Simple and efficient methods for selective preparation of α-mono or α,α-dichloro ketones and β-ketoesters by using DCDMH

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New processes that can selectively prepare α-mono or α,α-dichloro ketones and β-ketoesters using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) are reported. Using silica gel as the catalyst and methanol as the solvent and heating for 1 h under reflux, α-monochlorinated products were selectively obtained in 86–98% yield. However using a deep eutectic solvent (choline chloride: *p*-TsOH = 1:1) as the solvent and stirring for 45 min at room temperature, α,α-dichlorinated products were selectively obtained in 86–95% yield.

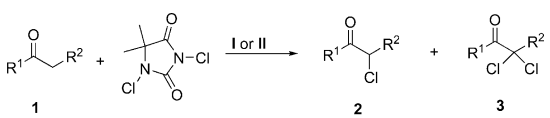
Introductions

Chlorinated organic compounds constitute an important class of intermediates as they can be converted into other functional molecules by simple chemical transformation.[1] α-Chlorinated ketones and β-ketoesters are among the most versatile intermediates used for medicine and agriculture, and their high reactivity makes them react with a large number of nucleophiles to provide a variety of useful compounds.[2] The previous methods to preparing the chlorinated organic compounds were based on molecular chlorine, some ammonium chlorides or *N*-chlorosuccinimide (NCS).[3] The novel methods of halogenating with high selectivity that satisfy the requirements of green chemistry have attracted a lot of attention.[4] However, developing selective monochlorination reactions or selective dichlorination reactions remains a challenge since these reactions in many cases always result in a mixture of mono- and dichlorinated products.[5] There are some excellent methods that have been reported to solve this challenge. M. Marigo *et al.* used NCS to prepare chlorinated ketones with high regioselectivity and stereoselectivity.[6] Wang *et al.* also used NCS to chlorinate ketones and accomplish high selectivity.[7] H. M. Meshram *et al.* used Amberlyst-15 as catalyst and obtained excellent results with high selectivity.[8] Recently, B. Sreedhar *et al.* also published a novel method to prepare chlorinated ketones rapidly with high selectivity.[9]

1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) is a disinfecting agent and bleaching agent that has been extensively used as a disinfectant for industrial and domestic water.[10] In contrast to common disinfectants, DCDMH does not have the odor of chlorine and is barely irritating to human beings.[11] Additionally, DCDMH can be used as a novel bactericide, so is also expected to be widely used for fruit storage.[12] Compared with *N*-chlorosuccinimide (NCS), a readily available N–Cl reagent that is widely used as electrophilic chlorinating agent, DCDMH is a widely used industrial product and is much cheaper. For example, the price of DCDMH was about three times lower than the price of NCS in 2006, according to the product catalogue of Alfa Aesar.[13] Z. Xu *et al.*[14] used DCDMH to chlorinate acetophenones in methanol, and the yields were good. Although DCDMH is cheap, Xu's process would produce much sewage containing *p*-toluenesulfonic acid, which was used as catalyst, so is not favorable for industry. We wish to discuss and develop a new process that can reduce the acid sewage while maintaining high selectivity.

Results and discussion

In order to reduce the acid sewage while retaining high selectivity, we tried various catalysts and found that when silica gel was added to the mixture of acetophenone **1a**, methanol and DCDMH, the chlorination took place quickly under reflux and only the α-chlorinated product was obtained easily (Scheme 1 and Table 1). So we used silica gel to substitute *p*-TsOH as the catalyst in the process. After that, we chose **1a** as the test substrate to optimize the reaction conditions (Table 1). When 1 g silica gel was added to the reaction mixture, a pure solid of **2a** was obtained in 95% yield; when 0.1 g silica gel was added, the yield of **2a** was increased to 97% (Table 1–Entry 2). So it seems that the larger amount of silica gel added to the reaction mixture was not so helpful to the process. When DCDMH was replaced by NCS under similar conditions, the conversion of acetophenone determined by GC was declined to 70%. When the process was without silica gel or was not heated at reflux but only at 40 °C,



