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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 4707–4710

Directed regioselectivity of bromination of ketones with NBS: solvent-free conditions versus water

Igor Pravst,[a] Marko Zupan[a,b] and Stojan Stavber[b,*]

[a]*Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia*
[b]*Laboratory for Organic and Bioorganic Chemistry, 'Jozef Stefan' Institute, Jamova 39, 1000 Ljubljana, Slovenia*

Received 15 February 2006; revised 19 April 2006; accepted 26 April 2006
Available online 22 May 2006

Abstract—The reaction conditions employed directed the site of functionalisation of ketones with NBS: under solvent-free conditions α-bromination was the exclusive process, while in water, ring functionalisation occurred in the case of methoxy substituted aromatic ketones.

Demands for sustainable and ecologically friendly organic syntheses have led to investigations of the conditions involved in reactions.[1] Among these conditions, solvent-free strategies[2] and the use of water[3] as the reaction medium represent important alternatives. Very recently, Sharpless and co-workers[4] reported an important observation that some organic molecules can react on the surface of water, and in some cases very strong enhancement in the reaction rate was noticed in comparison to reactions without solvent. On the other hand, Mayr and co-workers[5] reported an important modulation of the reactivity of organic molecules by water, enabling alkylation of aromatic molecules with benzyl halides without the use of Friedel–Craft catalysts, while water could also be used as a heat exchanger in exothermic reactions.[6] Halogenations have not been extensively studied under solvent-free conditions,[2a] while recently the important role of solvent vapour[7] in the efficiency of bromination in comparison to solvent-free conditions[8] has been reported. It has been demonstrated that the reactivity of NBS (*N*-bromosuccinimide) could be modulated with various catalysts, including the BF_3/H_2O couple and ammonium acetate.[9] Some new catalysts were reported recently for the bromination of ketones with NBS in organic solvents,[10] but to our knowledge these reactions in water or under solvent-free conditions have not been reported so far.

Aryl substituted ketones have been shown to be very sensitive model compounds in electrophilic functionalisation, and the site of their fluoro[11] and iodo[12] functionalisation could be selectively modulated by the solvent.

In continuation of our interest in organohalogen chemistry, we now report an investigation of the reactions of ketones with NBS under green reaction conditions: in water and under solvent-free conditions. It is known that NBS reacts with various aromatic compounds under solvent-free conditions;[13] however, an equimolar mixture of 5-methoxy-indanone (**1a**) and NBS when stirred in a mortar at room temperature remained unchanged after 5 h, while heating at 80 °C for 2 h gave a complex reaction mixture containing up to 24% of 2-bromo-5-methoxy-indanone (**2a**). Careful analysis showed that at this temperature the reaction mixture remains in the solid state (mp **1a**: 108 °C, mp NBS: 175–180 °C). In the next experiment we added 10 mol % of *p*-toluenesulfonic acid (PTSA) as catalyst, but unfortunately the reaction mixture remained unchanged after 5 h at room temperature, while a complex mixture containing up to 48% of **2a** was observed when the reaction mixture in the solid state was heated for 5 h at 40 °C. At 60 °C, the reaction mixture started to melt and after 10 min a substantial amount of **2a** (89%) was formed, while an almost quantitative conversion (Table 1) was achieved after 1 h at 80 °C. A similar high yield side chain bromination under these reaction conditions was also achieved in the case of 6-methoxytetralone (**1b**).

Keywords: Ketones; Bromination; NBS; Neat; Solvent-free; Water; Regioselectivity.
* Corresponding author. Tel.: + 386 1477 3660; fax: 386 1423 5400; e-mail: stojan.stavber@ijs.si

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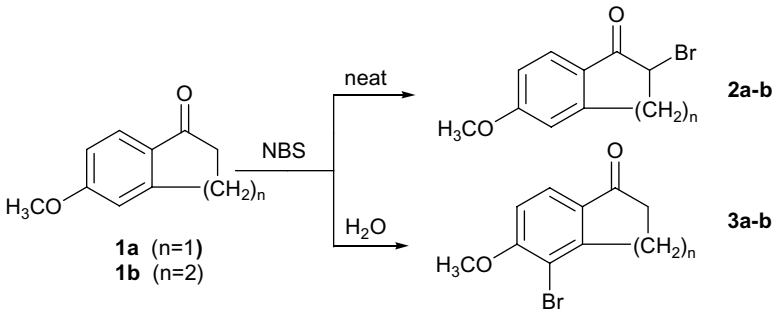
doi:10.1016/j.tetlet.2006.04.119

Table 1. Effect of reaction conditions[a] on the regioselectivity of bromination



Substrate	Solvent	Catalyst	Temperature (°C)	Time (min)	Product[b] (%)
1a ($n = 1$)	Neat	/	20	300	/
	Neat	PTSA	20	300	/
	Neat	PTSA	60	10	**2a** (89)
	Neat	PTSA	80	60	**2a** (97)
	H_2O		20	300	**3a** (60)
	H_2O	/	60	300	**3a** (78)
	H_2O	H_2SO_4	60	300	**3a** (87)
1b ($n = 2$)	Neat	PTSA	60	10	**2b** (97)
	H_2O	H_2SO_4	60	300	**3b** (81)

[a] Reaction conditions: ketone (1 mmol), NBS (1 mmol); *p*-toluenesulfonic acid (PTSA, 0.10 mmol) or H_2SO_4 (2 mmol) were used where noted.
[b] Conversion determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

We further studied the effect of water as solvent on the bromination of benzocycloalkanones **1** and found that in the case of **1a** the regioselectivity changed completely. In the reaction of **1a** with NBS in water, 4-bromo-5-methoxy-indanone (**3a**) was formed after 5 h at room temperature with 60% conversion. At 60 °C, 78% conversion was observed, but an even higher conversion was achieved in the presence of sulfuric acid as catalyst (Table 1). A similar regioselectivity was observed in the case of bromination of derivative **1b** in water.

