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An efficacious method for the halogenation of β-dicarbonyl compounds under mildly acidic conditions

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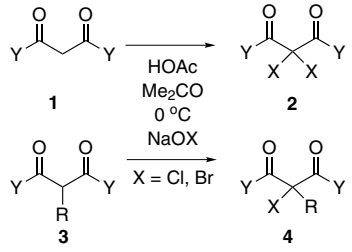
Abstract—A variety of 1,3-diketones, β-ketoesters and malonates can be chlorinated in high yields using sodium hypochlorite in a 5:2 mixture of acetone/acetic acid at 0 °C for 1 h. Similarly, bromination of these dicarbonyl substrates can be accomplished under the same conditions using sodium hypobromite.

A number of methods have previously been described in the literature for the halogenation of 1,3-dicarbonyl compounds.[1] Reagents which have been used inter alia for chlorination include sulfuryl chloride,[2] NaH/cupric chloride,[3] TEA/triflic chloride,[4] NaH/NCS[5] and (dichloroiodo)toluene.[6] In addition, a few scattered reports exist of chlorinations of simple malonate derivatives, which are unsubstituted at the α-position using hypochlorite in the presence of bases such as Na_2CO_3 or KOH.[7] Brominations of β-dicarbonyl compounds have often been effected with NBS,[2,5] NaH/cupric bromide[3] and NaH/Br_2.[8] We recently revealed that vinyl chlorides can be efficiently converted to α-chloro or α-bromoketones using sodium hypochlorite or sodium hypobromite, respectively, in a mixture of acetone/acetic acid.[9] Herein, we report that this same combination of reagents is also effective for the halogenation of a variety of β-dicarbonyl compounds.

Thus, it was found that a β-dicarbonyl compound **1** which is unsubstituted at the α-position undergoes dichlorination to afford high yields of **2** upon treatment with 3.0 equiv of commercially available 10–13% sodium hypochlorite solution in a 5:2 mixture of acetone/glacial acetic acid at 0 °C for 1 h (Scheme 1). Similarly, exposure of an α-monosubstituted system **3** to 1.5 equivs of sodium hypochlorite under the same



Scheme 1.

reaction conditions affords monochlorinated products **4**. Table 1 shows some representative examples of the transformations, which we have conducted.

It was observed using ethyl 2-oxocyclopentanecarboxylate as the substrate that omission of the acetic acid leads to a complex reaction mixture containing a significant amount of starting material. In addition, although diethyl malonate (entry f) and diethyl 2-bromomalonate (entry h) cleanly undergo chlorination, other 2-substituted malonates are less reactive. For example, diethyl 2-(*p*-tolyl)malonate is unchanged when exposed to the standard experimental conditions,[10] but can be chlorinated in good yield upon stirring at room temperature overnight (entry g). On the other hand, diethyl 2-methylmalonate and diethyl 2-ethylmalonate are totally unreactive even at room temperature. An attempt was made to monochlorinate diethyl malonate using 1.5 equiv of sodium hypochlorite, but in this case a mixture of mono- and dichlorinated products, along with starting

Keywords: Chlorination; Bromination; Vinyl chlorides; 1,3-Diketones; Malonates; β-Ketoesters.
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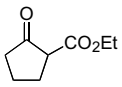
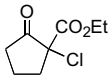
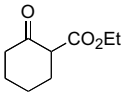
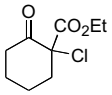
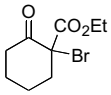
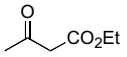
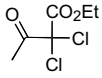
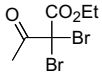
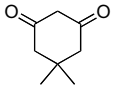
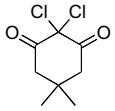
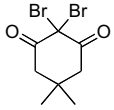
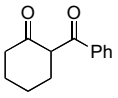
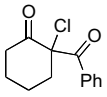
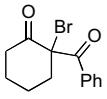
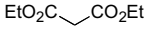
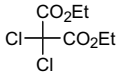
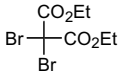
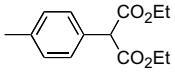
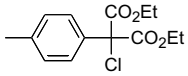
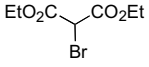
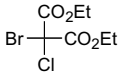
Table 1. Halogenation of representative 1,3-dicarbonyl compounds

