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Journal of Organometallic Chemistry 598 (2000) 348–352

Journal of Organo metallic Chemistry

Conversion of tributylstannylferrocene to a variety of heteroaryl ferrocenes

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Received 4 August 1999; received in revised form 4 November 1999; accepted 9 November 1999

Abstract

Tributylstannylferrocene (Fc–$SnBu_3$) was converted to a variety of heteroaryl ferrocenes, such as 2-thiophenyl, 3-thiophenyl, 3-pyridyl, 3-quinolyl, 4-oxazolyl and 4-isoxazolyl ferrocene, by using Pd-catalyzed reactions. The Stille-coupling catalyst ($PdCl_2$–PPh_3) promotes the reaction between Fc–$SnBu_3$ and electron-deficient heterocyclic bromides, while a modified catalyst (Pd–Ph_3P–CuO) proves to be the choice for the coupling of Fc–$SnBu_3$ with electron-rich heterocyclic bromides. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Tributylstannylferrocene; Heterocyclic bromides; Stille coupling; Heteroarylferrocene

1. Introduction

Procedures have been reported for the synthesis of ferrocene-containing heterocyclic rings [1–6]. These ferrocene derivatives are useful materials for their applications in electrochemistry [7,8], biochemistry and materials science [9]. Ring cyclization reactions have been useful methods for preparing ferrocene-attached heterocycles [1–3], since the cyclization chemistry can focus specifically on heterocyclic ring formations. Alternatively, procedures have been developed for the introduction of heteroaryl groups into Cp rings of ferrocene [3–6], giving 1,1′-bis(2-heteroaryl) ferrocene structures.

We are interested in developing methods for efficient synthesis of a variety of heterocyclic ferrocene compounds, in which one heteroaryl ring is bonded to ferrocene. Our methodology allows for the construction of compounds with multi-functional groups, including amide, amine, ester, halogen, ketone and nitro moieties. To avoid the tedious de novo synthesis of individual functionalized compounds, it is desirable to develop a protocol that would promote the coupling of bromo-substituted heterocyclic rings to a common intermediate such as tributylstannylferrocene (Fc–$SnBu_3$).

Tributylstannylferrocene (Fc–$SnBu_3$) was prepared decades ago and used as an additive of lubricating oil [10]. Recently, Kagan and co-workers reported procedures for efficient preparation of tributylstannylferrocene [11,12]. Although the reported methods gave some undesired bis-substituted ferrocenes, the desired mono derivative was produced in good yield (70%). Our laboratory described an alternative protocol [13], which features easy reaction conditions and less contamination of bis-stannyl ferrocene. Herein, we report the use of tributylstannylferrocene as a key intermediate for synthesizing a variety of heteroaryl ferrocenes via palladium-promoted coupling reactions.

2. Results and discussion

The palladium-catalyzed reactions were initially investigated by the coupling of bromo-substitued quinoline derivatives **1a**–**e** with tributylstannylferrocene (**2**) (Scheme 1). The use of a $PdCl_2(PPh_3)_2$ complex promoted the desired couplings by heating the mixture of starting materials at 100–120°C in DMF. It appears that the benzene ring of quinoline can be substituted with either electron-donating or -withdrawing groups. The desired compounds **3a**–**e** were generally obtained in good yields.

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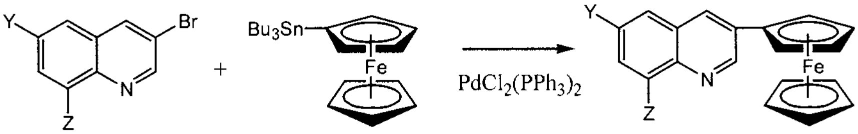
0022-328X/00/$ - see front matter
PII: S0022-328X(99)00733-0



1a: Y=Me, Z=NO$_2$
1b: Y=NO$_2$, Z=Me
1c: Y=OMe, Z=NO$_2$
1d: Y=NO$_2$, Z=OMe
1e: Y=Cl, Z=NO$_2$

2

3a, 89%
3b, 91%
3c, 87%
3d, 85%
3e, 80%

Scheme 1.

