Accepted Manuscript

Accepted Date:

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PII:	S0040-4039(17)30690-1
DOI:	http://dx.doi.org/10.1016/j.tetlet.2017.05.088
Reference:	TETL 48981
To appear in:	Tetrahedron Letters
Received Date:	20 April 2017
Revised Date:	24 May 2017

27 May 2017



Please cite this article as: Guo, S-r., Santhosh Kumar, P., Yuan, Y-q., Yang, M-h., Palladium Catalyzed Aroylation of NH-sulfoximines with Aryl Halides Using Chloroform as the CO Precursor, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.05.088

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Tetrahedron Letters

journal homepage: www.elsevier.com

Palladium Catalyzed Aroylation of NH-sulfoximines with Aryl Halides Using Chloroform as the CO Precursor

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ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online A palladium-catalyzed Aroylation of NH-sulfoximines for the efficient synthesis of N-aroyl sulfoximines from aryl halides and chloroform has been developed. The mild reaction conditions (temperature, catalyst loading) and the use of a CO surrogate render this transformation a useful method for the synthesis of N-aroyl sulfoximines from available feedstock.

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Keywords: Aroylation sulfoximines Chloroform Pd(OAc)₂ CO Precursor

Transition-metal catalyzed carbonylation reaction using carbon monoxide as C=O source has evolved as one of the most powerful protocol to introduce C1 building block into an organic molecule.¹ While the intrinsic odorless toxic and high pressure make it difficult to using normal flask in the application of CO gas. Aiming at this issue, some "CO-free" carbonylation methods have been devised to avoid CO gas directly by using such as Mo(CO)₆, formic acid, acid chloride or aryl formate.² Recently, the chloroform (CHCl₃) serves as a highly practical CO precursor for transition-metal-mediated carbonylation reactions attracted chemists attention.³ In 2015, Hull reported Pd-catalyzed aminocarbonylation of aryl halides with amines by using chloroform as CO source. ^{3a} The metal-catalyzed carbonylative Suzuki and Sonogashira coupling reaction using CHCl₃ as the CO source were also described in 2016 by the Jain, Lei and Han groups. 3c-3e This "CO-free" carbonylation shows some superior performance such as readily available and strong practical compared to direct use of CO gas, although remarkable advances have been achieved using CO gas as carbonyl surrogates. Undoubtedly, exploration of "CO-free" strategies to construct the carbonyl scaffold through a low cost and highly efficient process will be highly valuable.



Sulfoximines are mono-aza analogues of sulfones with an additional NH group which appear as a valuable structural unit in

biological and medicinal molecules or as exciting species for drug discovery programs.⁴ Some typical examples are exemplified by Figure 1.⁵ the compound AZD6738 from AstraZeneca is a novel and potent inhibitor of ATR kinase activity;^{5a} the heterocyclic sulfoximine Go 4962 is known as a partial benzodiazepine receptor agonist.^{5b} However, the more general use of the sulfoximine group in medicinal chemistry follows the development of BAY 1000394, a pan-CDK inhibitor for cancer in patients with advanced solid tumors.^{5c} In comparison to sulfones, the inherent nucleophilicity of N-H group allows sulfoximines for more valuable building blocks in organic synthesis.⁶ In the past decade, Bolm and others have developed many NH group functionalizations methods such as N-alkynylation,⁸ N-silvlation,9 N-arylations,⁷ Ntrifluoromethylation,¹⁰ N-thioetherification,¹¹ N-acylation ¹² and so on.¹³ In the case of direct N-aroylation of sulfoximines, Bolm reported some elegant work relative to transition-metal catalyzed oxidative N-acylation of sulfoximine using aldehyde, and methyl arenes as coupling partner.^{12e-12h} Very recently, Sekar disclosed a three-component strategy for the synthesis of N-aroyl sulfoximines skeleton, direct using CO gas as a carbonyl source.¹⁴ Stimulated by those pioneering works and continue to our ongoing project on the synthesis of functionalized sulfides, we herein demonstrate a simple and efficient aroylation of NHsulfoximines using CHCl₃ as in situ CO source.

