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A mild and environmentally acceptable synthetic protocol for chemoselective α-bromination of β-keto esters and 1,3-diketones☆

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This letter is dedicated to my mentor Professor K. C. Majumdar, Department of Chemistry, Kalyani University on the occasion of his 60th birthday

Abstract—A wide variety of unsubstituted β-keto esters can be brominated chemoselectively to the corresponding α-monobromo-β-keto esters by using a combination of vanadium pentoxide, hydrogen peroxide and ammonium bromide in a biphasic system, dichloromethane–water at 0–5 °C. In addition, α-mono substituted β-keto esters, cyclic β-keto-esters and 1,3-diketones can also be brominated selectively using the same protocol.

The chemoselective α-bromination of β-keto esters is an important organic transformation[1] because the resulting α-brominated products are valuable building blocks in organic synthesis.[2] The transformation is usually achieved by using either molecular bromine,[3] or Br_2/NaH,[4] or NBS/Et_3N,[5] or NBS/NaH,[6] or $CuBr_2$ with [hydroxy(tosyloxy)iodo]benzene[7] or NBS/$Mg(ClO_4)_2$.[8] Recently, other methods have also been reported employing NBS in combination with silica-supported $NaHSO_4$,[9] Amberlyst-15[10] or in ionic liquids.[11] Though all these methods provide good yields, most suffer from one or more disadvantages. From the green chemistry point of view,[12] the use of molecular bromine has several drawbacks: the reagent itself is harmful and hazardous and there are difficulties in handling and maintaining the stoichiometric ratio during the reaction. In addition, the reaction needs to be carried out under a dry and inert atmosphere and also uses expensive NaH. Moreover, NBS has also some limitations such as the requirement for dry[7] and harsh reaction conditions,[9] and NBS and the required solvents, such as an ionic liquids,[11] are expensive. Selective monobromination at the α position of β-keto esters is a challenging problem, since some of the α-monobrominated β-keto esters are unstable and readily disproportionate to dibrominated and debrominated products.[13,14] Therefore, there is scope to find an alternative methodology that would be environmentally benign and efficient.

Recently we reported the synthesis of 6,8-dibromoflavone, 8-bromoflavone, 5,7-dibromoaurone and 7-bromoaurone using V_2O_5–H_2O_2 catalyzed oxidation of ammonium bromide.[15] We also demonstrated the usefulness of the same combination in various organic transformations such as cleavage of dithioacetals,[16] hydrolysis of 1-thioglycosides[17] and deprotection of oxathioacetals.[18] Based on a knowledge of the reactivity of peroxovandate(V) complexes for the oxidation of bromide,[19] we have now developed an environmentally acceptable protocol for α-monobromination of β-keto esters and 1,3-diketones as shown in Scheme 1.

For the present study, ethyl acetoacetate was chosen as a model substrate to find optimal conditions, as shown in Table 1. We noted that a (1:1.5:0.5:19) substrate/ammonium bromide/vanadium pentoxide/hydrogen peroxide ratio, in dichloromethane/water (1:1, 2.5 mL per mmol of the substrate), provided the best results. For the same substrate, a combination of V_2O_5, NH_4Br and H_2O_2 (0.25:1.5:19) gave only a 40% conversion (calculated from the ^1H NMR spectrum) after 3.5 h with only α-monobrominated product (Table 1, entry 1). The chemical yield was 92% based on recovery of the starting material. The percent of conversion and the ratio of

Keywords: β-Keto esters; α-Bromination; Vanadium pentoxide; Hydrogen peroxide; Ammonium bromide; α-Bromo-β-keto esters.

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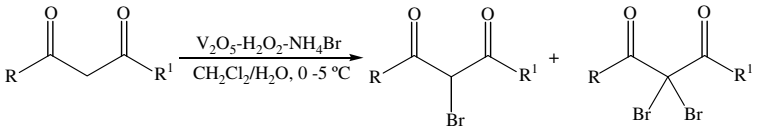


1 **2** **3**

R = Me/Ph

R^1 = OMe, OEt, OBn

Scheme 1.

Table 1. Optimization of the reaction conditions for selective α-bromination of ethyl acetoacetate

Entry	V_2O_5 (mmol)	NH_4Br (mmol)	50% H_2O_2 (mL)	Time (h)	Conversion[a] (%)	Yield[b] of product **2** (%)	Ratio of **2**:**3**[c]
1	0.25	1.5	1.3	3.5	40	92	100:0
2	0.50	1.5	1.3	3.5	92	85	10:1
3	0.50	2	1.3	2	86	84	9:1
4	0.75	6	2.1	9	100	13	1:9

[a] Quantities in the table are based on 1 mmol of ethyl acetoacetate, however, all reactions were carried out with 3.8 mmol scale of the substrate **2**.
[b] Isolated yield.
[c] Conversion and product ratio were determined using ^1H NMR.

