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Silver Nitrate Mediated Cyclization/N–N Bond-Cleavage Reaction for the Synthesis of 3-Arylisoquinolines

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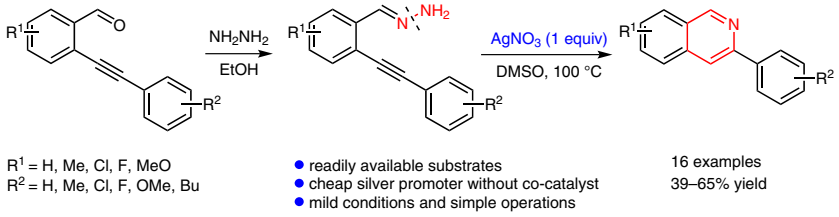

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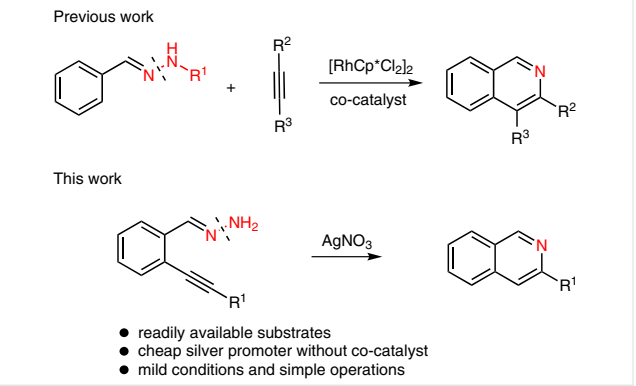
Abstract An unprecedented silver nitrate mediated novel transformation of aromatic hydrazones into various isoquinolines has been developed. This method involves a silver nitrate promoted cyclization of aromatic hydrazones followed by N–N bond cleavage, and has wide substrate scope under mild conditions.

Key words isoquinolines, bond cleavage, hydrazones, silver nitrate, alkynals, domino reactions

The isoquinoline skeleton, as a privileged substructure, is a key motif found in numerous natural products and pharmaceuticals with many biological activities.[1] Efficient constructions of functionalized isoquinoline motifs play critical roles in many syntheses toward natural products and pharmaceuticals.[2] Consequently, numerous efforts have been made to develop new synthetic approaches to isoquinolines.[3] Of these, transition-metal-catalyzed inter- or intramolecular cyclization/(hetero)annulation reactions are among the most popular strategies.[4] For example, isoquinoline derivatives can be obtained by silver-catalyzed cyclization of *ortho*-alkynylaryl aldimines.[5] Recently, transition-metal-catalyzed direct C–H bond functionalization of arenes bearing nitrogen-containing directing groups, followed by cyclization with the resulting internal alkynes, has been developed as a highly efficient method for constructing diverse isoquinolines with a wide range of functional groups.[6] The hydrazone group is widely used as a directing group, and cyclization to isoquinolines can be followed by hydrazone N–N bond cleavage, as demonstrated by elegant works from Cheng and Knochel and their respective co-workers.[7] In these reactions, noble-metal rhodium catalysts are usually required to achieve C–H functionalization (Scheme 1).[2f,8] On the other hand, Ag salts have also proved to be efficient catalysts for the formation of isoquinolines.[9] As part of our long-term interest in the development of methods for heterocycle synthesis,[10] we report here an efficient $AgNO_3$-mediated isoquinoline synthesis from aromatic hydrazones through cyclization and N–N bond cleavage. This approach has several advantages, including readily available substrates that can be prepared by simple condensation of *ortho*-alkynyl benzaldehydes with inexpensive hydrazine, a cheap silver promoter with no requirement for an external additive, mild conditions, and simple operations.



