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Direct Palladium-Catalyzed C-4 Arylation of Tri-substituted Furans with Aryl Chlorides: An Efficient Access to Heteroaromatics

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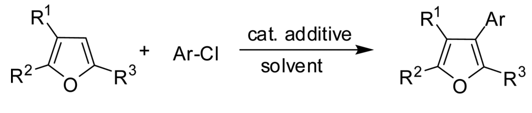
A series of functionalized furans were synthesized by way of a palladium -catalyzed coupling reaction of 2,3,5-trisubstituted furans with aryl chlorides through C-H bond cleavages at C-4 position. The feature of the reaction was facilitative preparation of furan derivatives with good functional group tolerance. All reactions gave the desired products in moderate to good yields in the presences of $BuAd_2P$ and *t*-BuOK in DMF at 120 °C after 15 h.

Key Words : Palladium catalyst, Coupling reaction, Furan, Arylation, Aryl chloride

Introduction

Palladium-catalyzed cross-coupling reactions are efficient methods for carbon-carbon bonds formations and play a crucial role in organic chemistry.[1-3] They have attracted significant attention because of their synthetic efficiency and high product yields in modern organic transformation.[4-8] Therefore, more and more synthetic organic chemists have focused much of their attention on the palladium-catalyzed cross-coupling reaction to develop efficient and convenient transformation for synthesis of biaryl compounds.[9-12] During the past decades, more efficient palladium-catalyzed coupling reactions have been reported to form carbon-carbon bonds.[1,13-15] Among them, particular attention has been paid to the Suzuki-Miyaura,[16] Mizoroki-Heck[17] and Sonogashira[18] coupling reaction which are one of the most powerful tools to form carbon-carbon in organic transformations.[19-21] Therefore, the development of new strategies and methodologies for construction of carbon-carbon bonds *via* palladium-catalyzed coupling reactions remains a continuing challenge reflecting the growing needs for pharmaceutical, food, and agricultural industries.[22-25] In this context, an efficient palladium-catalyzed coupling reaction with aryl chlorides[11,26,27] has been reported to construct heteroaromatics.

Heteroaromatics are always as one of the most important structural units frequently found in natural products, materials chemistry, pharmaceutically active substances, and agrochemicals, and they have been the focus of organic chemists for over one hundred years.[28-30] As a pharmacophore, these compounds exhibit a wide range of biological activities such as antibiotics, anti-inflammatories, anticancer and antifungal.[29] Due to their wide range of practical applications, more and more synthetic organic chemists have focused much of their attention on the palladium-catalyzed coupling reaction to synthesize biaryls for the formation of new carbon-carbon bonds.[31-33] Despite of several transition-metal-catalyzed coupling reactions have been reported to synthesize the biaryls during the last few years,[34-39] there is still an intrinsic need to develop and design novel and convenient coupling reaction of aryl halides with heterocycle for formation carbon-carbon bonds.



Scheme 1. Pd-catalyzed coupling reaction.

Herein we have successfully designed and developed an efficient way for the synthesis of biaryl compounds from inexpensive and facile aryl halides, aryl chlorides, with 2, 3, 5-trisubstituted furans in Scheme 1.

Experimental

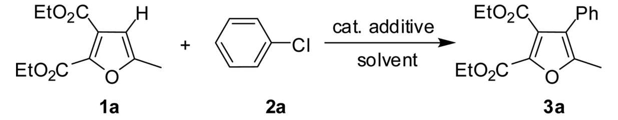
Typical Experimental Procedure for the Synthesis of **3a**: All reactions were performed under air atmosphere in a round bottom flask equipped with magnetic stir bar. To the mixture of $Pd(OAc)_2$ (0.05 equiv), $BuAd_2P$ (0.10 equiv), *t*-BuOK (2 equiv), **1a** (1 equiv), **2a** (1.2 equiv) and 3 mL DMF were added successively. The mixture was stirred at 120 °C for 15 h. After completion of the reaction (monitored by TLC), the water (10 mL) was added. The solution was extracted with ethyl acetate (3 × 15 mL), and the combined extract was dried with anhydrous $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography to give the pure sample **3a**.