Table 2. Selective α-bromination of β-keto esters and 1,3-diketones using $V_2O_5/NH_4Br/50\%$ H_2O_2 (0.5:1.5:19)

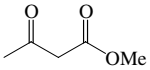
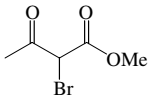
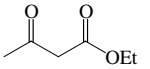
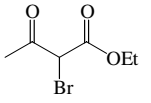
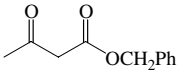
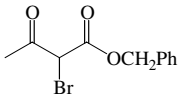
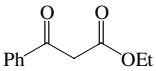
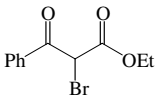
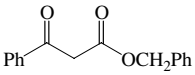
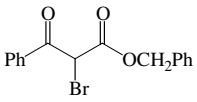
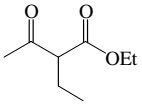
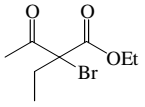
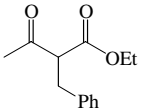
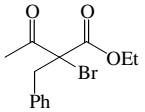
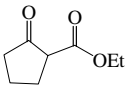
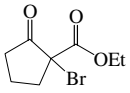
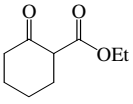
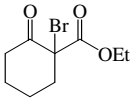
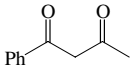
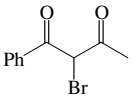
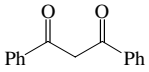
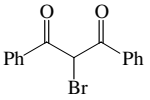
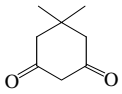
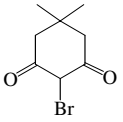
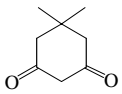
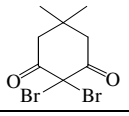
Entry	Substrate	Reaction time (h)	Product[a]	Yield[b,c] (%)
1		3.0		83[c]
2		3.5		85[c]
3		4.0		90
4		4.0		92
5		4.5		91
6		3.0		94
7		3.5		92
8		3.5		87
9		3.0		90

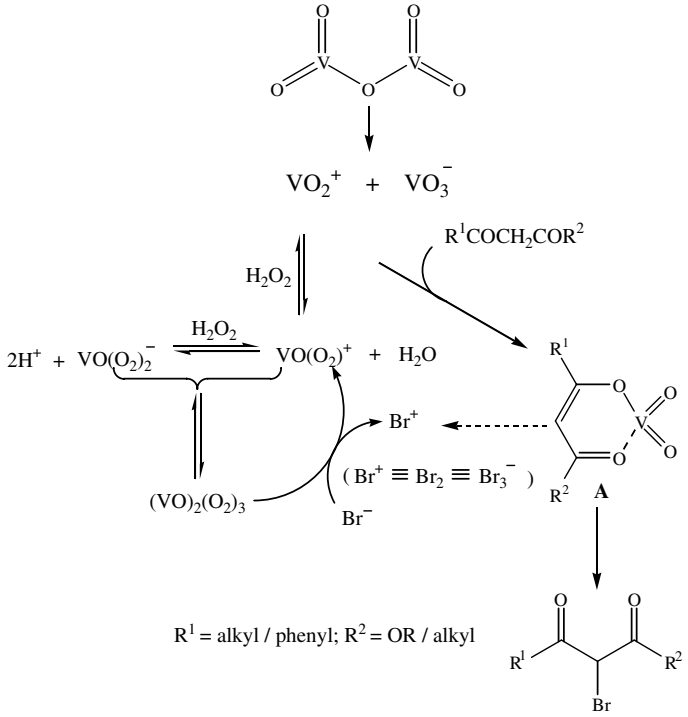
Table 2 (*continued*)

Entry	Substrate	Reaction time (h)	Product[a]	Yield[b,c] (%)
10		2.5		92
11		3.0		95
12		2.5		89
13		4.0		90

[a] Products were characterized by recording ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.
[b] Isolated yield.
[c] Yield was calculated based on starting material recovery.

mono- and dibrominated products were calculated directly from the integrations of NMR signals obtained from the crude reaction mixture. For the substrate ethyl acetoacetate, the methyl signal attached to the carbonyl group resonated at δ 2.27, whereas in the monobrominated product it appeared at δ 2.44. Next we varied the amount of V_2O_5. Using 0.5 equiv of V_2O_5 led to an increase in conversion from 40% to 92% within the same time interval (Table 1, entry 2). The chemical yield of monobrominated product was 85% and dibrominated product was less than 1%. When the amount of ammonium bromide was increased from 1.5 to 2.0 equiv, the conversion was 86% within 2 h with almost the same chemical yield (entry 3). It is clear that the reaction can be completed in shorter time if the amount of vanadium pentoxide, ammonium bromide and hydrogen peroxide are increased.

