#### Tetrahedron 73 (2017) 4317-4322

Contents lists available at ScienceDirect

## Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Cascade annulations of aryldiazonium salts, nitriles and halo-alkynes leading to 3-haloquinolines



Tetrahedro

"二金草

### Mani Ramanathan, Shiuh-Tzung Liu\*

Department of Chemistry, National Taiwan University, Taipei, 106, Taiwan

#### ARTICLE INFO

Article history: Received 23 April 2017 Received in revised form 23 May 2017 Accepted 28 May 2017 Available online 29 May 2017

Keywords: 3-Haloquinolines Diazonium Nitrile Alkyne Cascade annulation

#### ABSTRACT

A regiospecific access to 3-haloquinolines has been developed *via* a three-component annulation of aryldiazonium salts, nitriles and haloalkynes. This reaction proceeds through an initial formation of reactive nitrilium ion and further cascade annulation with haloalkynes. This method provides a straightforward access to a diverse array of functionalized quinolones (28 examples) under mild conditions and exhibits broad functional group tolerance. Applications of this method in a gram scale reaction and a formal synthesis of Pitavastatin are illustrated.

© 2017 Elsevier Ltd. All rights reserved.

#### 1. Introduction

Quinolines represent one of the most ubiquitous skeletons found in diverse natural products and pharmaceuticals.<sup>1</sup> Classical reactions such as Friedlander,<sup>2</sup> Conrad-Limpach-Knorr<sup>3</sup> and Combes<sup>4</sup> approaches are the most prevalent strategies for construction of the quinoline cores. Recent works in this regard, various transition metal catalyzed approaches<sup>5</sup> and metal-free protocols<sup>6</sup> were developed. Furthermore, syntheses of halo substituted quinolines are of special interest, because these molecules can serve as versatile precursors for further transformation *via* transition metal catalyzed coupling reactions including C–O, C–S and C–N bonds. Though several appealing approaches available for the synthesis of quinoline unit, established methods for the synthesis of halo-substituted quinolines are less reported and few are shown in Scheme 1.

An approach reported by Flynn et al. was *via* the electrophilic iodocyclization of 1-(2-*N*,*N*-dimethylamino-aryl)-2-yn-ols (Scheme 1a).<sup>7a</sup> Liang's group demonstrated the preparation of the desired compound through a 6-*endo*-dig iodocyclization of 2-tosylaminophenylprop-1-yn-3-ols with molecular iodine (Scheme 1b).<sup>7b</sup> Recently, Wang and co-workers described a synthesis of 3-

iodoquinolines *via* a Cu(OTf)<sub>2</sub> catalyzed tandem reaction of diaryliodonium salts, halogenated arylacetylenes and nitriles at elevated temperature (Scheme 1c).<sup>7c</sup> Another method by Tummatorn's group involved a cycloaddition strategy between benzyl azides and 1-bromoalkynes in presence of triflic acid followed by the aromatization (Scheme 1d).<sup>7d</sup> Despite the significance of these methods, there is still a need of the development of a general, mild and transition metal free method from easily accessible precursors leading to 3-haloquinolines.

Inspired by Wang's<sup>7c</sup> (Scheme 1c) and Yu's works,<sup>8</sup> herein we report an intermolecular cascade annulation protocol for the construction of 3-haloquinolines by the reaction of aryldiazonium salt (1) with a nitrile molecule to yield the *N*-arylnitrilium ion (2),<sup>9</sup> which could further react with halo-alkyne followed by a cyclization leading to the desired product (Scheme 2).

#### 2. Results and discussion

An investigation of the optimization was conducted with phenyldiazonium tetrafluoroborate (**1a**) and 1-iodo-phenylacetylene (**3a**) in anhydrous MeCN under heating conditions. Gratifying, the desired product **4a** was isolated in 62% isolated yield at 110 °C (Table 1, entry 1). By lowering the reaction temperature to 80 °C and with a slightly excess amount of nitrile, the yield can be improved up to 76% (Table 1, entry 3), but not at room temperature (entry 4).



<sup>\*</sup> Corresponding author. Tel.: +8862 3366 1661; fax: +8862 2366 0352. *E-mail address:* stliu@ntu.edu.tw (S.-T. Liu).



Scheme 1. Selected works for Synthesis of haloquinolines.



Scheme 2. Proposed synthetic approach.

