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A Simple and Efficient Method for the Preparation of α-Halogenated Ketones Using Iron(III) Chloride and Iron(III) Bromide as Halogen Sources with Phenyliodonium Diacetate as Oxidant

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Abstract. α-Halogenated ketones are both unique structure moieties existing in biologically natural products and valuable synthetic intermediates for the preparation of functional molecules. An efficient and scalable method for the preparation of α-halogenated ketone using iron (III) chloride and iron (III) bromide as halogen sources with phenyliodonium diacetate as oxidant has been developed, featuring mild reaction conditions, environmentally friendly reagents, and wide substrate scope. Notably, the three-step synthesis of drug prasugrel was achieved using this developed method as a key step with 30% yield on gram-scale. Additionally, the reaction mechanism involving chloride cation was proposed based on some preliminary control experiments.

Keywords: α-halogenated ketone; iron (III) bromide; iron (III) chloride; phenyliodonium diacetate; prasugrel.

α-Chlorinated ketone is a common structural unit in natural products, such as merochlorin C and D,[1a] and gomerone C.[1b] Due to the presence of a chloride adjacent to the carbonyl group, this unit has been widely used as a valuable intermediate, especially as an umpolung synthon,[2] for further chemical transformations to synthesize natural products, drugs, and other functional molecules.[3] Therefore, the preparation of this unit has been a center topic for synthetic chemistry, and numerous synthetic methods have been developed,[4] including Au-catalyzed transformation of terminal alkynes,[4b,c] electrochemical oxidation of olefin,[4i] oxidative hydrolysis of haloalkenes,[4e] photooxidation of vinyl silanes or vinyl sulfides, [4k] direct conversion of alcohols using trichloroisocyanuric acid as both a chloride source and an oxidant,[4h] Fe(III)-catalyzed cascade reaction of α-halo substituted styrenes,[4g] and various other approaches. Apart from these methods, the direct halogenation at α-position of a carbonyl compound is still a common and universal protocol.[5] In this context, the exploitation of new chloride sources[6] or new reaction procedures[7] such as in ionic liquid or under microwave irradiation has attracted the interests of synthetic chemists. Alternatively, the utilization of the known chlorinating reagents for this transformation has also been an active subject. Therefore, $SOCl_2$,[3c] Me_3SiCl,[8a,8c] NCS (*N*-chlorosuccinimide),[8b] MeCOCl,[5c] NH_4Cl,[8d] NaCl,[8e] $MgCl_2$,[8f] HCl,[8g] and ICl_3[8h] have been used. However, some disadvantages exist in the known methods, such as poor yields, narrow substrate scope, the use of relatively toxic and expensive chlorinating reagents, and tedious manipulation procedure. In contrast to the above-mentioned chloride sources, $FeCl_3{\cdot}6H_2O$ has its inherent advantages in organic synthesis because it is nontoxic, inexpensive, environmentally friendly, not sensitive to air and moisture, and thus easy to handle.[9] In continuation with our interest in organic synthesis involving iron (III) and hypervalent iodine (III) reagents,[10] herein, we report a novel method for the preparation of α-halogenated ketones, in which $FeCl_3{\cdot}6H_2O$ was used as the chloride source[11] with easily available phenyliodonium diacetate (PIDA) served as the oxidant.

In our investigation of the chlorination of 2-phenylcyclohexanone,[10a] we found that when phenylacetone (**1a**) was used as the substrate, the mono-chlorinated product **2a** was isolated in 57% yield (entry 1, Table 1). Encouraged by this initial result, we investigated other reaction parameters to further improve the reaction results. When Dess-Martin periodinane (DMP) was replaced by PIDA, the expected chlorination reaction also took place,

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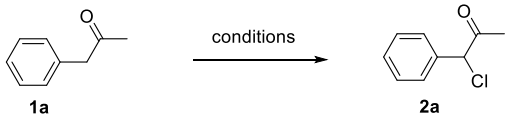
albeit affording **2a** in a decreased yield (entry 2, Table 1). Pleasingly, when the reaction was conducted in acetic

Table 1. The optimization of reaction conditions[a].



