Article

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$FeCl_3$ Catalyzed Barbier Homocoupling Reaction for Synthesis of Symmetric Biaryls

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A series of biaryls and biheteroaryls were synthesized by the Barbier reaction of aryl bromide with magnesium powder and 1,2-dibromoethane in the presence of $FeCl_3$ in THF under reflux reaction condition. The catalytic system differentiates itself from other homocoupling reactions catalyzed by iron salts in that it requires neither the preliminary preparation of Grignard reagent nor the addition of an oxidant.

Keywords: Biaryl; Barbier homocoupling reaction; Iron salt.

INTRODUCTION

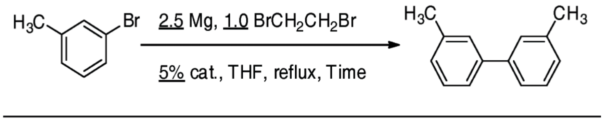
Biaryls constitute core structural motifs for a wide range of functional molecules and their potential applications in optoelectronic materials and molecular devices are well-recognized.[1] The original and most widely used route to biaryls is the copper-mediated homocoupling reactions of aryl halides (Ullmann reaction).[2] The need to avoid the harsh reaction conditions typically required for Ullmann couplings has motivated the search for milder variations. The iron-catalyzed homocoupling reaction of aryl halides has recently received considerable attention because the reactions proceed under milder reaction conditions which compared to the classical Ullmann reaction conditions.[3] Homocoupling reactions of aryl Grignard reagents are an easy and efficient access to symmetrical Biaryls. Hayashi and co-worker have demonstrated the efficiency of the iron-catalyzed homocoupling of aryl Grignard reagents using stoichiometric amount of 1,2-dichloroethane as an oxidant.[4] However, for industrial applications, these methods are limited since they require preparation of Grignard reagent and a stoichiometric amount of organic oxidant.[5] Herewith, we wish to report a simple method for synthesis of biaryls from aryl bromide with a catalytic amoumt of $FeCl_3$ under Barbier reaction condition (Scheme I).[6] This homocoupling reaction of aryl bromide was performed in one pot by a combination of unactivated magnesium powder[7] and a catalytic amount of iron salt. The catalytic system differentiates itself from other homocoupling reactions catalyzed by iron salts in that it requires neither the preparation of Grignard reagent nor the addition of an oxidant.

Scheme I

$$\text{Ar-Br} \xrightarrow[\text{THF, reflux}]{5\%\ \text{FeCl}_3\text{, Mg, BrCH}_2\text{CH}_2\text{Br,}} \text{Ar-Ar}$$

The first feasibility of our approach was tested by adding 1,2-dibromoethane (1.0 mmol) to a mixture of 3-bromotoluene (1.0 mmol), magnesium powder (2.5 mmol), CuCl (0.05 mmol) in THF (5 mL) and the reaction mixture was refluxed for 15 hours (Scheme II). The expected product biphenyl was only obtained with 40%. Others copper salts such as CuBr, CuI, $CuCl_2$, $CuBr_2$ and $Cu(OAc)_2$ also were investigated and $CuBr_2$ as catalyst improved the biphenyl formation yield to 72%. The formation yield of bi-

Scheme II



Entry	Catalyst	Time (hr)	Yield(%)[a]
1	CuCl	15	40
2	CuBr	15	37
3	CuI	12	40
4	$CuCl_2$	12	64
5	$CuBr_2$	12	72
6	$Cu(OAc)_2$	20	N.R.[b]
7	$FeCl_3$	1.5	80
8	$FeBr_3$	1.5	62
9	FeF_3	20	45

[a] Isolated yields were measured and based on 3-bromotoluene.
[b] No reaction and starting material was recovered.

Dedicated to the memory of Professor Yung-Son Hon (1955–2011).

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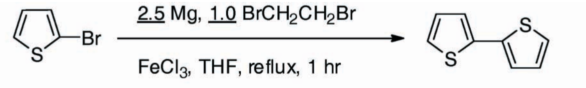
phenyl was improved to 80% when $FeCl_3$ was used as catalyst under the reaction condition. The reaction time by using iron salt catalyst under the reaction condition was much shorter than using copper salt catalyst.