^1H NMR spectra and ^{13}C NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer and referenced to 7.26 ppm and 77.0 ppm for chloroform solvent with TMS as internal standard, respectively. IR spectra were got as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Brucker Vector 22 spectrometer. Mass spectra were obtained on a Shimadzu GCMS-QP5050A at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter = 0.25 mm, length = 30 m). Elemental analysis was performed on a Vario EL elemental analyzer. TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF254), and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.

Results and Discussion

Diethyl 5-methylfuran-2,3-dicarboxylate **1a** and chlorobenzene **2a** were chosen as model substrates to optimize the reaction conditions for the formation of biaryl compounds in our initial study, and these results were summarized in Table 1. Various catalysts were firstly examined for the direct arylation process. As shown in Table 1, it's pleased to observe that the desired product **3a** was formed in 46% yield in the presence of $PdCl_2$ and Cs_2CO_3 (Table 1, entry 1) in *N*,*N*-dimethylformamide (DMF) for 15 h at 120 °C. It was undoubted that palladium was an efficient catalyst for this transformation. The other palladium catalysts, such as $Pd(dba)_2$ and $Pd(OAc)_2$, were also employed in this reaction and the arylation product **3a** was obtained in 13% and 51% yields, respectively (Table 1, entries 2-3). And then the effects of various bases were also examined, it can be seen that the *t*-BuOK was proved to be the most efficiency in this coupling reaction and the isolated yield was improved to 59% (Table 1, entry 4). On the contrary, lower isolated yield were observed when Cs_2CO_3 (51%) and K_2CO_3 (44%) were used (Table 1, entries 3 and 4). Stimulated by those results, and then a variety of phosphane ligands, such as PPh_3, PBu_3 and $BuAd_2P$, were tested in the presence of $Pd(OAc)_2$ and *t*-BuOK (Table 1, entries 6-8). Interestingly, the reaction yield of **3a** was dramatically increased to 78% (Table 1, entry 8) by using $BuAd_2P$ as ligands. Subsequently, solvent effects were also investigated. It was found that arylation product **3a** could be isolated in very good yields in dimethyl phthalate (DMP) (Table 1, entry 9), but when tetrahydrofuran (THF), *N,N*-dimethylacetamide (DMA), Toluene and dimethyl sulfoxide (DMSO) were employed, these reactions were severely retarded (Table 1, entries 10-12). Lastly, the effects of temperature was also detected (Table 1, entries 13-15) and it was evident that 120 °C was the most optimal one for this transformation.

Table 1. Condition Screening for the Palladium-catalyzed Direct Arylation Reaction of **1a** with **2a**



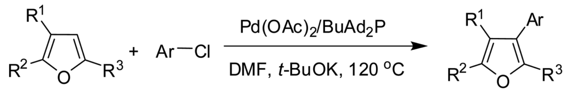
Entry	Catalyst (mol %)^a	Base	Solvent	T (°C)	Yield (%)^b
1	$PdCl_2$	Cs_2CO_3	DMF	120	46
2	$Pd(dba)_2$	Cs_2CO_3	DMF	120	13
3	$Pd(OAc)_2$	Cs_2CO_3	DMF	120	51
4	$Pd(OAc)_2$	K_2CO_3	DMF	120	44
5	$Pd(OAc)_2$	*t*-BuOK	DMF	120	59
6	$Pd(OAc)_2$	PPh_3/*t*-BuOK	DMF	120	47
7	$Pd(OAc)_2$	PBu_3/*t*-BuOK	DMF	120	50
8	$Pd(OAc)_2$	$BuAd_2P$/*t*-BuOK	DMF	120	78
9	$Pd(OAc)_2$	$BuAd_2P$/*t*-BuOK	DMP	120	75
10	$Pd(OAc)_2$	$BuAd_2P$/*t*-BuOK	THF	reflux	58
11	$Pd(OAc)_2$	$BuAd_2P$/*t*-BuOK	DMA	120	77
12	$Pd(OAc)_2$	$BuAd_2P$/*t*-BuOK	Toluene	reflux	68
13	$Pd(OAc)_2$	$BuAd_2P$/*t*-BuOK	DMF	100	45
14	$Pd(OAc)_2$	$BuAd_2P$/*t*-BuOK	DMF	140	71
15	$Pd(OAc)_2$	$BuAd_2P$/*t*-BuOK	DMF	reflux	trace

^{a}Reactions condition: **1** (0.5 mmol) and aryl chloride (0.7 mmol), Pd-catalyst (5 mol %), base (1.0 mmol), phosphane ligands (10 mol %), solvent (3 mL), 15 h. ^{b}GC yields.

