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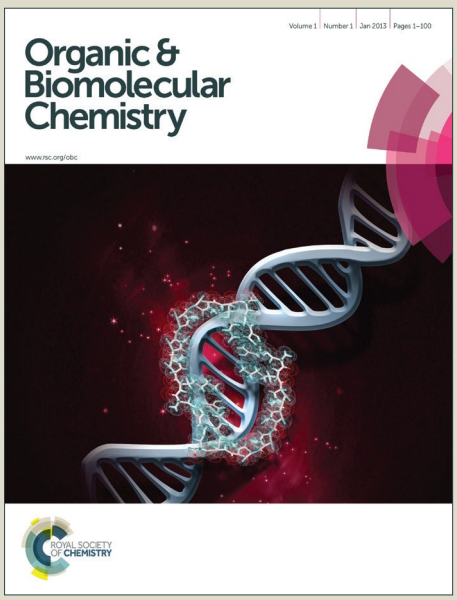

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Palladium-Catalyzed Carbonylative Sonogashira Coupling between Aryl Triazenes and Alkynes

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We disclosed a palladium-catalyzed carbonylative Sonogashira reaction with aryl triazenes and alkynes as substrates and methanesulfonic acid as the additive. A series of *α,β*-ynones were synthesized by this alternative procedure. Notably, bromides, iodides and hydroxyl groups could be well-tolerated under these reaction conditions.

α,β-Ynones are an important class of compounds with many special biological activities.[1] Besides, they provided versatile intermediates for numerous heterocycles[2] and natural products synthesis.[3] Traditionally, these structures were obtained from the nucleophilic addition of acetylide reagents to aldehydes[4] or carboxylic acid derivatives,[5] which required either two-step procedure or laborious work-up. The cross-coupling between acid chlorides and alkynes or alkynylboronates under metal-catalyzed[6] or metal-free[7] conditions represent a more convenient way to their synthesis, but the poor substrate stability and narrow functional group tolerance often curtailed this methodology for synthetic applications.

Since the seminal work by Kobayashi and Tanaka in 1981,[8] palladium-catalyzed carbonylative Sonogashira coupling using aryl (pseudo)halides has become an efficient route to *α,β*-ynones.[9] Aryl amines are relatively inexpensive and abundantly available chemicals and usually acted as nucleophiles in many organic reactions. However, after being converted to diazonium salts by some well-known procedures, they become more active than aryl halides in many palladium-catalyzed cross-coupling reactions.[10] One of the practical concerns when dealing with diazonium salts is their instability and explosive potential.[11] To overcome these disadvantages, in 2011, some of us developed a carbonylative Sonogashira protocol with in situ generated diazonium salts from aryl amines and *tert*-butyl nitrite in presence of acetic acid.[12] Recently, the using of triazenes as diazonium precursors or directing groups has attracted much attention due to their easy preparation and good stability and facile conversion to other functional groups.[13] For example, aryl triazenes have been often employed in Sonogashira reactions for the synthesis of some phenylacetylene oligomers,[14] molecular wires[15] and annulenes.[16] To the best of our knowledge, carbonylative Sonogashira coupling using aryl triazenes has been hitherto unreported in the literature. Herein, we report the palladium-catalyzed carbonylation of aryl triazenes with alkynes and carbon monoxide.

At the outset, we chose the carbonylation between 3,3-diethyl-1-(*p*-tolyl)triaz-1-ene (**1a**) and phenylacetylene (**2a**) as the model reaction in the presence of a catalytic amount of $Pd(OAc)_2$ to optimize the reaction conditions. When Lewis acid $BF_3{\cdot}OEt_2$ was added as the activator for **1a**, only a trace amount of 3-phenyl-1-(*p*-tolyl)prop-2-yn-1-one (**3aa)** was detected on GC (entry 1, Table 1). Under the same ligand-free conditions, several other protic acids were screened (entries 2-6, Table 1). Formic acid and acetic acid were as inefficient as $BF_3{\cdot}OEt_2$. Trifluoroacetic acid, which has been often used as activators for triazenes, led to only 33% yield of **3aa** (entry 4, Table 1). Finally we discovered that sulfonic acids were more effective than other acids and $MeSO_3H$ was the best additive, which furnished **3aa** in 55% yield (entries 6, Table 1).

