RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2016, **6**, 28442

Received 27th January 2016
Accepted 11th March 2016

DOI: 10.1039/c6ra02424f

www.rsc.org/advances

A facile and efficient method for the synthesis of alkynone by carbonylative Sonogashira coupling using $CHCl_3$ as the CO source†

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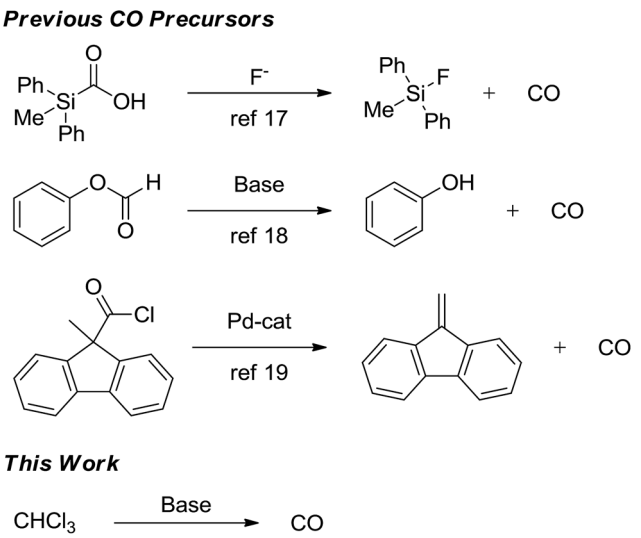
A facile and efficient method for the synthesis of alkynones by a Pd-catalyzed carbonylative Sonogashira coupling reaction starting from aryl iodide, terminal alkyne and chloroform ($CHCl_3$) as the CO source is described. This procedure proves that $CHCl_3$ is a cheap and efficient CO source in the presence of $CsOH \cdot H_2O$ as the base. Furthermore, it is applied successfully for the modification of natural products, such as vindoline and tabersonin, to obtain the corresponding products in good yields.

Alkynones are important intermediates in various organic syntheses of heterocyclic derivatives due to their multifunctional nature, such as pyrimidines,[1,2] quinolones,[3] furans,[4,5] pyrazoles,[6–9] pyrroles,[10,11] flavones,[12] and benzodiazepines.[13] Furthermore, they are also used for the synthesis of many natural products (*e.g.*, azaspiracid,[14] calystegine B2,[15] anthrapyran metabolite[16]). In addition, alkynones have been reported to possess diverse pharmacological properties such as antiinflammatory and analgesic activities,[17] PKC inhibitors,[18] CCR2 antagonists,[19] and so on.[20–23] Due to the unique structural feature and also to the biological activities of alkynones,[14–23] the synthesis of alkynones has received a considerable attention.

Recently, many methods have been reported for the synthesis of alkynones: (1) oxidation of propargylic alcohols;[24–27] (2) reaction of acyl chlorides with terminal alkynes;[28–34] (3) reaction of nitriles with terminal alkynes;[35] (4) reaction of aldehydes with terminal alkynes;[36] (5) carbonylative Sonogashira coupling reaction;[37–41] (6) other methods.[42–46] Among all of the methods mentioned above, carbonylative Sonogashira coupling reaction of aryl iodide, terminal alkyne and CO plays a key role due to its good yields, mild reaction conditions, and excellent functional group tolerance. However, a high CO pressure is always required to achieve efficient carbonylative coupling for the preparation of alkynones. High toxicity and pressure of CO severely limits the using of this method in organic synthesis. In recent years, to avoid using CO directly, several precursors of CO have been reported to replace the CO in organic synthesis.[47–51] As shown in Scheme 1, methyldiphenylsilanecarboxylic acid,[47,48] phenyl formate[49] and 9-methyl-9*H*-fluorene-9-carbonyl chloride[50,51] are applied successfully in organic synthesis as CO precursors. However, the use of these precursors has been limited due to their high prices, especially on a large scale organic synthesis. Therefore, there is a need to search a better precursor of CO for the application in organic synthesis in terms of operational simplicity and economic viability.

During the course of our studies, a Pd(II)-mediated carbonylative Sonogashira coupling reaction for the synthesis of alkynones using $CHCl_3$ as the CO precursor in the presence of $CsOH \cdot H_2O$ was also discovered.[52–55] Herein, we describe a Pd(II)-catalyzed carbonylative Sonogashira coupling reaction of aryl iodide, terminal alkyne and $CHCl_3$ to synthesis of alkynones.



Scheme 1 Reported CO precursors.

