Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201701623

Link to VoR: http://dx.doi.org/10.1002/adsc.201701623

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DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Silver-Catalyzed Isocyanide Insertion into N–H Bond of Ammonia: [5 + 1] Annulation to Quinazoline Derivatives

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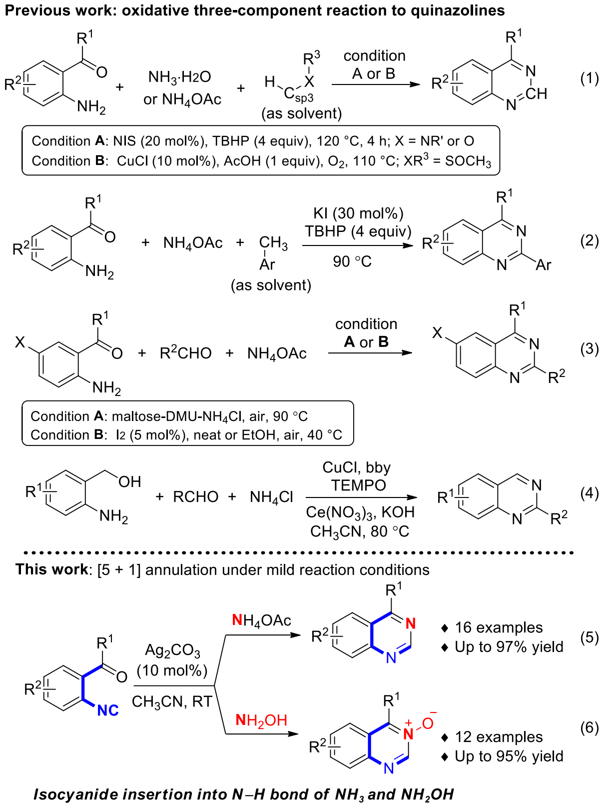
Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A silver-catalyzed [5 + 1] annulation of *o*-acylaryl isocyanides with ammonium acetate and hydroxlamine was developed for the efficient and practical synthesis of quinazolines and quinazoline 3-oxides in good to excellent yields, respectively. The domino process involved an unprecedented isocyanide insertion into the N−H bond of ammonia or hydroxylamine and followed by condensation reaction at ambient conditions.

Keywords: silver-catalyzed; [5 + 1] annulation; isocyanide insertion; quinazolines; quinazoline 3-oxides

Due to its abundance and low cost, ammonia, one of commodity chemicals, has long been recognized as an ideal nitrogen source for the preparation of nitrogen-containing compounds.[1] Especially, the domino transformation of ammonia to assemble of the valuable N-heterocycles is more appealing. Quinazoline derivatives are present in a wide variety of natural products and pharmaceuticals with significant physiological and biological activity.[2] Thus, a large number of new synthetic strategies for their preparations have been developed to date.[3-9] Among the existing methods, the direct assemble of quinazolines using NH_3 as nitrogen source attracted much attention. In 2012, Wang and co-workers developed an iodine-catalyzed oxidative amination of C(sp3)-H bonds for the synthesis of quinazolines from 2-aminobenzophenones, ammonia, and N-alkylamides (Scheme 1, eq 1, condition A).[4] Later, the three-component reaction involving 2-aminobenzophenones, aldehydes, and ammonium acetate for the direct access to quinazolines was independently reported by the research groups of Ma (Scheme 1, eq 1, condition B),[5] Li (Scheme 1, eq 2),[6] Zhang (Scheme 1, eq 3, condition A),[7] Saha (Scheme 1, eq 3, condition B).[8] In addition, Wu and co-worker reported a copper-catalyzed cascade reaction of (2-aminophenyl)methanols with aldehydes using the combination of cerium nitrate hexahydrate and ammonium chloride for the synthesis of quinazolines (Scheme 1, eq 4).[9] Despite these achievements, the development of new strategies for the efficient synthesis of quinazolines using ammonia as nitrogen source under mild conditions is still desirable.

