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Desulfitative palladium-catalyzed direct C-3 arylation of indolizines with arylsulfonyl chlorides

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An efficient Pd-catalyzed desulfitative approach to C-3 arylation of indolizine derivatives has been developed, and the protocol uses readily available arylsulfonyl chlorides as the arylation reagent under nitrogen. This transformation was performed in a mixed solvent of 1-methyl-2-pyrrolidone and dimethoxyethane using simple triphenylphosphine as a ligand, which provides a new method for the C-3 arylation of indolizines. Copyright © 2015 John Wiley & Sons, Ltd.

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Keywords: desulfitative arylation; indolizines; arylsulfonyl chlorides

Introduction

Nowadays, indolizines have emerged as important N-based heterocycles, which are commonly present in pharmaceutical building blocks.[1–8] Consequently, many synthetic methodologies for functionalized indolizines have been reported.[9–11] Many efforts have aimed to decorate the indolizine core and produce derivatives.[12–27] C-3 arylation methods for indolizine have been developed in the last ten years. In 2004, Gevorgyan and co-workers reported the first Pd-catalyzed C-3 arylation reaction with aryl bromides, and then Fagnou and co-workers reported a similar catalytic system.[28–30] Aryl chloride is a more challenging substrate in Pd-catalyzed chemistry for its poor reactivity and the strength of the aryl–Cl bond which is difficult to oxidize with Pd species. You and co-workers[31,32] applied aryl chlorides as arylation partners to achieve this target successfully. Arylboronic acid derivatives are regarded as important reagents. In 2009, Xia and You reported an approach to achieve indolizine C-3 arylation with arylboronic acids using C-3 chlorination and Suzuki–Miyarua cross-coupling.[31] Direct arylation of indolizines with arylboronic acids was reported recently by Hu and co-workers, which can be successfully achieved via a $Pd(OAc)/O_2$ system using picolinic acid as a ligand.[23] In 2012, we reported an indolizine C-3 arylation with $ArBF_3K$ to afford corresponding products.[33]

Transition metal-catalyzed desulfitative arylation of heteroarenes with sodium arylsulfinates and/or arylsulfonyl chlorides, arylsulfonyl hydrazides and arylsulfinic acids has emerged as a novel arylation approach.[34–44] Arylsulfonyl chlorides are inexpensive and readily available reagents, which have been demonstrated as a class of coupling partners in Pd-catalyzed desulfitative C–C cross-coupling reactions.[45–58] Prompted by our continuing interest in metal-catalyzed cross-coupling reactions with $ArSO_2R$ derivatives such as $ArSO_2Na$ or $ArSO_2Cl$,[58–62] herein, we describe a new application of arylsulfonyl chloride in arylation reactions with indolizines to afford C-3 arylation products using a more convenient Pd-catalyzed desulfitative reaction (Scheme 1).

Results and discussion

We initiated our investigation using the model reaction of methyl 2-methylindolizine-1-carboxylate with phenylsulfonyl chloride to optimize the reaction conditions. The results of optimization of the reaction conditions are summarized in Table 1. The desulfitative arylation occurs with $Pd(PPh_3)_4$ (5 mol%) in the presence of $NaHCO_3$ in DMF under nitrogen, providing methyl 2-methyl-3-phenylindolizine-1-carboxylate in 51% yield (Table 1, entry 1). We investigated the effect of solvents which influence the reaction activities. The optimization results are summarized in Table 1. The yields obtained in other polar aprotic solvents such as N,N-Dimethylacetamide (DMA), DMSO and 1-methyl-2-pyrrolidone (NMP) are in the range 60–72% (Table 1, entries 2–4). Other organic solvents have been tested; however, no better results are obtained (Table 1, entries 5–8). Subsequently, we further considered the application of a mixed solvent to enhance the efficiency. We chose NMP (which showed the best results in the initial solvent testing) to mix with other solvents. To our delight, the yields of the reaction increase with mixtures of various solvents (53–79%; Table 1, entries 9–11). The reaction proceeds smoothly in a solvent comprised of NMP and dimethoxyethane (DME) (Table 1, entry 12). Finally, we adjusted the proportions of NMP and DME (Table 1, entries 13–20), and in general, increasing NMP favors the formation