Mono heterocyclic rings were then used to probe the influence of ring electronic properties on the palladium-catalyzed carbon–carbon bond formation (Table 1). The complex of palladium chloride and triphenylphosphine promoted the coupling reactions between tributylstannylferrocene and a variety of functionalized pyridines (entries 9–12 and 14) and thiophenes (entries 17–20, 23–25). It was interesting to note that PdCl$_2$(PPh$_3$)$_2$ did not catalyze the coupling reactions of Fc–SnBu$_3$ with simple pyridines such as 2-bromopyridine (entry 6). Similar results were also observed for 3-bromopyridine (entry 9), several amino pyridines (entries 15–16) and 3-thiophene (entry 21). Results were not improved by using other related catalysts: PdClBz(PPh$_3$)$_2$ or PdCl$_2$(dppf) (not shown). We attempted to change the electronic property of 2-amino-5-bromopyridine by forming its hydrochloride salt, but the coupling of the salt with Fc–SnBu$_3$ gave fruitless results (trace to 25% yields, not shown). It can be generalized that PdCl$_2$(PPh$_3$)$_2$ promoted the desired couplings of FcSnBu$_3$ with only electron-deficient mono-heterocyclic systems.

For electron-rich heterocyclic bromides, we investigated the use of co-catalyst with the hope of generating a reactive palladium species or increasing the reactivity of heterocyclic rings by chelation. It was found that addition of CuO significantly improved the yield of compounds **3f** (entries 6–7). Similar results were obtained from 3-bromopyridine, 2-amino-3,5-dibromopyridine and 3-bromothiophene (entries 8, 13 and 22). Although the Pd(PPh$_3$)$_4$–CuO system had no catalytic effect on two pyridine derivatives (entries 13–14), it gave satisfactory yields for isoxazole and oxazole (entries 26–27). It was also observed that the Pd–PPh$_3$–CuO catalytic system gave the desired products (68–95% yield) in a relatively short period of time (about 1–4 h).

Tributylstannylferrocene was shown to be a suitable starting material for the synthesis of mono-substituted heteroarylferrocene compounds via Pd-catalytic coupling reactions. The standard complex of PdCl$_2$ and triphenylphosphine was the first choice, since the reactions can be simply carried out by heating the reaction mixtures for several hours to give the desired products in high yields. The co-catalyst system (Pd–PPh$_3$–CuO) offers an excellent option for electron-rich heterocyclic derivatives. Both systems use one-step procedures to synthesize efficiently a variety of functionalized heteroarylferrocenes, which are otherwise difficult to obtain.

3. Experimental

Infrared (IR) spectra were recorded in KBr on a Nicolet 179SX FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a FC-80A spectrometer using CDCl$_3$ as a solvent. Mass spectra were obtained on a VG ZBA-HS or HP5989A mass spectrometer.

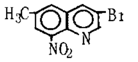
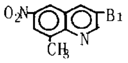
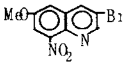
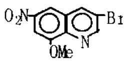
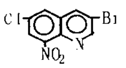
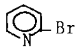
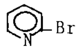
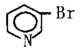
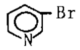
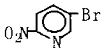
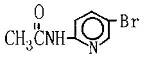
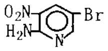
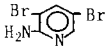
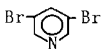
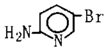
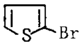
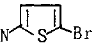
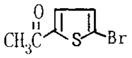
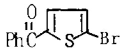
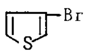
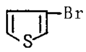
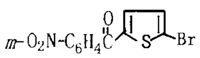
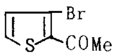
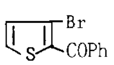
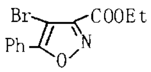
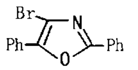
3.1. Coupling procedure using PdCl$_2$(PPh$_3$)$_2$

A mixture of bromosubstituted heteroarene (0.5 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.025 mmol) and Fc–SnBu$_3$ (0.55 mmol) in dry DMF (4 ml) was stirred at 120–130°C for the time given in Table 1. After the mixture was cooled to room temperature, water (8 ml) was added and the resulting solution was extracted with ether or dichloromethane. The organic layer was sequentially washed with saturated KF solution, water, and dried over MgSO$_4$. Evaporation of solvents gave a residue that was purified by chromatography on a silica gel column (eluant: petroleum–acetone in a ratio that was determined by the TLC studies of each product).