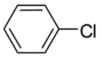
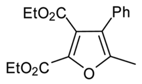
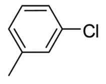
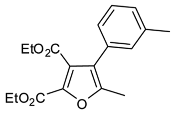
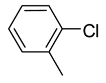
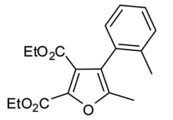
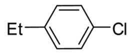
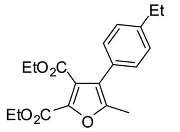
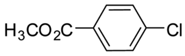
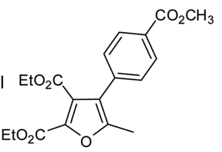
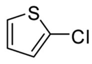
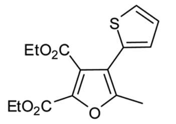
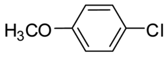
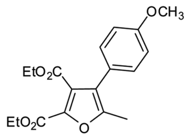
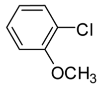
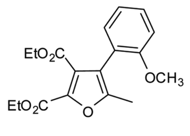
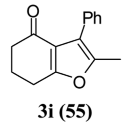
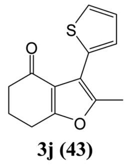
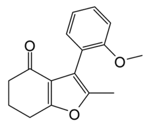
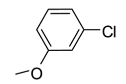
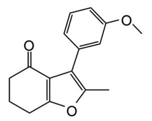
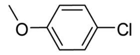
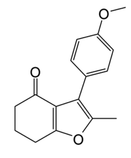
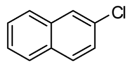
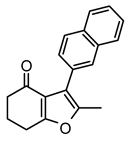
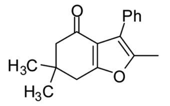
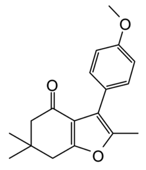
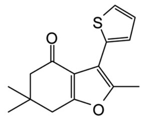
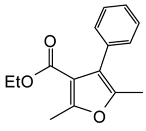
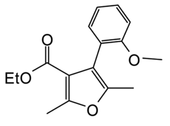
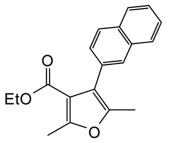
With optimal reaction conditions in hand, the next step was to explore the scope of this arylation reaction. Firstly, diethyl 5-methylfuran-2,3-dicarboxylate (**1a**) was chosen as the fixed substrate, we carried out the reactions with various types of aryl chlorides, and the results were outlined in Table 2. It can be seen that the arylation products **3a-h** were got in moderate yield by using a series of aryl chlorides **2a-h** (Ar = ph, *m*-Meph, *o*-Meph, *p*-Etph, *p*-MeO_2Cph, 2-thienyl, *p*-MeOph and *o*-MeOph) under the previously optimized conditions (Table 1, entry 8). These results revealed that all of the aryl chlorides, regardless of their electronic or steric properties, proceeded smoothly in moderate yields to afford the expected biaryls. However, relative higher isolated yields (83%) were gained when electron-withdrawing substituents were on the aromatic ring (Table 2, entry 5). On the other hand, sterically demanding *ortho* substituents did not hamper the arylation reaction obviously (Table 2, entries 3 and 8). Subsequently, different substituted furans substrates were also examined. From these results, when subtracts of tri-substituted furans were changed to 2-methyl-6,7-dihydrobenzofuran-4(5*H*)-one (**1b**) and 2,6,6-trimethyl-6,7-dihydrobenzofuran-4(5*H*)-one (**1c**), the isolated yields were between 43% and 61% (Table 2, entries 9-17). These results indicated that no matter what substituted group, electron-withdrawing or electron-denoting group, on C-2 positions in furan ring, all of them could react to aryl chlorides smoothly. Moreover, the similar phenomena were also found when the substrate of ethyl 2,5-dimethylfuran-3-carboxylate (**1d**) was employed, and the isolated yields between 41% and 71% were acquired (Table 2, entries 18-20). From these above-mentioned results, it can be concluded that various substituted furan substrates owning electron-withdrawing group, carboxyl group, on C-3 position could react more smoothly with aryl chlorides in the presence of $Pd(OAc)_2$/$BuAd_2P$. Although aryl chlorides were lower reaction activity than aryl bromides and aryl iodides, and the corresponding desired products were achieved in moderate to good yields.

