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Efficient Synthesis of Isoquinolines by $AgNO_3$-Catalyzed Sequential Imination−Annulation of 2-Alkynyl Aldehydes with Ammonium Bicarbonate

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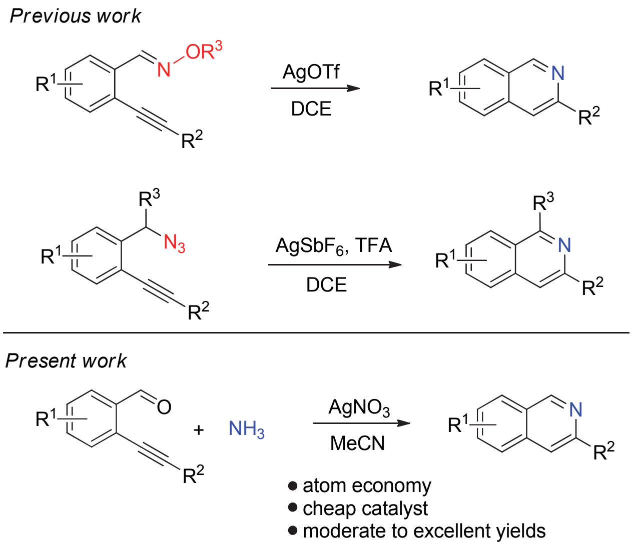
An operationally simple approach for the tandem synthesis of isoquinolines by the reaction of *o*-alkynylaldehydes with ammonium bicarbonate *via* Ag-catalyzed 6-endo-dig ring closure is described. The reaction conditions and the scope of the reaction are examined, and a variety of substituted isoquinolines are prepared in moderate to excellent yields.

Keywords isoquinolines, annulation, imination, silver nitrate, *o*-alkynyl aldehydes

Introduction

Isoquinoline derivatives are found in numerous natural products and pharmaceuticals and display a wide range of biological activities.[1] Therefor, the isoquinoline subunits have been employed as the valuable building block for the preparation of biologically active compounds including alkaloids, natural products and pharmaceuticals.[2] Numerous synthetic methods have been developed to construct the isoquinoline core skeleton due to its importance.[3] The Bischler-Napieralski,[4] Pomeranz-Fritsch, [5] and Pictet-Spengler[6] reactions were applied to the preparation of isoquinoline in the initial years. In order to avoid the harsh conditions or tedious reaction procedures required in the above reactions, Pfeffer, [7] Heck, [8] and Widdowson[9] reported the transition metal methodology to synthesize substituted isoquinolines. And the transition metal catalyzed inter- or intramolecular cyclization or heteroannulation strategy for preparation of isoquinoline is the most useful method owing to its efficience and mild conditions.[10] Among the transition metals, such as Pd, Ag, Cu, Ni, Rh and Zr, used in synthesizing isoquinolines,[11] the silver catalyzed protocols have received the most attention due to the significant role silver plays in annulation reactions of alkynes.[12] Liang utilized Ag-catalyzed cyclization of 2-alkynyl benzyl azides for the synthesis of substituted isoquinoline.[13] Shin demonstrated that O-alkyl benzaldoxime derivatives undergo a cyclization-induced N—O bond cleavage to provide isoquinolines co-catalyzed by AgOTf and TfOH.[14] These two reactions would undergo a N—N or N—O bond cleavage process and the residue is waste (Scheme 1). Then Abbiati reported a three-component cascade reaction for the

Scheme 1 Ag-catalyzed isoquinolines synthesis



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synthesis of isoquinolines using aqueous ammonia as the reagent for the imination step providing product with low to moderate yields.[15] Consistent with our former reports,[16] we report here a highly efficient $AgNO_3$-catalyzed isoquinolines synthesis from *o*-alkynyl aldehydes and ammonium bicarbonate. This approach has several advantages: a) the ammonia source is provided by ammonium bicarbonate without other waste formed; b) the reaction can work well under air condition without other external co-catalysts or additives; c) and the catalyst is cheap and easily available.