I: SiO_2,MeOH,reflux,1h; Yield: **2a~2l**(86~98%)
II: DES, rt, 45 min.; Yield: **3a~3l**(86~95%)

1a: R^1=phenyl, R^2=H
1b: R^1=*p*-Cl-phenyl, R^2=H
1c: R^1=*p*-Br-phenyl, R^2=H
1d: R^1=*p*-Me-phenyl, R^2=H
1e: R^1=*p*-NO_2-phenyl, R^2=H
1f: R^1=*m*-NO_2-phenyl, R^2=H
1g: R^1=4'-Br-biphenyl, R^2=H
1h: R^1=*p*-OMe-phenyl, R^2=H
1i: R^1=Me, R^2= -COOEt
1j:R^1=benzoyl, R^2= -COOEt
1k: R^1=*p*-NO_2-benzoyl, R^2= -COOEt
1l:R^1= *t*-butyl, R^2=H

Scheme 1

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Table 1 Conditions of the α-chlorination of acetophenone with DCDMH using silica gel[a]

Entry	SiO_2/g	Solvent	Temperature/°C	Product	Yield (%)
1	1	methanol	reflux	solid (m.p. 51–52 °C)	95[b]
2	0.1	methanol	reflux	solid (m.p. 51–52 °C)	97[b,e]
3	0	methanol	reflux	oil	80[c]
4	0.1	methanol	40	oil	66[c]
5	0.1	acetonitrile	reflux	oil	(29 + 8)[d]

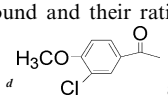
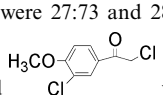
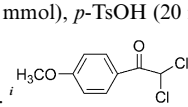
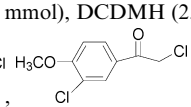
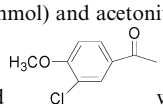
[a] All reactions were run with 10 mmol of acetophenone using 7.5 mmol of DCDMH for 1 h. [b] Isolated yield. [c] A mixture of α-monochloroacetophenone and acetophenone was obtained and the conversion of acetophenone was determined by GC. [d] A mixture of α-mono-, α,α-dichloroacetophenone and acetophenone was obtained and the ratio determined by GC was 29:8:63. [e] Using NCS to replace DCDMH with the same conditions, a mixture of α-monochloroacetophenone and acetophenone was obtained; their ratio determined by GC was 70:30.

the conversion of **1a** that was determined by GC declined and a mixture of α-monochloroacetophenone and acetophenone was obtained (Table 1-Entry 3 and 4). When acetonitrile was used as solvent, replacing methanol, the conversion of **1a** determined by GC declined obviously and the dichlorinated product was found. So we thought silica gel as the catalyst and methanol as the solvent were necessary and helpful for the reaction rate and selectivity.

The process involving 10 mmol of **1a**, 7.5 mmol of DCDMH and 0.1 g of silica gel was heated at reflux for 1 hour to offer the product is, perhaps, the best reaction conditions without *p*-TsOH (Table 1–Entry 2). After that, we chose **1b**, **1c** and **1d** as the tested substrate and the selectivity, reaction rate and yields were good (Table 2). High purity products **2b**–**2d** were directly obtained even without any further purification. The conversion of α-monochlorination of **1e** was almost 100%, but among the products 73% was obtained in the form of the α-monochlorinated ketal (Table 2–Entry 5). The case of **1f** was similar (Table 2–Entry 6). Research into ketals is in progress. The reaction of **1g** did not take place, as the substrate hardly