At the beginning of the reaction, the model substrate S-methyl-S-phenylsulfoximine (**1a** 1.0 equiv) was treated with iodobenzene (**2a** 1.2 equiv.), and CHCl₃ (10.0 equiv). To our delight, the desired aroylation product **3aa** was obtained in 79% yield using Pd(OAc)₂ (2 mol%) as catalyst, PPh₃ (20 mol %) as ligand and KOH (6.0 equiv) as base in toluene after 12 h at 80 °C (table 1, entry 1). The reported relative reaction mechanism suggested that the Pd-catalyst serves two purposes: to catalyze the hydrolysis of CHCl₃ and to catalyze the subsequent formation

of aroyl intermediate, and it is obvious that the CO group is from chloroform. Screening of other catalyst revealed that no aroylation was observed when using FeCl₂, Cu(OAc)₂, Ru₃(CO)₁₂, AgOAc as catalyst (entries 2-5). Other palladium catalysts such as PdCl₂ and Pd(dba)₂ were also examined, and both were found to be active and yielded 3aa in 36 and 58 % yields, respectively (entries 6 and 7). Since Pd(OAc)₂ was found to have the highest activity, it was used for further optimizations. Next, the effect on selected ligands toward the process was examined. It turned out that the reaction failed with 1,10phenanthroline and BINAP as the ligand (entries 8 and 9), In contrast, other ligands such as DBU, DMAP, and 2,6-lutidine led to the formation of the desired product 3aa (entries 10-12), DBU was found to be the best ligand giving 3aa in 85% yield, albeit with lower efficiency lowering or raising the amount of DBU to 10 or 40 mol %. Following the above investigation, the screening of base was conducted. A low yield was observed with NaOH and LiOH (entries 13 and 14), while CsOH·H₂O resulted in an 88% yield. However, taking into account the higher cost as well as hygroscopic nature of CsOH·H₂O, we used KOH as base. After a brief solvent screening, we found out that toluene was the best solvent under our optimized reaction parameters (entries 15-18). Therefore, optimal reaction conditions involved heating 1 equiv of 1a. 1.2 equiv of 2a. 2 mol % of Pd(OAc)₂, 20 mol % of DBU as ligand, 6 equiv of KOH and 10 equiv of CHCl₃ at 80 °C for 12 h in the toluene solvent. It is noteworthy that no desired product 3aa was obtained in the absence of palladium or base (entries 19 and 20).

Table 1. Optimization of the Reaction Conditions [a]

	,NH _ S_ _{CH3} + 1a	CHCl ₃ cat./base/ligand solvent 2a		O CH ₃ Jaa	
Entry	Cat.	Ligand/Base	Solvent	Yield (%) [b]	
1	$Pd(OAc)_2$	PPh₃/KOH	toluene	79	
2	FeCl ₂ ,	PPh₃/KOH	toluene	0	
3	$Cu(OAc)_2$,	PPh₃/KOH	toluene	0	
4	Ru ₃ (CO) ₁₂ ,	PPh₃/KOH	toluene	0	
5	AgOAc	PPh ₃ /KOH	toluene	0	
6	$PdCl_2$ and	PPh ₃ /KOH	toluene	36	
7	Pd(dba)2	PPh ₃ /KOH	toluene	58	
8	$Pd(OAc)_2$	1,10- phenanthroline/KOH	toluene	0	
9	$Pd(OAc)_2$	BINAP/KOH	toluene	0	
10	$Pd(OAc)_2$	DBU/KOH	toluene	85	
11	$Pd(OAc)_2$	DM AP/KOH	toluene	80	
12	$Pd(OAc)_2$	2,6-lutidine/KOH	toluene	82	
13	$Pd(OAc)_2$	DBU/NaOH	toluene	75	
14	$Pd(OAc)_2$	DBU/LiOH	toluene	70	
15	$Pd(OAc)_2$	DBU/CsOH·H ₂ O	toluene	88	
16	$Pd(OAc)_2$	DBU/KOH	dioxane	20	
17	$Pd(OAc)_2$	DBU/KOH	DMF	0	
18	$Pd(OAc)_2$	DBU/KOH	DCE	50	
19	$Pd(OAc)_2$	-	toluene	0	
20		DBU/KOH	toluene	0	
[a] Reaction conditions: S-methyl-S-phenylsulfoximine (0.5 mmol),					

iodobenzene (0.6 mmol), chloroform (5 mmol, 10 equiv.), Ligand (20 mol%) and base (3 mmol, 6 equiv.) and solvent (2 mL) heated at 80 °C for 12 h. [b] Isolated yield.

