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# Catalytic Three-Component One-Pot Reaction of Hydrazones, Dihaloarenes, and Amines

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## ABSTRACT


**A new three-component assembly reaction between *N*-tosylhydrazones, dihalogenated arenes, and various primary and secondary amines was devised, producing nitrogen-containing 1,1′-diarylethylenes in good yields. The two C−C and C−N bonds formed through this coupling have been catalyzed by a single Pd-catalyst in a one-pot fashion.**

The search for practically simple and highly efficient methods to access complex structures is an ongoing challenge for the organic chemist. In this context, transition-metal-catalyzed multicomponent reactions (MCRs), most notably using palladium, allow the efficient construction of elaborate molecules from simple precursors, in a single step without isolation of any intermediate.[1] In these types of reactions, various bonds can be successively created in one operation, and it is of great interest when a single catalyst is able to initiate two or more mechanistically distinct reactions in a multicomponent transformation (autotandem catalysis).[2] Such a process is particularly attractive in view of ecological and economical concerns (e.g., catalyst and solvent economy, operational simplicity, etc.).

In recent years, *N*-tosylhydrazones have attracted extensive attention because of their various useful applications in organic synthesis.[3] In particular, they are valuable and readily available reagents in C−C[4] and C−heteroatom[5] bond-forming reactions through metal-catalyzed processes. Because there are many different reactions that can be catalyzed by the same catalyst, great potential exists to link these reactions in a sequence. Recently, *N*-tosylhydrazones containing an amino group have been coupled with *o*-dihalobenzenes[6] through an efficient sequential C=C bond formation and intramolecular C−N cross-coupling to produce phenanthridine and acridine derivatives.

Although significant progress has been achieved on sequential transformations of *N*-tosylhydrazones through autotandem catalysis,[7] to our knowledge, only one study

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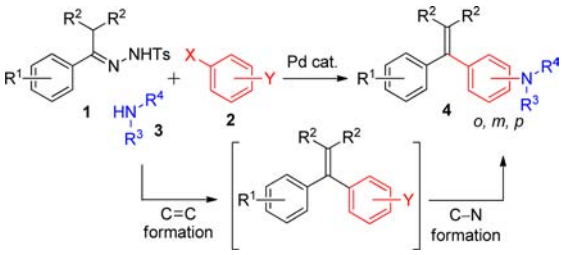
**Scheme 1.** MCRs of Tosylhydrazones with Dihaloarenes and Amines through Palladium-Catalyzed Carbene Migratory Insertion and C−N Cross-Coupling

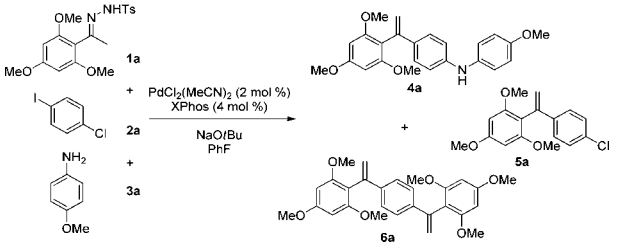



has explored MCRs of *N*-tosylhydrazones with an aryl halide and a terminal alkyne.[8]

As a continuation of our interest in the 1,1-diarylethylene unit synthesis,[9] as a promising cytotoxic agent,[10] combined with the development of MCRs,[11] we report here a novel Pd-catalyzed three-component coupling between *N*-tosylhydrazones **1**, dihaloarenes **2**, and amines **3** leading to a faster C═C bond formation and an efficient intermolecular C—N cross-coupling (Scheme 1). The value of this MCR is in its brevity and ease of synthesis of the desired substrates **4**, as well as in the palladium-based catalytic system preventing both the formation of symmetrical disubstituted byproducts from dihaloarenes **2** and reaction of amines **3** with *N*-tosylhydrazones **1**.[5b] In addition, the availability of amines and dihaloarenes makes this approach sufficiently diversity-oriented, thus fulfilling the recent demand for the generation of large combinatorial chemical libraries.