Table 2 α-Chlorinations of ketones and β-ketoesters with DCDMH

Entry	Substrate	Product	Isolated yield (%)	mp/°C
1[a]	**1a**	**2a**	97	51–52 (lit: 51–52[15])
2[a]	**1b**	**2b**	98	99–101 (lit: 101–101.5[16])
3[a]	**1c**	**2c**	93	114–116 (lit: 113.5–115[17])
4[a]	**1d**	**2d**	92	52–54 (lit: 54.5–55[18])
5[a]	**1e**	**2e**	(27 + 73)[b]	—
6[a]	**1f**	**2f**	(28 + 72)[b]	—
7[a]	**1g**	**2g**	0[c]	—
8[a]	**1h**	**2h**	—[d]	—
9[a]	**1i**	**2i**	88 **2i** and methyl ester[e]	—
10[a]	**1j**	**2j**	86 **2j** and methyl ester[e]	—
11[a]	**1k**	**2k**	88 **2k** and methyl ester[e]	—
12[a]	**1l**	**2l**	—[f]	—
13[g]	**1a**	**3a**	95	oil (lit: 19–20.5[20])
13[g]	**1b**	**3b**	94	56–58 (lit: 58–59[20])
15[g]	**1c**	**3c**	96	59–61 (lit: 61–62[20])
16[g]	**1d**	**3d**	94	52–54 (lit: 54–56[21])
17[h]	**1e**	**3e**	86	oil (lit: 26.8–27.8[20])
18[h]	**1f**	**3f**	89	50–51 (lit: 52.5–54[20])
19[h]	**1g**	**3g**	93	138–140
20[g]	**1h**	**3h**	—[i]	—
21[g]	**1i**	**3i**	94	—
22[g]	**1j**	**3j**	92	—
23[g]	**1k**	**3k**	92	—
24[g]	**1l**	**3l**	88	50–51 (lit: 50–51[22])

[a] Substrate (10 mmol), methanol (10 ml), DCDMH (7.5 mmol), silica gel (0.1 g), reflux for 1 hour. [b] The α-monochloroketones and the α-monochlorinated ketals as products were found and their ratios were 27:73 and 28:72. [c] The substrate hardly resolved in the methanol and the process of chlorination did not take place. [d]  and  were found as the products. The ratio of the two products determined by ^{1}H NMR was 4:1. [e] Ester exchange reaction took place in the process. The conversion of substrates was complete and the yields of the products, which include methyl ester and ethyl ester, were determined by ^{1}H NMR. The ratio of methyl ester:ethyl ester = 1:5. [f] A mixture of α-chloropinacolone and α,α-dichloropinacolone was obtained and the ratio of the compounds determined by ^{1}H NMR was 2.7:1. [g] Substrate (10 mmol), choline chloride (20 mmol), *p*-TsOH (20 mmol), DCDMH (11 mmol) and acetonitrile (0.5 ml). The mixture and DES were stirred at room temperature for 45 minutes. [h] Substrate (2 mmol), choline chloride (20 mmol), *p*-TsOH (20 mmol), DCDMH (2.2 mmol) and acetonitrile (0.5 ml). The mixture and DES were stirred at room temperature for 45 minutes. [i]  ,  and  were found in the products and the ratio of three compounds determined by ^{1}H NMR was 1:3:3.

dissolved in the solvent. Substrates with a strong electron-donating group, such as **1h**, were also chlorinated on the benzene ring, and a mixture of 3-chloro-4-methoxyacetophenone and α,3-dichloro-4-methoxyacetophenone was obtained after work-up. β-Ketoesters, such as **1i**, **1j** and **1k**, were completely transferred to the products but the ester exchange reaction took place in the process. Some chlorinated methyl esters were found among chlorinated ethyl esters. In the case of aliphatic ketone pinacolone **1l**, a mixture of α-chloropinacolone and α,α-dichloropinacolone was obtained and the ratio of the compounds determined by ^{1}H NMR was 2.7:1. It seems the selectivity of our methods declined slightly when an aliphatic ketone (pinacolone) was used as the substrate. In short, this process of α-monochlorination of some acetophenones and β-ketoesters was rapid with high selectivity and much greener than the previous method using DCDMH.

