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A simple and efficient method for α-bromination of carbonyl compounds using *N*-bromosuccinimide in the presence of silica-supported sodium hydrogen sulfate as a heterogeneous catalyst☆

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Abstract—α-Bromination of carbonyl compounds (cyclic and acyclic ketones, amides and β-ketoesters) has been achieved efficiently by treatment with *N*-bromosuccinimide (NBS) and catalyzed by silica-supported sodium hydrogen sulfate ($NaHSO_4{\cdot}SiO_2$). The products were formed in high yields under mild reaction conditions and in short reaction times.

α-Bromination of carbonyl compounds is an important transformation in organic synthesis as the α-brominated products are useful synthetic intermediates.[1] Bromine in the presence of protic and Lewis acids is generally used to achieve this transformation.[2] *N*-Bromosuccinimide (NBS), which is a superior brominating agent in terms of availability and in terms of ease of handling is now being used increasingly for α-bromination of carbonyl compounds.[3] However, the catalysts and any accompanying reagent used with NBS should also be easily available, mild and make the procedure simple and efficient. Previously, NBS has been utilized for α-bromination of carbonyl compounds using a radical initiator [such as, azobisisobutyronitrile (AIBN) or dibenzoyl peroxide (BPO)][4], or in strongly basic media[3a–d] or in the presence of $Mg(ClO_4)_2$[3e] or NH_4OAc.[3f] α-Hydroxylation of carbonyls has recently been carried out using iodine under basic conditions.[5] In continuation of our work[6] on the applications of heterogeneous catalysts in organic synthesis we have found that silica-supported sodium hydrogen sulfate is an efficient catalyst for α-bromination of carbonyl compounds using NBS (Scheme 1).

Scheme 1.

Several ketones (cyclic and acyclic) were treated with NBS in the presence of $NaHSO_4{\cdot}SiO_2$ in ether or CCl_4 to obtain the corresponding α-monobrominated products (Table 1). Cyclic ketones were converted at room temperature while acyclic ketones at 80 °C. The products were obtained in high yields. For an α-monosubstituted cyclic ketone (entry c), monobromination occurred at both the α-positions, though mainly at the substituted position. An unsymmetrical acyclic ketone also afforded two products derived from monobromination at the two α-positions (entry g).

The present method was also found to be applicable for α-bromination of lactams. Earlier studies on such conversion using NBS are limited.[3] $Mg(ClO_4)_2$ combined with NBS was previously used for α-bromination of amides.[3e] Our procedure afforded α-monobromolactams in good to excellent yields.

The preparation of α-monobromo products of α-unsubstituted β-ketoesters is difficult as such bromo compounds are unstable and undergo disproportionation to dibrominated and debrominated products. In the

Keywords: Carbonyl compounds; α-Bromination; NBS; $NaHSO_4{\cdot}SiO_2$; Heterogeneous catalyst.

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Table 1. α-Bromination of carbonyl compounds[a]