Using the typical reaction protocol,[20] methyl acetoacetate (Table 2, entry 1) also reacted smoothly to give the α-monobrominated product in 83% yield along with 7% dibrominated product based on starting



Scheme 2. A plausible mechanism for the α-bromination of β-keto esters and 1,3-diketones showing the dual role of vanadium.

material recovery. Other unsubstituted β-keto esters (entries 3–5) were exclusively α-monobrominated in good yields.

Various monoalkyl substituted β-keto esters (entries 6–9) were also brominated chemoselectively at the α-position (Table 2). Following identical reaction conditions, 1-benzoylacetone (entry 10) was smoothly converted to the corresponding α-monobrominated product in good yield. Likewise, dibenzoylmethane (entry 11) and dimedone (entry 12) were transformed chemoselectively to the corresponding α-monobrominated products, respectively, in good yields. It is important to point out that α,α-dibromodimedone can be obtained exclusively by increasing the amount of ammonium bromide from 1.5 to 3.0 equiv.

We believe that the promoter (V_2O_5) is used not only for the oxidation of ammonium bromide by H_2O_2 but also acts as a Lewis acid for chelation with the two carbonyl groups present in β-keto esters or 1,3-diketones as shown in Scheme 2. This promotes enol formation for chemoselective monobromination.

In conclusion, we have developed a general method for mild α-bromination of β-keto esters and 1,3-diketones using a combination of V_2O_5–H_2O_2–NH_4Br, avoiding the use of the conventional reagent NBS for this transformation. Additionally, all these reagents are environmentally acceptable. We suggest that vanadium pentoxide plays the dual role in: (i) formation of peroxo complexes, which oxidize bromide ion to the bromonium ions and (ii) promotion of enol formation by chelating with the two carbonyl groups of the β-keto ester or 1,3-diketone. We also note, that the ester functionality does not undergo hydrolysis under the experimental conditions. We believe our protocol will find a position in the arsenal of synthetic organic chemistry because of its high selectivity, high yields, simplicity and economic viability.

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20. General procedure: To a stirred solution of vanadium pentoxide (1.9 mmol, 345 mg) in water (5 mL) was added 50% hydrogen peroxide (5 mL, 73.5 mmol) at ice-bath temperature with stirring. The colour changed from light orange to deep red after 25–30 min. Then, ammonium bromide (5.7 mmol, 560 mg) was added and the reaction mixture was stirred for another 10 min. Subsequently, ethyl acetoacetate (495 mg, 3.8 mmol) in CH_2Cl_2 (5 mL) was added and the reaction mixture was then stirred for a further 3.0 h at the same temperature. After completion of the reaction as monitored by TLC, it was extracted with dichloromethane (25 mL × 2) and the organic layer was washed with saturated sodium metabisulfite solution to destroy unreacted molecular bromine. Finally, it was washed with water and dried over anhydrous sodium sulfate. Removal of the organic layer provided a crude residue, which was purified by short path distillation. Some of the compounds were purified through silica gel column (60–120 mesh, SRL) chromatography by eluting with a mixture of (2% ethyl acetate in hexane) to obtain the pure products.
Spectroscopic data of the α-monobrominated product of benzyl acetoacetate: IR (neat): 1747, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H, $COCH_3$), 4.79 (s, 1H, CHBr), 5.23 (s, 2H, OCH_2Ph), 7.35 (bs, 5H, ArH). Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09. Found: C, 48.52; H, 4.01. For α-monobrominated product of benzoylacetone: IR (neat): 1726, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H, $COCH_3$), 5.61 (s, 1H, CHBr), 7.48 (t, 2H, $J = 7.6$ Hz, ArH), 7.61 (t, 1H, $J = 7.6$ Hz, ArH), 7.95 (t, 2H, $J = 7.2$ Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 53.3, 127.2, 128.8, 129.2, 130.9, 133.9, 134.6, 190.0, 198.2. Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76. Found: C, 49.56; H, 3.70.