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Ag(I)-Catalyzed Three-Component Reaction of 2-Alkynylbenzaldehydes, Amines, and Diazo Compounds

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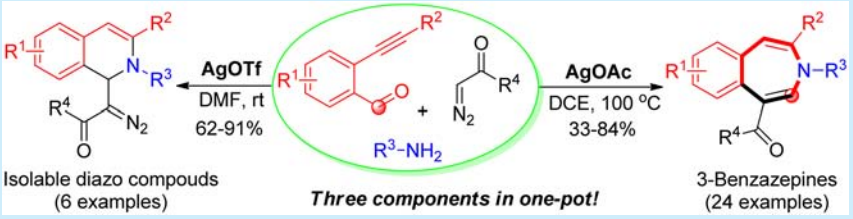
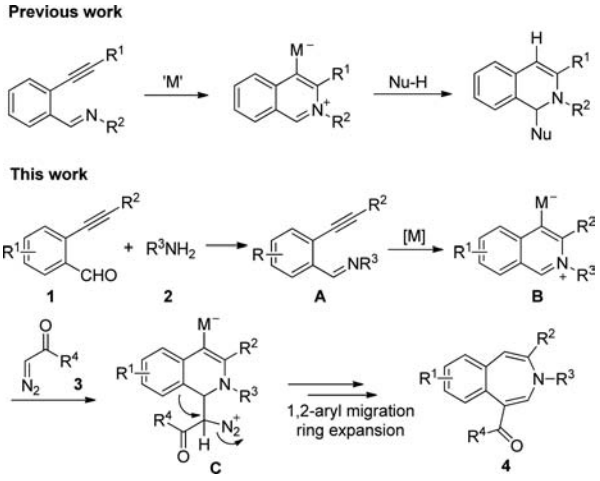
Supporting Information



ABSTRACT: Diazo compounds have been employed as the nucleophile in a silver-catalyzed three-component reaction with amines and 2-alkynylbenzaldehydes. Various 3-benzazepines were prepared in a one-pot manner based on a cascade imine−-yne cyclization/nucleophilic addition/1,2-aryl migration process. Moreover, this Ag(I)-mediated reaction also provides a practical route to diazo-containing dihydroisoquinolines under slightly modified conditions.

Multicomponent reactions are among the most efficient synthetic methods, and they allow the construction of complex molecular architectures from simple precursors with high levels of stereocontrol in a single operation.[1] In the past decades, transition-metal-catalyzed tandem reactions of 2-alkynylbenzaldehydes, amines, and nucleophiles have been developed as efficient methods for the generation of 1,2-dihydroisoquinoline derivatives (Scheme 1).[2] A variety of different nucleophiles, such as terminal alkynes,[3] organic metal reagents,[4] ketones,[5] indoles,[6] phosphites,[7] and $TMSCF_3$,[8] have been used. However, diazo compounds have never been reported as one of the key reactants in the coupling reactions with 2-alkynylbenzaldehydes and amines.[9] We assumed that the related nucleophilic addition of the diazo compound to isoquinolinium **B** would form intermediate **C**,[10] which might afford a 3-benzazepine skeleton via a 1,2-aryl migration process.[11] The challenge in the development of an efficient imine−yne cyclization/nucleophilic addition/1,2-aryl migration cascade process lies in the restraint of possible side reactions, such as the formation of β-ketone esters[12] or N−H insertion of amines with diazo compounds.[13] Moreover, 1,2-*H*[14] and 1,2-*N* migration[15] can also compete with 1,2-aryl migration from intermediate **C**. We envisioned that employing judicious reaction conditions, in particular an appropriate transition-metal catalyst, would allow the reaction to proceed along the desired pathway. As part our recent interest in the nucleophilic addition of diazo compounds to in situ generated iminium ions,[16] herein we report a silver-catalyzed three-component reaction of 2-alkynylbenzaldehydes, amines, and diazo compounds. This novel reaction provides an efficient and convenient synthetic route to 3-benzazepines, which are a prominent substructure in numerous pharmaceuticals and naturally occurring alkaloids.[17]

Scheme 1. Three-Component Reaction of 2-Alkynylbenzaldehydes, Amines, Nucleophiles, and Our Design