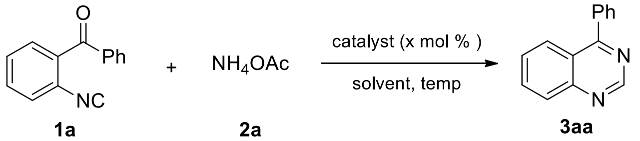


Scheme 1. Assemble of quinazolines with ammonia

Isocyanide insertion reaction has been widely involved in the preparation of nitrogen-containing compounds.[10,11] Among these transformations, isocyanide insertion into N–H bonds of amines has proven to be a promising protocol for the construction of N-heterocycles.[10,12] Although the reactions involving isocyanide insertion into N–H bonds of primary and secondary amines have been reported,[12] to our knowledge, isocyanide insertion into the N–H bonds of ammonia has not been explored so far. We have focused our study on isocyanide-based annulations in the synthesis of heterocycles for years.[13] And very recently, we developed an unprecedented chemoselective double annulation of *o*-acylaryl isocyanides with *α*-trifluoromethylated isocyanides for the synthesis of trifluoromethylated oxadiazino[3, 2-*a*]indoles, in which a formal isocyanide insertion into C=O is involved.[14] Herein, we report a silver-catalyzed domino [5 + 1] annulation of *o*-acylaryl isocyanides with ammonium acetate for the efficient and practical synthesis of quinazolines (Scheme 1, eq 5). Although isocyanides have already been used to synthesize quinazoline derivatives,[15] this quinazoline synthesis involved the first example of isocyanide insertion into N–H bonds of the commodity chemical ammonia. Silver nitrate-catalyzed insertion of 2-isocyanobenzoate into the N−H bond of primary amines for the synthesis of quinazolinones were developed by Zhu recently,[12a] however, only two examples (with benzylamine and tryptamine) were reported and the reaction was performed at 60 ºC. In contrast, our domino reaction provides a general protocol for the synthesis of various aromatic quinazolines with broad substrate scope at room temperature. In addition, a series of quinazoline 3-oxides were also synthesized by the same transformation of *o*-acylaryl isocyanides and hydroxylamine (Scheme 1, eq 6).

Originally, the exploration started with *o*-acylphenyl isocyanide **1a** and ammonium acetate **2a** to give the corresponding 4-phenylquinazoline **3aa** to optimize the reaction conditions. It was found that the product **3aa** can be isolated in 94% yield in the presence of Ag_2CO_3 (30 mol %) in CH_3CN under 80 ºC for 0.25 h (Table 1, entry 1). Selected metal salts, such as AgOTf, AgF and CuCl, were also examined but gave **3aa** in lower yields (entries 2-4). No obvious difference in terms of yield was observed when decreasing the reaction temperature (entries 5-7). Decreasing the amount of Ag_2CO_3 to 10 mol % had no obvious influence on the yield of reaction except slight prolonging of reaction time (entries 8 and 9). Then, we found that the reaction was insensitive when $NH_3{\cdot}H_2O$ or NH_4Cl was used as N–H source (entries 10 and 11). Solvent screening showed that CH_3CN gave the highest yield of **3aa** (entries 12-14). It was found that the reaction did not proceed at all when silver salt was absence or replaced Ag_2CO_3 by Na_2CO_3 and Cs_2CO_3 (entries 16-18). The yield of **3aa** was decreased to 85% when the amount of ammonium acetate was reduced to 1.5 equivalent (entries 16-17). Hence, the optimal condition for the insertion reaction involves Ag_2CO_3 (10 mol %) in CH_3CN at room temperature using ammonium acetate as N–H source (**Table 1**, entry 8).

Table 1. Optimization of reaction conditions [a]