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† Electronic supplementary information (ESI) available: Experimental procedures, copies of the ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c6ra02424f

Initially, to exam whether the $CHCl_3$ could be used as CO precursor, we carried out the reaction of iodobenzene **1a**, ethynylbenzene **2a**, and $CHCl_3$ using $Pd(OAc)_2$ as catalyst, BINAP as ligand and $CsOH \cdot H_2O$ as base in toluene. After stirred for 8 h at 80 °C, the desired product **3aa** was obtained in 70% yield. This result clearly indicated that $CHCl_3$ could be as CO precursor to synthesis of alkynone. To further improve the efficiency of this reaction, a series of optimization experiments were performed, and the results are summarized in Table 1.

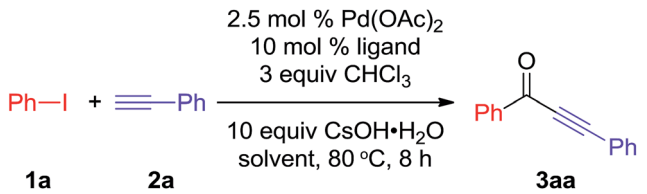
Preliminary experiments suggested that the ligands had a significant impact on the yields of **3aa**. Hence, various ligands such as BINAP, dppf, dppp, PPh_3, DPEphos, CEMTPP, $(2\text{-furyl})_3P$, and *o*-phenanthroline were applied to promote this coupling reaction. As shown in Table 1, the reaction could not proceed smoothly to obtain the corresponding product **3aa** under ligand-free conditions (Table 1, entry 1). All the ligands studied on this reaction showed good ligand effect in terms of the yields of **3aa** (50–96%) but *o*-phenanthroline (15%). By screening of ligands, PPh_3 was found to be the superior one than others to obtained **3aa** in 96% yield determined by LC-MS and in 91% isolated yield, respectively. Therefore, PPh_3 was chosen as the ligand for all further reactions.

Furthermore, to examine the solvent effect, various solvents such as toluene, 1,4-dioxane, DMF, MeCN, EtOH, and THF were applied to this coupling reaction. As shown in Table 1, the reaction could not proceed smoothly in DMF and MeCN and only 5% yield of **3aa** was obtained in EtOH (Table 1, entries 11–13). Moderate to excellent yields were obtained when using toluene, 1,4-dioxane, and THF as the solvent (65–96%) (Table 1, entries 5, 81 and 14), and toluene displayed the best solvent effect.

In addition, the other factors, such as catalyst, base and temperature, were also investigated and these contents were provided in ESI.† Having established the optimized reaction conditions, we then carried out the reaction under the similar conditions using aromatic compounds with different leaving groups, such as Br-, Cl-, TsO-, and TfO-, as substrates to replace iodobenzene. In these cases, the results showed that only 1,4-diphenylbuta-1,3-diyne was obtained in 75% yield, and the desired **3aa** was not formed (see ESI†).

To explore the generality and scope of the carbonylative Sonogashira coupling reaction, the reaction of various aryl iodides and phenylacetylene was carried out under the optimized conditions (Table 2). As shown in Scheme 2, *ortho*, *meta* and *para* substituted substrates were chosen to exam the steric hindrance on this reaction. The desired products **3aa–na** were obtained in 78–91% yields. These results clearly indicated that the steric

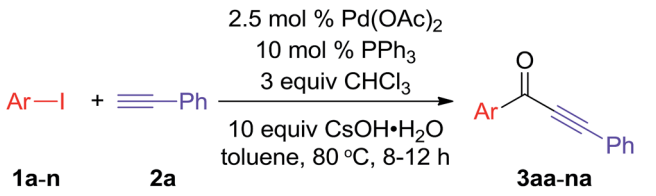
Table 1 Optimization of the reaction conditions[a]