1a 2a

Entry	Cl source (2.0 equiv)	Oxidant (1.2 equiv)	Solvent	Coversion (%)[b,12]	Yield (%/)[c]
1[d]	$FeCl_3·6H_2O$	DMP	EA/AcOH	100	57
2[e]	$FeCl_3·6H_2O$	PIDA	EA/AcOH	100	43
3	$FeCl_3·6H_2O$	PIDA	AcOH	100	68
4	$FeCl_3·6H_2O$	PIDA	DMF	28	trace
5	$FeCl_3·6H_2O$	PIDA	THF	32	trace
6	$FeCl_3·6H_2O$	PIDA	CH_3CN	91	26
7	$FeCl_3·6H_2O$	PIDA	DMSO	22	NR[f]
8	$FeCl_3·6H_2O$	PIDA	DCM	47	trace
9	$FeCl_3·6H_2O$	PIDA	hexane	94	43
10	$FeCl_3·6H_2O$	PIDA	toluene	27	trace
11[g]	$FeCl_3·6H_2O$	PIFA	AcOH	100	66
12	$FeCl_3·6H_2O$	Na_2IO_4	AcOH	92	42
13[h]	$FeCl_3·6H_2O$	*m*CPBA	AcOH	99	42
14	$FeCl_3·6H_2O$	I_2	AcOH	99	15
15[i]	$FeCl_3·6H_2O$	DDQ	AcOH	50	trace
16	$FeCl_3·6H_2O$	$K_2S_2O_8$	AcOH	42	NR
17	$FeCl_3·6H_2O$	O_2	AcOH	50	NR
18	$FeCl_3·6H_2O$	air	AcOH	28	NR
19[j]	$FeCl_3·6H_2O$	PIDA	AcOH	97	41
20[k]	$FeCl_3·6H_2O$	PIDA	AcOH	100	50
21[l]	$FeCl_3·6H_2O$	PIDA	AcOH	100	70
22[m]	1.0 M HCl	PIDA	AcOH	100	56
23	$CuCl_2·2H_2O$	PIDA	AcOH	5	trace
24	$CoCl_2·6H_2O$	PIDA	AcOH	33	trace
25	$NiCl_2·6H_2O$	PIDA	AcOH	5	NR
26	$MgCl_2$	PIDA	AcOH	26	trace
27	NaCl	PIDA	AcOH	13	trace
28	$SnCl_2$	PIDA	AcOH	27	NR
29	$ZnCl_2$	PIDA	AcOH	22	trace
30	$AlCl_3$	PIDA	AcOH	100	55
31	$SnCl_4$	PIDA	AcOH	100	59
32	$TiCl_4$	PIDA	AcOH	100	58
33[n]	NCS	PIDA	AcOH	33	NR
34	$FeCl_3·6H_2O$	-	AcOH	50	0[l]

a) Reactions were performed using phenylacetone (0.2 mmol), $FeCl_3·6H_2O$ (0.4 mmol), oxidant (0.24 mmol) in 1.0 mL solvent at room temperature under an argon atmosphere; b) determination by using isopropyl-benzene as interior label;[12] c) isolated yield; d) DMP = Dess-Martin Periodinane; e) PIDA = phenyliodonium diacetate; f) NR = no reaction; g) PIFA = phenyliodonium bis(trifluoroacetate); h) *m*-CPBA = *meta*-chloroperbenzoic acid; i) DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; j) 1.0 equiv $FeCl_3·6H_2O$ was used; k) 1.5 equiv $FeCl_3·6H_2O$ was used; l) 2.5 equiv $FeCl_3·6H_2O$ was used; m) 6.0 equiv HCl was used n) NCS = *N*-chloro-succinimide; l) the starting material was partically consumed without **2a**.

acid (AcOH), the product yield increased to 68% (entry 3, Table 1). Therefore, further screening of other solvents were carried out, and the results indicated that AcOH was superior (entries 4-10, Table 1). Various other oxidants were then examined. Except for phenyliodonium bis(trifluoroacetate) (PIFA), which gave a similar reaction result in comparison to PIDA, no reaction or unsatisfactory reaction results were generally observed (entries 11-18, Table 1). Next, the amount of $FeCl_3·6H_2O$ was investigated. Lowering

