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Facile and efficient preparation of α-halomethyl ketones from α-diazo ketones catalyzed by iron(III) halides and silica gel

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ABSTRACT

An efficient and mild method for the synthesis of α-halomethyl ketones from α-diazo ketones was developed using ferric chloride or bromide as the halogen source and silica gel as the hydrogen source, with good to excellent yields.

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Recently, α-halomethyl ketones have become increasingly important building blocks in organic synthesis,[1] and have been widely applied in various fields, including pharmaceutical synthesis, pesticides, and spices.[2] Several methods for constructing α-halomethyl ketones have been developed in the past decade. Generally, these processes involve the direct halogenation of ketones or their derivatives, using *N*-halosuccinimides (NBS, NCS, NBA, NCA),[3] metal halides,[4] halogens,[5] or DCDMH/DBDMH,[6] to form α-mono- or α,α-dichloroketones as halogenating reagents.[7] On the other hand, a new approach involving the hydration of haloalkynes or oxyhalogenation of alkynes has been developed in recent years and become a hot topic.[8] However, the aforementioned halogen reactions are inefficient due to their long reaction times, costly catalysts, or use of strong protic acids. Another method involves the addition of α-diazoacetophenones with monohalides, or molecular halogens to obtain α-haloketones in good yields.[9] But this has the relative disadvantages of using a strong acid as catalyst and harsh reaction conditions. Considering these challenges, we herein report a mild and efficient synthesis of α-halomethyl ketones from α-diazo ketones in the presence of $FeCl_3$ or FeBr with silica gel in good to excellent yields at room temperature. More significantly, compared with the traditional method using strong protic acids, iron halides are easy to operate.

Initially, the reaction conditions were optimized using α-diazoacetophenone[10] (**1a**) as a model substrate for chlorination. Compound **1a** was treated with 0.5 equiv. of $FeCl_3$ in dichloromethane (DCM), with the results shown in Table 1. The temperature had almost no effect on the reaction (entries 1–3), with similar yields obtained at lower temperatures, so room temperature was chosen for subsequent experiments. Regarding solvent selection, as protic solvents would attack the carbine carbon, leading to the formation of acetophenone or a mixed product (entries 4 and 5), only nonprotic solvents were tested for this reaction. Unfortunately, the reaction did not proceed in THF, a result which remains to be explored (entry 6). Halogenated solvents were more appropriate, affording the best yields of up to 70%, while toluene only produced yields of up to 60% (entries 1 and 7). When using nitrogenous solvents, such as CH_3CN or DMF, only poor yields were obtained (entries 10 and 11). When other metal chlorides were screened, stronger Lewis acids participated in the reaction, but afforded slightly lower yields (entries 13 and 14). When $CuCl_2$ or neutral salt KCl was used, no product was found (entries 15 and 16). When a protic acid was used instead of silica gel, a lower yield was obtained (entry 18).

Based on the above optimization, we next examined the substrate scope of this reaction. Various substituents on the phenyl ring afforded the corresponding α-chloromethyl ketones in

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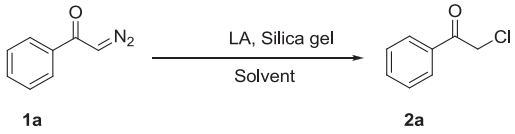
Table 1
Optimization of experimental conditions.[a]