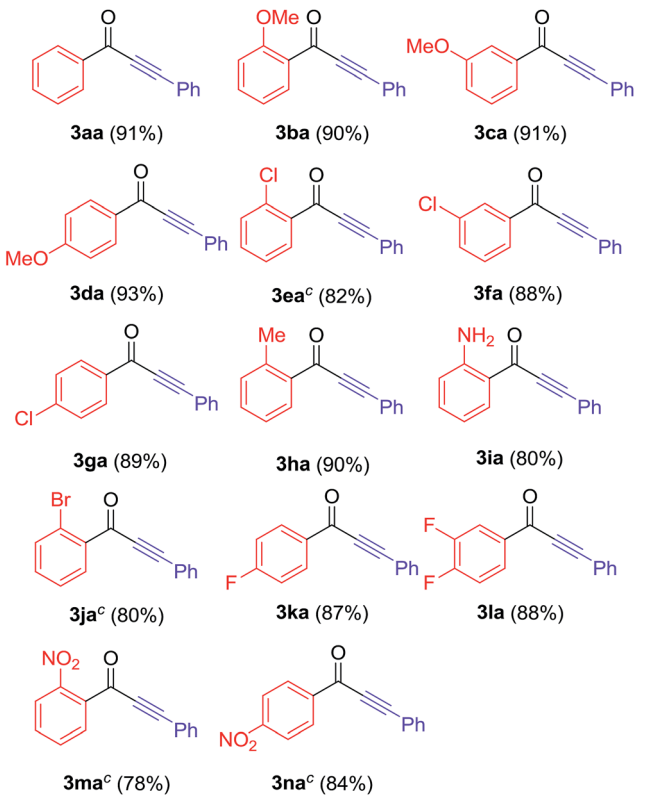


Entry	Ligand	Solvent	Yield[b] (%)
1	—	Toluene	0
2	BINAP	Toluene	70
3	dppf	Toluene	80
4	dppp	Toluene	76
5	PPh_3	Toluene	96 (91)
6	DPEphos	Toluene	85
7	CEMTPP	Toluene	91
8	$(2\text{-Furyl})_3P$	Toluene	50
9	*o*-Phenanthroline	Toluene	15
10	PPh_3	1,4-Dioxane	81
11	PPh_3	DMF	0
12	PPh_3	MeCN	0
13	PPh_3	EtOH	5
14	PPh_3	THF	65

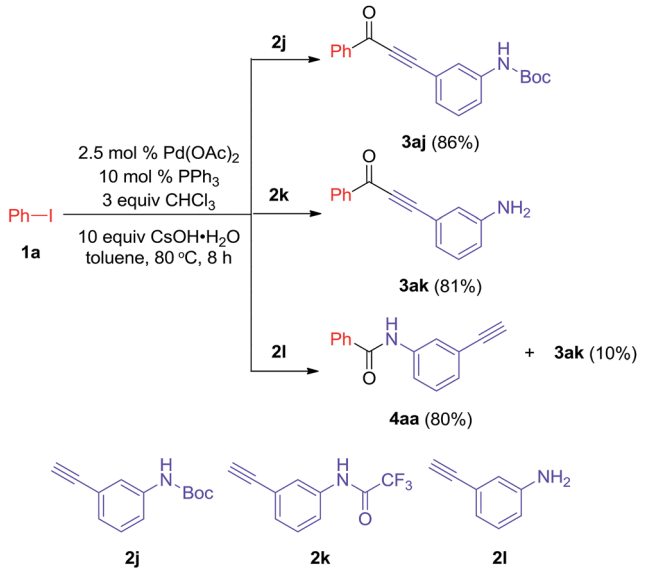
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), $CHCl_3$ (1.5 mmol), $Pd(OAc)_2$ (2.5 mol%), ligand (10 mol%), $CsOH \cdot H_2O$ (5 mmol), solvent (3 mL), 80 °C, 8 h. [b] Yields were determined by LC-MS; the number in parentheses refers to the yield of isolated **3aa**.

Table 2 Reaction of aryl iodides with ethynylbenzene[a,b]

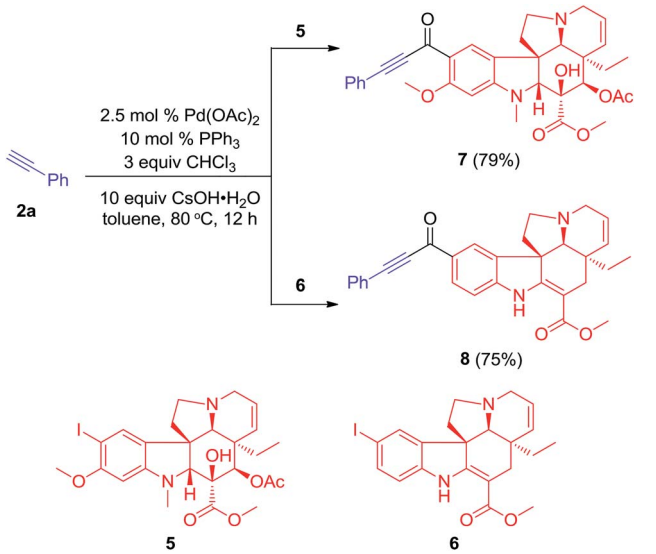




[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), $CHCl_3$ (1.5 mmol), $Pd(OAc)_2$ (2.5 mol%), PPh_3 (10 mol%), $CsOH \cdot H_2O$ (5 mmol), toluene (3 mL), 80 °C, 8 h. [b] Isolated yields. [c] The reaction proceeded for 12 h.



