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A mild and efficient procedure for α-bromination of ketones using *N*-bromosuccinimide catalysed by ammonium acetate

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Cyclic ketones reacted with *N*-bromosuccinimide (NBS) catalysed by NH_4OAc in Et_2O at 25 °C to give the corresponding α-brominated ketones in good yields, while acyclic ketones were efficiently brominated in CCl_4 at 80 °C.

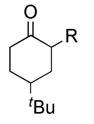
As α-bromoketones are highly useful synthetic intermediates, α-bromination of ketones is an important transformation in synthetic chemistry.[1] The most commonly used reagent for this purpose is molecular bromine in the presence of protic or Lewis acids.[2] However, the monosubstituted product is often accompanied by a small amount of the disubstituted product in the presence of an excess of the ketone.[2,3]

In terms of ease of handling and availability, *N*-bromosuccinimide (NBS) is a superior brominating reagent.[4,5] It has been reported that ketones are α-brominated by reactions with NBS initiated by azobisisobutyronitrile (AIBN) or dibenzoyl peroxide (BPO) in refluxing CCl_4.[6]

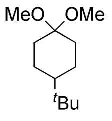
Recently, Das *et al.* reported the deprotection of aromatic acetates using NH_4OAc as a neutral catalyst, but the mechanism was not mentioned.[7] We were interested in the properties of NH_4OAc and planned to generate Br_2 and HBr by the redox reactions between NBS and NH_3, which was generated by the dissociation of NH_4OAc.

Here we report that various ketones react with NBS in the presence of the neutral catalyst, NH_4OAc, to give the corresponding α-monobrominated ketones in good yields.

First, 4-*tert*-butylcyclohexanone (**1**) was chosen as a model for bromination. Compound **1** was treated with 1.05 equiv. of NBS in the presence of 10 mol% of NH_4OAc at 25 °C in various solvents. The results are shown in Table 1. In CCl_4, the reaction completed within 0.5 h to give α-brominated product **2** in 71% yield together with the recovery of **1** (17%) (entry 1). The reactions in $CHCl_3$, CH_2Cl_2 and CH_3CN required longer reaction times and unreacted **1** remained (entries 2, 3 and 6). In Et_2O, bromination completed within 0.5 h to give **2** in 92% yield (entry 4). The reaction in THF gave **3** (60%) as well as **2** (26%) (entry 5). In MeOH, **2** (43%) and acetal **4** (57%) were yielded (entry 7). The most effective solvent was Et_2O for the bromination of **1**. Reactions in Et_2O require cooling with water in order to avoid sudden boiling of the solvent.



1: R = H
2: R = Br
3: R = O(CH₂)₄Br



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Next, we examined the bromination of various cyclic ketones and the results are summarized in Table 2. Cyclic ketones reacted with 1.05 equiv. of NBS in the presence of 10 mol% of NH_4OAc in Et_2O at 25 °C to give the corresponding α-monobrominated ketones in good yields. In all cases, the yields of dibromo derivatives were < 1%. Cyclohexanone (**5**) was transformed to 2-bromocyclohexanone (**10**) in 87% yield (entry 2). Even when 2.1 equiv. of NBS was employed, monobromoketone **10** was obtained in 78% yield together with 9% of 2,6-dibromocyclohexanone (**39**). In the case of 2-methylcyclohexanone (**6**), the more substituted position was brominated predominantly (entry 3).[2] Bromination of 3,4-dihydro-1(2*H*)-naphthalenone (**9**) led to the α-brominated ketone **15** in 99% yield (entry 6). When **9** was treated with NBS in the presence of AIBN or BPO in CCl_4 at 80 °C for 1 h, bromination occurred at the benzylic position exclusively to give 4-bromo-3,4-dihydro-1(2*H*)-naphthalenone (**40**) in quantative yield.