3.2. Coupling procedure using Pd(PPh$_3$)$_4$–CuO

A mixture of bromosubstituted heteroarene (0.5 mmol), Pd(PPh$_3$)$_4$ (0.025 mmol) and CuO (0.5 mmol) in dry DMF (4 ml) was heated to 130°C under argon for 30 min. Tributylstannylferrocene (0.55 mmol) was then added in one portion at 100°C, and heating was continued at 120–130°C for the time given in Table 1. The aforementioned work-up procedure was used for obtaining the desired product.

Table 1
Coupling results between Fc–$SnBu_3$ and various heterocyclic bromides

Entry	Product	Bromide	Catalyst	Time (h)	Yield (%)
1	3a		$PdCl_2(PPh_3)_2$	4.0	89
2	3b		$PdCl_2(PPh_3)_2$	4.0	91
3	3c		$PdCl_2(PPh_3)_2$	13.0	87
4	3d		$PdCl_2(PPh_3)_2$	13.0	85
5	3e		$PdCl_2(PPh_3)_2$	10.0	80
6	3f		$PdCl_2(PPh_3)_2$	10.0	trace
7	3f		$Pd(PPh_3)_4$-CuO	3.5	95
8	3g		$Pd(PPh_3)_4$-CuO	1.5	85
9	3g		$PdCl_2(PPh_3)_2$	8.0	17
10	3h		$PdCl_2(PPh_3)_2$	1.0	96
11	3i		$PdCl_2(PPh_3)_2$	1.3	97
12	3j		$PdCl_2(PPh_3)_2$	1.5	90
13	3k		$Pd(PPh_3)_4$-CuO	3	68
14	3l		$PdCl_2(PPh_3)_2$	10	58
15	3m		Various Pd-complexes	~ 10	trace
16	3n		Various Pd-complexes	~ 10	trace
17	3o		$PdCl_2(PPh_3)_2$	2.0	80
18	3p		$PdCl_2(PPh_3)_2$	1.0	95
19	3q		$PdCl_2(PPh_3)_2$	1.5	89
20	3r		$PdCl_2(PPh_3)_2$	2.0	90
21	3s		$PdCl_2(PPh_3)_2$	8.0	13
22	3s		$Pd(PPh_3)_4$-CuO	1.5	90
23	3t		$PdCl_2(PPh_3)_2$	2.0	56
24	3u		$PdCl_2(PPh_3)_2$	3.0	78
25	3v		$PdCl_2(PPh_3)_2$	4.0	36
26	3w		$Pd(PPh_3)_4$-CuO	1.5	95
27	3x		$Pd(PPh_3)_4$-CuO	1.5	89

3a was obtained as deep red solid, d.p. 155°C ^{1}H-NMR: δ 2.6 (s, 3H), 4.05 (s, 5H), 4.46 (m, 2H), 4.77 (m, 2H), 7.73 (s, 1H), 7.8 (s, 1H), 8.01 (s, 1H), 9.13 (s, 1H); IR: 1065, 1503, 1101, 999, 486 cm^{-1}; FAB MS: *m*/*z* 372 (M$^+$, 18%).

3b was obtained as deep red solid, d.p. 145°C ^{1}H-NMR: δ 2.8 (s, 3H), 4.0 (s, 5H), 4.4 (m, 2H), 4.74 (m, 2H), 8.07 (s, 1H), 8.17 (s, 1H), 8.47 (s, 1H), 9.13 (s, 1H); IR: 1603, 1478, 1092, 1000, 490 cm^{-1}; FAB MS: *m*/*z* 372 (M$^+$, 28%).

3c: deep red solid, d.p. 150°C ^{1}H-NMR: δ 3.9 (s, 3H), 4.0 (s, 5H), 4.4 (m, 2H), 4.71 (m, 2H), 7.15 (s, 1H), 7.55 (s, 1H), 7.94 (s, 1H), 8.9 (s, 1H); IR: 1625, 1496, 1252, 1096, 1009, 481 cm^{-1}; FAB MS *m*/*z* 388 (M$^+$, 6%).

3d: deep red solid, d.p. 160°C ^{1}H-NMR: δ 3.95 (s, 5H), 4.05 (s, 3H), 4.37 (m, 2H), 4.7 (m, 2H), 7.61 (s, 1H), 8.05 (s, 1H), 8.20 (s, 1H), 9.07 (s, 1H); IR: 1611, 1489, 1258, 1085, 996, 499 cm^{-1}; FAB MS *m*/*z* 388 (M$^+$, 18%).