We began the exploration of this MCR process with a model reaction between *N*-tosylhydrazone **1a** (1.2 equiv), 4-chloroiodobenzene **2a** (1 equiv), and *p*-anisidine **3a** (1 equiv) using our previously optimized protocol:[12] $PdCl_2(MeCN)_2$ (2 mol %), Xphos (4 mol %), and NaO*t*Bu (3 equiv) in fluorobenzene (Table 1). Under these conditions, the desired product **4a**, formed through two consecutive processes, C−C cross-coupling and intermolecular C−N bond forming reactions, was isolated in a moderate 47% yield after 14 h at 110 °C. Careful analysis by NMR showed a significant amount of C—C monocoupling compound **5a**, together with symmetrically disubstituted byproduct **6a** (entry 1). Products derived from undesired side reactions, such as mono- or diamination of **2a**, were not observed,[13] clearly suggesting that the C═C bond formation occurred faster than C—N cross-coupling. Examination of reaction parameters revealed that increasing the amount of base to 3.5 equiv slightly raised the yield of **4a** (entry 2). We were delighted to find that the use of a 1/1 ratio of *p*-anisidine **3a** and hydrazone **1a** leads to improvement in performance of this MCR, and **4a** was isolated in a 72% yield (entry 3). Finally, fine-tuning of the temperature and the reaction time led to **4a** in an excellent isolated yield of 92% (entry 5), showing that this MCR is viable and indeed highly selective.

**Table 1.** Optimization of the One-Pot Reaction Conditions[a]




| entry | aniline (equiv) | time (h)/ temp °C | ratio[b] 4a | 5a | 6a | yield of 4a (%)[c] |
|---|---|---|---|---|---|---|
| 1 | 1.0 | 14/110 | 62 | 33 | 5 | 47 |
| 2 | 1.0 | 14/110 | 72 | 17 | 11 | 55[d] |
| 3 | 1.2 | 14/110 | 92 | 0 | 8 | 72[d] |
| 4 | 1.2 | 6/110 | 94 | 0 | 6 | 75[d] |
| 5 | 1.2 | 6/120 | 100 | 0 | 0[e] | 92[d,f] |

[a] The reactions were carried out in a sealed tube with hydrazone **1a** (1.2 mmol), **2a** (1 mmol), **3a** (*x* equiv), $PdCl_2(MeCN)_2$ (2 mol %), Xphos (4 mol %), and NaO*t*Bu (3 equiv) at mentioned temperature in PhF (4.0 mL). [b] Ratio was determined by $^1$H NMR in the crude mixture; see Supporting Information. [c] Yield of isolated product **4a**. [d] 3.5 equiv of NaO*t*Bu were used. [e] Not detected by $^1$H NMR in the crude reaction. [f] Using $Pd_2(dba)_3$, $Pd(OAc)_2$, or $Pd(acac)_2$ in place of $PdCl_2(MeCN)_2$ furnished **4a** in 51%, 78%, and 69% yield, respectively.

Next, the substrate diversity and the efficiency of the $PdCl_2(MeCN)_2$/Xphos catalytic system on this three-component coupling were examined with various hydrazone, dihaloarene, and amine components (Table 2). Initially, the scope of the reaction was examined with respect to the dihalogenated aromatic system and the nature of amine, including primary and secondary anilines as well as aliphatic amines. Reactions with *para*-, *meta*-, and *ortho*-anisidines **3a**−**c** proceeded efficiently to form the expected products **4a**−**c** in good yields (entries 1−3). The electronic nature of the substituents on the anilines did not have a significant effect on the reaction. Electron-donating or -withdrawing substrates all reacted to give the