On the other hand, the mechanism for the palladium-catalyzed direct C-H arylation was also discussed, and a plausible mechanism was depicted in Scheme 2 as previous studies reported.[39,40] Firstly, the intermediate **A** was formed

Table 2. Pd-catalyzed Direct Arylation Reaction of α-carbonyl Furan with Aryl Chlorides



1 a-f **2 a-h** **3 a-u**

Entry	Substituted Furan	ArCl	Product (Yield %)[a]
1	**1a** $R^1 = R^2 = CO_2Et$; $R^3 = CH_3$	 **2a**	 **3a (74)**
2	**1a**	 **2b**	 **3b (62)**
3	**1a**	 **2c**	 **3c (66)**
4	**1a**	 **2d**	 **3d (67)**
5	**1a**	 **2e**	 **3e (83)**
6	**1a**	 **2f**	 **3f (64)**
7	**1a**	 **2g**	 **3g (65)**
8	**1a**	 **2h**	 **3h (60)**
9	**1b** $R^1 + R^2 = -CO(CH_2)_3-$; $R^3 = -CH_3$	**2a**	 **3i (55)**
10	**1b**	**2f**	 **3j (43)**
11	**1b**	**2h**	 **3k (47)**
12	**1b**	 **2i**	 **3l (49)**
13	**1b**	 **2j**	 **3m (52)**
14	**1b**	 **2k**	 **3n (59)**
15	**1c** $R^1+R^2 =$ $-COCH_2C(CH_3)_2CH_2-$; $R^3 = -CH_3$	**2a**	 **3o (57)**
16	**1c**	**2j**	 **3p (59)**
17	**1c**	**2f**	 **3q (61)**
18	**1d** $R^1 = CO_2Et$; $R^2 = R^3 = CH_3$	**2a**	 **3r (71)**
19	**1d**	**2h**	 **3s (55)**
20	**1d**	**2k**	 **3t (41)**

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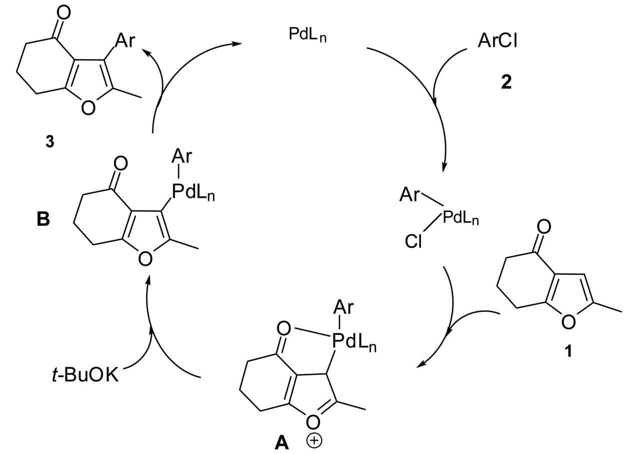
[a]Reactions condition: **1** (0.5 mmol) and aryl chloride (0.7 mmol), $Pd(OAc)_2$ (5 mol %), *t*-BuOK (1.0 mmol), $BuAd_2P$ (10 mol %), solvent (3 mL), 120 °C, 15 h. [b]Isolated yields.



Scheme 2. Plausible reaction mechanism.

trough the reaction **1** with the palladium species, and a five-member Pd cycle was generated with the help of α-carbonyl group.[41,42] Subsequently, under the abstraction of strong base, *t*-BuOK, on acidic hydrogen, the C-H bond was cleaved at C-4 position in furan ring and the intermediate **B** was produced. Lastly, reductive elimination of **B** gave the desired product **3** and released the Pd catalyst.

Conclusion

In summary, we have developed a convenient palladium-catalyzed direct arylation reaction of 2,3,5-trisubstituted furans with aryl chlorides by utilizing catalytic amounts of $Pd(OAc)_2$ in conjunction with $BuAd_2P$ at 120 °C for 15 hours. It was especially noteworthy that not only a series of aryl chlorides but also various tri-substituted furans could take place to afford a range of biaryl compounds in moderate to good yield.

Supplementary Data. Supplementary data (characterization data for desired products) associated with this article can be found, in the online version, at XXX.

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