To further improve the yield of **3aa**, we tried to add some ligands to the catalytic system. When bidentate phosphine ligands

Table 1. Optimization of the reaction conditions[a]

Entry	Acid	Ligand	Solvent	Yield (%)[b]
1	$BF_3{\cdot}OEt_2$	no	dioxane	trace
2	HCOOH	no	dioxane	trace
3	CH_3COOH	no	dioxane	trace
4	CF_3COOH	no	dioxane	33
5	$TsOH{\cdot}H_2O$	no	dioxane	48
6	$MeSO_3H$	no	dioxane	55
7	$MeSO_3H$	DPPP	dioxane	11
8	$MeSO_3H$	DPEPhos	dioxane	5
9	$MeSO_3H$	XantPhos	dioxane	7
10	$MeSO_3H$	*n*-BuPAd$_2$	dioxane	51
11	$MeSO_3H$	PPh_3	dioxane	60
12	$MeSO_3H$	P(*p*-FC_6H_5)$_3$	dioxane	41
13	$MeSO_3H$	P(*p*-OC_6H_5)$_3$	dioxane	57
14	$MeSO_3H$	PCy_3	dioxane	58
15	$MeSO_3H$	P(*o*-toyl)$_3$	dioxane	66
16	$MeSO_3H$	P(*o*-toyl)$_3$	^{t}BuOMe	11
17	$MeSO_3H$	P(*o*-toyl)$_3$	DME	55
18	$MeSO_3H$	P(*o*-toyl)$_3$	THF	76[c] (71[d])

[a]Reaction conditions: **1a** (57.4 mg, 0.3 mmol), **2a** (50 µL, 0.45 mmol), $MeSO_3H$ (20 µL, 0.33 mmol), $Pd(OAc)_2$ (2.02 mg, 9 µmol) and solvent (2

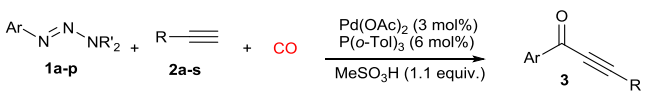
mL). 20 bar CO, 70 °C. [b]Determined by GC using *n*-hexadecane as the internal standard. [c] Corresponding to 73% isolated yield.[d] The CO pressure was 10 bar.

like DPPP, DPEPhos and XantPhos were employed, the yield of **3aa** decreased to a very low level (entries 7-9, Table 1). Therefore, we tried to use some monophosphines instead. *n*-BuPAd$_2$, which has been used in many palladium-catalyzed carbonylations of aryl halides,[17] led to somewhat lower yield of **3aa** (51% vs 55%) than ligand-free conditions (entry 10, Table 1). Substituted triphenylphosphines with either electron-donating or electron-withdrawing groups on the phenyl rings did not show much improvement for this reaction (entries 11-13, Table 1). The electron-richer ligand like tricyclohexylphosphine (PCy$_3$) led to 58% yield of **3aa**. To our satisfaction, when P(*o*-toyl)$_3$ was used in place of PPh$_3$, the yield of **3aa** increased from 60% to 66% under the same conditions (entries 11 vs. 15, Table 1). When the solvent was changed from dioxane to THF, the yield of **3aa** was increased further to 76%. But in other ether solvents like ^{t}BuOMe and DME, the yields were much lower (entries 16 and 17, Table 1). At elevated temperature as 80 °C, the yield in THF dropped from 76% to 65%, which may be caused by the partial decomposition of the diazonium methanesufonate that was likely to be presented as an intermediate during the reaction. In other solvents like MeCN, toluene and DMSO, the yield of **3aa** were 44, 15 and 62% respectively Therefore, THF was the optimal solvent for the carbonylation between **1a** and **2a**. Besides, the lower CO pressure caused decrease in the yield.

