo-4-thienylmanganese bromide and 4-substituted 3-thienylmanganese bromides were prepared from the reactions of Rieke manganese with 3-bromothiophene, 3,4-dibromothiophene and 4-substituted 3-bromothiophenes, respectively. The resulting thienylmanganese bromides underwent cross-coupling reactions under mild reaction conditions. © 1997, Elsevier Science Ltd. All rights reserved.

In our continuing studies on the applications of active metals to synthetic organic chemistry, Rieke manganese (Mn*) was shown to exhibit superior reactivity towards oxidative addition to organic halides.[1] This discovery prompted us to investigate whether we could apply this finding to 3,4-dibromothiophene and 4-substituted 3-bromothiophene. Due to the possibility of functional group conversion of both bromine atoms of the thiophene ring, 3,4-dibromothiophene appears to be an ideal starting material[2] for the preparation of symmetrical and/or unsymmetrical 3,4-disubstituted thiophene derivatives, which are currently of interest in drug design and for the construction of new polymers.[3]

Acylation-reduction, lithiation-alkylation, thiophene ring construction and Grignard cross-coupling with bromothiophene are the representative methods for the preparations of alkyl- and aryl-thiophenes.[4]

In this letter, we would like to report a facile synthesis of 3-bromo-4-thienylmanganese bromide and 4-substituted 3-thienylmanganese bromides via the direct oxidative addition of Rieke manganese to 3,4-dibromothiophene and 4-substituted 3-bromothiophenes, respectively. And, the coupling reaction of the resulting thienylmanganese bromides with various electrophiles will be described. Also, the coupling reaction of 3-thienylmanganese bromide will be included.

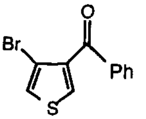
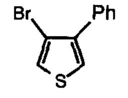
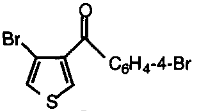
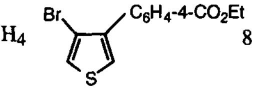
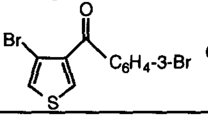
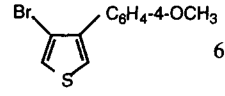


Scheme I

As shown in Table I, 3-bromo-4-thienylmanganese bromide was formed as a major product from the reaction of 1 equiv of 3,4-dibromothiophene and 2 equiv of Mn*.[5] and easily underwent cross-coupling reaction with acid chlorides and aryl iodides. According to the high resolution mass spectra of the products of entries 1, 4, 5, and 6 in Table 1, the second bromine atom of thiophene ring is still retained.

The coupling reaction of 3-bromo-4-thienylmanganese bromides with acid chlorides gave the corresponding ketones in good isolated yields (Table 1, entries 1, 2, and 3) without requiring any transition metal catalysts. Coupling reactions with aryl iodides were also examined. Using a catalytic amount of $Pd(PPh_3)_4$ catalyst, the corresponding C-C bond forming products were obtained in good yields (Table 1, entries 4, 5, and 6). It is noteworthy that the consecutive two precedures, oxidative addition and coupling step, can be completed at room temperature in a few hours.

Table 1. Coupling Reaction of 3-Bromo-4-thienylmanganese Bromide

Entry	Electrophile	Product [a]	Yield (%) [b]	Entry	Electrophile	Product [a]	Yield (%) [b]
1	PhCOCl		80	4 [c]	PhI		65
2	$4\text{-}BrC_6H_4COCl$		83	5 [c]	$4\text{-}EtO_2CC_6H_4$		86
3	$3\text{-}BrC_6H_4COCl$		62	6 [c]	$4\text{-}CH_3OC_6H_4$		69

a) ^1H, ^{13}C NMR , HRMS spectra were consistent with literature. b) Isolated yields (based on electrophile).
c) 10 mole % $Pd(PPh_3)_4$ was used as a catalyst (based on electrophile).

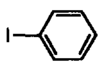
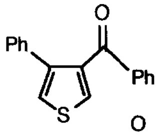
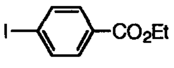
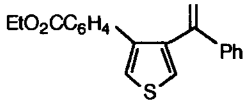
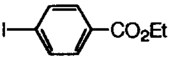
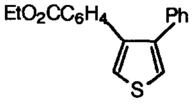
The same strategy was applied to 4-substituted 3-bromothiophenes to make unsymmetrical 3,4-disubstituted thiophenes. As shown in Table 2, cross-coupling products were obtained in moderate yields (36 - 66 %) under mild conditions. Oxidative additions of Mn* to the 4-substituted bromothiophenes were performed at rt in 5h and the successive coupling reactions of thienylmanganese bromides with benzoyl chlorides afforded unsymmetrical 3,4-disubstituted thiophenes at rt in 30 min without a catalyst (Table 2, entries 1 and 2). With a Pd(0) catalyst, C-C bond formation was completed from the reaction of the thienylmanganese bromide with 4-iodobenzene (Table 2, entry 3).