With the optimized reaction conditions, scope of this transformation was investigated. The reactivity of S-methyl-S-phenylsulfoximine **1a** toward different substituted aryl iodides was seen. As shown in table 2, the electron-withdrawing as well as electron-donating functional groups in aromatic ring of aryl iodides were well tolerated. Aryl iodides bearing alkyl or alkoxyl group at the para position, such as $-CH_3$, $-OCH_3$, coupled smoothly with **1a** to give the corresponding products in 89% (**3ab**) and 82% (**3ac**) yields, respectively (entries 2-3). Halogen

substituents on the benzene ring, including 4-F and 4-Cl, were compatible for this kind of coupling reaction (entries 4-5). The electron-withdrawing functional group, such as 4-CF₃ and 4-CN were well tolerated to give the desired product in 90% and 82% yield (entries 6-7). In addition, a slight steric effect was observed since the substrates bearing a meta-substituent such as -CH₃, -OCH₃, -SCH₃, -F, Br, -NO₂ and -CF₃ led to relatively lower yields compared to para-substituted variant (entries 8-14). Heterocyclic compounds such as thiophenes are also readily functionalized (entries 15-16). Unfortunally, the ortho-substituted aryl iodides failed to afford the desired products. These results obviously suggested that the steric hindrance of aryl iodides has significant effect on this carbonylative coupling reaction. The reaction was also applied for gram-scale synthesis starting from 1g of S-methyl-S-phenylsulfoximine 1a and 1579 mg of iodobenzene to yield **3aa** in a 70 % yield (1169 mg).

Table 2. Pd(OAc)₂ catalyzed N-aroylation of 1a with aryl iodides ^{a,b}





Subsequently, the reaction scope with respect to NHsulfoximine substrates is presented in Table 3. They proved to efficiently couple with meta- and para-substituted aryl iodides under the optimize conditions and no significant electronic effects were observed to sulfoximine (entries 1-7). A slight decline of yields was observed using ortho-substituted NHsulfoximine comparable with meta- and para-substituted NHsulfoximines (entries 8-9). The S-ethyl-S-arylsulfoximine coupled well with any iodides to provide 3aj and 3ak in 89% and 91% yields respectively (entries 10-11). Even the sterically diphenylsulfoximine also smoothly reacted with iodobenzene to provide the product **3al** in 80% yield (entry 12). Further, the reaction is not limited to aryl iodides, the aromatic bromides also afford the desired product, but aryl bromides were proved to be a less efficient coupling partner, resulted in the desired product in low yields (entries 1-3).

Table 3. Pd(OAc)₂ catalyzed N-aroylation of sulfoximines with aryl halides





O N Ph

entry 11, **3bk** (91%) entry 12, **3bl** (80%) ^[a] Reaction conditions: S-methyl-S-arylsulfoximine (0.5 mmol), ArI (0.6 mmol), chloroform (5 mmol), KOH (3 mmol), Pd(OAc)₂ (2 mol%) and DBU (20 mol%), toluene (2 mL), heated at 80 °C for 12 h. ^[b] Isolated yield. ^[c] ArBr (1.5 equiv.) used.

With respect to the reaction mechanism, this transformation would be a typical carbonylation reaction.³ Initially, chloroform decomposed to generate CO in situ, which undergoes the insertion process to generate the acyl palladium complex. Then this key intermediate is attacked by N-H nucleophiles to give the products.

In summary, we have developed a convenient and efficient palladium-catalyzed aroylation process of aryl halides with sulfoximines to construct N-aroyl sulfoximines derivatives using $CHCl_3$ as CO precursor. A wide range of aryl halides and sulfoximines reacted smoothly under the optimized reaction conditions to give the corresponding products in moderate to good yields. Further this work will provide an alternate pathway for the construction of various N-aroylation reactions in the use of CO releasing molecules for the transition metal mediated carbonylation reactions.

Acknowledgments

This work was supported by the Natural Science Foundation of Zhejiang Province P.R. China (No. Y16B020018) and Public Welfare Technology Application Foundation of Lishui (2014JYZB49).

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/ xxxxxxxxxx.

Highlights:

- "CO-free" carbonylation shows readily available and easy to handle.
- Palladium-catalyzed aroylation of sulfoximines using CHCl₃ as CO precursor.
- Various aryl halides and sulfoximines reacted smoothly in moderate to good yields.
- Providing an alternative carbonylation in the use of CO releasing molecules.
- Mild reaction condition and avoids harsh reaction conditions.