We tried to use the same process of silica gel and methanol to prepare dichlorinated acetophenones. When the reaction time was prolonged from 1 hour to 3 hours and the amount of DCDMH was increased from 7.5 mmol to 11 mmol, a mixture of α-monochloroacetophenone and α,α-dichloroacetophenone was obtained, the ratio determined by GC was 68:32. So a novel and rapid method of preparing α,α-dichlorinated ketones needed to be developed. Deep eutectic solvents (DES) formed between choline chloride and acids are thought to be versatile alternatives to ionic liquids and have been shown to be good solvents for many reactions.[19] Herein, we tried to use a DES to accomplish the dichlorinating process.

Firstly, to prepare a proper DES we tried some ratios of two compounds in the mixture such as hydantoin with TsOH, hydantoin with choline chloride, hydantoin with $ZnCl_2$, hydantoin with $FeCl_3$, hydantoin with $AlCl_3$, urea with $FeCl_3$, urea with $AlCl_3$ and urea with TsOH. After heating, the mixture turned into sticky liquid but the liquid easily became solid again at room temperature. After obtaining many negative results, we found only the mixture of choline chloride and *p*-TsOH could be transferred to DES easily and the ratio of these two substances was 1:1.

So we used this new DES to prepare α,α-dichlorinated acetophenones. After that, we chose **1a** as the test substrate to optimize the reaction condition (Table 3). When the ratio of DES and **1a** was 1:10, the conversion of **1a** to α,α-dichlorination was 56% (Table 3–Entry 1). When the ratio was decreased to 2:1, the conversion was increased to 86% (Table 3–Entry 3). After that, we tried to add a little acetonitrile to speed up the reaction and the conversion of **1a** was complete after stirring the reaction mixture for 0.75 hour (Table 3–Entry 5).

We found that the mixture of substrate (10 mmol), choline chloride (20 mmol), *p*-TsOH (20 mmol), DCDMH (11 mmol), acetonitrile (0.5 ml) being stirred at room temperature for 45 minutes was a good reaction condition for selective preparation of α,α-dichloroacetophenones, and the yield of **3a** was 95% (Table 2–Entry 13). The amount of DES made the products easy to be extracted by an organic solvent such as MTBE and made the DES easy to be reused to reduce the usage of *p*-TsOH. We reused DES five times and the yield of **3a** did not decline obviously. After that, the other substrates were tested and the yields of the products were also high (Table 2). High purity α,α-dichlorinated products **3a**–**3f** were directly obtained. For the solid substrates, such as **1g**, that hardly dissolved in the DES, we reduced the amount of the substrate (Table 2–Entries 17–19). As for **1h**, 3-chloro-4-methoxyacetophenone and α,3-dichloro-4-methoxyacetophenone were also found with the product **3h**, and the ratio of these three compounds determined by ^{1}H NMR was 3:3:1. The yields of the tested β-ketoesters, such as **1i**, **1j** and **1k**, were also good (Table 2–Entries 21–23). In the case of aliphatic ketone **1l**, α,α-dichloropinacolone **3l** as a pure and white solid was obtained in 88% yield.

As mentioned above, when acetonitrile, which is without a hydroxyl group, was used as solvent, replacing methanol, in the process that used silica gel as catalyst, the reaction did not take place so rapidly and without high selectivity (Table 1-Entry 5). It seems the hydroxyl in the solvent is maybe helpful and necessary for the reaction. To prove this, a DES formed from *p*-TsOH and tributylmethylammonium chloride (1:1) that is without hydroxyl was used in the process of preparing α,α-dichlorinated acetophenone, and the yield of product declined to 56%. This perhaps also points to the necessity of the hydroxyl in the solvent.

NCS as a good chlorinating agent catalyzed by acid functionalized silica has been reported.[23] In our process catalyzed by silica gel without acid, when DCDMH was replaced by NCS, the conversion of acetophenone declined, as mentioned above. In our process, it seems that NCS was not more efficient than DCDMH. Samant *et al.*[24] suggested the mechanism of keto-enol tautomerism in the process of the bromination of substituted acetophenones using NBS and we thought the mechanism of our processes was possibly similar to the one that Samant *et al.* mentioned.