Toward this objective, we started our optimization by using 2-(phenylethynyl)benzaldehyde **1a** (0.2 mmol), aniline **2a** (1.05 equiv), and ethyl diazoacetate **3a** (1.1 equiv) as the model substrates. Initially, various transition-metal catalysts, such as $Cu(OTf)_2$, $FeCl_3$, $InCl_3$, and $PdCl_2$, were tested. Although

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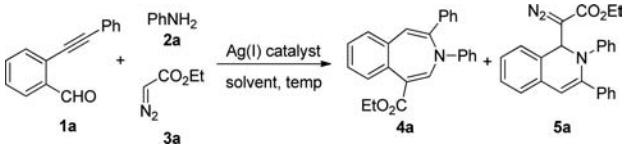
these metal salts have been reported as good catalysts for imine−yne cyclization,[3a,4b,18] their application in the present three-component reactions resulted in complex mixtures (Table 1, entries 1−4). Gratifyingly, when 10 mol % of AgOTf was

Table 1. Optimization of Reaction Conditions[a,b]



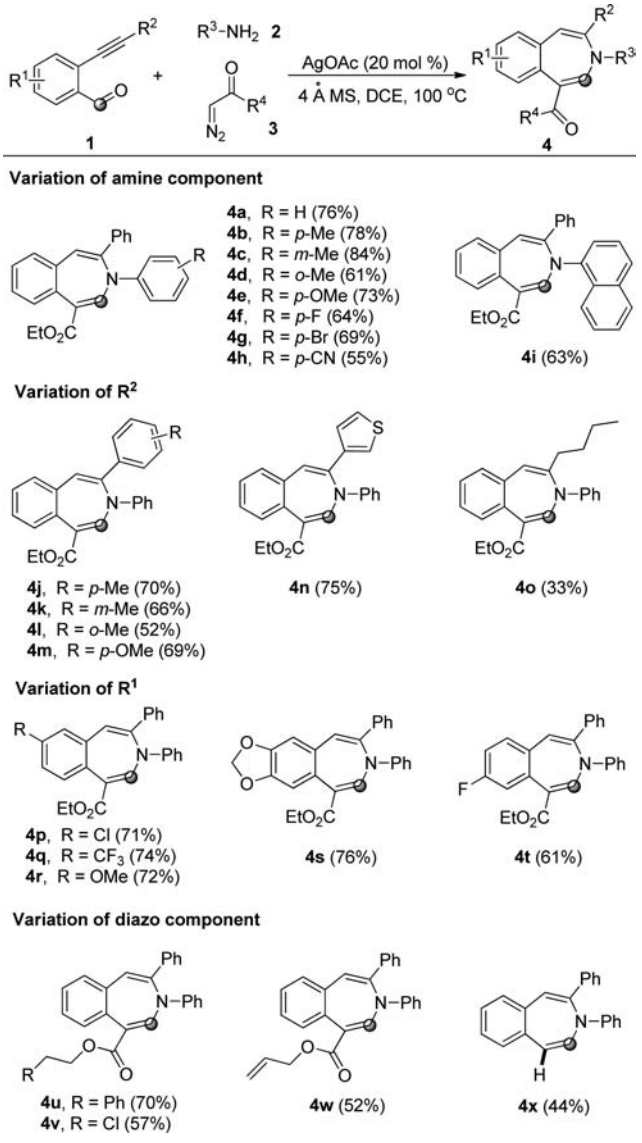
entry	catalyst (mol %)	temp (°C)	solvent	4a (%)	5a (%)
1	$Cu(OTf)_2$ (10)	75	DCE	9	0
2	$FeCl_3$ (10)	75	DCE	0	7
3	$InCl_3$ (10)	75	DCE	0	13
4	$PdCl_2$ (10)	75	DCE	0	0
5	AgOTf (10)	75	DCE	21	25
6	AgF (10)	75	DCE	15	37
7	$AgNO_3$ (10)	75	DCE	19	29
8	Ag_2CO_3 (10)	75	DCE	28	24
9	$AgSbF_6$ (10)	75	DCE	16	28
10	AgOAc (10)	75	DCE	47	23
11	AgOAc (10)	85	DCE	68	15
12	AgOAc (10)	100	DCE	77	9
13	AgOAc (10)	120	DCE	51	5
14	**AgOAc (20)**	**100**	**DCE**	**83**	**<2**
15	AgOAc (20)	100	MeCN	21	65
16	AgOAc (20)	100	DMF	17	63
17	AgOAc (20)	100	dioxane	27	51
18	AgOAc (20)	100	toluene	19	58
19	AgOTf (10)	25	DMF	0	91[c]