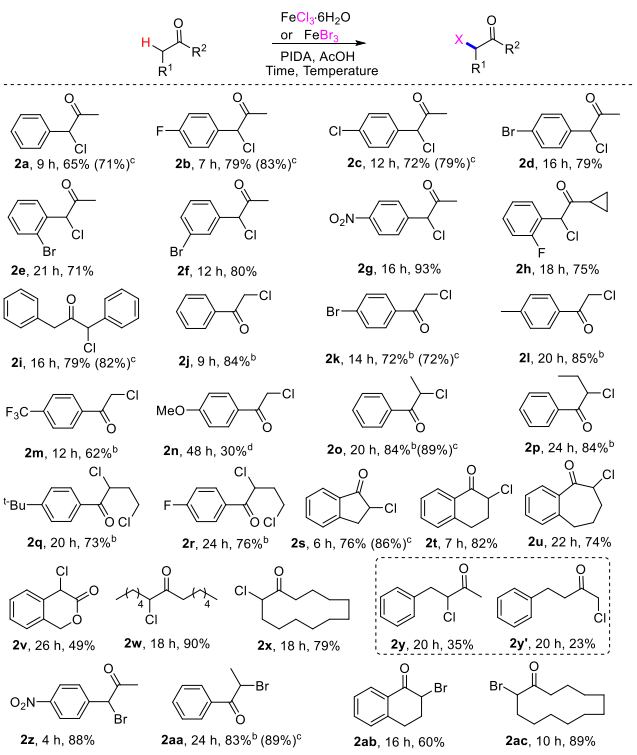
the amount of $FeCl_3·6H_2O$ dramatically diminished the yield of this transformation (entries 19-20, Table 1), while increasing the $FeCl_3·6H_2O$ to 2.5 equivalent slightly enhanced the yield (entry 21, Table 1). Considering the marginal difference in product yield, we selected 2.0 equivalent of $FeCl_3·6H_2O$ as the standard amount. Finally, other chloride sources were also investigated, with inferior result obtained in each case (entries 22-33, Table 1). Therefore, the reaction conditions listed in entry 3 (Table 1) was selected as the optimal reaction conditions.

With the optimal reaction conditions in hand, we investigated the generality of this chlorination reaction. Various benzyl ketones, aromatic ketones, cyclic benzoketones, and aliphatic ketones were subjected to the optimal conditions, and the reaction results were shown in Table 2. Firstly, a series of phenylacetones containing either F, Cl, Br or NO_2 substituents at *para*-position or Br at *meta*- or *ortha*- position of the aryl ring were investigated, and all the reactions performed well, providing the corresponding products **2a**-**2g** in good to excellent yields. However, the strong electron-donating OMe group of the aryl ring has a detrimental effect on the reaction, which gave a complex mixture. Notably, 1-cyclopropyl-2-(2-fluorophenyl)-ethanone (**1h**) was also an amenable substrate, affording the product **2h** in 75% yield. Interestingly, when the symmetric 1,3-diphenylpropan-2-one was used, the mono-chlorinating product **2i** was obtained with 79% yield without the isolation of symmetric dichlorinated product. Next, a range of acetophenone derivatives were studied, which also provided the expected phenacyl chlorides **2j**-**2r** with good yield. Except for the preparation of product **2n**, an elevated reaction temperature (50 ^oC) was generally required for achieving the satisfactory yields. In these reactions, the substituents at *para*-position of the aryl ring, the length of the alkyl group, as well as the chloride at the alkyl chain have little influence on the reaction outcomes. However, product **2n** bearing strong electron-donating OMe group at *para*-position of the aryl ring was isolated only in a low yield (30%), along with recovery of **1n** (38%). Remarkably, propiophenone and 1-phenylbutan-1-one were ideal substrates,