In order to realize the optimized reaction condition of this Barbier homocoupling reaction, 2-bromothiophene was selected as the testing substrate for synthesis of bisthiophene which was well known as the important synthetic intermediate of optoelectronic material.[8] The introducing amount of $FeCl_3$ in different solvent was investigated and the results were shown in Scheme III.

Scheme III



Entry	$FeCl_3$ (mol%)	Solvent	Yield(%)[a]
1	3	THF	65
2	5	THF	82
3	10	THF	71
4	15	THF	66
5	20	THF	56
6	5	Toluene	N.R.[b]
7	5	Hexane	N.R.[b]

[a] Isolated yields were measured and based on 2-bromothiophene.
[b] No reaction and starting material was recovered.

1,2-Dibromoethane (2.0 mmol) was added to a reaction mixture of 2-bromothiophene (2.0 mmol), magnesium powder (5.0 mmol), $FeCl_3$ (0.1 mmol) in THF (10 mL) and the reaction mixture was refluxed for 1 hour and the bisthiophene was obtained with 82% yield. Different introducing amount of catalyst $FeCl_3$ was investigated and the experimental results showed that 0.05 molar ratio of $FeCl_3$ to substrate is the best choice for this Barbier homocoupling reaction. It should be noted that the Barbier homocoupling reaction did not proceed when toluene or hexane was used as solvent.

RESULTS AND DISCUSSION

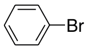
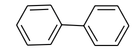
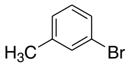
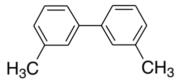
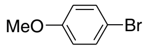
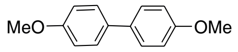
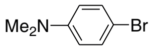
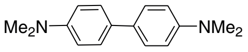
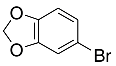
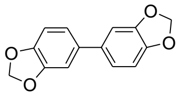
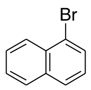
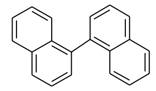
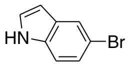
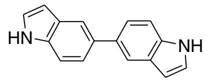
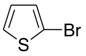
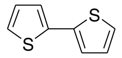
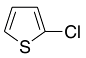
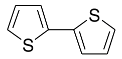
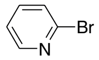
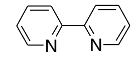
To understand and expand the scope for synthesis of biaryls by this Barbier homocoupling reaction, a series of aryl bromides was investigated and the results are shown in Table 1. Various aromatic bromides underwent the homocoupling smoothly affording the corresponding symmetrical biaryls in moderate to excellent yields. It is interesting to know that 1*H*,1′*H*-5,5′-biindoyl compound was obtained with the starting unprotected 5-bromoindole under the Barbier reaction condition (Table 1, Entry 7).

A representative procedure for synthesis of a biaryl is as follows: 1,2-Dibromoethane (2.0 mmol) was added to a mixture of aryl bromide (2.0 mmol), magnesium powder (5.0 mmol), $FeCl_3$ (0.1 mmol) in anhydrous THF (10 mL) and the reaction mixture was refluxed for 1 hour. The cooled reaction mixture was filtrate by a paper filter and the filtrate was extracted with ether (20 mL × 3). The combined organic layer was washed with brine (20 mL), dried with $MgSO_4$, filtered, and then the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexane as eluant.

As a conclusion, we demonstrate here an efficient

Table 1. Synthesis of biaryls

$$\mathrm{Ar{-}X} \xrightarrow[\underline{5}\%\ \mathrm{FeCl_3,\ THF,\ reflux,\ 1\ hr}]{\underline{2.5}\ \mathrm{Mg},\ \underline{1.0}\ \mathrm{BrCH_2CH_2Br}} \mathrm{Ar{-}Ar}$$

Entry	Aryl-X	Product	Yield(%)[a]
1			80
2			80
3			80
4			75
5			79
6			81
7			81
8			82
9			40
10			49

[a] Isolated yields were measured and based on introducing amount of Ar-X.

method for the synthesis of symmetric biaryls under Barbier reaction condition. The Barbier homocoupling reaction of aryl bromides was successfully performed in one pot by a combination of unactivated magnesium powder and a catalytic amount of iron trichloride. This catalytic system differentiates itself from other homocoupling reactions catalyzed by iron salts in that it requires neither the preliminary preparation of Grignard reagent nor the addition of an oxidant.