Scheme 1 Synthesis of isoquinolines by cleavage of N–N bonds

Initially, we used [2-(phenylethynyl)benzylidene]hydrazine as a model substrate to screen the reaction parameters (Table 1). On the basis of our previous study on isoquinoline synthesis, we first tested CuI in the reaction (Table 1, entry 1), and we obtained the desired isoquinoline product **2a** in

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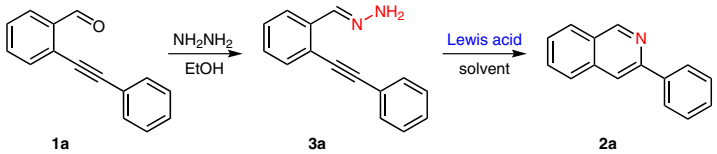
moderate yield by heating with a catalytic amount of CuI in DCE at 80 °C for 12 hours. Although the reaction with $PdCl_2$ gave a similar result (entry 2), further studies revealed that $AgNO_3$ is a superior catalyst, affording product **2a** in 36% isolated yield (entry 3). With $AgNO_3$ as the catalyst, we next examined the effects of a wide range of solvents (entries 4–12), and the reaction in DMSO as the solvent gave the best yield (entry 12). To further improve the yield, we studied the effect of catalyst loading on the reaction. The reaction efficiency was improved by increasing the catalyst loading to 30 mol% (entry 13). The yield increased to 53% on further increasing the $AgNO_3$ loading to 50 mol% (entry 14). The yield of the isoquinoline product increased markedly to 57% with one equivalent of $AgNO_3$ (entry 15), but no further improvement was observed when more catalyst was used (entry 16).

Having identified the optimal reaction conditions [$AgNO_3$ (100 mol%), DMSO, 100 °C], we next examined the scope of the reaction (Table 2). Generally, the domino reactions provided substituted isoquinolines in moderate to good yields. Various substitutions on the aryl rings, including chloro, methyl, fluoro, and methoxy groups, were well tolerated. Better results were usually observed with substrates bearing electron-donating groups at the *para*-position of the phenyl ring (Table 2, entries 11 and 12), whereas those with electron-withdrawing groups at the same position gave slightly lower yields (entries 13 and 14). A substrate bearing chloro substituents on both aryl rings showed poor reactivity, and the corresponding product **2g** was isolated in only 39% yield (entry 7). Furthermore, when the reaction was tested with a substrate bearing an alkyl-terminated alkyne, none of the desired product was obtained under the standard conditions (entry 16).

On the basis of these experiment results and reported precedents for silver-catalyzed cyclization of *ortho*-alkynylaryl aldimines,[11] we propose a possible mechanism for the present cyclization reaction, shown in Scheme 2. First, activation of the alkyne triple bond by silver(I) facilitates a 6-*endo*-dig cyclization of the hydrazine and alkyne groups in **1a** to afford intermediate **I**. Protonation of intermediate **I** then gives intermediate **II**, which undergoes N–N bond cleavage to afford product **2a**. The strong tendency toward aromatization is possibly the driving force for the critical N–N bond cleavage. The byproduct NH_2OH might form a stable silver–amine complex, thereby hampering catalyst recycling; a stoichiometric amount of $AgNO_3$ is therefore required to promote the reaction.

Table 1 Optimization of the Reaction Conditions[a]



1a 3a 2a

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	CuI (10%)	DCE	80	12	21
2	$PdCl_2$ (10%)	DCE	80	12	24
3	$AgNO_3$ (10%)	DCE	80	0.5	36
4	$AgNO_3$ (10%)	$CHCl_3$	80	12	36
5	$AgNO_3$ (10%)	CCl_4	80	12	35
6	$AgNO_3$ (10%)	toluene	80	12	25
7	$AgNO_3$ (10%)	THF	80	10	33
8	$AgNO_3$ (10%)	MeCN	80	10	34
9	$AgNO_3$ (10%)	MeOH	80	0.5	41
10	$AgNO_3$ (10%)	DMF	80	12	35
11	$AgNO_3$ (10%)	H_2O	80	12	32
12	$AgNO_3$ (10%)	DMSO	100	12	44
13	$AgNO_3$ (30%)	DMSO	100	12	47
14	$AgNO_3$ (50%)	DMSO	100	10	53
15	**$AgNO_3$ (100%)**	**DMSO**	**100**	**0.5**	**57**
16	$AgNO_3$ (400%)	DMSO	100	0.2	56

[a] Reaction conditions: **1a** (0.3 mmol), solvent (3.0 mL).
[b] Isolated yield.