[a]Reaction conditions: 2-(phenylethynyl)benzaldehyde **1a** (0.2 mmol), aniline **2a** (1.05 equiv), ethyl diazoacetate **3a** (1.1 equiv), 4 Å molecular sieves (200 mg), and sliver catalyst in 1 mL of solvent for 24 h. [b]Yields were determined using mesitylene as an internal standard. [c]Isolated yield.

employed, the desired 3-benzazepine **4a** was obtained in 21% yield concomitant with the formation of an isolable diazo product **5a** in 25% yield (Table 1, entry 5). Since the reaction was carried out under neutral conditions, the formation of diazo compound **5a** must occur through the nucleophilic addition of diazoacetate **3a** to isoquinolinium **B**, followed by deprotonation/protonation from intermediate **C**. Encouraged by this result, several silver salts, including AgF, $AgNO_3$, Ag_2CO_3, $AgSbF_6$, and AgOAc, were examined; among them, AgOAc gave the best yield of 3-benzazepine **4a** (Table 1, entries 6−10). We found that the formation of **4a** was more favorable at elevated temperatures (Table 1, entries 11 and 12). However, increasing the temperature to 120 °C has a negative impact on the reaction, resulting in the fast decomposition of ethyl diazoacetate **3a** (Table 1, entry 13). We found the yield of diazo compound **5a** could be further suppressed by using 20 mol % of AgOAc as the catalyst, in which the desired 3-benzazepine **4a** was obtained in 83% yield (Table 1, entry 14). Varying the solvent from DCE to MeCN, DMF, 1,4-dioxane, or toluene gave low yields of **4a** (Table 1, entries 15−18). In these cases, the diazo compound **5a** was obtained as the major product. Notably, 91% yield of **5a** could be isolated when the reaction was carried out in DMF at room temperature by using 10 mol % of AgOTf as the catalyst (Table 1, entry 19).

Having established the optimized reaction conditions, an investigation into the versatility and functional group tolerance of this reaction process was performed. First, the amine component was varied, and their coupling with 2-(phenylethynyl) benzaldehyde **1a** and ethyl diazoacetate **3a** were investigated. As shown in Scheme 2, the reaction proceeded

Scheme 2. Scope of the Ag(I)-Catalyzed Three-Component Reactions[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (1.05 equiv), **3** (1.1 equiv), AgOAc (20 mol %), and 4 Å molecular sieves (200 mg) in 1 mL of DCE at 100 °C for 24 h. [b]Isolated yields.

smoothly with *o*-, *p*-, and *m*-methyl-substituted anilines as the substrates. The optimal conditions were compatible with a variety of substitutents, including methoxy, fluoro, and cyano groups. It is noteworthy that a bromo substituent could survive in the reaction, which provided the possibility of functionalizing the resulting 3-benzazepines by using palladium-catalyzed coupling reactions. We were delighted to find that 1-aminonaphthalene was also consistent with the optimal conditions, leading to 3-benzazepine **4i** in 63% yield. Unfortunately, when alkylamines such as 1-hexylamine and

