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## Iron (III) catalyzed halo-functionalization of alkynes

Bryant Catano<sup>1</sup>, John Lee<sup>1</sup>, Claudia Kim<sup>1</sup>, David Farrell<sup>1</sup>, Jeffrey L. Petersen<sup>2</sup> and Yalan Xing<sup>1</sup>\*

<sup>1</sup>Department of Chemistry, William Paterson University, 300 Pompton Rd, Wayne, NJ 07470, US

<sup>2</sup>Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26506, US

xingy@wpunj.edu

## Graphic abstract



### Keywords

Alkyne, halo-functionalization, one-pot, iron.

### Abstract

Aromatic and aliphatic alkynes can be halo-functionalized to  $\alpha, \alpha$ -dihalodimethyl ketals catalyzed by FeCl<sub>3</sub> in excellent yields. MeOH is used as a nucleophilic solvent and *N*-halosuccinimide as the halogen source for this efficient transformation. The resulting  $\alpha, \alpha$ -dibromodimethyl ketals can be converted to the corresponding  $\alpha, \alpha$ -dibromoketones by treatment with 8% FeCl<sub>3</sub> in silica gel.

#### Introduction

The transition metal catalyzed functionalization of carbon-carbon multiple bonds is of prime importance in synthetic organic chemistry.<sup>1</sup> Alkynes are readily available as synthetic starting materials and can be converted to a variety of different functional groups. In the past few decades, the development of transition metal catalyzed functionalizations of alkynes has seen an increased amount of research. Halo-functionalization of alkenes and alkynes is one of the most widely used strategies for the synthesis of halogen containing compounds, which are versatile intermediates and substrates in organic synthesis.<sup>2</sup>

Herein we report our investigation of the iron (III) catalyzed formation of  $\alpha, \alpha$ -dihalodimethyl ketals from alkynes and *N*-halosuccinimide in the presence of nucleophilic solvent MeOH, as well as the treatment of the crude  $\alpha, \alpha$ -dihalodimethyl ketals with 8% FeCl<sub>3</sub> in silica gel to generate  $\alpha, \alpha$ -dihaloketones according to known literature procedures.<sup>3</sup> Only limited methods are currently available in the literature for the preparation of these compounds. Phukan and coworkers have recently reported a facile generation of  $\alpha, \alpha$ -dibromodimethyl ketals from terminal alkynes;<sup>4</sup> however, this reaction requires the reagent *N*,*N*-dibromo-*p*-

toluenesulfonamide (TsNBr<sub>2</sub>), which is not readily available.<sup>5</sup> Bromine<sup>6</sup> and tetrabutylammonium tribromide<sup>7</sup> have been reported as halogen sources in reaction with alkynes, leading to only moderate yields of  $\alpha,\alpha$ -dibromodimethyl ketals with a significant amount of the *E*- $\alpha,\beta$ -dibromoalkene byproduct being generated. The preparation of  $\alpha,\alpha$ -dihalodialkoxyl ketals using *N*halosuccinimide as the halogen source has been reported using catalytic amount of acids, such as *p*-toluenesulfonic acid<sup>8</sup> and H<sub>2</sub>SO<sub>4</sub>,<sup>9</sup> which give relatively harsh conditions. As part of our investigations into novel methods of the transition metal catalyzed functionalizations of alkynes, we developed a highly efficient iron (III) catalyzed halo-functionalization reaction under mild and simple conditions.

### **Results and discussion**

The optimal reaction conditions were first screened for with phenyl acetylene chosen as a model substrate. Initially, the reaction was conducted with four different transition metal catalysts in the presence of *N*-bromosuccinimide (NBS) and the nucleophilic solvent methanol at room temperature (Table 1). The reaction process was monitored using TLC and GC-MS and the structure of the products determined by NMR. The use of AgNTf<sub>2</sub> produced only trace amounts of the  $\alpha,\alpha$ -dibromodimethyl ketal product **2a**<sup>10</sup> with the major product being bromoacetylene **2c** (Entry 3). A 56% yield of **2a** was observed when AuCl<sub>3</sub> was used as the catalyst; however, a significant amount of the methyl ketone hydration product **2b** was detected (Entry 4). Iron (III) chloride both gave similar yields of the desired product **2a** at room temperature (Entries 5 and 6) with similar reaction times. Due to the abundance and lower cost of iron catalysts,<sup>11</sup> the use of FeCl<sub>3</sub> as a catalyst was investigated further. The conversion of the starting material under FeCl<sub>3</sub> gave 100% GC conversion and 98% isolated yield of the desired product **2a** for the same 5 h reaction time (Entry 7). When performed without any transition metal catalyst, either at rt or elevated temperature and longer reaction times, this reaction gave very low yield of **2a** (Entries 1 and 2). Instead, a significant amount of the (1,2-dibromovinyl)benzene product **2d**, generated by a radical reaction mechanism,<sup>12</sup> was observed.

la	+ MeC	H+NBS <u>catalyst</u> 5h		D OMe Br + 2a	0 + 2b	C 2c	+	Br Br 2d
	entry	catalyst	1a%	2a%	2b%	2c%	2d%	$\sim$
	1	none	10	35			40	0
	2 <sup>b</sup>	none		<b>1</b> 5			51	
	3	AgNTf <sub>2</sub>		11		55		Q
	4	AuCl <sub>3</sub>		56	28			
	5	RuCk		58				
	6	FeCl <sub>3</sub>	35	60				
	7°	FeCl <sub>3</sub>		98	_			