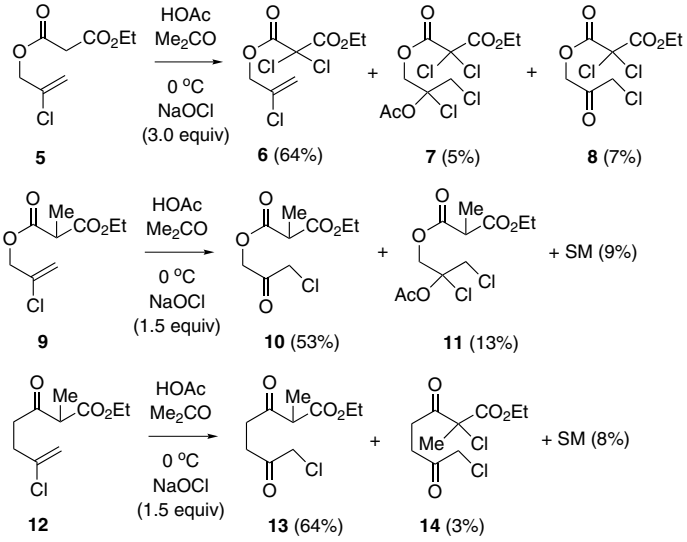
Entry	1,3-Dicarbonyl substrate	Chlorinated product	Brominated product
a		 88 %	—
b		 94 %	 95 %
c		 98 %	 96 %
d		 67 %	 81 %
e		 96 %	 98 %
f		 88 %	 90 %
g		 87 %[a]	—
h		 99 %	—

[a]After sodium hypochlorite addition at 0 °C, reaction mixture was warmed to rt and stirred for 17 h.

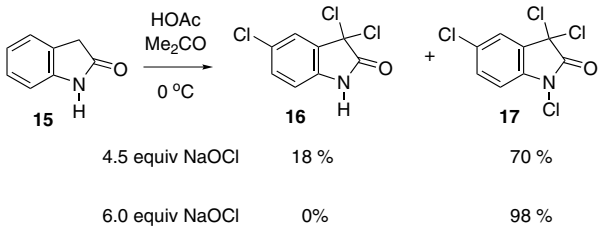
material, was isolated. It is also possible to brominate these β-dicarbonyl substrates if one replaces the sodium hypochlorite with a freshly prepared solution of sodium hypobromite.[10] The data in Table 1 indicate that these bromination reactions generally proceed in good yields.

In order to probe some selectivity issues with regard to this chemistry, vinyl chloride malonate **5** was exposed to 3.0 equiv of sodium hypochlorite under the standard conditions[10] leading to chemoselective α,α-dichlorination, with compound **6** formed as the major product (Scheme 2). In addition, small amounts of trichloro acetate **7** and α-chloroketone **8** were produced. On the other hand, with the 2-substituted malonate vinyl chloride substrate **9**, halogenation is completely chemoselective for the vinyl chloride functionality, producing α-chloroketone **10** as the major product. In addition, acetate **11** is also produced (an inseparable mixture of diastereomers) along with a small amount of starting material. This result is not surprising based on our observation that 2-substituted malonates are resistant to chlorination under these conditions (vide supra). Interestingly, in the case of the β-ketoester vinyl chloride **12**, chlorination again proved to be highly selective for the vinyl chloride moiety, leading to α-chloroketone **13** as the major product. In addition, a very small amount of the α-chloroketone product **14** resulting from halogenation of the β-ketoester moiety of **12** was formed in this system.

Finally, we have briefly investigated the chlorination of oxindole (**15**) with this reagent.[11,12] Treatment of **15** with 4.5 equiv of sodium hypochlorite under the usual conditions[10] (2.5 h reaction time) led to the formation of a mixture of trichlorinated compound **16** along with tetrachlorooxindole **17** as the primary product (Scheme 3). However, with 6.0 equiv of sodium hypochlorite, only tetrachloro product **17** was formed in high yield. The structure of compound **17** was confirmed by X-ray crystallography.[13]



Scheme 2.



Scheme 3.