3e: deep red solid, d.p. 150°C ^{1}H-NMR: δ 3.98 (s, 5H), 4.4 (m, 2H), 5.7 (m, 2H), 7.8 (s, 2H), 7.9 (s, 1H), 9.05 (s, 1H); IR: 1603, 1489, 1092, 997 cm^{-1}; FAB MS *m*/*z* 392 (M$^+$, 9.5%).

3f: orange solid, m.p. 93–94°C (reported 91–92°C [5]); ^{1}H-NMR: δ 8.52 (d, $J = 4.88$ Hz, 1H), 7.72–7.38 (m, 2H), 7.09 (m, 1H), 4.97 (m, 2H), 4.44 (m, 2H), 4.09 (s, 5H); FAB MS *m*/*z* 263 (M$^+$, 100%).

3g: orange solid, m.p. 52–54°C (reported 57–59°C [5]); ^{1}H-NMR: δ 4.07 (s, 5H), 4.38 (m, 2H), 4.68 (m, 2H), 7.18 (m, 1H), 7.73 (m, 1H), 8.44 (m, 1H), 8.75 (s, 1H); IR: 3060, 1591, 1496, 1100, 1000, 496 cm^{-1}; FAB MS *m*/*z* 263 (M$^+$, 100%).

3h: purple solid, m.p. 236–238°C; ^{1}H-NMR: δ 4.11 (s, 5H), 4.56 (m, 2H), 4.81 (m, 2H), 7.98 (dd, $J = 8.29$. 2.07 Hz, 1H), 8.19 (d, $J = 8.29$ Hz, 1H), 8.68 (d, $J = 2.07$ Hz, 1H); IR: 3049, 1576, 1523, 1494, 1107, 1021, 501 cm^{-1}; FAB MS *m*/*z* 308 (M$^+$, 100%).

3i: bright brownish yellow solid, m.p. 171–173°C; ^{1}H-NMR: δ 2.23 (s, 3H), 4.07 (s, 5H), 4.37 (m, 2H), 4.64 (m, 2H), 7.79 (dd, $J = 8.161$, 76 Hz, 1H), 8.17 (d, $J = 8.61$ Hz, 1H), 8.38 (d, $J = 1.76$ Hz, 1H), 8.92 (NH); IR: 3238, 3088, 1663, 1579, 1442, 1102, 999, 489 cm^{-1}; FAB MS *m*/*z* 320 (M$^+$, 100%).

3j: purple solid, m.p. 198–200°C; ^{1}H-NMR: δ 4.10 (s, 5H), 4.38 (m, 2H), 4.63 (m, 2H), 8.40 (d, $J = 2.42$ Hz, 1H), 8.53 (d, $J = 2.42$ Hz, 1H); IR: 3467, 3280, 3055, 1641, 1564, 1522, 1440, 1107, 1000, 471 cm^{-1}; FAB MS *m*/*z* 323 (M$^+$, 100%);

3k: reddish orange solid, m.p. 123–124°C; ^{1}H-NMR: δ 4.22 (s, 5H), 4.46 (m, 2H), 4.57 (m, 2H), 5.32 (NH_2), 7.61 (d, $J = 2.33$ Hz, 1H), 8.03 (d, $J = 2.33$ Hz, 1H); IR: 3446, 3288, 1619, 1560, 1448, 1105, 1000, 493 cm^{-1}; FAB MS *m*/*z* 356 (M$^+$, 99.43%), 358 (M$^+$, 100%).

3l: orange solid, m.p. 46–49°C; ^{1}H-NMR: δ 4.09 (s, 5H), 4.43 (m, 2H), 4.68 (m, 2H), 8.04 (m, 1H), 8.77 (m, 2H); IR: 3037, 1588, 1496, 1102, 1009, 485 cm^{-1}; FAB MS *m*/*z* 341 (M$^+$, 50%), 343 (M$^+$, 48%).

3o: orange red solid, m.p. 90–92°C (reported 116.5–117.5°C [6]); ^{1}H-NMR: δ 7.28–6.87 (m, 3H), 4.79 (m, 2H), 4.43 (m, 2H), 4.27 (s, 5H); IR: 3084, 1597, 1540, 1456, 1104, 1000, 507 cm^{-1}; FAB MS *m*/*z* 268 (M$^+$, 72.5%).