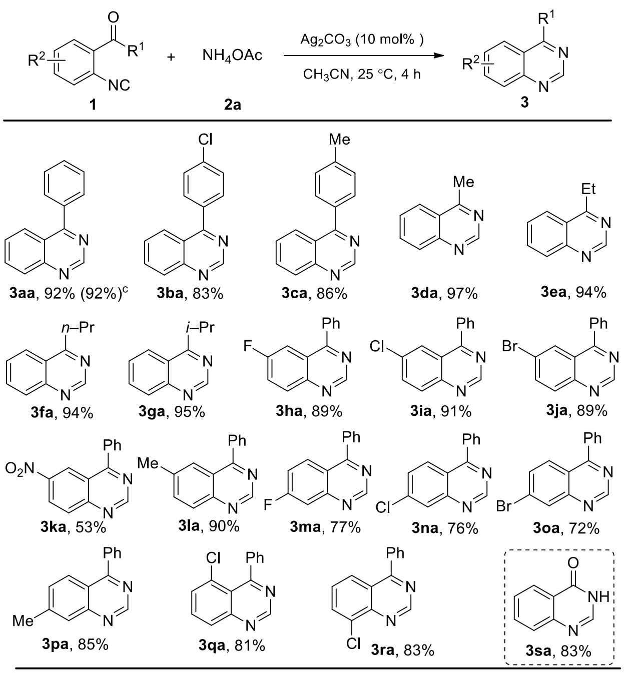
Entry	Cat. (mol %)	N source	T. (ºC)	Time (h)	**3aa** (%) [b]
1	Ag_2CO_3 (30)	NH_4OAc	80	0.25	94
2	AgOTf (30)	NH_4OAc	80	0.25	72
3	AgF (30)	NH_4OAc	80	0.25	82
4	CuCl (30)	NH_4OAc	80	0.25	48
5	Ag_2CO_3 (30)	NH_4OAc	60	0.5	93
6	Ag_2CO_3 (30)	NH_4OAc	40	1.5	93
7	Ag_2CO_3 (30)	NH_4OAc	25	2.0	92
8	***Ag_2CO_3 (10)***	***NH_4OAc***	***25***	4.0	***92***
9	Ag_2CO_3 (5)	NH_4OAc	25	14	85
10	Ag_2CO_3 (10)	$NH_3{\cdot}H_2O$	25	4.0	60
11	Ag_2CO_3 (10)	NH_4Cl	25	4.0	-
12 [c]	Ag_2CO_3 (10)	NH_4OAc	25	4.0	83
13 [d]	Ag_2CO_3 (10)	NH_4OAc	25	4.0	81
14 [e]	Ag_2CO_3 (10)	NH_4OAc	25	4.0	71
15 [f]	Ag_2CO_3 (10)	NH_4OAc	25	4.0	92
16	--	NH_4OAc	25	24	-
17	Na_2CO_3 (10)	NH_4OAc	25	24	-
18	Cs_2CO_3 (10)	NH_4OAc	25	24	-
19 [g]	Ag_2CO_3 (10)	NH_4OAc	25	10.0	85

[a] reaction conditions: **1a**, (0.3 mmol), NH_4OAc, (0.6 mmol) metal salts, (10 mol %), CH_3CN, (3 mL); [b] isolated yields; [c] EtOH as solvent; [d] THF as solvent; [e] DCE as solvent; [f] N_2 atmosphere; [g] NH_4OAc, (0.45 mmol).

Subsequent work was to investigate the substrate scopes of this efficienct and mild domino protocol under the optimized condition (Scheme 2). Satisfactorily, the diversity of the R^1 groups including electron-neutral/poor/rich aryl (Scheme 2, **1a-c**) or aliphatic groups (Scheme 2, **1d-g**) and R^2 groups including electron-withdrawing/donating substituents (Scheme 2, **1h-r**) on isocyanides **1** were allowed. All of corresponding products **3aa-3ra** were obtained with good to high yields. Moreover, it was noted that the reaction tolerated a wide range of R^2 substitutents on the 5-8 positions of quinazolines (**3ha-3ra**). Interestingly, quinazolin 4-(3*H*)-one **3sa** was also constructed in high yield using methyl 2-isocyanobenzoate as substrate under the same condition. Furthermore, the practicability of this domino reaction was demonstrated by a gram-scale synthesis of **3aa** (Scheme 2, 1.142g, 92%).

It has been found that quinazoline N-oxides frequently applied in organic synthesis and the pharmaceutical industry.[16] Recently, an elegant Rh(III)- and Zn(II)-catalyzed C−H amidation-cyclization of oximes was developed for the synthesis of quinazoline N-Oxides by Li and co-workers.[17]

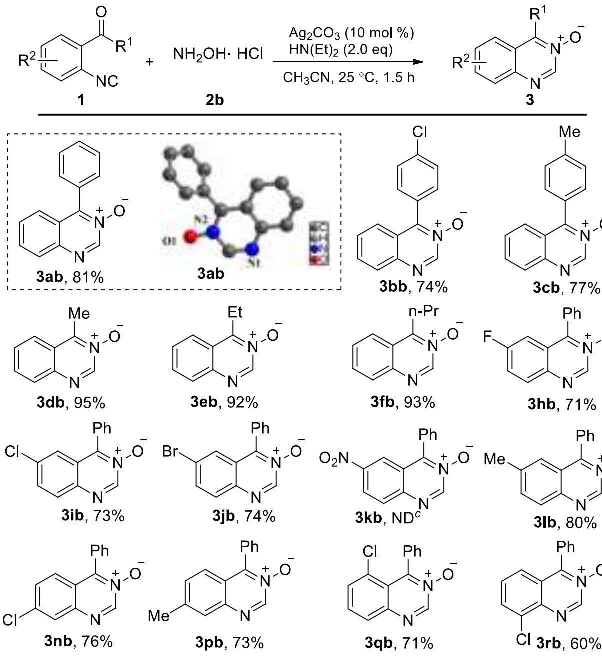
Scheme 2. Synthesis of substituted quinazolines [a,b]



