Molybdenum(VI) Dichloride Dioxide Catalyzed Conversion of β-Hydroxycarbonyls into α-Bromo 1,3-Dicarbonyls by *N*-Bromosuccinimide

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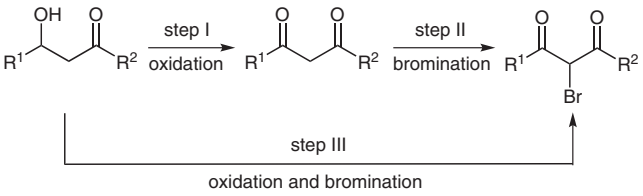
Dedicated to the 70th birthday anniversary of Prof. Gopa B. Behera

Abstract: A novel and efficient method for the one-pot transformation of β-hydroxycarbonyl compounds to α-brominated 1,3-dicarbonyl compounds is achieved with MoO_2Cl_2 in the presence of *N*-bromosuccinimide. All the reactions were carried out under mild conditions and provide good yields of the products. No bromination occurs at benzylic and allylic positions.

Key words: β-hydroxycarbonyl compounds, oxidation, bromination, molybdenum, *N*-bromosuccinimide



Scheme 1

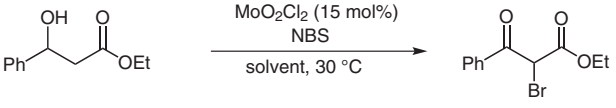
Multi-coupling reagents such as 1,3-diketones and β-keto esters possess electrophilic and nucleophilic centers and hence can be derivatized to obtain a variety of functionalized organic molecules.[1] Two major routes are available for the synthesis of 1,3-dicarbonyl compounds, namely, oxidation of β-hydroxycarbonyl compounds[2] and the reaction of enolates with acylating reagents such as esters, acid halides, and acylimidazoles.[3] Oxidation methods provide 1,3-dicarbonyl compounds in better yields as compared to acylation methods.[2] The α-brominated 1,3-dicarbonyl compounds are valuable building blocks for the synthesis of various organic molecules,[4] which are usually achieved by the bromination of 1,3-dicarbonyl compounds using various brominating reagents.[5]

Although, several methods are available for the oxidation of β-hydroxycarbonyl compounds (Scheme 1, Step **I**)[2] and bromination of 1,3-dicarbonyl compounds (Scheme 1, Step **II**),[5] to the best of our knowledge there is no report on the one pot conversion of β-hydroxycarbonyl compounds into α-brominated 1,3-dicarbonyl compounds (Scheme 1, Step **III**).

The role of MoO_2Cl_2 as a catalyst for various organic transformations has gained considerable interest during the past few years.[6] We have also developed MoO_2Cl_2 as a mild and selective catalyst for the oxidation of sulfides,[7a] aerobic oxidation of alcohols,[7b] ring-opening reactions of epoxides,[7c] and C–H insertion of ethyl diazoacetate into aldehydes.[7d] Recently, *N*-bromosuccinimide (NBS) is employed as a convenient co-oxidant for metal-catalyzed oxidation of alcohols,[8] and epoxides and aziridines.[9] *N*-Bromosuccinimide is also used as an efficient reagent for the bromination of 1,3-dicarbonyl compounds in the presence of Lewis acid.[5e] Thus, it should be possible to develop and optimize a combination of NBS and a catalyst suitable for both oxidation of alcohols and bromination of active methylene carbons. In this paper, we wish to report an application of MoO_2Cl_2 as a catalyst for the one-pot conversion of β-hydroxycarbonyl compounds into α-brominated 1,3-dicarbonyl compounds in the presence of NBS.

Initially, we studied the fate of ethyl 3-hydroxy-3-phenylpropanoate (**1**) when treated with various combinations of MoO_2Cl_2 and NBS at ca. 30 °C (Table 1). The optimum yield of ethyl 2-bromo-3-oxo-3-phenylpropanoate (**9**) was observed with 2.5 equivalents of NBS in the presence of 15 mol% MoO_2Cl_2 in dichloromethane at ca. 30 °C (Table 1, entry 3). Further, various β-hydroxycarbonyl compounds were oxidized to the corresponding α-brominated 1,3-dicarbonyl compounds and the results are summarized in Table 2.

Table 1 Oxidation of Ethyl 3-Hydroxy-3-phenylpropanoate Followed by Bromination[a]



1 **9**

Entry	Solvent	NBS (equiv)	Time (h)	Yield (%)[b]
1	MeCN	1.1	5	30
2	MeCN	2.5	5	72
3	CH_2Cl_2	2.5	5	89
4	toluene	2.5	5	50

[a] A mixture of β-hydroxy ester (1 mmol), MoO_2Cl_2 (15 mol%), and NBS (as indicated) was stirred in the solvent (10 mL) at ca. 30 °C.
[b] Isolated yield.