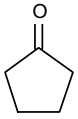
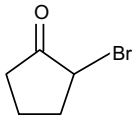
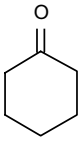
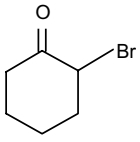
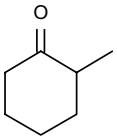
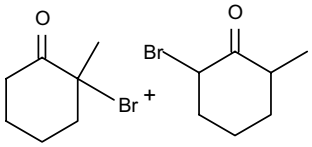
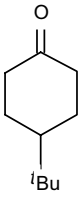
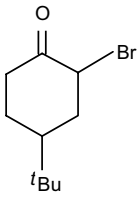
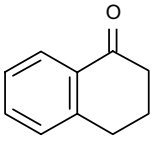
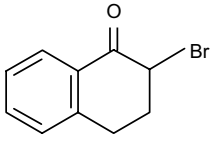
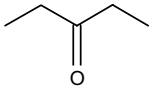
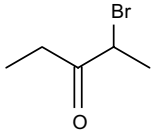
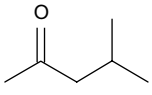
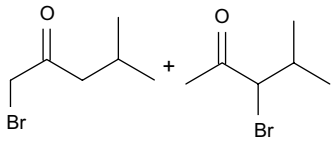
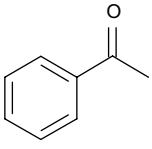
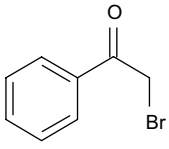
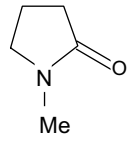
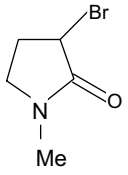
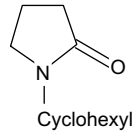
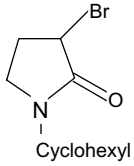
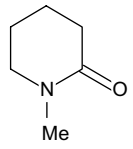
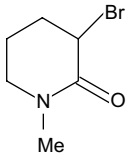
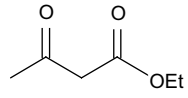
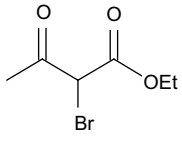
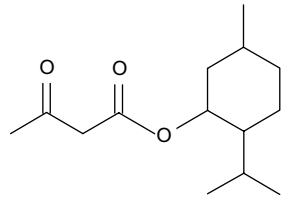
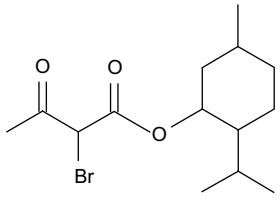
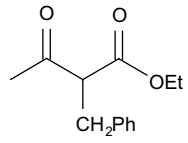
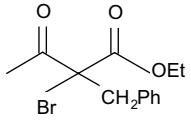
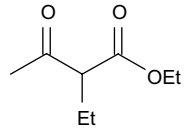
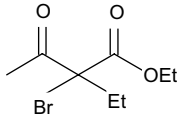
Entry	Substrate	Product	Time (h)	Isolated yield (%)
a		 **2a**	1.5	91
b		 **2b**	0.5	93
c		 **2c$_1$** **2c$_2$**	1.5	91 and 4, respectively
d		 **2d**	0.5	90
e		 **2e**	1.0	97
f		 **2f**	1.0	80
g		 **2g$_1$** **2g$_2$**	1.5	61 and 19, respectively
h		 **2h**	2.5	87

Table 1 (*continued*)

Entry	Substrate	Product	Time (h)	Isolated yield (%)
i		 **2i**	3.0	95
j		 **2j**	3.0	84
k		 **2k**	3.0	62
l		 **2l**	2.0	68
m		 **2m**	1.0	72
n		 **2n**	2.5	95
o		 **2o**	2.0	95

[a] The structures of the products were determined from their spectroscopic (IR, ^{1}H and ^{13}C NMR and MS) and elemental analyses data.

present study, treatment of α-unsubstituted β-ketoesters with NBS in the presence of $NaHSO_4{\cdot}SiO_2$ at room temperature produced the corresponding α-monobromo products in good yields (entries l, m). α,α-Dibromo compounds were formed as minor products only. However, α-monosubstituted β-ketoesters afforded the α-brominated products in excellent yields (entries n, o).

The catalyst, $NaHSO_4{\cdot}SiO_2$ can be easily prepared[7] from the readily available reagents, $NaHSO_4$ and silica

gel (finer than 200 mesh). It works under heterogeneous conditions and can easily be handled and removed from the reaction mixture. The experimental procedure is simple and structures of all the products were determined from their spectroscopic (IR, ^1H and ^{13}C NMR and MS) and elemental analyses data.[8]

In conclusion, we have developed a mild and efficient method for α-monobromination of carbonyl compounds (cyclic and acyclic ketones, amides and β-ketoesters) by treatment with NBS and catalyzed by $NaHSO_4{\cdot}SiO_2$. The simple experimental procedure, high yields of the monobrominated products, application of a heterogeneous catalyst and short reaction times are advantages of the present procedure.