Conclusions

We used DCDMH, which is cheap and clean, as a chlorination reagent to prepare chlorinated acetophenones and β-ketoesters

Table 3 Conditions of α,α-dichlorination of **1a** with DCDMH in DES[a]

Entry	Choline chloride: *p*-TsOH:**1a**/mmol	Reaction time/h	Acetonitrile/ml	Conversion of **1a** (%)[b]
1	1:1:10	1	0	56
2	1:1:1	1	0	69
3	2:2:1	1	0	86
4	2:2:1	1	0.5	100
5	2:2:1	0.75	0.5	100

[a] **1a** was 10 mmol, DCDMH was 11 mmol and the reaction mixture was stirred in room temperature. [b] The conversion of **1a** was determined by GC.

rapidly and with high selectivity. These two processes can easily offer α-monochlorinated acetophenones and β-ketoesters or α,α-dichlorinated acetophenones and β-ketoesters with high selectivity; and these two processes, that are greener than the previous methods, using DCDMH are easy to scale up in industry.

Experimental

Typical procedure for preparation of α-chloroacetophenone (2a)

Silica gel (0.1 g) and DCDMH (1.48 g, 7.5 mmol) were added into a mixture of **1a** (1.2 g, 10 mmol) and methanol (10 ml) in a flask equipped with a magnetic stirring bar. The solution was heated at reflux for 1 hour and then was cooled to room temperature. After the mixture was filtered, solvent was distilled under reduced pressure and MTBE (20 ml) was added to the residue. The MTBE layer was washed twice by water (20 ml) and was dried over $MgSO_4$. After that, the organic layer was filtered and solvent was removed under reduced pressure. The product was obtained as a white solid (1.5 g, 97% yield). mp: 51–52 °C (lit: 51–52 °C).[15] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.72 (s, 2H, CH_2Cl), 7.51 (t, J= 7.8 Hz, 2H, ArH), 7.63 (t, J= 7.4 Hz, 1H, ArH), 7.96–7.98 (m, 2H, ArH).[25]

Typical procedure for preparation of α,α-dichloroacetophenone (3a)

A mixture of choline chloride (2.8 g, 20 mmol) and TsOH (3.4 g, 20 mmol) was added into a flask with a magnetic stirring bar under N_2 atmosphere. The flask was heated in an oil bath at 100 °C for 40 minutes and then was cooled to room temperature slowly. When the mixture was heated, there was a little HCl released from the mixture. After cooling down, the colourless DES was prepared in the flask. **1a** (1.2 g, 10 mmol), acetonitrile (0.5 ml) and DCDMH (2.2 g, 11 mmol) were added into the flask and the mixture was stirred for 45 minutes at room temperature. MTBE (30 ml) was added slowly to extract the product and the MTBE layer was separated from the flask carefully. The organic layer was washed twice by water (30 ml) and was dried over $MgSO_4$. After that, the organic layer was filtered and solvent was removed under reduced pressure. The product was obtained as light yellow oil (1.8 g, 95% yield, 98% GC area purity). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.69 (s, 1H, $CHCl_2$), 7.52 (t, J = 7.8 Hz, 2H, ArH), 7.65 (t, J= 7.4 Hz, 1H, ArH), 8.08–8.10 (m, 2H, ArH).[26]

Preparation of α,α-dichloromethyl-4′-bromobiphenyl ketone (3g)