Experimental

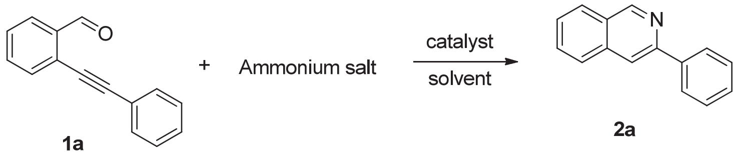
General procedure for Ag-catalyzed sequential imination-annulation of 2-alkynyl aldehydes

To a solution of 2-(phenylethynyl)benzaldehyde **1a** (62.0 mg, 0.3 mmol) in MeCN (3 mL), NH_4HCO_3 (79 mg, 1 mmol) and $AgNO_3$ (10 mg, 0.06 mmol) were added. The mixture was stirred at 120 ℃ until all starting materials were consumed. The reaction mixture was diluted with saturated brine and extracted with ethyl acetate. The organic layers were combined and washed with water and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel to afford the desired product 3-phenylisoquinoline **2a** as white solid.[13]

Results and Discussion

Initially, we tested the reaction of substrate 2-(phenylethynyl)benzaldehyde **1a** with 20 mol% of $AgNO_3$ in aqueous ammonia (mass percentage 25%—28%) at 80 ℃, and the desired product **2a** was obtained in 25% yield after 12 h (Table 1, Entry 1). By increasing the temperature to 100 ℃, a higher yield of 40% was observed (Entry 2). No beneficial effect was observed when using THF as a co-solvent in aqueous ammonia (Entry 3). Then, NH_4Cl, NH_4HCO_3 and NH_4OAc were investigated instead of aqueous ammonia at 80 ℃ to provide product **2a** in 50%, 65% and 48% yields, respectively (Entries 4—6). Therefore, NH_4HCO_3 was chosen as the ammonia source for the following experiments. By further increasing the reaction temperature to 100 ℃, the yield of product was dramatically raised to 79% (Entry 7). Other solvents such as EtOH, 1,2-dichloroethane (DCE) and dimethylsulfoxide (DMSO) were screened. They afforded the desired product **2a** in lower yields (Entries 8—10). CuI was also investigated as a catalyst but showed an inferior result to $AgNO_3$ (Entry 11). Interestingly, the reaction could provide product **2a** with 39% yield without addition of catalyst (Entry 12). In order to further improve the efficiency of this reaction, changing the conditions to a higher reaction temperature (120 ℃) gave the best result of 86% yield (Entry 13). When the catalyst loading was reduced to 10 mol% of $AgNO_3$, the chemical yield

Table 1 Optimization of reaction conditions[a]



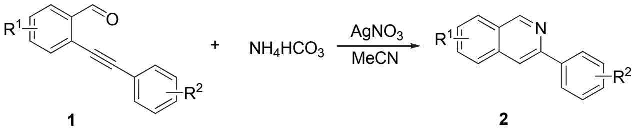
Entry	Catalyst/%	Solvent	Ammonium salt	*T*/℃	*t*/h	Yield[b]/%
1	$AgNO_3$ (20)	—	NH_3•H_2O	80	12	25
2	$AgNO_3$ (20)	—	NH_3•H_2O	100	12	40
3	$AgNO_3$ (20)	THF	NH_3•H_2O	100	12	42
4	$AgNO_3$ (20)	MeCN	NH_4Cl	80	12	50
5	$AgNO_3$ (20)	MeCN	NH_4HCO_3	80	12	65
6	$AgNO_3$ (20)	MeCN	NH_4OAc	80	12	48
7	$AgNO_3$ (20)	MeCN	NH_4HCO_3	100	12	79
8	$AgNO_3$ (20)	EtOH	NH_4HCO_3	100	12	16
9	$AgNO_3$ (20)	DCE	NH_4HCO_3	100	12	50
10	$AgNO_3$ (20)	DMSO	NH_4HCO_3	100	12	42
11	CuI (20)	MeCN	NH_4HCO_3	100	12	70
12[c]	—	MeCN	NH_4HCO_3	100	12	39
13	$AgNO_3$ (20)	MeCN	NH_4HCO_3	120	12	86
14	$AgNO_3$ (10)	MeCN	NH_4HCO_3	120	12	75