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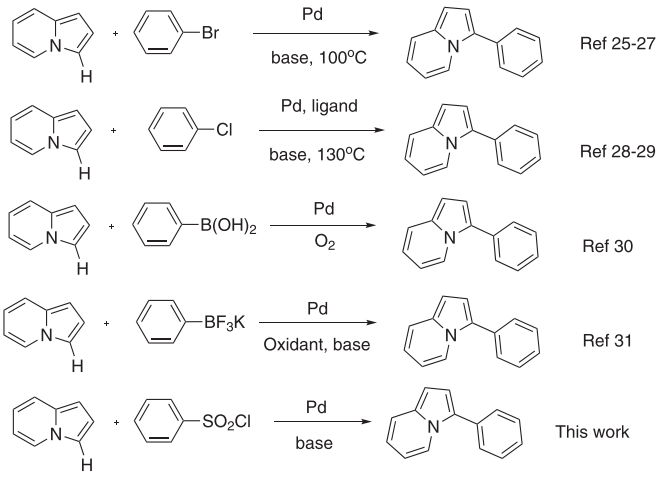
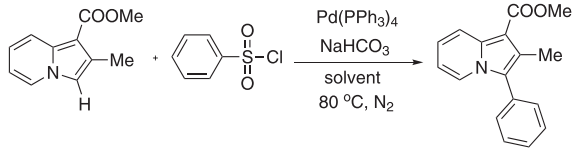


Scheme 1. Methods for indolizine C-3 arylation.

Table 1. Solvent selection for desulfitative Pd-catalyzed C-3 arylation[a]



Entry	Solvent[b]	Yield(%)[c]	Entry	Solvent[b]	Yield(%)[c]
1	DMF	51	11	NMP–toluene (1:1)	53
2	DMA	60	12	NMP–DME (1:1)	85
3	DMSO	66	13	NMP–DME (9:1)	90
4	NMP	72	14	NMP–DME (4:1)	95
5	CH_3CN	52	15	NMP–DME (3:1)	86
6	Toluene	10	16	NMP–DME (2:1)	80
7	1,4-Dioxane	22	17	NMP–DME (1:2)	70
8	DME	49	18	NMP–DME (1:3)	74
9	NMP–dioxane (1:1)	79	19	NMP–DME (1:4)	77
10	NMP–CH_3CN (1:1)	71	20	NMP–DME (1:9)	69

[a]Reaction conditions: 2-methylindolizine-1-carboxylate (0.5 mmol), phenylsulfonyl chloride (0.6 mmol), $Pd(OAc)_2$ (5 mol%), $NaHCO_3$ (0.5 mmol), solvent (2.0 ml) at 80 °C under nitrogen for 3 h unless otherwise indicated.

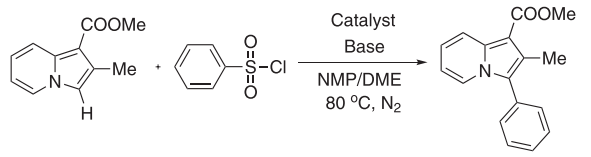
[b]Solvent proportion by volume in parentheses.

[c]Isolated yield.

of C-3 arylation product. A volume ratio of NMP to DME of 4:1 shows the best efficiency (Table 1, entry 14).

The effects of catalysts and bases were also investigated. As evident from Table 2, we initially tested various palladium catalysts for this desulfitative coupling reaction using NMP–DME (4:1) as the solvent. Among the Pd catalysts explored, $PdCl_2$, PdI_2 and $PdCl_2(CH_3CN)_2$ afford the desired product with 47, 45 and 56% yields. Increased yields are obtained with the introduction of phosphine ligands (Table 2, entries 4 and 5). Transformation using Pd(0) catalysts leads to good yields (Table 2, entries 6–8). No product is formed in the absence of Pd catalyst (Table 2, entry 9). Thus, $Pd(PPh_3)_4$ was selected for further optimization. In this reaction various bases seem to play key roles in promoting efficacy. Intriguingly, when K_3PO_4 is used as the base, it gives an 81% yield of arylation

Table 2. Screening of various catalysts and bases for Pd-catalyzed arylation[a]



Entry	Catalyst	Base	Yield(%)[b]
1	$PdCl_2$	$NaHCO_3$	47
2	PdI_2	$NaHCO_3$	45
3	$PdCl_2(CH_3CN)_2$	$NaHCO_3$	56
4	$PdCl_2$(dppf)	$NaHCO_3$	72
5	$PdCl_2(PPh_3)_3$	$NaHCO_3$	80
6	$Pd(PPh_3)_4$	$NaHCO_3$	95
7	$Pd_2(dba)_3$	$NaHCO_3$	92
8	$Pd(dba)_2$	$NaHCO_3$	88
9	—	$NaHCO_3$	—
10	$Pd(PPh_3)_4$	K_3PO_4	81
11	$Pd(PPh_3)_4$	NaOH	15
12	$Pd(PPh_3)_4$	Et_3N	10
13	$Pd(PPh_3)_4$	KOAc	75
14	$Pd(PPh_3)_4$	K_2CO_3	80
15	$Pd(PPh_3)_4$	Na_2CO_3	86
16	$Pd(PPh_3)_4$	—	—
17	$Pd(PPh_3)_4$	$NaHCO_3$	62[c]

[a]Reaction conditions: 2-methylindolizine-1-carboxylate (0.5 mmol), phenylsulfonyl chloride (0.6 mmol), catalyst (5 mol%), base (0.5 mmol), DMSO–DME (2.0 ml; 9:1 v/v) at 80 °C for 3 h unless otherwise indicated.