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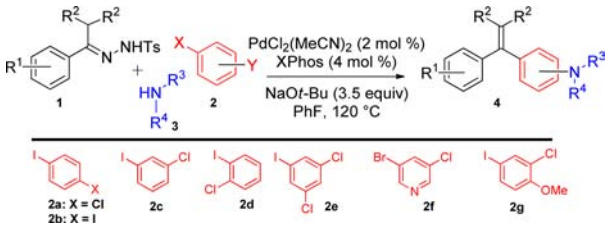
**Table 2.** Scope of One-Pot, Three-Component Reaction of *N*-Tosylhydrazones with Dihalogenated Arenes and Amines[a]




| entry | 1 | 2 | 3 | compound 4 | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 1a | 2a | 3a | 4a | 92 |
| 2 | 1a | 2a | 3b | 4b | 76 |
| 3 | 1a | 2a | 3c | 4c | 77 |
| 4 | 1a | 2c | 3a | 4d | 82 |
| 5 | 1a | 2d | 3a | 4e | 73[c] |
| 6 | 1a | 2a | 3d | 4f | 71 |
| 7 | 1a | 2a | 3e | 4g | 67 |
| 8 | 1a | 2a | 3f | 4h | 65 |
| 9 | 1a | 2g | 3a | 4i | 70 |
| 10 | 1a | 2a | 3g | 4j | 55 |
| 11 | 1a | 2a | 3h | 4k | 72 |
| 12 | 1a | 2a | 3i | 4l | 85 |
| 13 | 1a | 2c | 3i | 4m | 81 |
| 14 | 1a | 2a | 3j | 4n | 78 |
| 15 | 1a | 2e | 3i | 4o | 72 |
| 16 | 1a | 2f | 3i | 4p | 51 |
| 17 | 1a | 2b | 3k | 4q | 50 |
| 18 | 1a | 2a | 3l | 4r | 57 |
| 19 | 1a | 2a | 3m | 4s | 72 |
| 20 | 1a | 2a | 3n | 4t | 45[d] |
| 21 | 1b | 2a | 3a | 4u | 88 |
| 22 | 1c | 2a | 3i | 4v | 56 |
| 23 | 1d | 2b | 3a | 4w | 35 |
| 24 | 1e | 2a | 3i | 4x | 72 |
| 25 | 1f | 2a | 3i | 4y | 93 |
| 26 | 1g | 2a | 3i | 4z | 90 |
| 27 | 1h | 2a | 3a | 4aa | 75 |
| 28 | 1i | 2a | 3i | 4ab | 68 |

[a] The reactions were carried out in a sealed tube with hydrazones **1** (1.2 mmol), aryl halides **2** (1 mmol), amines **3** (1.2 mmol), $PdCl_2(MeCN)_2$ (2 mol %), Xphos (4 mol %), and NaO*t*Bu (3.5 equiv) at 120 °C in PhF (4.0 mL). [b] Isolated yield of product **4**. [c] Aniline **3a** was added after 1 h of coupling between **1a** and **2d**. [d] **4r** was obtained by acidic hydrolysis of *N*-aryl imine adduct in a THF/HCl solution; see Supporting Information.

corresponding products **4a**–**g** in good yields (entries 1–7). In the same manner, switching the halide group from the *para*-position to the *meta*- or *ortho*-position on the aryl ring of **2** does not significantly influence the overall yield of the reaction, demonstrating that steric factors have little influence on the rate of C=C and C—N bond formation (compare entries 1 and 4, 5). Interestingly, this three-component coupling was found also to proceed successfully with heterocyclic amines, such as 5-aminoquinoline **3f**, furnishing **4h** in a 65% yield (entry 8). To illustrate the usefulness of this MCR, we prepared from hydrazone **1a** and dihalogenated aromatic compound **2g** the

1,1-diarylethylene **4i** in one step, which could be regarded as an analogue of antivascular *iso*$NH_2$-combretastatin-A4[14] (entry 9).

Next we examined the efficiency of this MCR with secondary anilines. Thus, reactions with diphenylamine **3g**, *N*-methylaniline **3h**, indoline **3i**, and 1,2,3,4-tetrahydroquinoline **3j** all reacted to give the corresponding coupling products with yields ranging from 55 to 85% (entries 10−14). It is intersting to note that this reaction can be applied successfully to a trihalogenated aromatic system. A good yield of **4o** was obtained when using 1,3-dichloro-5-iodobenzene **2e** as a coupling partner. Accordingly, one C=C bond and two C—N bonds were formed efficiently, representing an average 90% yield for each of the three steps of this MCR (entry 15). In addition, we found also that our coupling conditions proved also to be successful with dihalogenated heteroaromatic partner **2f**; in this case, compound **4p** was obtained in a satisfactory 51% yield (entry 16).