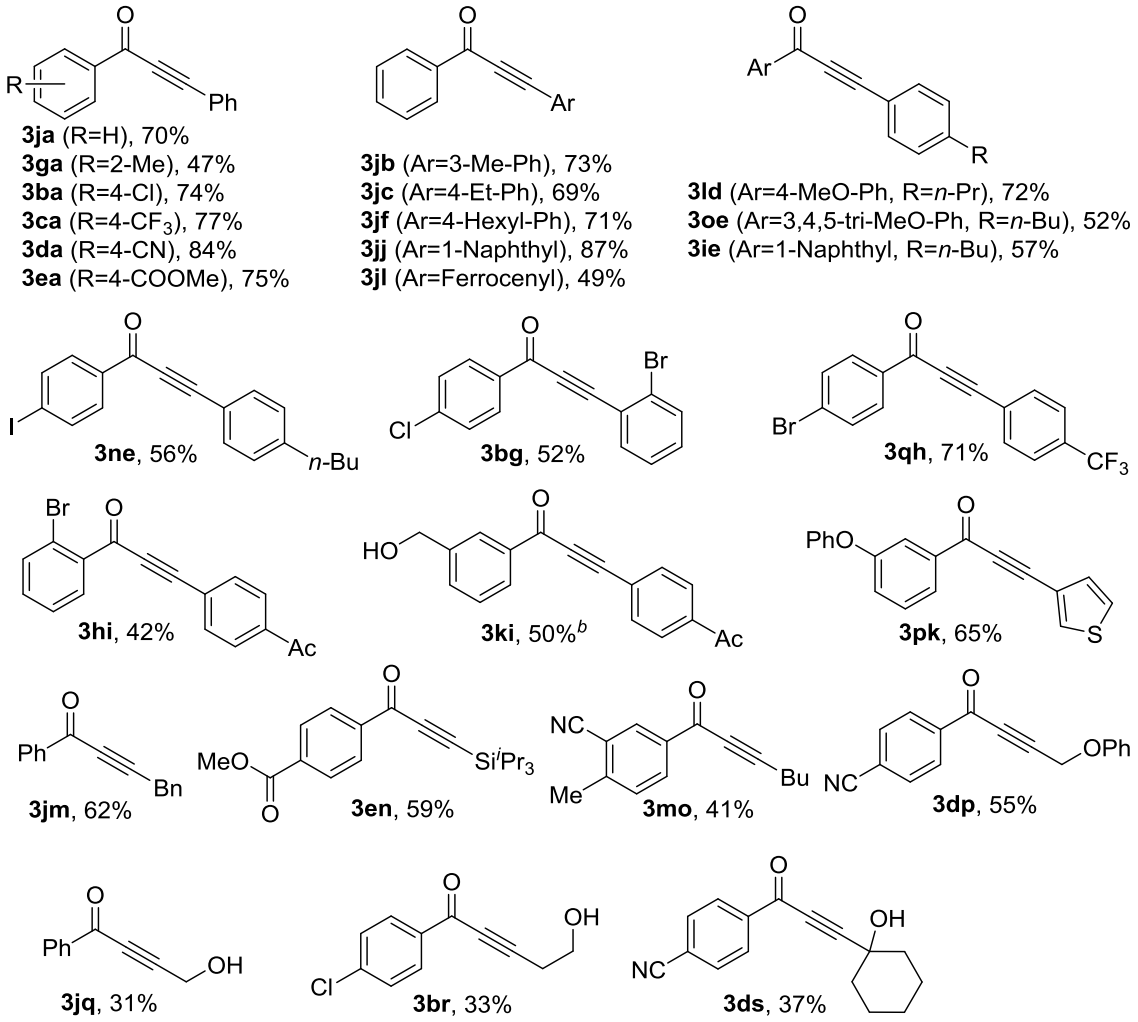
Having the optimized reaction conditions in hand, we next examined the substrates scope of the above procedure with other triazenes and commercially available alkynes (Table 2). These triazenes (**1a-q**) were easily prepared from the corresponding anilines and secondary amines in high yields (see Experimental Section). Firstly, we carried out the reactions between several *ortho* and *para*-substituted aryl triazenes and phenyl acetylenes. Obvious lower yields were found when *ortho* substituents were on the phenyl group. Aryl triazenes with some electron-withdrawing groups on *para* positions gave higher yield of the products. These may be attributed to the less stability of those aryl triazenes with electron rich or *ortho* groups.[11] Next, 1-(phenyldiazenyl)pyrrolidine (**1j**) was reacted with several substituted phenyl acetylenes and good to excellent yields were obtained. For example, when 1-ethynyl naphthene (**2j**) was employed, **3jj** was isolated in 87% yield. Notably, **3jl** was obtained from ferrocenylethyne (**2l**) in 49% yield, which has some potential applications in photoactive semiconductors and liquid crystals.[18] More investigation on the substituent effect on both aryl triazenes and aryl alkynes were performed and we were glad to see that aryl iodide (**1n**) and bromides (**1h**, **1q**, **2g**) and were well-tolerated. These aryl halides could undergo further palladium-catalyzed cross-couplings to introduce various functional groups.[19] The free hydroxyl in **1k** and **2q-s** were also tolerated under these acidic conditions. Unfortunately, some basic functional groups like pyridines and amine were not tolerated under our conditions.

Finally, we tried the carbonylative Sonogashira reactions with some aliphatic alkynes (**2m-s**) and the yields were in overall lower than the aryl counterparts. The masked form of gaseous acetylene, (triisopropylsilyl)acetylene (**2n**), was smoothly converted to protected aryl ethynyl ketone, which is a very versatile intermediates for many organic synthesis.[20] Besides, the alkynols (**2q-s**) were also coupled with aryl triazenes but the yields were even lower.