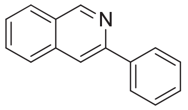
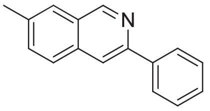
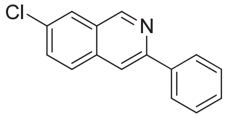
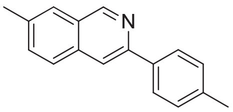
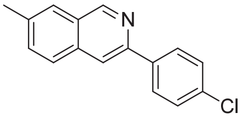
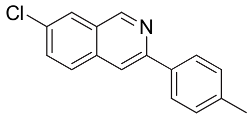
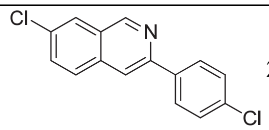
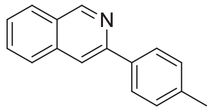
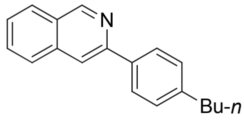
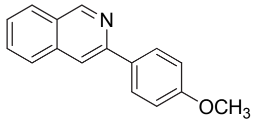
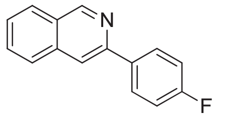
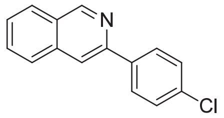
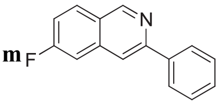
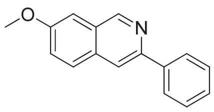
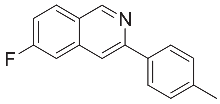
[a] The reactions were performed using 0.3 mmol of 2-(phenylethynyl)benzaldehyde **1a** and 1 mmol of ammonium salt in 3.0 mL of solvent. [b] Isolated yield. [c] No catalyst was added.

decreased to 75% (Entry 14).

Under the optimized reaction condition [$AgNO_3$ (20 mol%), MeCN, 120 ℃], the scope of the reactions of *o*-alkynyl aldehydes **1** was explored. The results are summarized in Table 2. Generally, the imination-cyclization reactions provided substituted isoquinlines in moderate to excellent yields. The results listed in Table 2 showed that various R^1 and R^2, including hydrogen, chloro, methyl, fluoro, methoxyl were well tolerated. Better yields were observed when electron-donating groups were on the phenyl ring in *para*-positions in most cases (Table 2, Entries 6, 8, 10). Whereas the phenyl group bearing electron-withdrawing groups gave inferior results (Table 2, Entries 5, 11, 12). The substituents on the aromatic ring were also investigated. Introducing electron-withdrawing groups onto the aromatic ring slightly enhanced the yields (Table 2, Entries 3, 6, 7, 13, 15). However, when the electron-donating groups were used, the yields of target products were slightly lower (Table 2, Entries 2, 5, 14). To our disappointment, cyclization could not proceed when the terminus of the carbon-carbon triple bond was substituted by an alkyl group. Thus, there was no product obtained when *o*-hexynyl aromatic aldehyde reacted under the optimized reaction condition.

Table 2 The scope of reaction substrates[a]



Entry	R^1, R^2	**1**	Product	**2**	Yield[b]/%
1	H, H	**1a**		**2a**	86
2	7-Me, H	**1b**		**2b**	67
3	7-Cl, H	**1c**		**2c**	71
4	7-Me, 4-Me	**1d**		**2d**	76
5	7-Me. 4-Cl	**1e**		**2e**	66
6	7-Cl, 4-Me	**1f**		**2f**	91
7	7-Cl, 4-Cl	**1g**		**2g**	69
8	H, 4-Me	**1h**		**2h**	87
9	H, 4-*n*-Bu	**1i**		**2i**	68
10	H, 4-MeO	**1j**		**2j**	80
11	H, 4-F	**1k**		**2k**	75
12	H, 4-Cl	**1l**		**2l**	67
13	6-F, H	**1m**		**2m**	82
14	7-MeO, H	**1n**		**2n**	66
15	6-F, 4-Me	**1o**		**2o**	91

[a] The reactions were performed using 0.3 mmol of 2-(phenylethynyl)benzaldehyde **1** and 1 mmol of NH_4HCO_3 in 3.0 mL of MeCN. [b] Isolated yield.

Conclusions

In summary, we have developed a convenient domino reaction to synthesize various substituted isoquinlines with moderate to excellent yields. This methodology featured using NH_4HCO_3 as the ammonia source catalyzed by silver nitrate in the absence of an external metal.

Acknowledgement

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