[b]Isolated arylation yield under nitrogen.

[c]Isolated arylation yield under air.

product, whereas the use of NaOH and Et_3N gives yields less than 15% (Table 2, entries 10–12). KOAc, K_2CO_3 and Na_2CO_3 were tested, and, to our delight, Na_2CO_3 give a better result (86%; Table 2, entries 13–15). Furthermore, the reaction does not occur at all when carried out without bases, indicating that base may be an important factor for this reaction (Table 2, entry 16). Notably, only 62% yield of arylation product is isolated under air (Table 2, entry 17). Finally, the desulfitative arylation proceeds well with a catalytic system composed of $Pd(PPh_3)_4$ (5 mol%) and $NaHCO_3$ (1 equiv.) in NMP–DME (4:1) at 80 °C under nitrogen for 3 h.

With the optimized conditions in hand, we next set out to explore the scope of the method with respect to this Pd-catalyzed desulfitative arylation of indolizines with arylsulfonyl chlorides. To expand the scope of substrates, several indolizines were surveyed under the present reaction conditions, as shown in Fig. 1. It should be noted that the yield of desired product is slightly decreased along with increasing carbon chain of ester (**3a** to **3b** to **3c** to **3d**). When 2-methylindolizine-1-carbonitrile and 2-methylindolizin-1-yl acetate react with phenylsulfonyl chloride, the desired products are obtained in 89 and 91% yields, respectively (Fig. 1, **3e** and **3f**). The reaction also proceeds well when the methyl substituent is removed from the C-2 position of indolizine. Different functionalities on the C-3 position of the indolizine ring, whether electron-withdrawing or electron-donating groups, are compatible. As shown in Fig. 1, this reaction is compatible with ester, keto, cyano, carbamyl and acetoxyl substituents, and furnishes the desired product in good yields (Fig. 1, **3 g–3 k**). Gratifyingly, a variety of substituents on other positions of the indolizine successfully couple with

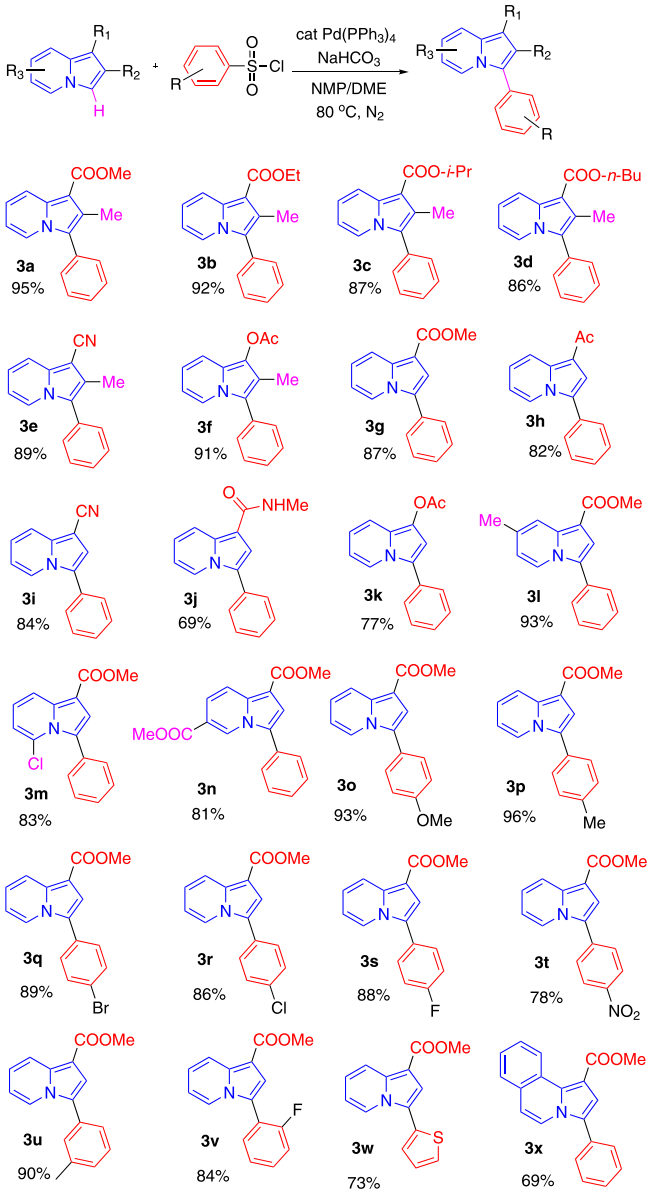
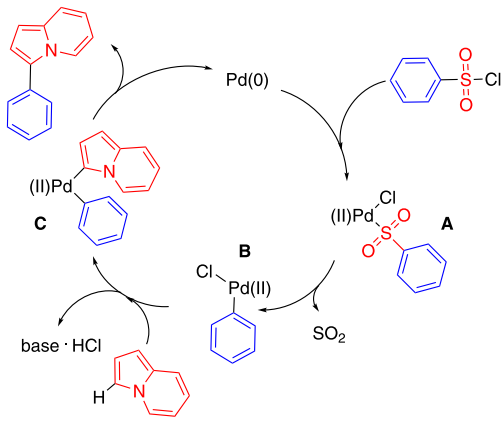


