Mn(III)-Mediated Chlorination of Conjugated Ketones

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Mn(III)-Cl formed by the reaction of $Mn(OAc)_3$ and hydrochloric acid *in situ*, reacted with *α*,*β*-unsaturated ketones readily to afford *α*,*β*-dichloroketones in good yields under mild conditions. The products are key precursors for synthesis of conjugated alkynones and other organic compounds.

Keywords chlorination, $Mn(OAc)_3$, *α*,*β*-unsaturated ketone

Introduction

Halogenated organic compounds are very important intermediates which can be transformed to other functionality easily.[1] Generally, they could be synthesized by the reaction of molecular halogen and unsaturated compounds,[2] however, this method is limited in many cases, so developing new and efficient ways to halogenated organic compounds is neccessary.

$Mn(OAc)_3$ is widely used in the formation of C—C bond.[3] Recently, our group reported the $Mn(OAc)_3$-mediated C—S and C—P bond formations.[4] Fristad reported the chlorination of alkenes through Mn(III)-chloride species oxidatively transferring a Cl ligand directly to the carbon-carbon double bond.[5] To the best of our knowledge, no such reagent has ever been used for the chlorination of conjugated ketones. As the continuation of our research on $Mn(OAc)_3$-promoted reaction, herein, we would like to report the synthesis of *α*,*β*-dichloroketones by the reaction of *α*,*β*-unsaturated ketones and Mn(III)-Cl species formed by the reaction of $Mn(OAc)_3$ and hydrochloric acid *in situ*.

Experimental

^1H and ^{13}C NMR spectra were determined in $CDCl_3$ or DMSO-d_6 on an Inova-400 MHz spectrometer and chemical shifts reported from internal TMS (*δ*). Melting points were determined on an XT-4 melting point apparatus and uncorrected. High resolution mass spectra were recorded on a Micromass OA-TOF (EI) mass spectrometer. All of the reagents were used directly as obtained commercially unless otherwise noted.

General procedure for Mn(III)-mediated chlorination of conjugated ketones

Typical experimental procedure for preparation of 2a—2k Manganese(III) acetate (3 mmol) was added to an ice-cooled mixture of acetic acid (3 mL) and 36% hydrochloric acid (1 mL), followed by addition of conjugated ketones (1 mmol) 5 min later, then, the mixture was stirred at 25 ℃ for 1 h. After the reaction was completed (TLC monitored), saturated Na_2CO_3 solution was added, extracted with ethyl acetate, and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (eluted with ethyl acetate/petroleum ether, *V*∶*V*=1∶50) to afford the pure products **2** in good yields.

Spectral data of 2a—2k

2a: Yield 82%, m.p. 116—117 ℃ (lit.[6] 116 ℃). ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.09 (d, *J*=7.6 Hz, 2H, ArH), 7.68—7.64 (m, 1H, ArH), 7.57—7.52 (m, 4H, ArH), 7.44—7.42 (m, 3H, ArH), 5.53—5.47 (m, 2H, 2CH); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 191.6, 137.2, 134.8, 134.6, 129.6, 129.3, 129.0, 128.6, 60.3, 57.2. HRMS: *m/z* (%), calcd for $C_{15}H_{12}{}^{35}Cl_2O$ (M^+) 278.0265, found 278.0254 (M^+, 0.02).

2b: Yield 81%, m.p. 149—150 ℃ (lit.[7] 139—143 ℃). ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.00 (d, *J*=8.0 Hz, 2H, ArH), 7.53 (d, *J*=7.3 Hz, 2H, ArH), 7.46—7.41 (m, 3H, ArH), 7.35 (d, *J*=7.8 Hz, 2H, ArH), 5.53—5.45 (m, 2H, 2CH), 2.46 (s, H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 191.4, 146.0, 137.6, 132.5, 130.2, 129.8, 129.6, 129.2, 128.8, 60.6, 57.3, 22.3. HRMS: *m/z* (%), calcd for $C_{16}H_{14}{}^{35}Cl_2O$ (M^+) 292.0422, found 292.0419 (M^+, 0.13).