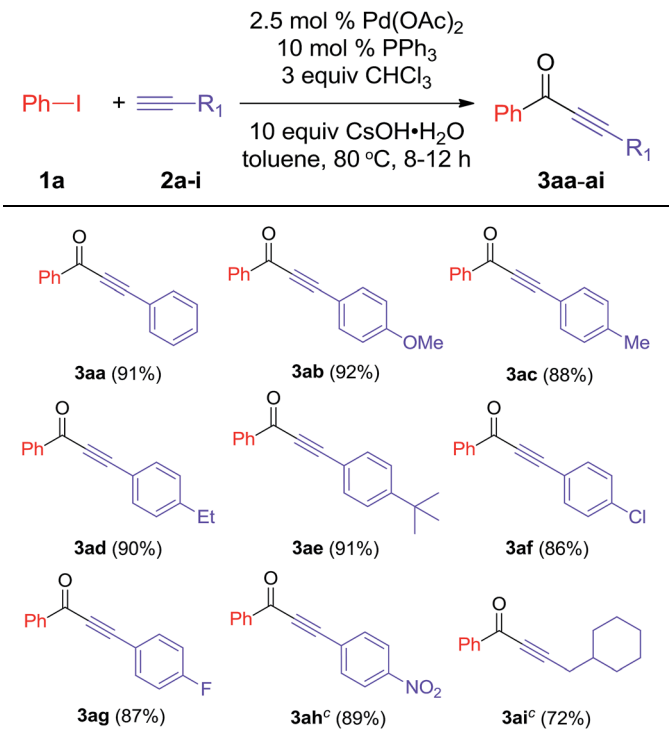
Scheme 2 Reaction of iodobenzene with substituted amino-ethynylbenzene.



Scheme 3 Reaction of ethynylbenzene with natural products.

hindrance of aryl iodides without significant effect on this carbonylative Sonogashira coupling reaction. Moreover, both electron-rich and electron-deficient aryl iodides could afford the corresponding alkynones **3aa–na** in good yields (78–91%).

Table 3 Reaction of iodobenzene with terminal alkynes[a,b]



[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), $CHCl_3$ (1.5 mmol), $Pd(OAc)_2$ (2.5 mol%), PPh_3 (10 mol%), $CsOH \cdot H_2O$ (5 mmol), toluene (3 mL), 80 °C, 8 h. [b] Isolated yields. [c] The reaction proceeded for 12 h.

We further investigated the reactions of iodobenzene with various terminal alkynes (Table 3). All of the aryl alkynes were coupled with iodobenzene to afford the alkynones **3aa–ah** in good yields (86–92%). The reaction of 3-cyclohexyl-1-propyne with iodobenzene proceeded to yield 72% of the desired product **3ai**.

In addition, several substituted amino-ethynylbenzenes (**2j**, **2k** and **2l**) were selected for this reaction, and some interesting results were obtained (Scheme 2). Normal product **3aj** was formed when using 3-(Boc-amino)-ethynylbenzene **2j** as starting material. However, only detrifluoroacetyl product **3ak** was obtained under similar conditions when using 3-(trifluoroacetyl-amino)-ethynylbenzene **2j**. If the amino without any protection group **2l**, both **4aa** and **3ak** were formed in 80% and 10% yields, respectively. These results provided an alternative approach to synthesis corresponding products as needed.

Furthermore, this carbonylative Sonogashira coupling reaction was also applied in natural products (Scheme 3). At first, vindoline and tabersonin were chosen as starting materials, which were iodinated by NIS to form 15-iodo-vindoline **5** and 10-iodo-tabersonin **6**.[56,57] Then, the reaction of **5** or **6** with phenylacetylene was carried out under standard conditions for 12 h. The corresponding products 15-alkynone-vindoline **7** and 10-alkynone-tabersonin **8** were obtained in 79% and 75% yields, respectively.

Conclusions

In conclusion, we have developed a convenient and efficient procedure for the carbonylative Sonogashira coupling of aryl iodides with terminal alkynes using $CHCl_3$ as the CO precursor. It is noteworthy that this protocol is also suitable for the modification of natural products. The mild reaction conditions, short reaction time, high yields of the products, and compatibility with various functional groups, will make the present

method a useful and important addition to the present methodologies for the synthesis of alkynones.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grants 81273397 and 81561148011), the Chinese National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program" (grant 2013ZX09508104).

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