Figure 1. Desulfitative Pd-catalyzed C-3 arylation of indolizines with arylsulfonyl chlorides. Reaction conditions: indolizines (0.5 mmol), arylsulfonyl chlorides (0.6 mmol), $Pd(OAc)_2$ (5 mol%), $NaHCO_3$ (0.5 mmol), DMSO–DME (2.0 ml; 9:1 v/v) at 80 °C under nitrogen for 3 h. The yields indicated for each product are isolated arylation yields.

phenylsulfonyl chloride, such as methyl 7-methylindolizine-1-carboxylate, methyl 5-chloroindolizine-1-carboxylate and dimethyl indolizine-1,6-dicarboxylate (Fig. 1, **3 l–3n**). Subsequently, we applied our method to other arylsulfonyl chlorides to prepare an array of methyl 3-arylindolizine-1-carboxylates with either electron-withdrawing groups or electron-donating groups successfully engaged in this reaction (Fig. 1, **3o–3 t**). Notably, bromo, chloro and fluoro substituents on the sulfonyl chloride moiety do not affect the yields of the desired arylation products, and offers the potential for highly chemoselective transformations (Fig. 1, **3q–3 s**). An *ortho*- or *meta*-substituent group on the aromatic ring of the arylsulfonyl chloride does dramatically decrease the reaction yield (Fig. 1, **3u** and **3v**). Heteroaromatic sulfonyl chlorides, such as thiophene-2-sulfonyl chloride, are tolerated, albeit with a slightly decreased yield



Scheme 2. Possible mechanism.

(Fig. 1, **3w**). Finally, methyl pyrrolo[2,1-*a*]isoquinoline-1-carboxylate is also desulfitatively arylated in reasonable yield (Fig. 1, **3x**).

Mechanism

On the basis of previous work and the results of our study,[23,28–33] a plausible Pd(0)/Pd(II) mechanism for the desulfitative arylation as shown in Scheme 2 is proposed. First is the oxidative addition of Pd(0) with phenylsulfonyl chloride to form intermediate A. Accompanied with the release of sulfur dioxide, electrophilic palladation occurs at the preferential C-3 position of indolizine with intermediate B to form intermediate C, with base being necessary for the removal of HCl. The subsequent reductive elimination of intermediate C generates the arylation products, and then the formed Pd(0) is regenerated to complete the cycle (Scheme 2).

Experimental: typical procedure

A mixture of indolizine (0.5 mmol), arylsulfonyl chloride (0.6 mmol), $Pd(PPh_3)_4$ (5 mol%) and $NaHCO_3$ (0.5 mmol) was stirred in DMSO–DME (2.0 ml; 9:1 v/v) at 80 °C under nitrogen for 3 h. Afterwards, 2 ml of water was added to the reaction solution which was then filtered through a filter paper and the solution was extracted three times with Et_2O (2 ml). The organic phase was combined and evaporated under reduced pressure. The residue was purified with a SiO_2 column (ethyl acetate–hexane) to afford the desired product.

Conclusions

A novel method for desulfitative C-3 arylation was developed through the reaction of indolizines with arylsulfonyl chlorides catalyzed by 5 mol% $Pd(PPh_3)_4$. The reaction proceeded under mild conditions in air without external oxidants and ligands. This methodology provides an effective and cheap way for the synthesis of indolizine derivatives. The transformation was promoted by a mixed solvent and carried through via the release of SO_2.

Acknowledgements

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