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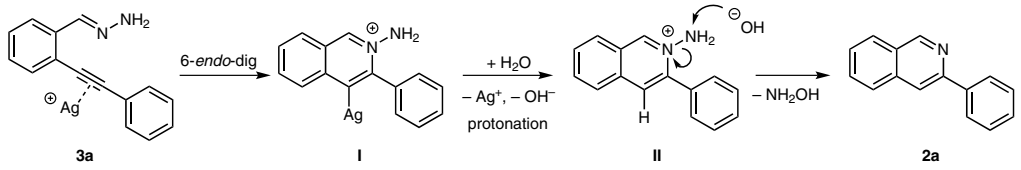
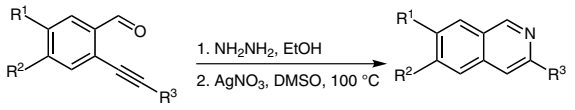


Scheme 2 Proposed mechanism for the $AgNO_3$-promoted cyclization/N–N bond-cleavage reaction

Table 2 Substrate Scope[a]



1 2

Entry	Product	R^1	R^2	R^3	Yield[b] (%)
1	**2a**	H	H	Ph	57
2	**2b**	Me	H	Ph	56
3	**2c**	Cl	H	Ph	48
4	**2d**	Me	H	4-MeC_6H_4	51
5	**2e**	Me	H	4-ClC_6H_4	60
6	**2f**	Cl	H	4-MeC_6H_4	55
7	**2g**	Cl	H	4-ClC_6H_4	39
8	**2h**	H	H	4-MeC_6H_4	61
9	**2i**	H	H	4-BuC_6H_4	60
10	**2j**	H	H	4-$MeOC_6H_4$	62
11	**2k**	H	H	4-FC_6H_4	56
12	**2l**	H	H	4-ClC_6H_4	52
13	**2m**	H	F	Ph	56
14	**2n**	MeO	H	Ph	50
15	**2o**	H	F	4-MeC_6H_4	65
16	**2p**	H	H	Bu	–

[a] Reaction conditions: *o*-alkynyl aldehyde **1** (0.3 mmol), solvent (3.0 mL).
[b] Isolated yield.

In summary, we have developed a convenient domino reaction for synthesizing various substituted isoquinolines in moderate to good yields.[12] This method involves a silver nitrate promoted cyclization/N–N bond cleavage in the absence of an external additive.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562609.

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(12) **3-Phenylisoquinolines (2a);**[13] **Typical Procedure**
To a solution of 2-(phenylethynyl)benzaldehyde (**1a**; 62.0 mg, 0.3 mmol) in EtOH (5 mL) was added N_2H_4·HCl (30.6 mg, 0.45 mmol), and the mixture was stirred at r.t. for 3 h. The solid was then collected by filtration and used in the next step without further purification. The crude aromatic hydrazones **3a** was dissolved in DMSO (3 mL) and $AgNO_3$ (51.0 mg, 0.3 mmol) was added. The mixture was stirred at 100 °C until all starting material was consumed. The solvent was evaporated and the residue was purified by column chromatography, eluting with hexanes/EtOAc (5:1) to give a white solid; yield: 35 mg (57%); mp 97–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 8.16 (d, *J* = 7.5 Hz, 2 H), 8.10 (s, 1 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 7.91–7.89 (d, *J* = 8.0 Hz, 1 H), 7.75–7.70 (m, 1 H), 7.63–7.60 (m, 1 H), 7.56–7.53 (m, 2 H), 7.47–7.44 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.5 , 151.3, 139.6, 136.7, 130.6, 128.8, 128.6, 127.8, 127.6, 127.1, 127.0, 126.9, 116.6. The NMR data agreed with those previously reported.

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