affording the expect products **2o** and **2p** with 84% and 84% yield, respectively. It is noteworthy that the substrates bearing a chloride at distal site of the alkyl chain reacted smoothly, resulting in the 1,3-dichlorides **2q** and **2r** with satisfied yields. Cyclic benzoketones were also proved to be suitable substrates, which could be easily transformed to the corresponding five-, six-, and seven-membered ring products **2s-2u** with good to excellent yields, respectively. Moreover, isochroman-3-one was also tested, giving the expected product **2v** with 49% yield. Finally, when 7-tridecanone and cyclododecanone were subjected to the optimal conditions, the expected products **2w** and **2x** was isolated with 90% and 79% yields, respectively, while 4-phenylbutan-2-one was selected as a substrate, products **2y** and **2y'** were isolated with low regioselectivity.

Similarly, the α-brominated ketone not only is a key structural scaffold in natural products,[1a] but also serves as a building block in the design and exploration of new chemical reaction.[13] In order to further expand this α-chlorinated reaction to a corresponding bromination process, $FeBr_3$ was used in place of $FeCl_3·6H_2O$ under the optimal conditions. The reaction proceeded smoothly, affording the expected brominated products **2z-2ac** with good to excellent yields. These results demonstrate that the present transformation could be applied for the preparation of α-brominated ketone, either the linear benzylketone or phenylketone or the cyclic benzoketone or aliphatic ketone.

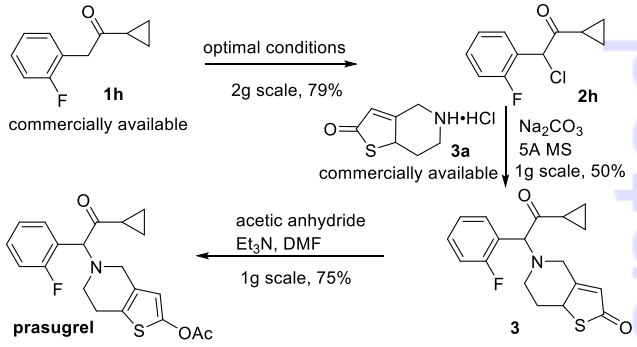
Table 2. Scope of Substrates[a].



a) Unless otherwise noted, reactions were performed using ketone derivatives (0.2 mmol) in 1.0 mL AcOH at room temperature under an argon atmosphere and the starting materials were completely conversed; b) the reaction was performed at 50°C; c) 10 mmol scale; d) the recovery starting material (38%).

To verify the synthetic utility of this transformation, eight representative substrates were carried out on a gram-scale reaction (10.0 mmol) under the optimal conditions, and a slightly improved or similar yield were obtained, respectively, along with some minor byproducts (Table 2).[12] These results indicated that the present protocol could be applied for the preparation of α-chlorinated/α-brominated ketones on gram-scale.

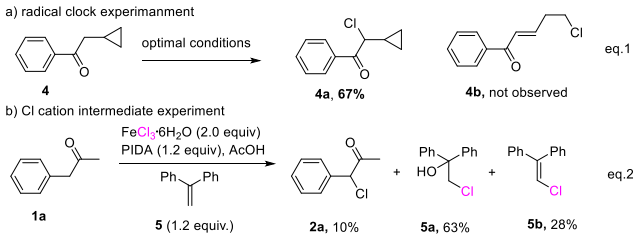
The synthetic application of this protocol was further demonstrated through the gram-scale synthesis of prasugrel,[14] a clinically used pharmaceutical for preventing the formation of blood clots. The product **2h** could be achieved in 79% yield when the gram-scale reaction of the commercially available substrate **1h** (2.14 g, 12.0 mmol) was conducted. Condensation of the chlorinated product **2h** (1.0 g) with the commercially available 5,6,7,7α-tetrahydrothieno [3,2-c] pyridine-2(4*H*)-one (**3a**, 1.10 g) gave intermediate **3** in 50% yield, and the subsequent acylation **3** (1.14 g) with acetic anhydride (0.53 g) afforded the target compound in 75% yield. The overall yield of the three-step synthesis is 30% from two commercially available materials **1h** and **3a** (Scheme 1).