3-Substituted thiophene derivatives have attracted much attention in both material[6] and pharmaceutical science.[7] To date, the most widely used methods for the preparation of 3-substituted thiophene derivatives are the coupling reactions of 3-thienyl organometallic reagents with electrophiles. The intermediates used in these reactions are generally obtained via either a metal-halogen exchange reaction of 3-bromothiophene with n-butyllithium[8] or the metathesis of the 3-lithiothiophene with different metal halides.[9] However, these reactions suffer from a lack of regiospecificity as well as decomposition of the thiophene ring at rt.[8b,10] 3-Thienyl organometallic reagents can be prepared by the direct oxidative addition of active metals to 3-iodothiophene.[11] However, 3-iodothiophene is rather difficult to prepare.

3-Thienylmanganese bromide was easily prepared from the reaction of Mn* (2 equiv) and 3-bromothiophene (1 equiv). The oxidative addition of Mn* to 3-bromothiophene was accomplished in THF at rt. The reactions of 3-thienylmanganese bromide with acid chlorides gave the corresponding ketones in moderate to high yields (Table 3, entries 1 and 2). In the absence of additional electrophile, 3-thienylmanganese bromide underwent homocoupling reaction to give 3,3'-bithienyl with Pd(0) catalyst at rt (Table 3, entry 3). Under our reaction conditions, successful cross-coupling products were obtained from Pd(0)-catalyzed reactions with aryl electrophiles in good yields (Table 3, entries 4 and 5).

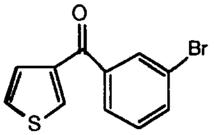
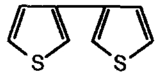
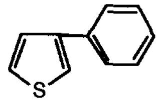
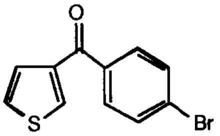
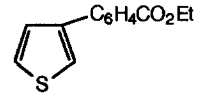
In conclusion, thienylmanganese bromide reagents are easily prepared via the direct oxidative addition of Rieke manganese to 3-bromothiophene 3,4-dibromothiophene and 4-substituted 3-bromothiophenes. These resulting thienylmanganese bromides undergo coupling reactions with acid chlorides to give the corresponding ketones and Pd(0) catalyzed C-C bond formation with aryl iodides afforded the corresponding aryl substituted thiophenes under mild reaction conditions.

Table 2. Coupling Reaction of 4-substituted 3-Bromothiophene

Entry	Electrophile1 (E_1)	Electrophile 2 (E_2)	Product[a]	Yield (%)[b]
1		PhCOCl		66
2		PhCOCl		46
3[c]		PhI		36

a) ^1H, ^{13}C NMR , HRMS spectra were consistent with literature. b) Isolated yields (based on electrophile).
c) 10 mole % $Pd(PPh_3)_4$ was used as a catalyst (based on electrophile).

Table 3. Coupling Reactions of 3-Thienylmanganese Bromide

Entry	Electrophile	Product[a]	Yield (%)[b]	Entry	Electrophile	Product[a]	Yield (%)[b]
1	3-BrC_6H_4COCl		91	3[c]	-		58
				4[c]	PhI		61
2	4-BrC_6H_4COCl		79	5[c]	$4\text{-IC}_6H_4CO_2Et$		70

a) ^1H, ^{13}C NMR , HRMS spectra were consistent with literature. b) Isolated yields (based on electrophile).
c) 10 mole % $Pd(PPh_3)_4$ was used as catalyst (based on electrophile).

The following is a representative procedure : to a slurry of Rieke manganese[12] (10.0 mmol) in THF (10 mL) under argon was added 3,4-dibromothiophene (5.0 mmol) at rt and the mixture was stirred at rt for 5h.[13] 1,2-Dibromoethane[14] (6.0 mmol) was added neat to the reaction mixture at 0 °C and the mixture was allowed to warm to rt over 20min. The resulting thienylmanganese bromide reagent was transfered via cannula to a flask containing a THF solution of ethyl 4-iodobenzoate (4.0 mmol) and $Pd(PPh_3)_4$ (0.4 mmol) at rt over 30min. The resulting mixture was sitrred at rt for 30min. The reaction mixture was quenched with 3M HCl (10 mL), extracted with ether (2x10 mL), and the combined organic layers were sequentially washed with saturated $NaHCO_3$, $Na_2S_2O_3$ and NaCl solutions, dried over $MgSO_4$, and concentrated. Flash chromatography (ethyl acetate/ hexanes) afforded Ethyl 4-(3-bromo-4-thienyl) benzoate in 70% isolated yield.