Table 1 The reactions of **1** with NBS catalysed by NH_4OAc

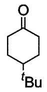
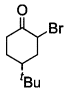
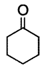
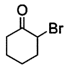
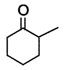
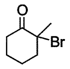
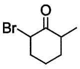
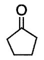
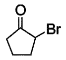
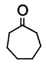
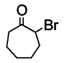
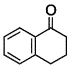
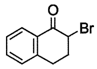
Entry	Solvent	Time/h	Yield (%)[a]
1	CCl_4	0.5	71[b]
2	$CHCl_3$	7	68[c]
3	CH_2Cl_2	56	53[d]
4	Et_2O	0.5	92
5	THF	1	26[e]
6	CH_3CN	7	75[f]
7	CH_3OH	5	43[g]

[a] Isolated yields. [b] 17% of **1** was recovered. [c] 19% of **1** was recovered. [d] 34% of **1** was recovered. [e] **3** was obtained in 60% yield. [f] 21% of **1** was recovered. [g] **4** was obtained in 57% yield.

In the cases of acyclic ketones, heating at 80 °C in CCl_4 was necessary. The results are shown in Table 3. In all cases, the reactions proceeded smoothly to give the corresponding α-brominated ketones. Bromination occurred at the more substituted positions predominantly (entries 1–3).

Table 4 shows the bromination of β-keto esters. A mild method for the bromination of β-keto esters using NBS catalysed by $Mg(ClO_4)_2$ was devised recently.[8] α-Monobromination of α-unsubstituted β-keto esters has been a challenging problem, since some compounds such as **34** and **36** were reported to be unstable and readily disproportionated to dibrominated and debrominated

Table 2 Bromination of various cyclic ketones[a]

Entry	Substrate	Time/h	Products (Yield (%))
1	 **1**	0.5	 **2** (92)
2	 **5**	0.5	 **10** (87)
3	 **6**	1.5	 **11** (93)  **12** (2)
4	 **7**	0.5	 **13** (81)
5	 **8**	0.5	 **14** (92)
6	 **9**	1.5	 **15** (99)

[a] *Reagents and conditions*: Substrate 10 mmol, NBS 10.5 mmol, NH_4OAc 1 mmol, Et_2O 10 mL, temp. 25 °C.

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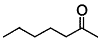
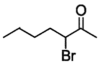
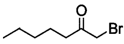
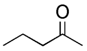
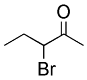
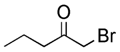
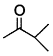
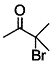
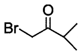
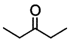
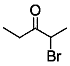
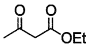
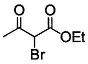
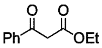
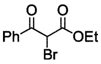
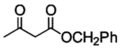
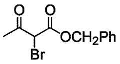
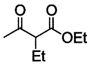
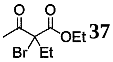
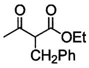
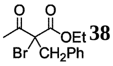
Table 3 Bromination of various acyclic ketones[a]

Entry	Substrate	Time/h	Products (Yield (%))	
1	 **16**	0.5	 **21** (74)	 **22** (16)
2	 **17**	0.5	 **23** (65)	 **24** (15)
3	 **18**	1	 **25** (70)	 **26** (10)
4	 **19**	0.5	 **27** (81)	
5	$PhCOCH_3$ **20**	3	$PhCOCH_2Br$ **28** (84)	

[a] *Reagents and conditions*: Substrate 10 mmol, NBS 10.5 mmol, NH_4OAc 1 mmol, CCl_4 10 mL, temp. 80 °C.

Table 4 Bromination of various β-keto esters[a]

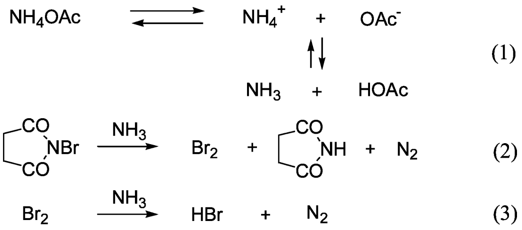
Entry	Substrate	Solvent	*T*/°C	Time/h	Products (Yield (%))
1	 **29**	Et_2O	25	1.5	 **34** (82)
2	 **30**	Et_2O	25	3	 **35** (92)
3	 **31**	Et_2O	25	3	 **36** (83)
4	 **32**	CCl_4	80	0.5	 **37** (97)
5	 **33**	CCl_4	80	1	 **38** (98)

[a] *Reagents and conditions*: Substrate 10 mmol, NBS 10.5 mmol, NH_4OAc 1 mmol, solvent 10 mL.