Scheme 1. The Concise Synthesis of Prasugrel on Gram-scale.

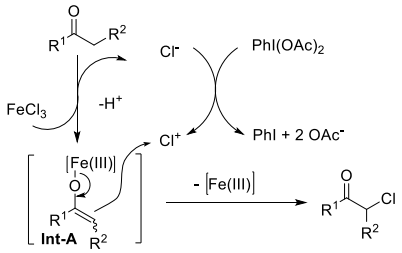
To elucidate the possible reaction mechanism, some designed control experiments were carried out (Scheme 2). First, the compound **4**[15a] was subjected to the optimal reaction conditions, and the chlorinated product **4a** was isolated without the ring-opening product **4b** being observed (eq. 1, Scheme 2.);[12] this result excluded a possible radical reaction process involving Cl·. Second, the model reaction was performed under the standard condition in the presence of 1,1-diphenylethene (DPE, **5**), the compounds **5a**[15b] and **5b**[15c] were isolated along with product **2a** (eq.2, Scheme 2.), these experimental results

ruled out the possibility of chloride anion participation in the reaction and suggested that a chloride cation might be involved in the current transformation based on the combinition of the formation of product **5a** and radical clock experiment. Third, when $FeCl_3·6H_2O$ was replaced by 1.0 mol/L HCl as both of an acid and chloride source, the reaction led to the desired product **2a** with 56% yield (entry 22, Table 1). Finally, various metal chlorides were used to replace $FeCl_3·6H_2O$ under the optimal conditions. The results demonstrated that the Lewis activity of metal chlorides dramatically effect the expected transformation (entries 23-32, Table 1) and proved that the enolized process is a crucial for the success of the reaction. Because some metal chlorides with weaker Lewis acidity could not efficiently promote the enolization of substrate and the activation of the oxidant PIDA, [16] the expected chlorination could not occur in these cases. However, $FeCl_3·6H_2O$ could acted as "three birds with one stone" reagent,[10a] i.e. the acceleration of the enolized transformation, the activation of the oxidant PIDA,[16] and the chloride source in the current transformation.



Scheme 2. Some Control Experiments.

Based on the above-mentioned experimental results including entry 34 (Table 1) and the reported literatures,[16,17] a possible reaction mechanism was proposed (Scheme 3). The enolized intermediate **Int-A** was generated by the activation of $FeCl_3$, and the Cl anion was simultaneously released. Subsequently, the resulting Cl anion was oxidized by PIDA to generate the active Cl cation,[17] which was trapped by the intermediate **Int-A** to afford the chlorated product and release a Fe(III) species.



Scheme 3. The Proposed Reaction Mechanism.

In conclusion, a new, efficient and scalable method for introduction of chloride at α-position of ketones have been developed under the mild conditions, and environmentally friendly $FeCl_3·6H_2O$ and phenyliodonium diacetate were applied as the chloride source and the oxidant, respectively. This methodology has been extended to α-bromination of ketones. Notably, a clinically drug prasugrel was concisely synthesized in three steps with 30% yield on gram-scale.

Experimental Section

Under an argon atmosphere, to a 15 mL reaction tube were added sequentially a magnetic stir-bar, ketone substrates (0.2 mmol), $FeCl_3·6H_2O$ (0.4 mmol, 108.1 mg), $PhI(OAc)_2$ (0.24 mmol, 77.3 mg) and AcOH (1.0 mL). The reaction mixture was stirred at room temperature (procedure A) or at 50°C (procedure B) until the starting material disappeared (monitored by TLC), and the reaction mixture was diluted with EtOAc and H_2O. The mixture was extracted with EtOAc (30 mL × 3) and the combined organic layers were washed successively with water and brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude product, which was purified by silica gel column with petroleum ether/EtOAc as the eluent to afford the desired product.

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A simple and efficient method for the preparation of α-halogenated ketones using iron(III) chloride and iron(III) bromide as halogen sources with phenyliodonium diacetate as oxidant

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