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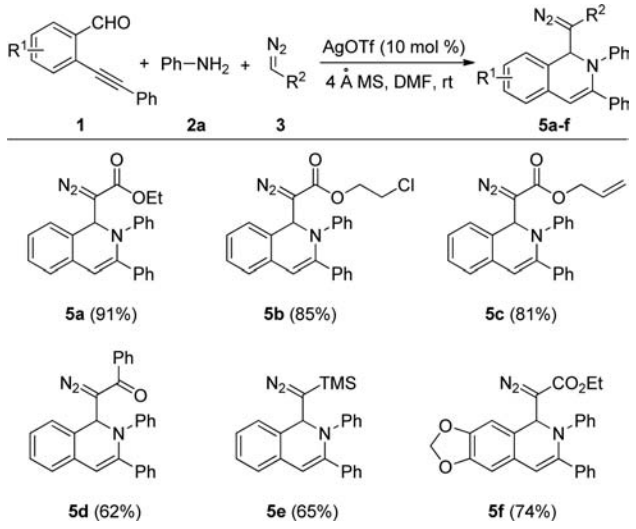
benzylamine were employed as the substrates, the reactions gave complex mixtures, and only trace amounts of the desired products were detected. Next, various 2-alkynyl benzaldehydes **4j−t** were examined under the optimized reaction conditions. The reaction was not significantly affected by the substitutent on the phenyl ring at the acetylenic center (R^2); products **4j−m** were isolated in 52−70% yields. Benzaldehyde with triple-linked thiophene also underwent the reaction smoothly with phenylamine and ethyl diazoacetate to assemble the desired 3-benzazepine **4n** in 75% yield. Notably, *o*-alkylacetylenic-substituted benzaldehyde was also suitable substrate for the reaction but afforded the 4-butyl-3-benzazepine **4o** in low yield. When a substitutent was introduced to the *para* or *meta* position of the aldehyde, the three-component coupling products **4p−s** were obtained in good yields. Both electron-withdrawing groups, such as Cl, F, and CF_3, and electron-donating groups, such as OMe and OCH_2O, could be well tolerated in this transformation. Finally, we tested the reactions with different α-diazo esters, and they all underwent smooth reactions with **1a** and **2a** to give the corresponding 3-benzazepines **4u**, **4v**, and **4w** in yields of 70%, 57%, and 52%, respectively. In the case of $TMSCHN_2$, product **4x** with deprotection of TMS group was isolated as the major product.

As shown in Table 1, the reaction could afford an isolable diazo-containing dihydroisoquinoline **5a** in an excellent yield by varying the solvent and temperature (entry 19). The scope of the present Ag(I)-mediated three-component reaction for the preparation of these diazo-containing cycloadducts was also examined (Scheme 3). To our delight, the reaction proved to

Scheme 3. Sliver-Catalyzed Synthesis of Diazo-Containing 1,2-Dihydroisoquinolines[a,b]

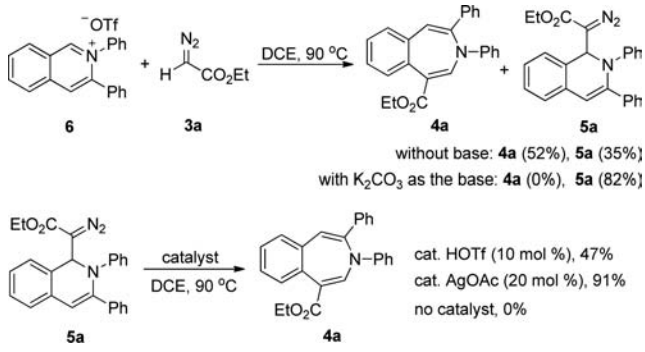


[a]Reaction conditions: benzaldehyde **1** (0.2 mmol), aniline **2** (1.05 equiv), diazo compound **3** (1.1 equiv), AgOTf (10 mol %), and 4 Å molecular sieves (200 mg) in 1 mL of DMF at rt for 12 h. [b]Isolated yields.

be quite general with various diazo compounds, including α-diazo esters, α-diazo ketone, and $TMSCHN_2$ as the substrates. In all cases, the desired β-amino-α-diazo compounds **5a−f** were isolated in good yields, and no ring-expansion products were detected.