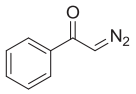
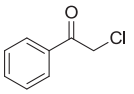
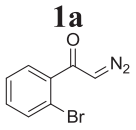
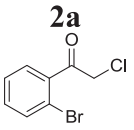
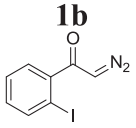
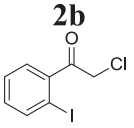
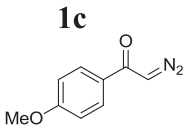
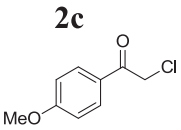
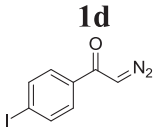
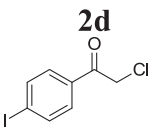
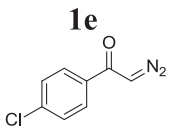
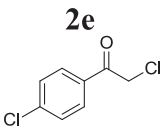
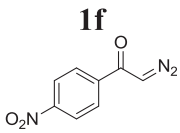
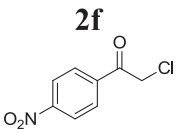
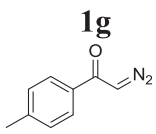
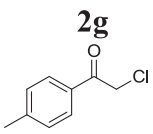
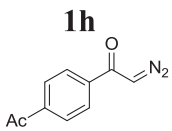
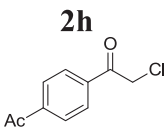
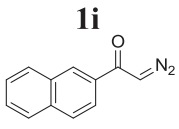
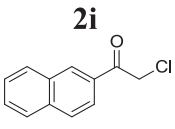
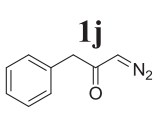
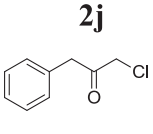
Entry	Lewis acid	Temperature	Solvent	Yield[b] (%)
1	$FeCl_3$	RT	DCM	70
2	$FeCl_3$	0 °C	DCM	71
3	$FeCl_3$	−30 °C	DCM	70
4	$FeCl_3$	RT	H_2O	Mix
5	$FeCl_3$	RT	CH_3OH	85[c]
6	$FeCl_3$	RT	THF	NR
7	$FeCl_3$	RT	$PhCH_3$	60
8	$FeCl_3$	RT	$CHCl_3$	63
9	$FeCl_3$	RT	DCE	67
10	$FeCl_3$	RT	CH_3CN	Mix
11	$FeCl_3$	RT	DMF	Mix
12	$FeCl_2$	RT	DCM	36
13	$InCl_3$	RT	DCM	37
14	$TiCl_4$	RT	DCM	63
15	$CuCl_2$	RT	DCM	NR
16	KCl	RT	DCM	NR
17	$FeCl_3$	RT	DCM	70[d]
18	$FeCl_3$	RT	DCM	15[e]

[a] Reaction conditions: **1a** (0.5 mmol), Lewis Acid (0.25 mmol, 0.5 equiv.) and silica gel 100 mg in 2 mL solvent with 10 min.
[b] Isolated yields.
[c] The resulting product was acetophenone.
[d] The reaction time was 1 h.
[e] 2.0 equiv. acetic acid was used instead of silica gel, 24 h.

moderate to good yields. Firstly, the efficiency of different halogen-substituted substrates was investigated. The results showed that the substituent position had a significant effect on the reaction (Table 2, entries 2–5). For example, *ortho*-iodoacetophenone gave a higher yield (**2c**, entry 3) than its *para*-substituted counterpart (entry 5). Other *para*-substituted substrates, with either electron-donating or electron-withdrawing groups, reacted smoothly, giving desired products **2e**–**2 h** in 56–75% yield. Among these, *para*-methyl-substituted **1h** gave a lower yield of 56% (entry 8), *para*-acetyl-substituted **1i** gave the yield of 70% comparing with similar *para*-benzoyl-substituted structure was reported by using HCl to give the yield of 25%.[11] Furthermore, the substrate bearing a naphthyl ring gave the highest yield, with corresponding product **2l** isolated in 82% yield (entry 10). Dialkyl ketone substrates were also tested, with **1k** reacting smoothly under the optimized conditions to give the desired nitrile **2k** in a highest yield of 68%. When **1l**, **1m**, **1n** were subjected to this optimal conditions, the expected products **2l**, **2m**, **2n** was isolated with similar lower yield about 45%. Unfortunately, substituting a methoxy group at the *ortho* position of the substrate failed to provide the desired chloric product, instead affording coumaranone in excellent yield (97%), which is commonly obtained from same starting material using a large excess of protic acid as catalyst, such as HCl, AcOH, or CF_3COOH.[12,13]

In order to understand well this reaction mechanism, some designed experiments were carried out. As previously reported by Xiang and Zhang,[14] α-chloro/bromo methyl ketones could be obtained when 1,2-dichloroethane or 1,2-dibromoethane were used as solvent. Therefore, chloride or bromide apparently came from the halogenated reaction solvent. To better understand where the halide came from in our reaction, we verified our conjecture by

Table 2
Chlorination of various α-diazo-methyl ketones.[a]

Entry	Substrate	Product	Yield (%)[b]
1			70
2	**1a** 	**2a** 	65
3	**1b** 	**2b** 	81
4	**1c** 	**2c** 	65
5	**1d** 	**2d** 	73
6	**1e** 	**2e** 	75
7	**1f** 	**2f** 	65
8	**1g** 	**2g** 	56
9	**1h** 	**2h** 	70
10	**1i** 	**2i** 	82
11	**1j** 	**2j** 	68
	1k	**2k**	

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