2c: Yield 84%, m.p. 110—111 ℃ (lit.[7] 100—105 ℃). ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.09 (d, *J*=6.8 Hz, 2H, ArH), 7.70—7.66 (m, 1H, ArH), 7.57 (d, *J*=7.0 Hz, 2H, ArH), 7.45 (d, *J*=6.9 Hz, 2H, ArH), 6.96 (d, *J*=6.9 Hz, 2H, ArH), 5.54—5.40 (m, 2H, 2CH), 3.85 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 191.9, 160.7,

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135.1, 134.7, 130.0, 129.5, 114.6, 60.5, 57.5, 55.8. HRMS: *m/z* (%), calcd for $C_{16}H_{14}{}^{35}Cl_2O_2$ (M^+) 308.0371, found 308.0366 (M^+, 0.45).

2d: Yield 84%, m.p. 157—158 ℃ (lit.[7] 155—157 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.03 (d, J=8.3 Hz, 2H, ArH), 7.54—7.51 (m, 4H, ArH), 7.46—7.41 (m, 3H, ArH), 5.48—5.41 (m, 2H, 2CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 190.6, 141.4, 137.3, 133.3, 130.8, 129.9, 129.3, 128.7, 60.4, 57.4. HRMS: *m/z* (%), calcd for $C_{15}H_{11}{}^{35}Cl_3O$ (M^+) 311.9875, found 278.0067 (M^+−Cl, 6.62).

2e: Yield 85%, m.p. 167—168 ℃ (lit.[8] 167—168 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.08 (d, J=7.3 Hz, 2H, ArH), 7.68—7.66 (m, 1H, ArH), 7.58—7.54 (m, 2H, ArH), 7.48—7.41 (dd, J=7.7, 19.6 Hz, 4H, ArH), 5.46 (s, 2H, 2CH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 192.1, 137.0, 135.5, 134.5, 134.4, 131.5, 129.9, 129.8, 129.3, 59.8, 55.9. HRMS: *m/z* (%), calcd for $C_{15}H_{11}{}^{35}Cl_3O$ (M^+) 311.9875, found 311.9908 (M^+, 0.01).

2f: Yield 80%, m.p. 96—97 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.10 (d, J=7.2 Hz, 2H, ArH), 7.66 (t, J=7.4 Hz, 1H, ArH), 7.55 (t, J=7.7 Hz, 2H, ArH), 7.48 (dd, J=1.4, 7.6 Hz, 1H, ArH), 7.41—7.36 (m, 1H, ArH), 7.04 (t, J=7.5 Hz, 1H, ArH), 6.98 (d, J=8.3 Hz, 1H, ArH), 5.93—5.87 (m, 2H, 2CH), 3.95 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 190.5, 156.5, 133.8, 133.1, 129.6, 128.7, 128.0, 127.9, 124.0, 119.8, 110.4, 54.8, 54.6. HRMS: *m/z* (%), calcd for $C_{16}H_{14}{}^{35}Cl_2O_2$ (M^+) 308.0371, found 308.0372 (M^+, 0.87).

2g: Yield 66%, m.p. 117—119 ℃ (lit.[7] 108—114 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.31 (d, J=8.6 Hz, 2H, ArH), 8.09 (d, J=7.9 Hz, 2H, ArH), 7.74—7.68 (m, 3H, ArH), 7.58 (t, J=7.7 Hz, 2H, ArH), 5.57 (d, J=10.3 Hz, 1H, CH), 5.46 (d, J=10.4 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 189.4, 147.2, 142.9, 133.6, 133.1, 128.5, 128.1, 128.0, 127.7, 122.9, 57.3, 55.4. HRMS: *m/z* (%), calcd for $C_{15}H_{11}{}^{35}Cl_2NO_3$ (M^+) 323.0116, found 287.0344 (M^+−Cl, 6.64).

2h: Yield 78%, m.p. 139—141 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.08 (d, J=8.8 Hz, 2H, ArH), 7.45 (d J=8.6 Hz, 2H, ArH), 7.02 (d, J=8.8 Hz, 2H, ArH), 6.95 (d, J=8.6 Hz, 2H, ArH), 5.46 (s, 2H, 2CH), 3.91 (s, 3H, CH_3), 3.84 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 188.8, 163.4, 159.1, 130.4, 128.5, 128.2, 126.4, 113.2, 113.0, 59.1, 55.9, 54.6, 54.3. HRMS: *m/z* (%), calcd for $C_{17}H_{16}{}^{35}Cl_2O_3$ (M^+) 338.0476, found 338.0482 (M^+, 0.10).