To understand the mechanism of the reaction, several control experiments were performed (Scheme 4). First, heating

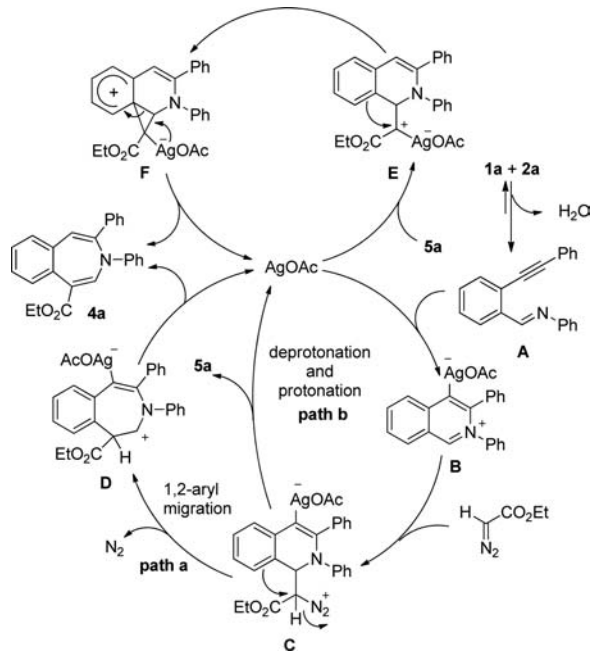
Scheme 4. Control Experiments



the solution of diazoacetate **3a** and isoquinolinium salt **6** gave a mixture of 3-benzazepine **4a** and diazo compound **5a** in a ratio of 1.5:1. When 1 equiv of K_2CO_3 was added, the formation of **4a** was completely suppressed, and compound **5a** was isolated as the sole product in 82% yield. These results indicated K_2CO_3 might promote the deprotonation to form **5a**. Since the reaction of **6** and **3a** generates HOTf, which can be used as a catalyst for 1,2-aryl migration,[19] the addition of a base also neutralized the HOTf in the solution. To evaluate the catalytic efficiency of HOTf for the reaction, diazo compound **5a** was heated in DCE at 100 °C in the presence of 10 mol % of HOTf. The reaction afforded 3-benzazepine **4a** in a yield of 44%, and 51% yield of **5a** remained unreacted. As a comparison, we found the reaction delivered 91% yield of **4a** when AgOAc (20 mol %) was used as the catalyst, while no reaction occurred without the catalyst.

Therefore, a tentative mechanism for the Ag(I)-catalyzed three-component coupling reaction of 2-alkynylbenzaldehydes, amines, and diazo compounds is proposed in Scheme 5. The condensation of 2-(phenylethynyl)benzaldehyde and aniline affords imine **A**, followed by an intramolecular imine−yne cyclization in the presence of Ag(I) catalyst to give isoquinolinium intermediate **B**.[2] Intermolecular nucleophilic

Scheme 5. Proposed Reaction Mechanism



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attack of diazo compound to **B** forms intermediate **C**. The direct 1,2-aryl migration of **C** leads to the formation of ring-expansion intermediate **D** with the extrusion of nitrogen (path a). Subsequently, deprotonation and protonation with regeneration of the Ag(I) catalyst produce the 3-benzazepine product. Since AgOAc is also a good catalyst for the conversion of diazo compound **5a** to 3-benzazepine and the reaction can be efficiently promoted by increasing the amount of the catalyst loading, another stepwise route was also proposed (path b). The direct deprotonation/protonation from intermediate **C** gives the isolable diazo compound **5a** with concomitant release of AgOAc. The stability of the resulting α-diazo ester **5a** is decreased owing to the presence of an amino group on its β-position, which could be decomposed by Ag(I) to form the metal-bound carbene intermediate **E**.[14b,d] Finally, 1,2-aryl migration through a tricyclic intermediate **F** gives the ring-expansion product **4a** and regenerated the silver catalyst.[19a,20]

In conclusion, we have developed an efficient three-component reaction of 2-alkynylbenzaldehydes, amines, and diazo compounds, leading to 3-benzazepine derivatives by using Ag(I) as the catalyst. The reaction provides a straightforward method for the construction of a biologically important 3-benzazepine skeleton from easily available starting materials with the tolerance of a wide range of functional groups. Mechanistically, the reaction is supposed to proceed via a cascade imine−yne cyclization/nucleophilic addition/1,2-aryl migration process. It is the first instance where Ag(I)-mediated 1,2-aryl migration is used in the synthesis of medium-sized heterocycles where no 1,2-*H* and 1,2-*N* migration are observed as competitive side reactions.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http//pubs.acs.org. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02159.

Experimental details, characterization data, and NMR spectra of all new products (PDF)

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Notes

The authors declare no competing financial interest.

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