Table 2. Palladium-catalyzed carbonylative Sonogashira coupling of various aryl triazenes and alkynes[a]

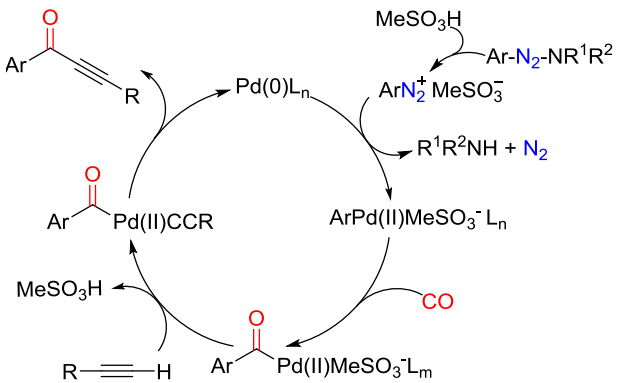


R'=Et	**R'=Et**	**R'=-(CH$_2$)$_4$**	**R'=-(CH$_2$)$_5$**
1a (Ar=4-Me-Ph)	**1f** (Ar=3-I-Ph)	**1j** (Ar=Ph)	**1n** (Ar=4-I-Ph)
1b (Ar=4-Cl-Ph)	**1g** (Ar=2-MePh)	**1k** (Ar=3-CH$_2$OH-Ph)	**1o** (Ar=3,4,5-*tri*-MeO-Ph)
1c (Ar=4-CF$_3$-Ph)	**1h** (Ar=2-Br-Ph)	**1l** (Ar=4-MeO-Ph)	**1p** (Ar=3-PhO-Ph)
1d (Ar=4-CN-Ph)	**1i** (Ar=1-Naphthyl)	**1m** (Ar=4-Me-5-CN-Ph)	**NR'$_2$=4-methylpiperidiyl**
1e (Ar=4-COOMe-Ph)			**1q** (Ar= 4-Br-Ph)
Structure of the alkynes **2a-s**			
2a (R=Ph)	**2f** (R=4-*n*-Hex-Ph)	**2k** (R=3-thienyl)	**2p** (R=CH$_2$OPh)
2b (R=3-Me-Ph)	**2g** (R=2-Br-Ph)	**2l** (R=ferrocenyl)	**2q** (R=CH$_2$OH)
2c (R=4-Et-Ph)	**2h** (R=4-CF$_3$-Ph)	**2m** (R=Bn)	**2r** (R=(CH$_2$)$_2$OH)
2d (R=4-*n*-Pr-Ph)	**2i** (R=4-Ac-Ph)	**2n** (R=TIPS)	**2s** (R=(1-cyclohexanol)yl)
2e (R=4-*n*-Bu-Ph)	**2j** (R=1-Naphthyl)	**2o** (R=*n*-Bu)	



[a]Reaction conditions: **1** (0.6 mmol), **2** (0.9 mmol), $MeSO_3H$ (40 µL, 0.66 mmol), $Pd(OAc)_2$ (4.04 mg, 18 µmol), P(*o*-Tol)$_3$ (11.0 mg, 36 µmol), and solvent (4 mL), 70°C, 20 h. Isolated yield. [b]The product was contaminated with some unreacted **2i**.

Based on these results, a most possible reaction mechanism has been proposed. As shown in Scheme 1, the aryl triazenes were firstly transformed into the corresponding aryl diazonium salts under the assistant of methane sulfonic acid. Then the formed aryl diazonium salts will go oxidative addition with Pd(0) to give the arylpalladium complex which will give the acylpalladium intermediate after the coordination and insertion one molecular of CO. Then the terminal alkynes come and form a new Pd-C bond under the assistant of $MeSO_3^-$, which will give the desired alkynones after reductive elimination and also Pd(0) for the next catalytic cycle. In this procedure, methane sulfonic acid might have three roles: (1) produce aryl diazonium salts from aryl triazenes; (2) $MeSO_3^-$ will deprotonate of terminal alkynes and reform methane sulfonic acid; (3) the regenerated methane sulfonic acid will react with pre-released free amines to avoid the nucleophilic attract of the amines to the acylpalladium intermediate and produce non-desired amides.



Scheme 1. Proposed reaction mechanism.

Conclusions

In conclusion, we have developed a carbonylative Sonogashira procedure for the synthesis of *α,β*-ynones using aryl triazenes, which has been transformed to aryl diazonium salts in the presence of methane sulfonic acid. This procedure has the following features: (1) Acidic conditions are used instead of basic conditions and aryl

bromides and iodides remained unreactive; (2) Aryl triazenes are easily prepared and stable to store for long time; (3) Free alcohols in the substrates can be tolerated. Owing to these advantages, we believe that this alternative method will be useful in the synthesis of some special functionalized ynones for multiple step synthesis.

Notes and references

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†Electronic Supplementary Information (ESI) available: [NMR spectrums and data, reaction procedure]. See DOI: 10.1039/c000000x

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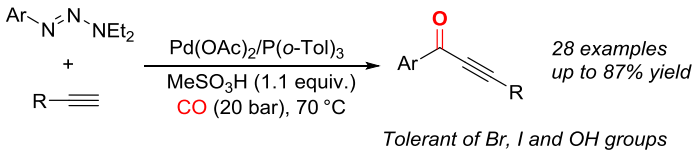

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