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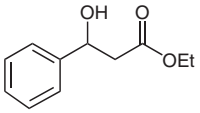
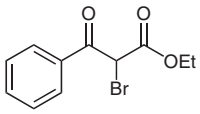
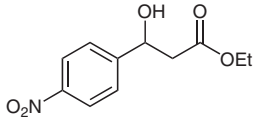
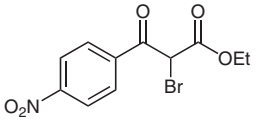
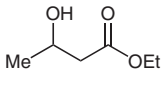
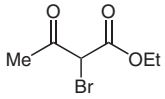
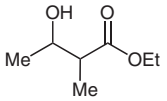
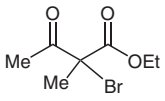
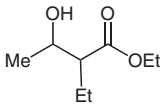
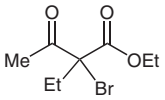
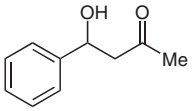
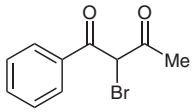
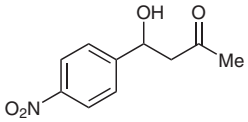
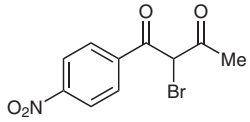
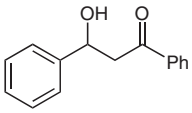
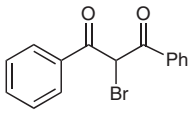
Table 2 Oxidation Followed by Bromination of β-Hydroxy Esters and Ketones[a]

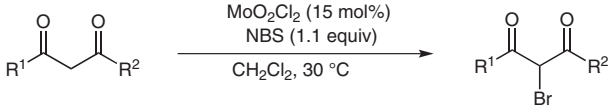
Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	**1** 	**9** 	5	89
2	**2** 	**10** 	5	73
3	**3** 	**11** 	12	49
4	**4** 	**12** 	12	63
5	**5** 	**13** 	12	65
6	**6** 	**14** 	5	81
7	**7** 	**15** 	5	70
8	**8** 	**16** 	5	78

[a] A mixture of β-hydroxy carbonyl compound (1 mmol), MoO_2Cl_2 (15 mol%), and NBS (2.5 mmol) was stirred in CH_2Cl_2 (10 mL) at ca. 30 °C.
[b] Isolated yield.

Aryl-substituted β-hydroxy esters (Table 2, entries 1 and 2) were smoothly converted into the corresponding mono-α-brominated β-keto esters in 73–89% yields at room temperature within 5 hours. However, aliphatic β-hydroxy esters took 12 hours and the corresponding mono α-brominated β-keto esters were obtained in 49–65% yields (Table 2, entries 3–5). Further, the oxidation of β-hydroxy ketones was examined under similar conditions to obtain 70–81% of corresponding mono α-brominated diketones (Table 2, entries 6–8).

We have also separately investigated the α-bromination of various 1,3-dicarbonyl compounds using 15 mol% of MoO_2Cl_2 with 1.1 equivalents of NBS in dichloromethane (Scheme 2) and the results are summarized in Table 3.

The α-unsubstituted β-keto esters were selectively monobrominated within 5 minutes to give 71–95% of yields (Table 3, entries 1–3). In the case of α-alkyl substituted β-keto esters (Table 3, entries 4 and 5) bromination was quantitative, however, within 45 minutes. Bromination of

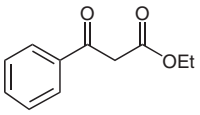
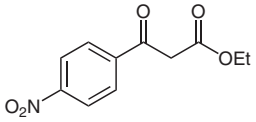
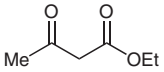
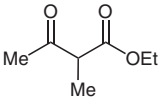
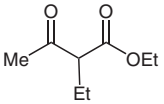
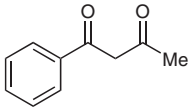
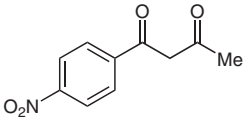
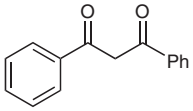


Scheme 2 Bromination of 1,3-dicarbonyl compounds using MoO_2Cl_2 and NBS

1,3-diketones were also performed where 69–91% of monobrominated diketones were obtained (Table 3, entries 6–8).

In order to determine the scope of this methodology, we have studied the bromination of benzylic and allylic substituted β-keto esters using the MoO_2Cl_2 and NBS system (Table 4). It is interesting to note that, benzylic (Table 4, entries 1–3) and allylic (Table 4, entry 4) positions were tolerated while active methylene carbons were brominated in 74–89% yields.