products.[8,9] α-Unsubstituted β-keto esters were treated with NBS catalysed by NH_4OAc in Et_2O at 25 °C to afford the corresponding α-brominating products in good yields (entries 1–3). α-Substituted β-keto esters reacted with NBS in the presence of NH_4OAc in CCl_4 at 80 °C to give the corresponding α-brominated β-keto esters (entries 4 and 5). Bromination of **33** afforded α-brominated β-keto ester **38** in 98% yield. Under Wohl–Ziegler bromination conditions (NBS, AIBN, CCl_4, 80 °C, 8 h), the generation of the desired product **38** (62%) was accompanied by ethyl 2-bromophenylmethyl-3-oxobutyrate (**41**) (18%) which was substituted at the benzylic position.

Chlorination or iodination of compound **1** using *N*-chlorosuccinimide (NCS) or *N*-iodosuccinimide (NIS) at 25 °C in CCl_4, Et_2O or CH_3CN did not occur. (**CAUTION**!: When NH_4OAc was added to a mixture of **1** and NIS in CH_3CN at 25 °C, an explosion occurred. It has been reported that explosive NI_3 is generated when I_2 is mixed with ammonia although explosive products of the present reaction are not clear.[10])

A possible mechanism for the generation of Br_2 and HBr is shown in Scheme 1. Since NH_4OAc is a salt which consists of a weak acid and a base, the behaviour of NH_4OAc in an organic solvent may be represented by the parallel equations shown in eqn. (1).[11] NH_4OAc is dissociated into NH_4^+ and OAc^-. Proton transfer from NH_4^+ to OAc^- affords NH_3 and HOAc. NBS may be reduced by NH_3 to give Br_2, succinimide and N_2 (eqn. (2)). Reduction of Br_2 by NH_3 may lead to HBr and N_2 (eqn. (3)).



Scheme 1

Supports for this mechanism may be provided by the following experiments. (i) Treatment of NBS with aqueous ammonia (25%) afforded Br_2, succinimide and N_2. The reaction of Br_2 with aqueous ammonia gave HBr and N_2.[12] (ii) When NH_4OAc was mixed with 1.0 equiv. of NBS in CCl_4 at 0 °C, the yellow Br_2–succinimide complex was precipitated with the formation of N_2 and CH_3COOH. The complex decomposed at 85–86 °C to give Br_2 and succinimide.[13] The ratio $[Br_2]/[\text{succinimide}] = 0.2$, which was determined by iodometric titration. The complex was soluble in Et_2O, CH_3CN, MeOH and H_2O to give Br_2 and succinimide, but not in CCl_4 and CH_2Cl_2. This complex can be used as a brominating agent. The reaction with cyclooctene in Et_2O at 25 °C gave 1,2-dibromocyclooctane (98%).

In conclusion, the present procedure provides a highly efficient method for α-monobromination of ketones. In addition, it is possible to carry out α-bromination of ketones without benzylic bromination.

A typical experimental procedure is as follows: to a mixture of **1** (10 mmol) and NBS (10.5 mmol) in dry Et_2O (10 mL) was added NH_4OAc (1 mmol). After stirring at 25 °C for 0.5 h, the mixture was filtered and the filtrate was washed with water, dried and evaporated. The residue was chromatographed (hexane–acetone = 10 : 1) on silica gel to give **2** (92%).

Notes and references

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12 M. Grayson, *Kirk-Othmer Concise Encyclopedia of Chemicla Technology*, John Wiley and Sons, New York, 1985 (Japanese translation,Maruzen, Tokyo, 1988, p. 98).
13 Similarly, the colourless Cl_2-succinimide complex was isolated from the reaction of NH_4OAc with NCS in CCl_4 at 15 °C The complex decomposed at 98–107 °C to give Cl_2 and succinimide. The ratio $[Cl_2]/[\text{succinimide}] = 0.2$. The complex was soluble in MeOH and H_2O to give Cl_2 and succinimide, but not in less polar solvents (CCl_4, CH_2Cl_2, $CHCl_3$, Et_2O and CH_3CN). The reaction with cyclooctene in MeOH at 25 °C gave 1-chloro-2-methoxycyclooctane (77%). The fact that chlorination of ketones using NCS and NH_4OAc did not proceed might be attributed to the high stability of the complex.