Intrigued by the expected outcome, a comprehensive investigation on the scope of the arvldiazonium salts was examined under the optimized reaction conditions. A diverse set of aryldiazonium salts with functional groups including esters, ethers, cyano and benzovl were found to be compatible with the reaction conditions and provided the corresponding 2,4-disubstituted-3iodoquinolines in good yields (Table 2, entries 4–9). In general, electron-donating groups on the arenediazonium salts led to slightly better yields than electron-withdrawing groups. Notably, the ortho-substituted substrates deliver the desired product in low yields such as **4h** (36%) and **4j** (41%), presumably due to the steric hindrance posed by the substituents (Table 2, entries 10 and 12). The reaction worked well with the aryldiazonium salt containing terminal alkyne to afford 4g in 63% yield, leading to a useful handle for further cross-coupling reactions. The structure of 4h was unambiguously confirmed by x-ray crystallography and ORTEP plot of 4h is shown in Fig. 1. Thus, the regio-selectivity of this reaction is established. As expected, meta-substituted aryldiazonium salt afforded a mixture of separable regio-isomeric 3-iodoquinolines

#### Table 1

Reaction optimization.<sup>a</sup>

$ \underbrace{ \begin{array}{c} & & \\ &$						
1a		3a	4a			
Entry	Alkyne	Nitrile	Temp (°C)	Time (h)	Yield(%) <sup>b</sup>	
1	<b>3a</b> (1.3 eq)	1 mL	110	3	62	
2	<b>3a</b> (1.3 eq)	1 mL	100	12	51	
3	<b>3a</b> (1.2 eq)	2 mL	80	2	76	
4	<b>3a</b> (1.2 eq)	2 mL	rt	12	<5%	

 $^{\rm a}$  Conditions: Reaction conditions:  $1a~(0.52~{\rm mmol})$  and  $3a~{\rm in}$  anhydrous acetonitrile in a sealed reaction tube.

<sup>b</sup> Isolated yields.

#### Table 2

Substrate scope of aryldiazonium salts with 3 in MeCN.<sup>a</sup>



Entry	Product (position-substitutent)	Yield <sup>b</sup>
1	<b>4a</b> $(R^1 = H, X = I)$	76%
2	<b>4a</b> ' ( $R^1 = H, X = Br$ )	64%
3	<b>4a</b> " ( $R^1 = H, X = CI$ )	19%
4	<b>4b</b> $(R^1 = 6-OMe, X = I)$	78%
5	<b>4c</b> $(R^1 = 6$ -COOEt, $X = I)$	72%
6	<b>4d</b> $(R^1 = 6$ -CN, $X = I)$	63%
7	<b>4e</b> $(R^1 = 6$ -CF <sub>3</sub> , $X = I)$	66%
8	<b>4f</b> ( $R^1 = 6$ -COPh, $X = I$ )	55%
9	<b>4g</b> $(R^1 = 6-C \equiv CH, X = I)$	63%
10	<b>4h</b> $(R^1 = 8$ -CN, $X = I)$	36%
11	<b>4i</b> ( $R^1 = 5$ -Me, 7-Me, $X = I$ )	74%
12	<b>4j</b> $(R^1 = 6$ -Me, 8-Br, X = I)	41%
13	<b>4k</b> ( $R^1 = 7$ -Br, $X = I$ )	38%
	<b>4k</b> ' ( $R^1 = 5$ -Br, $X = I$ )	33%

 $<sup>^</sup>a$  Conditions: 1a (0.52 mmol), 3 (0.62 mmol) and anhydrous MeCN (2 mL) in a scaled reaction tube, 80 °C, 2 h.

<sup>b</sup> Isolated yields.

(**4k** and **4k'**) in good yields (Table 2, entry 13). The bromo and chloro analogs were also investigated. Reactions of **1a** with **3b** gave 2-methyl-3-bromo-4-phenylquinoline (**4a'**) in 64% isolated yield, but the chloro-substituted **4a"** was obtained in poor yield (Table 2, entries 2 and 3). In fact, reaction of **1a** with **3c** gave a mixture of various products.

When aryldiazonium salt with an adjacent benzoyl (**5**) or phenyl (**6**) moiety involved in this reaction, the intermediate rapidly underwent the intramolecular aromatic electrophilic substitution to deliver 9*H*-fluoren-9-one (**7**) and 6-methylphenanthridine (**10**), respectively (Scheme 3). The expected compound **8** was not formed when using **5** as the substrate. As for **6**, the rate of the intramolecular cyclization is apparently faster than that of the electrophilic addition of *N*-arylnitrilium ion **9** toward the alkyne molecule.

We then contemplated the scope of the reaction with varieties of readily available aromatic and aliphatic nitriles (Table 3). Anhydrous benzonitrile was smoothly reacted with various aryldiazonium salts to furnish the desired products in good yields (Table 3,



Fig. 1. ORTEP plot of 4h. I(1)-C(1) 2.093(5)Å; C(17)-N(2) 1.145(8) Å. (Drawn with 30% probability ellipsoids).

Download English Version:

# https://daneshyari.com/en/article/5212239

Download Persian Version:

https://daneshyari.com/article/5212239

Daneshyari.com