Acknowledgements

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7. Breton, G. W. *J. Org. Chem.* **1997**, *62*, 8952–8954.
8. Typical experimental procedure: To a mixture of a carbonyl compound (1 mmol) and NBS (1.2 mmol) in Et_2O or CCl_4 (5 mL), $NaHSO_4{\cdot}SiO_2$ (100 mg) was added. The mixture was stirred at room temperature (for a cyclic ketone or a β-ketoester) or heated at 80 °C (for an acyclic ketone or a lactam). After completion of the reaction (as indicated by TLC) the mixture was filtered, the filtrate was concentrated and the residue was purified by column chromatography over silica gel using hexane–EtOAc (10:1) as eluent to obtain the pure α-brominated carbonyl compound. The spectral data of some representative compounds are given below.
Compound **2b**: IR (neat): 1717, 1450, 1339, 1176 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.34 (1H, dd, J = 8.0, 2.0 Hz), 2.96 (1H, m), 2.33–2.19 (3H, m), 2.08–1.95 (2H, m), 1.83–1.65 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 203.2, 53.5, 38.2, 37.1, 26.6, 22.4; EIMS: *m/z* 178, 176 ($M^{+\cdot}$). Anal. Calcd for C_6H_9BrO: C, 40.68; H, 5.08%. Found: C, 40.72; H, 5.02%.
Compound **2e**: IR (neat): 1685, 1583, 1462, 1374 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.22 (1H, dd, J = 8.0, 2.0 Hz), 7.62–7.54 (3H, m), 4.06 (1H, t, J = 6.0 Hz), 2.36–2.34 (1H, m), 2.31–2.29 (1H, m), 2.28–2.24 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.2, 136.0, 135.7, 130.2, 129.8, 128.2, 128.1, 50.2, 34.1, 28.4; EIMS: *m/z* 226, 224 ($M^{+\cdot}$). Anal. Calcd for $C_{10}H_9BrO$: C, 53.33; H, 4.00%. Found: C, 53.42; H, 4.04%.
Compound **2g$_1$**: IR (neat): 1710, 1462, 1376, 1183 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.76 (2H, s), 2.54 (2H, d, J = 7.0 Hz), 1.79 (1H, m), 0.94 (6H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 201.5, 54.1, 36.4, 24.1, 21.4; EIMS: *m/z* 180, 178 ($M^{+\cdot}$). Anal. Calcd for $C_6H_{11}BrO$: C, 40.22; H, 6.15%. Found: C, 40.17; H, 6.18%.
Compound **2g$_2$**: IR (neat): 1712, 1460, 1385, 1205 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.97 (1H, d, J = 7.0 Hz), 2.37 (3H, s), 1.61 (1H, m), 0.91 (6H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 201.7, 58.7, 28.7, 28.4, 21.2, 19.0; EIMS: *m/z* 180, 178 ($M^{+\cdot}$). Anal. Calcd for $C_6H_{11}BrO$: C, 40.22, H, 6.15%. Found: C, 40.26, H, 6.12%.
Compound **2l**: IR (neat): 1718, 1462, 1227 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.67 (1H, s), 4.28 (2H, q, J = 7.0 Hz), 2.43 (3H, s), 1.32 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.6, 167.3, 61.8, 54.6, 27.1, 14.2; EIMS: *m/z* 210, 208 ($M^{+\cdot}$). Anal. Calcd for $C_6H_9BrO_3$: C, 34.45; H, 4.31%. Found: C, 34.50; H, 4.27%.
Compound **2n**: IR: 1726, 1460, 1360, 1244 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.29–7.18 (5H, m), 4.27 (2H, q, J = 7.0 Hz), 3.62 (1H, d, J = 12.0 Hz), 3.48 (1H, d, J = 12.0 Hz), 2.32 (3H, s), 1.22 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.8, 168.2, 136.1, 130.2, 128.2, 127.5, 62.0, 54.8, 42.2, 27.1, 14.2; EIMS: *m/z* 300, 298 ($M^{+\cdot}$); Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.17; H, 5.02%. Found: C, 52.24; H, 5.11%.