3p: purple solid, m.p. 120–122°C; ^{1}H-NMR: δ 7.79 (d, $J = 4.2$ Hz, 1H), 6.94 (d, $J = 4.2$, 1H), 4.70 (m, 2H), 4.50 (m, 2H), 4.16 (s, 5H); IR: 3048, 1535, 1485, 1462, 1103, 1001, 489 cm^{-1}; FAB MS *m*/*z* 313 (M$^+$, 57.5%).

3q: deep red solid, m.p. 151–154°C (reported 148–151°C [14]); ^{1}H-NMR: δ 7.53 (d, $J = 3.9$, 1H), 7.02 (d, $J = 3.9$, 1H), 4.67 (m, 2H), 4.40 (m, 2H), 4.12 (s, 5H), 2.55 (s, 3H); IR: 3082, 2949, 1648, 1100, 1022, 491 cm^{-1}; FAB MS *m*/*z* 310 (M$^+$, 100%).

3r: deep red solid, m.p. 125–128°C; ^{1}H-NMR: δ 7.94–7.55 (m, 5H), 7.47 (d, $J = 3.9$, 1H), 7.04 (d, $J = 3.9$, 1H), 4.72 (m, 2H), 4.44 (m, 2H), 4.15 (s, 5H); IR: 3084, 3025, 1682, 1575, 1475, 1446, 1106, 999, 506 cm^{-1}; FAB MS *m*/*z* 372 (M$^+$, 2%), 371 (8.3%).

3s: orange solid, m.p. 100–102°C; ^{1}H-NMR: δ 7.6–7.15 (m, 3H), 4.67 (m, 1H), 4.57 (m, 1H), 4.31 (m, 2H), 4.08 (s, 5H); IR: 3092, 1599, 1549, 1514, 1450, 1101, 999 cm^{-1}; FAB MS *m*/*z* 268 (M$^+$, 90.5%).

3t: purple solid, m.p. 92–94°C; ^{1}H-NMR: δ 8.70 (s, 1H), 8.48 (d, $J = 7.32$ Hz, 1H), 8.22 (d, $J = 7.78$ Hz, 1H), 7.73 (m, 1H), 7.47 (d, $J = 3.99$ Hz, 1H), 7.09 (d, $J = 3.99$ Hz, 1H), 4.57 (m, 2H), 4.33 (m, 2H), 4.10 (s, 5H); IR: 3091, 1628, 1529, 1481, 1091, 998 cm^{-1}; FAB MS *m*/*z* 417 (M$^+$, 67.3%).

3u: deep red liquid; ^{1}H-NMR: δ 7.67 (d, $J = 4.2$, 1H), 7.16 (d, $J = 4.2$, 1H), 4.712 (m, 2H), 4.43 (m, 2H), 4.21 (s, 5H), 2.38 (s, 3H); IR: 3093, 1649, 1528, 1459, 1106, 1002 cm^{-1}; FAB MS *m*/*z* 310 (M$^+$, 10%), 309 (61%).

3v: deep red solid, m.p. 37–40°C; ^{1}H-NMR: δ 7.73–7.21 (m, 7H), 4.50–4.07 (m, 9H); IR: 3092, 1630, 1596, 1534, 1447, 1108, 1000, 500 cm^{-1}; FAB MS *m*/*z* 372 (M$^+$, 77.6%).

3w: red solid, m.p. 124–126°C; ^{1}H-NMR: δ 7.35–7.66 (m, 5H), 4.66 (q, $J = 7.2$, 2H), 4.54 (m, 2H), 4.31 (m, 2H), 4.06 (s, 5H), 1.54 (t, $J = 7.2$, 3H); IR: 3088, 1735, 1614, 1475, 1440, 1101, 1007, 492 cm^{-1}; FAB MS *m*/*z* 401 (M$^+$, 100%)

3x: red solid, m.p. 125–127°C; ^{1}H-NMR: δ 8.09–8.28 (m, 2H), 7.80–7.93 (m, 2H), 7.30–7.65 (m, 6H), 4.75 (m, 2H), 4.37 (m, 2H), 4.25 (s, 5H); IR: 3055, 1551, 1453, 1449, 1109, 1001, 487 cm^{-1}; FAB MS *m*/*z* 405 (M$^+$, 100%).

Acknowledgements

This research has been supported by Middle-Young Science Foundation of Gansu Province no. ZQ-97-002.

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