In conclusion, we have described a mild, convenient and inexpensive method for the bromination and chlorination of a variety of 1,3-dicarbonyl compounds. These reactions occur rapidly at 0 °C and provide the halogenated products in high yields. Although a plethora of reagents and reaction conditions have been reported for halogenation of dicarbonyl compounds, many involve the use of a base to initially deprotonate the substrate.[1] The procedure outlined here allows one to effect this transformation under mild acidic conditions, and should provide a good alternative to existing methodology.

Acknowledgements

We are grateful to the National Institutes of Health (GM-32299) for financial support of this research.

References and notes

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10. General procedure for halogenation of 1,3-dicarbonyl compounds: To a solution of the 1,3-dicarbonyl compound (1.20 mmol) in acetone (5 mL) and glacial acetic acid (2 mL) cooled to 0 °C was added dropwise sodium hypochlorite solution (0.83 mL, 1.80 mmol, 1.21 g/mL, 10–13% v/v, Aldrich). The mixture was stirred for 1 h at 0 °C, then poured into saturated Na_2CO_3 solution and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 10:1) to afford the monochlorinated product. Dichlorination was effected using the same procedure with 3.60 mmol of sodium hypochlorite.
Brominations were conducted as described above using freshly prepared sodium hypobromite solution. A solution of sodium hypobromite was prepared by slowly adding bromine (0.85 mL, 16.6 mmol) to a solution of sodium hydroxide (2.0 g, 50.0 mmol) in water (25 mL) at 0 °C. The mixture was stirred for 15 min and used immediately.
Spectral data for new compounds—**6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 4.31 (q, J = 7.1 Hz, 2H), 4.78 (s, 2H), 5.42 (d, J = 2.0 Hz, 1H), 5.50 (d, J = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 162.5, 134.2, 117.0, 69.4, 65.3, 65.1, 14.1. **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H), 2.08 (s, 3H), 3.90 (d, J = 12.1 Hz, 1H), 4.34 (m, 3H), 4.74 (d, J = 2.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 164.3, 163.6, 96.4, 79.2, 69.5, 67.0, 47.5, 23.5, 15.7. **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 4.12 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 5.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 162.8, 162.7, 69.3, 65.5, 45.9, 30.1, 14.1. **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3H), 1.40 (d, J = 7.3 Hz, 3H), 3.51 (q, J = 7.3 Hz, 1H), 4.15 (m, 4H), 4.95 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 168.5, 168.4, 66.0, 60.8, 44.8, 44.7, 13.0, 12.6. **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3H), 1.39 (d, J = 7.3 Hz, 3H), 2.08 (s, 3H), 3.44 (q, J = 7.3 Hz, 1H), 3.91 (d, J = 2.0 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.39 (d, J = 2.0 Hz, 1H), 4.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.1, 167.7, 95.5, 65.8, 62.1, 46.4, 46.0, 21.9, 14.5, 13.9; ESI (+/−): $[M+Na]^+$ calcd for $C_{11}H_{16}O_6Cl_2Na$, 337.0; found 337.0. **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3H), 1.42 (d, J = 7.2 Hz, 3H), 2.90 (m, 4H), 3.57 (q, J = 7.2 Hz, 1H), 4.17 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 201.5, 170.5, 61.7, 52.9, 48.4, 35.4, 33.5, 14.3, 13.0. **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 1.79 (s, 3H), 2.82 (m, 2H), 2.97 (m, 1H), 3.18 (m, 1H), 4.09 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H); ESI (+/−): $[M+Na]^+$ calcd for $C_{10}H_{14}O_4Cl_2Na$, 291.0; found 291.0. **16**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.89 (d, J = 8.4 Hz, 1H), 7.29 (dd, J = 8.4, 2.1 Hz, 1H), 7.54 (d, J = 2.1 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.2, 136.7, 132.5, 131.4, 130.2, 125.9, 112.9, 74.2; ESI (+/−): $[M+H]^+$ calcd for $C_8H_3NOCl_3$, 233.928; found 233.928. **17**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.98 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 8.4, 2.0 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 163.9, 137.9, 132.7, 131.5, 130.3, 125.6, 111.8, 72.3; ESI (+/−): $[M+H]^+$ calcd for $C_8H_4NOCl_4$, 267.890; found 267.890.
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13. We are grateful to Dr. Hemant Yennawar for this X-ray analysis. CCDC 271465 contains the supplementary crystallographic data, which can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.