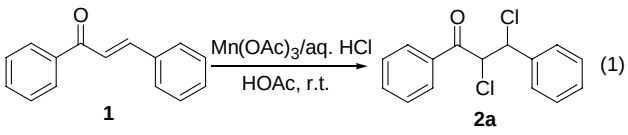
2i: Yield 73%, m.p. 140—141 ℃ (lit.[9] 142—144 ℃). ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 11.78 (s, 1H, OH), 7.85 (d, J=8.3 Hz, 1H, ArH), 7.58 (t, J=7.8 Hz, 1H, ArH), 7.45 (d, J=8.6 Hz, 2H, ArH), 7.08 (d, J=8.5 Hz, 1H, ArH), 7.03—6.99 (m, 1H, ArH), 6.96 (d, J=8.7 Hz, 2H, ArH), 5.55—5.40 (m, 2H, 2CH), 3.85 (s, 3H, OCH_3).

2j: Yield 71%, m.p. 116—118 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.79 (d, J=4.7 Hz, 1H, pyridine-H), 8.23 (d, J=7.0 Hz, 1H, pyridine-H), 8.00—7.92 (m, 1H, pyridine-H), 7.60—7.56 (m, 3H, ArH), 7.46—7.40 (m, 3H, ArH), 6.45 (d, J=11.0 Hz, 1H, CH), 5.51 (d, J=11.0, 1H, CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 192.9, 151.3, 149.8, 137.8, 137.6, 129.8, 129.2, 128.8, 128.7, 124.1, 60.5, 55.5. HRMS: *m/z* (%), calcd for $C_{14}H_{11}{}^{35}Cl_2NO$ (M^+) 279.0218, found 279.0228 (M^+, 0.06).

2k: Yield 85%, m.p. 91—92 ℃ (lit.[10] 92—93 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42—7.40 (m, 5H, ArH), 5.15 (d, J=10.5 Hz, 1H, CH), 4.60 (d, J=10.5 Hz, 1H, CH), 2.44 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 199.5, 136.7, 129.7, 129.0, 128.5, 63.6, 60.4, 27.2.

Results and discussion

At the initial stage, the chlorination of 1,3-diphenylpropenone (chalcone) with $Mn(OAc)_3$/HCl(aqueous) was explored (Eq. 1), fortunately, a major product was isolated and its structure was characterized to be 2,3-dichloro-1,3-diphenylpropanone (Table 1, Entry 1). Solvent scanning was then conducted with CH_2Cl_2, CH_3CN, EtOH and MeOH, which indicated that HOAc was the best medium (Table 1, Entries 2—5). Increasing reaction temperature reduced the reaction time without improving the yields (Table 1, Entries 6—7). Based on the experimental results obtained, the optimal reaction conditions were determined to be that 1,3-diphenylpropenone (1 mmol) and $Mn(OAc)_3$•$2H_2O$ (2 mmol) were reacted in the mixture of HOAc (2 mL) and 36% aq. HCl (1 mL) at 25 ℃, and this was used for other chalcones.



1 2a (1)

Table 1 Effects of solvent and temperature on the chlorination

Entry[a]	Solvent	Temp./℃	Time/h	Yield[b]/%
1	HOAc	25	1	82
2	CH_2Cl_2	25	1	complicated
3	CH_3CN	25	1	43
4	EtOH	25	1	50
5	MeOH	25	1	45
6	HOAc	40	0.5	82
7	HOAc	60	0.4	81

[a] 1,3-Diphenylpropenone (1 mmol), $Mn(OAc)_3$•$2H_2O$ (2 mmol) were reacted in the mixture of HOAc (2 mL) and 36% aq. HCl (1 ml). [b] Isolated yields.

Chlorination results for a series of conjugated ketones are summarized in Table 2, which showed that all the reactions were completed in 1 h to afford the desired products in moderate to good yields (66%—85%) except for substrate bearing NO_2 group (Table 2, Entry 7).