The reaction was carried out as described in typical procedure for preparation of α,α-dichloroacetophenone (**3a**). 0.55 g (2 mmol) of methyl 4′-bromobiphenyl ketone **1g** was used to give a white solid **3g**: 0.65 g (yield 93%). mp: 138–140 °C. A white crystal was obtained by recrystallation from methanol. mp: 144–145 °C (methanol). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.70 (s, 1H, $CHCl_2$), 7.52 (d, J= 8.5 Hz, 2H, ArH), 7.64 (d, J= 8.5 Hz, 2H, ArH), 7.72 (d, J= 8.5 Hz, 2H, ArH), 8.20 (d, J= 8.5 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 67.9 ($CHCl_2$), 123.2 (ArCBr), 127.3 (ArCH), 128.9 (ArCH), 129.3 (ArCH), 130.5 (ArCH), 132.3 (ArCH), 138.3 (ArCH), 146.0 (ArCH), 185.5 (CO). Element Analysis: found: C, 48.71%; H, 2.70%. Calculated for $C_{14}H_9BrCl_2O$ (344.03): C, 48.83%; H, 2.62%.

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References

1 C. Chiappe, E. Leandri and M. Tebano, *Green Chem.*, 2006, **8**, 742–745.
2 N. D. Kimpe and R. Verhe, *In the Chemistry of* α-*Haloketones,* α-*Haloaldehydes and* α-*Haloimines*, ed. S. Patai and Z. Rappoport, John Wiley &, Sons, Chichester, UK, 1988.
3 J. C. Lee and H. J. Park, *Synth. Commun.*, 2007, **37**, 87–90 and references therein.
4 I. Pravst, M. Zupan and S. Stavber, *Green Chem.*, 2006, **8**, 1001–1005.
5 R. V. Hoffman, W. S. Weiner and N. Maslouh, *J. Org. Chem.*, 2001, **66**, 5790–5795.
6 M. Marigo, S. Bachmann, N. Halland, A. Braunton and K. A. Jorgenson, *Angew. Chem., Int. Ed.*, 2004, **43**, 5507–5510.
7 C. Wang and J. Tunge, *Chem. Commun.*, 2004, **23**, 2694–2695.
8 H. M. Meshram, P. N. Reddy, K. Sadashiv and J. S. Yadav, *Tetrahedron Lett.*, 2005, **46**, 623–626.
9 B. Sreedhar, P. S. Reddy and M. Madhavi, *Synth. Commun.*, 2007, **37**, 4149–4156.
10 T. Mitchenko, P. Stender and N. Makarova, *Solvent Extr. Ion Exch.*, 1998, **16**, 75–149.
11 Z. Rao, X. Zhang and W. R. G. Baeyens, *Talanta*, 2002, **57**, 993–998.
12 N. Fan and W. Wang, *HuaXue ShiJie*, 1998, **39**, 297–300.
13 http://www.alfa.com/Alf/laboratory_chemical_suppliers.htm.
14 Z. Xu, D. Zhang and X. Zou, *Synth. Commun.*, 2006, **36**, 255–258.
15 A. F. Diaz, Y. Y. Cheng and M. Ochoa, *J. Am. Chem. Soc.*, 1977, **99**, 6319–6322.
16 A. J. Sisti and W. Memeger, *J. Org. Chem.*, 1965, **30**, 2102–2104.
17 S. Sawada, *Chem. Pharm. Bull.*, 1977, **25**, 3370–3375.
18 C. R. Noller and R. Adams, *J. Am. Chem. Soc.*, 1924, **46**, 1889–1896.
19 A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, *J. Am. Chem. Soc.*, 2004, **126**, 9142–9147 and references therein.
20 A. O. Terent'ev, *Synthesis*, 2004, **17**, 2845–2848.
21 A. Bandyopadhyay, *J. Indian Chem. Soc.*, 1989, **66**, 239–240.
22 I. A. Savost'yanova, *Zhurnal Obshchei Khimii*, 1977, **47**, 1197–1198.
23 B. Das, K. Venkateswarlu, H. Holla and M. Krishnaiah, *J. Mol. Catal. A: Chem.*, 2006, **253**, 107–111.
24 M. V. Adhikari and S. D. Samant, *Ultrasonics Sonochem.*, 2002, **9**, 107–111.
25 J. Kagan, *J. Org. Chem.*, 1983, **48**, 703–706.
26 J. Barluenga, *J. Chem. Soc. Perkin Transaction 1*, 1991, **2**, 297–300.