## Table 1. Optimization of reaction conditions for the synthesis of α,α-dibromodimethyl ketals<sup>a</sup>

<sup>a</sup> Reaction condition: phenylacetylene (1.0 mmol), NBS (2.0 mmol), MeOH (5 mL) and catalyst (5 mol %) at room temperature for 5 h. <sup>b</sup> At 50 °C for 5 h and 12 h, results were the same. <sup>c</sup> At 50 °C

With the optimal conditions in hand, we then explored the substrate scope and limitations of this reaction by investigating a variety of alkynes, as shown in Table 2. The  $\alpha,\alpha$ -dibromodimethyl ketals and  $\alpha,\alpha$ -diiododimethyl ketals were both synthesized in good yields using NBS and *N*-iodosuccinimide under the standard conditions. When *N*-chlorosuccinimide was used, none of the corresponding  $\alpha,\alpha$ -dichlorodimethyl ketals were detected. In addition, aromatic alkynes underwent the halo-functionalization in good yields with both electron-donating and electron-withdrawing groups on the benzene ring. In particular, substrates with a halogen group at any position on the benzene ring gave excellent yields of over 90%. The aliphatic alkynes 1-nonyne and 1-hexyne afforded the products **2d** and **2t**, respectively, in good yields while maintaining the high regioselectivity. The phenyl-substituted internal alkynes 5-phenyl-1-pentyne, prop-1-yn-1-ylbenzene, and 1,2-diphenylethyne also afforded the products **2p**, **2u**, and **2v**, respectively, in good yields. A single crystal of **2h** was obtained and the X-ray crystallographic analysis confirmed the structure and stereochemistry of the  $\alpha,\alpha$ -dibromodimethyl ketal (Figure 1).<sup>13</sup>

## Table 2. Substrate scope



A plausible mechanism for this transformation is proposed in Scheme 1. The iron (III) catalyst first activates the triple bond. Nucleophilic methanol then adds to the benzylic position to give the vinyl iron intermediate **3**, which reacts with the electrophilic halogen  $Br^+$  to generate a vinyl bromide **4**. The nucleophilic methanol and electrophilic  $Br^+$  again regioselectively add to the resulting double bond to give the  $\alpha, \alpha$ -dibromodimethyl ketal.

### Scheme 1. Proposed mechanism I



A second possible mechanism is also proposed in Scheme 2. The iron (III) catalyst may coordinate with one of the carbonyl oxygen atoms of NBS to give complex **II**, in which the Br is more electrophilic. Treatment of phenyl acetylene with this more electrophilic bromination reagent generates intermediate **III**, which reacts with methanol to provide intermediate **4**. Similar to the proposed mechanism I, intermediate **4** further reacts with methanol and Br<sup>+</sup> to give the  $\alpha, \alpha$ -dibromodimethyl ketal.

### Scheme 2. Proposed mechanism II



Both of these proposed mechanisms involve the generation of intermediate **4**. A test reaction was performed to confirm the formation of this intermediate. In the test reaction, one equivalent of NBS was used to react with phenyl acetylene under the standard condition. Intermediate **4** was not detected by GC-MS while the isolated yield of **2a** dropped to 45%. We believe that intermediate **4** is very reactive with too short of a life time to be detected; once formed it would react immediately with methanol and NBS to give the ketal.

It was found that when the acetal **2a** was treated with a preprepared reagent of 8% FeCl<sub>3</sub> by mass in chromatographic silica gel, the dimethyl acetal was cleaved to give the  $\alpha, \alpha$ -dibromoketone **5a**<sup>14</sup> (Scheme 3).<sup>3</sup> Using this mild and convenient acetal deprotection procedure, we developed a one-pot strategy to directly prepare  $\alpha, \alpha$ -dibromoketones from alkyne starting materials.<sup>15</sup> First, the alkyne is treated with our optimal conditions to yield the  $\alpha, \alpha$ -dibromodimethyl ketal. Next, without isolation of the ketal product, 8% FeCl<sub>3</sub> in silica gel is added directly to the reaction flask after removal of the methanol solvent. The  $\alpha, \alpha$ -dibromoketone is obtained in comparable yield (96%) to the two-step reaction after 12 h of stirring. As shown in Scheme 2, a

variety of terminal and internal aromatic alkynes were smoothly converted to  $\alpha, \alpha$ -dibromoketones using this one-pot strategy in greater than 90% overall yield. However, a benzene ring-bearing methoxy group (**5c**) was observed to give a slightly lower yield of 80%. When  $\alpha, \alpha$ -diiododimethyl ketal **2q** was treated with this acetal deprotection procedure, a mixture of the corresponding  $\alpha$ -iodoketone and  $\alpha, \alpha$ -diiodoketone was observed.

### Scheme 3. Ketone formation



### Conclusion

In summary, we have developed a convenient and efficient synthesis of  $\alpha, \alpha$ -dihalodimethyl ketals and  $\alpha, \alpha$ dibromoketones from readily available alkynes. The first row transition metal iron is an excellent choice of catalyst for this transformation due to its low cost, high abundance, and minimal toxicity. This transformation has a broad substrate scope, able to be performed with a variety of aromatic and aliphatic alkynes, both terminal and internal. This reaction opens a new bridge between alkyne and carbonyl chemistry where the alkynes can be selectively converted to  $\alpha$ -halogenated ketones or the protected ketone acetals based on need by changing the conditions. The resulting products are versatile substrates for many S<sub>N</sub>2, carbonyl, and Reformatsky reactions<sup>16</sup>. The direct synthesis of  $\alpha$ -halogenated ketones from corresponding ketones using electrophilic halogen sources suffers poor regioselectivity; this alkyne functionalization strategy provides an alternative preparation to avoid this regioselectivity issue.

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