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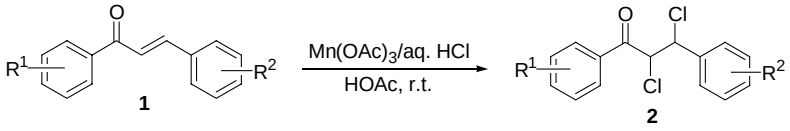
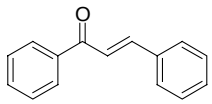
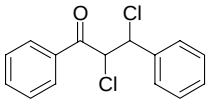
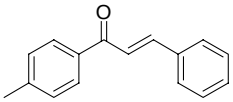
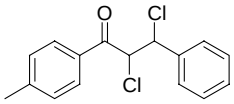
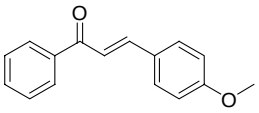
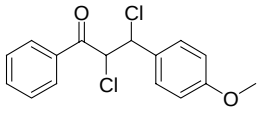
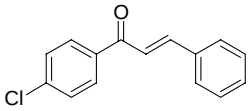
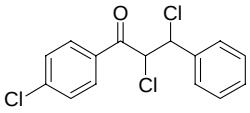
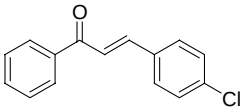
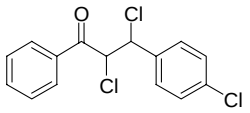
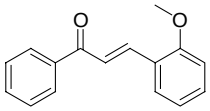
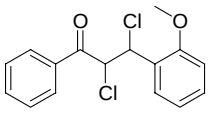
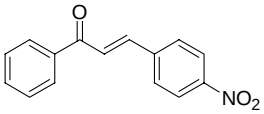
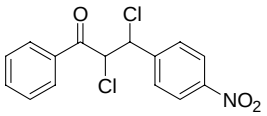
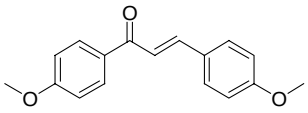
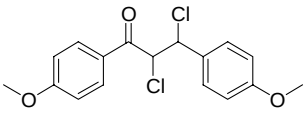
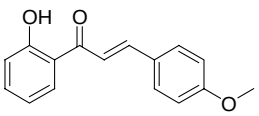
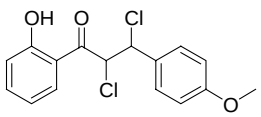
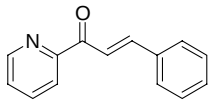
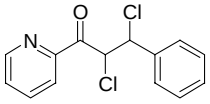
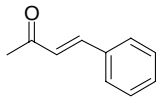
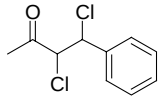


(2)

Table 2 Mn(III)-mediated chlorination of conjugated ketones[a]

Entry	Conjugated ketone	Time/h	Yield[b]/%	Product
1		1	82	 **2a**
2		1	81	 **2b**
3		0.5	84	 **2c**
4		1	84	 **2d**
5		1	85	 **2e**
6		0.5	80	 **2f**
7		1.2	66	 **2g**
8		0.2	78	 **2h**
9		0.5	73	 **2i**

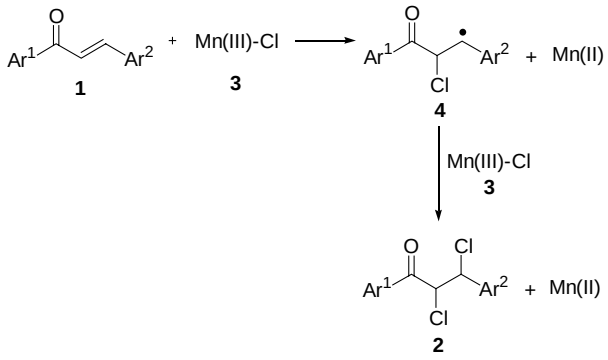
Continued

Entry	Conjugated ketone	Time/h	Yield [b]/%	Product
10		1	78	 **2j**
11		1	85	 **2k**

[a] Chalcone (1 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (2 mmol) were reacted in the mixture of HOAc (2 mL) and 36% aq. HCl (1 mL) at 25 ℃; [b] Isolated yields.

A plausible mechanism for the reaction is illustrated in Scheme 1. Mn(III)-Cl species (**3**) formed by the reaction of $Mn(OAc)_3$ and hydrochloric acid *in situ*, transfers a Cl ligand to C=C double bond in **1**[5] to yield radical **4**, which reacts with a second **3** to afford the product **2** through transferring a second Cl ligand.

Scheme 1



Conclusions

In summary, we have developed a new and efficient method for the synthesis of chlorinated organic compounds through Mn(III)-Cl species formed by the reaction of $Mn(OAc)_3$ and hydrochloric acid *in situ*, and conjugated ketones to afford *α*,*β*-dichloroketones under the mild and eco-friendly conditions. The *α*,*β*-dichloroketones are key precursors for synthesis of conjugated alkynones and other organic compounds.

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