[a] Reaction conditions: **1a**, (0.3 mmol), NH_4OAc, (0.6 mmol), Ag_2CO_3, (10 mol %), CH_3CN, (3 mL), room temperature, 4.0 h; [b] Yield of isolated product; [c] Gram-scale: 1.14 g, 92%.

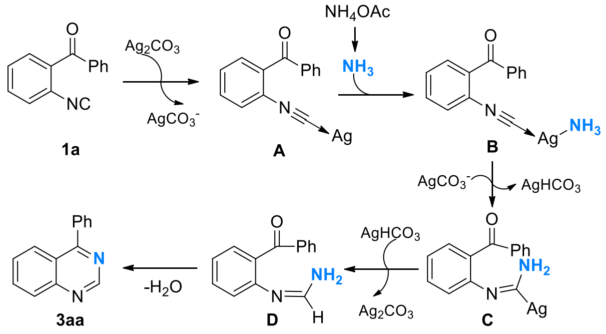
To our delight, a series of quinazoline-3-oxides **3ab**[18]-**3qb** were produced in good to excellent yields when *o*-acylphenyl isocyanides **1** was treated with hydroxylamine hydrochloride ($NH_2OH·HCl$) **2b** in the presence of Ag_2CO_3 (10 mol %) and 2.0 equiv of diethylamine (Scheme 3). This domino isocyanide insertion into N−H bond of hydroxylamine and condensation reaction tolerated various isocyanides **1** bearing arylacyl (**1a-c**) and alkylacyl groups (**1d-f**), halo (**1h-j**, **1n**, **1q** and **1r**) and alkyl groups (**1l** and **1p**) at ambient conditions.

Scheme 3. Synthesis of quinazoline-3-oxides [a,b]



[a] reaction conditions: **1a**, (0.3 mmol), $NH_2OH·HCl$, (0.6 mmol), Ag_2CO_3, (10 mol %), $HN(Et)_2$, (0.6 mmol), CH_3CN, (3 mL), 1.5 h; [b] Yield of isolated product. [c] ND = not detected.

On the basis of related reports[12,14] and the present results, a possible reaction mechanism is shown in Scheme 4 (exemplified by the generation of **3aa**). Ag_2CO_3 coordinates to isocyanide **1a** to form complex **A**, which coordination with ammonia generates complex **B**. In the presence of a base, migratory insertion from **B** affords imidoylsilver intermediate **C**. Then, salt metathesis of **C** produces *o*-carbonyl phenylamidine **D**, which was detected by high-resolution mass spectra ($[M + H]^+$ = 225.1025, **Fig. S1**). Finally, the intramolecular condensation of **D** leads to **3aa**.



Scheme 4. Plausible mechanism.

In summary, an efficient and practical method for the construction of polysubstituted quinazolines and quinazoline 3-oxides under ambient conditions has been successfully disclosed. This domino process involves an unprecedented silver-catalyzed isocyanide insertion into the N–H bonds of ammonia or hydroxylamine and an intramolecular condensation reaciton. This reaction features mild reaction conditions, operational simplicity, high to excellent product yields and amenability to gram-scale synthesis. Investigations on new isocyanide insertion reactions are ongoing.

Experimental Section

General procedure for the synthesis of 3a: To a mixture of (2-isocyanophenyl)(phenyl)methanone (**1**) (0.3 mmol) and ammonium acetate (**2a**) (46.7 mg, 0.6 mmol) in CH_3CN (3 mL) at 25 ºC was added Ag_2CO_3 (8.8 mg, 0.03 mmol). After the reaction was finished as indicated by TLC (4 h), the resulting mixture was poured into water (10 mL) and extracted with EtOAc (6 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product with flash column chromatography to give **3a**.

Acknowledgements

Financial support provided by NSFC (21402112, 21672034) and 1331 project of Shanxi Province is gratefully acknowledged.

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[18] CCDC 1810764 (**3ab**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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