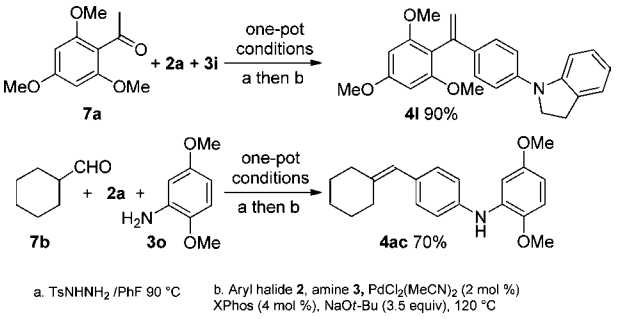
Furthermore, we investigated whether it might be possible to carry out this MCR with aliphatic amines. To our delight, satisfactory to good yields were obtained with primary and secondary amines, such as *n*-octylamine **3k**, dibutylamine **3l**, and 1-methylpiperazine **3m** (entries 17−19). Extending this MCR to include benzophenone imine **3n** as an ammonia surrogate allows the formation of the corresponding *N*-aryl imine adduct, which was then hydrolyzed to furnish the desired aniline **4t** with an overall acceptable yield of 45% (entry 20).

To broaden the substrate scope, we further investigated this MCR with respect to hydrazones **1**. Gratifyingly, as depicted in Table 2 (entries 21−28), the entire coupling proceeded cleanly and selectively in good to excellent yields. Functionalized *N*-tosylhydrazones containing electron-donating or -withdrawing groups proved to be suitable substrates in this MCR. It is noteworthy that the chloro substituent on the phenyl ring of hydrazone **1c** and **1d** was tolerated, enabling further metal-catalyzed functionalization processes (entries 22−23).

The effectiveness of our protocol was also demonstrated with *N*-tosylhydrazones **1g**,**h** containing a secondary carbon atom α to the hydrazone function to provide tetrasubstituted olefins **4z** and **4aa** having a cycloalkylidene unit in good yields (entries 26 and 27). Finally, cyclic *N*-tosylhydrazone **1i**, which is derived from cyclooctanone, also undergoes smooth MCR to afford **4ab** in 68% yield (entry 28).

As sulfonyl hydrazones could be simply prepared by mixing relative sulfonyl hydrazides and the carbonyl compounds, we investigated whether the reaction could be carried out in a one-pot fashion directly from carbonyl compounds **7**, avoiding the isolation of the tosylhydrazone intermediates **1**. After some experimentation, we were pleased to successfully achieve a one-pot MCR protocol. In this process, carbonyl compounds **7a**,**b** and sulfonyl hydrazide were stirred in PhF for 2 h at 90 °C, and then all the reagents were added to the reaction mixture. Following this procedure, yields similar to those from hydrazones **1** were obtained (Scheme 2).

**Scheme 2.** One-Pot MCR from Carbonyl Compounds **7a**,**b**




In conclusion, we have succeeded in developing a novel three-component reaction of *N*-tosylhydrazones, polyhaloarenes, and amines, allowing efficient sequential C=C bond formation and intermolecular C—N cross-coupling. Our optimized conditions allowed us to prepare 1,1-diarylethylene derivatives **4** of biological interest that accommodated a wider combination of nitrogen substituents at the aromatic ring. Good to excellent yields were obtained using a wide range of amine partners, including primary and secondary anilines as well as aliphatic amines. The process is very general with regard to other coupling partners, the tosylhydrazone and the dihalogenated aromatic system. Moreover, it is not necessary to isolate the tosylhydrazone partner, and the reaction can be conducted in a one-pot manner directly from the carbonyl compound. All of these features make this simple and general MCR of broad utility for the synthesis and development of new medicinal agents. Further studies on the scope and synthetic applications are in progress.

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**Supporting Information Available.** Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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