Table 3 Direct Bromination of 1,3-Dicarbonyl Compounds[a]

Entry	Substrate		Product	Time (min)	Yield (%)[b]
1	**17**		**9**	5	90
2	**18**		**10**	5	95
3	**19**		**11**	45	71
4	**20**		**12**	45	92
5	**21**		**13**	45	90
6	**22**		**14**	15	91
7	**23**		**15**	15	92
8	**24**		**16**	15	92

[a] A mixture of 1,3-dicarbonyl compound (1 mmol), MoO_2Cl_2 (15 mol%), and NBS (1.1 mmol) was stirred in CH_2Cl_2 (10 mL) at ca. 30 °C.
[b] Isolated yield.

In conclusion, we have developed a novel and efficient method for the one-pot transformation of β-hydroxycarbonyl compounds to α-brominated 1,3-dicarbonyl compounds. All the reactions were carried out under mild conditions with good yields. It is also interesting to note that benzylic and allylic positions are tolerant to bromination.

Alcohols, **1**–**8** were prepared using literature methods.[10] MoO_2Cl_2, NBS, and β-keto esters, **17**–**28** were purchased from Aldrich. The products were characterized by ^1H and ^{13}C NMR, IR, and melting points using Bruker 400 MHz NMR spectrometer, Jasco FT/IR 660 plus, and Toshnival-India melting point apparatus, respectively. The spectral data for products are comparable with the literature data: **9**,[5b] **11**,[5b] **12**–**13**,[11a] **14**–**16**,[5b] **29**,[11b] **30**,[5f] **31**–**32**.[5b] The product **10** is reported,[12] however, we could not find any spectral data for comparison. Thus, analytical data for **10** is provided in this work.

Oxidation of 3-Hydroxycarbonyl Compounds; General Procedure A

A mixture of 3-hydroxycarbonyl compound (1 mmol), NBS (0.443 g, 2.5 mmol) and 15 mol% MoO_2Cl_2 (0.030 g, 0.15 mmol) was stirred in CH_2Cl_2 (10 mL) at ca. 30 °C. The conversion was monitored by TLC. After completion, CH_2Cl_2 was evaporated and the crude mixture was diluted with H_2O (15 mL). The product was extracted with EtOAc (2 × 15 mL) and the combined organic extracts were dried (Na_2SO_4). The EtOAc was evaporated and the residue was purified by flash column chromatography (silica gel 60–120 mesh, EtOAc–hexane) to give the pure α-brominated 1,3-dicarbonyls **9**–**16**.

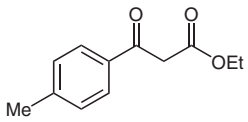
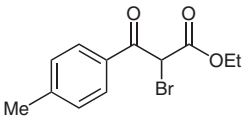
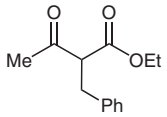
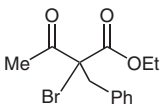
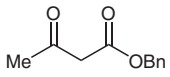
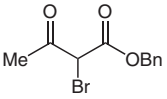
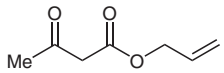
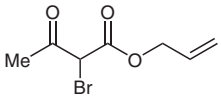
Bromination of 1,3-Dicarbonyl Compounds; General Procedure B

A mixture of 1,3-dicarbonyl compound (1 mmol), NBS (0.195 g, 1.1 mmol) and 15 mol% MoO_2Cl_2 (0.030 g, 0.15 mmol) was stirred in CH_2Cl_2 (10 mL) at ca. 30 °C. The conversion was monitored by TLC. After completion, CH_2Cl_2 was evaporated and the crude mixture was diluted with H_2O (15 mL). The product was extracted with EtOAc (2 × 15 mL) and the combined organic extracts were dried (Na_2SO_4). The EtOAc was evaporated and the residue was purified by flash column chromatography (silica gel 60–120 mesh, EtOAc–hexane) to give the pure α-brominated 1,3-dicarbonyls **9**–**16** and **29**–**32**.

Ethyl 2-Bromo-3-(4-nitrophenyl)-3-oxopropanoate (10)

Prepared by using the general procedure **A** or **B**; yield: 73%; solid; mp 85 °C.

Table 4 Regioselective Bromination of Allylic and Benzylic β-Keto Esters[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	**25** 	**29** 	10	80
2	**26** 	**30** 	30	89
3	**27** 	**31** 	15	81
4	**28** 	**32** 	10	74

[a] A mixture of β-keto ester (1 mmol), MoO_2Cl_2 (15 mol%), and NBS (1.1 mmol) was stirred in CH_2Cl_2 (10 mL) at ca. 30 °C.
[b] Isolated yield.

IR (neat): 1725 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.35 (d, *J* = 8.5 Hz, 2 H), 8.17 (d, *J* = 8.5 Hz, 2 H), 5.61 (s, 1 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 186.8, 166.4, 150.8, 137.9, 130.3, 123.9, 63.6, 46.0, 13.8.

MS (ESI): *m*/*z* = 338 and 340 ($M + Na^+$).

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