Acknowledgement

The authors thank Xiaoming Wu for helpful discussions regarding product identification. We gratefully acknowledge the financial support provided by the National Science Foundation.

References and Notes

1. Kim, S. H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *3,7,* 2197.
2. Gronowitz, S.; Moses, P.; Hornfeldt, A.-B.; Hakansson, R. *Ark. Kemi.* **1961**, *17,* 165.
3. (a) Daoust, G.; Leclerc, M. J. *Macromolecules* **1991**, *24,* 455. (b) Coffey, M.; McKellar, B. R.; Reinhardt, B. A.; Nijakowski, T.; Felda, W. A. *Synth. Commun.* **1996**, *26,* 2205 and references cited therein. (c) Leclerc, M.; Daoust, G.; *J. Chem. Soc., Chem. Commun.* **1990**, 273.
4. For representatives, see: (a) Sauter, F.; Stanetty, P.; Frohlich, H. *Heterocycles* **1987**, *26,* 2657. (b) Shu, P.; Chiang, L.-Y. *J. Chem. Soc., Chem. Commun.* **1981**, 920. (c) Chiang, L.-Y.; Shu, P.; Holf, D. *J. Org. Chem.* **1983**, *48,* 4713. (d) Reddinger, J. L.; Reynolds, J. R. *J. Org. Chem.* **1996**, *61,* 4833. (e) Tamao, K.; Kodama, S.; Nakajima, I.; Kumada, M.; Minato, A.; Suzuki, K. *Tetrahedron* **1982**, *38,* 3347 and references cited therein.
5. The formation of bis-organomanganese bromides can not be ruled out on the basis our gas chromatography monitoring. After acidic quenching of the reaction mixture followed by gas chromatography analysis, less than 5 % of thiophene was detected.
6. (a) Jen, K.-Y.; Miller, G. G.; Elsenbaumer, R. L. *J. Chem. Soc., Chem. Commun.* **1986**, 1346. (b) Hotta, S.; Rughooputh, S. D. D. V.; Heeger, A. J.; Wudl, F. *Macromolecules* **1987**, *20,* 212. (c) Sato, M.; Tanaka, S.; Kaeriyama, K. *J. Chem. Soc.,Chem. Commun.* **1986**, 873.
7. (a) Hartman, G. D.; Halczenko, W.; Smith, R. L.; Sugrue, M. F.; Mallorga, P. J.; Michelson, S. R.; Randall, W. C.; Schwam, H.; Sondey, J. M. *J. Med. Chem.* **1992**, *35,* 3822. (b) Holmes, J. M.; Lee, G. C. M.; Wijono, M.; Weinkam, R.; Wheeler, L. A.; Garst, M. E. *J. Med. Chem.* **1994**, *37,* 1646.
8. (a) Gronowitz, S. and Hakansson, R. *Arkiv. Kemi.* **1959**, *17,* 73. (b) Gronowitz, S. *Organic Sulphur Chemistry - Structure, Mechanism, and Synthesis;* Stering, C. J. M., Butterworths.**1975**, pp.203 - 228.
9. (a) Zhang, Y.; Hornfeldt, A. -B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32,* 435. (b) Ritter, S. K.; Noftle, R. E. *Chem. Mater.* **1992**, *4,* 872. (c) Arnswald, M.; Neumann, W. P. *J. Org. Chem.* **1993**, *58,* 7022. (d) Yamamura, K.; Miyake, H.; Nakatsuji, S. *Chem. Lett.* **1992**, 1213. (e) Gronowitz, S. *Arkiv. Kemi.* **1958**, *12,* 533.
10. Moses, P.; Gronowitz, S. *Arkiv. Kemi.* **1971**, *18,* 119.
11. Wu, X.; Rieke, R. D. *J. Org. Chem.* **1995**, *60,* 6658.; This report from our laboratory has shown that the direct oxidative additions to 3-iodothiophene were completed by using Rieke magnesium (Mg*) and Rieke zinc (Zn*). However, 3-bromothiophene was unreactive toward Mg* and Zn*.
12. In typical preparation, lithium (9.68 mmol), naphthalene (1.48 mmol), and anhydrous manganese iodide (4.71 mmol) under argon were stirred in freshly distilled THF (10 mL) for 1h at room temperature.
13. The formation of bis-organomanganese bromides can not be ruled out on the basis our gas chromatography monitoring. After acidic quenching of the reaction mixture followed by gas chromatography analysis, less than 5% of thiophene was detected.
14. 1,2-Dibromoethane was used to consume the remaining active manganese in the reaction mixture because Mn* was active to additional electrophile to give a homocoupling product.

(*Received in USA* 19 *November* 1996; *revised* 16 *December* 1996; *accepted* 17 *December* 1996)