EXPERIMENTAL

Biphenyl (Table 1, Entry 1)

^{1}H-NMR: δ 7.34 (2H, t, J = 7.2 Hz), 7.44 (4H, t, J = 7.2 Hz), 7.60 (4H, d, J = 7.5 Hz); ^{13}C-NMR: δ 127.3, 127.4, 128.9, 141.4.

3,3′-Dimethylbiphenyl (Table 1, Entry 2)

^{1}H-NMR: δ 2.48 (6H, s), 7.22 (2H, d, J = 7.5 Hz), 7.38 (2H, dt, J = 1.6 Hz, 7.5 Hz), 7.46 (2H, dd, J = 11 Hz), 7.47 (2H, s); ^{13}C-NMR: δ 21.7, 124.4, 128.1, 128.18, 128.8, 138.4, 141.5.

4,4′-Dimethoxybiphenyl (Table 1, Entry 3)

^{1}H-NMR: δ 3.84 (6H, s), 6.95 (4H, d, J = 9.0 Hz), 7.47 (4H, d, J = 9.0 Hz); ^{13}C-NMR: δ 55.5, 114.3, 127.9, 133.6, 158.9.

4,4′-Bis(dimethylamino)biphenyl (Table 1, Entry 4)

^{1}H-NMR: δ 2.95 (12H, s), 6.78 (4H, t, J = 8.5 Hz), 7.43 (4H, d, J = 8.5 Hz); ^{13}C-NMR: δ 40.8, 113.1, 126.9, 129.8, 149.2.

5,5′-Bi-1,3-benzodioxole (Table 1, Entry 5)

^{1}H-NMR: δ 5.89 (4H, s), 6.85 (2H, d, J = 7.3 Hz), 5.99 (4H, d, J = 7.3 Hz); ^{13}C-NMR: δ 101.3, 107.7, 108.7, 120.5, 135.6, 146.9, 148.2.

1,1′-Binaphthyl (Table 1, Entry 6)

^{1}H-NMR: δ 7.28-7.31 (2H, m), 7.38 (2H, d, J = 8.5 Hz), 7.44 (4H, m), 7.56 (2H, m), 7.93 (4H, m); ^{13}C-NMR: δ 125.5, 126.0, 126.1, 126.7, 128.0, 128.1, 128.3, 133.0, 133.7, 138.6.

1*H*,1′*H*-5,5′-Biindoyl (Table 1, Entry 7)

^{1}H-NMR: δ 6.62 (1H, d, J = 3 Hz), 7.24 (1H, d, J = 3 Hz), 7.26 (1H, d, J = 1 Hz), 7.46 (1H, dd, J = 8.1 Hz), 7.53 (1H, dd, J = 8.1 Hz), 7.90 (1H, d, J = 1 Hz), 8.14 (bs, 1H); ^{13}C-NMR: δ 102.9, 111.0, 119.3, 122.4, 124.6, 128.4, 134.7, 134.8.

2,2′-Bithiophene (Table 1, Entry 8)

^{1}H-NMR: δ 7.00 (2H, dd, J = 3.70, 4.95 Hz), 7.71-7.26 (4H, m); ^{13}C-NMR: δ 123.9, 124.5, 127.9, 137.6.

2,2′-Bipyridyl (Table 1, Entry 10)

^{1}H-NMR: δ 7.13 (2H, m, J = 7.2 Hz), 7.64 (2H, m, J = 7.2 Hz), 8.74 (2H, m, J = 7.5 Hz), 8.64 (2H, m J = 7.2 Hz); ^{13}C-NMR: δ 121.3, 123.9, 137.1, 149.4, 156.4.

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