The important role of the reaction conditions observed on the regioselectivity of this functionalisation of ketones stimulated us to investigate reactions with liquid ketones. A solvent-free mixture of acetophenone (**4**) and NBS at room temperature after 24 h gave only 19% of 2-bromo-1-phenyl-ethanone (**5**), while a catalytic amount of PTSA (2 mol %) sharply increased the degree of bromination and an 85% conversion of **4** was achieved after 3 h at room temperature, while in the presence of 10 mol % of PTSA, an almost quantitative conversion to **5** (Table 2) was achieved after 3 h.

Contrary to the above observed results, water almost completely stopped the bromination of **4** and even after 24 h at 60 °C, only 15% conversion was observed. A similar result was achieved after 4 h with 10 mol % of PTSA, while sulfuric acid proved to be a more convenient catalyst leading to an 80% conversion. Finally, we examined more ecologically friendly catalysts and found that the polymer supported analogue (DOWEX) or iodine gave comparable results (Table 2). Additionally, we studied the effect of other solvents on the bromination of **4** and found that in methanol or acetonitrile an almost quantitative conversion to **5** could be obtained in the presence of 10 mol % of PTSA.[14]

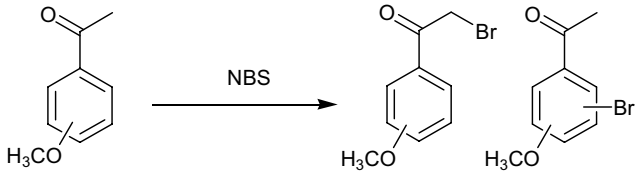
Table 2. Effect of the reaction conditions on the functionalisation of acetophenone (**4**) with NBS to give 2-bromo-1-phenyl-ethanone (**5**)[a]

Solvent	mol % of Catalyst	Temperature (°C)	Time (min)	Conversion[b] (%)
Neat	/	20	1440	19
Neat	2% PTSA	20	180	85
Neat	5% PTSA	20	180	93
Neat	10% PTSA	20	180	>95
H_2O	/	60	1440	15
H_2O	10% PTSA	60	240	15
H_2O	$2H_2SO_4$	60	240	80
H_2O	50% DOWEX	60	240	70
H_2O	10% I_2	60	240	72

[a] Reaction conditions: ketone (1 mmol), NBS (1 mmol); catalyst was used where noted.
[b] Conversion determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

The role of the reaction conditions and substrate aggregate state in the reactivity and regioselectivity stimulated us to study the bromination with two solid (**6a**, **6d**) and two liquid (**6b**, **6c**) methoxy substituted acetophenones (Table 3). All the isomeric acetophenones (**6a**–**c**) responded to the reaction conditions similarly, as in the case of **1**, and high yields of side chain bromination products were obtained under solvent-free conditions, while ring bromination occurred in water in the presence of PTSA or sulfuric acid (Table 3). However, the regioselectivity changed when an additional methoxy group was present on the aromatic ring (**6d**, solid); ring bromination also took place in the absence of a solvent. It

Table 3. Effect of the reaction conditions on the regioselectivity of the bromination of methoxy substituted acetophenones[a]



6	Solvent	Temperature (°C)	Time (min)	7 (%)	8[b] (%)
6a	Neat	20	120	73	
(4-Methoxy)	H_2O	60	300		72
6b	Neat	20	120	85	
(3-Methoxy)	H_2O	60	300		94
6c	Neat	20	120	91	
(2-Methoxy)	H_2O	60	300		95
6d	Neat	20	120		93
(2,4-Dimethoxy)	H_2O	60	60		97

[a] Reaction conditions: ketone (1 mmol), NBS (1 mmol); yield determined by ^{1}H NMR spectroscopy with 1,4-di-*tert*-butyl-benzene as an internal standard.
[b] Isomers: **8a**: 3-bromo; **8b**: 6-bromo, **8c** and **8d**: 5-bromo.

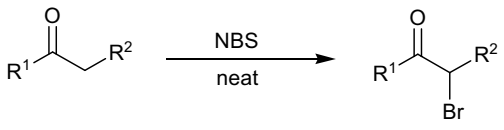
is also interesting to note the effect of water on the regioselectivity of ring bromination, since only one brominated isomer was formed; 3-bromo (**8b**), 5-bromo (**8c**) or 5-bromo (**8d**) substituted methoxy acetophenones in the bromination of the 3-methoxy (**6b**), 2-methoxy (**6c**) and 2,4-dimethoxy (**6d**) derivatives, respectively.

Finally, we evaluated the solvent-free bromination method on various structural types of ketones, 1,3-diketones and β-keto esters. In all cases good to excellent results were observed (Table 4). Bromination of 1,3-diketone **9c** and β-keto ester **9d** occurred at room temperature in the absence of a catalyst, while the bromination of solid ketones **9b** and **9f** initially required heating to achieve melting (~80 °C) and then transformation was completed in 10 min.

Under solvent-free conditions, we also effectively brominated various cycloalkanones to give their α-bromo derivatives (Table 5). Finally, we studied the possibility of further bromination under solvent-free conditions and established that 1-indanone (**15a**) could be successfully converted to 2,2-dibromo-indanone (yield 99%) after 1 h at 80 °C, when 2 mmol of NBS and 10 mol % PTSA were used. A similar reaction with an excess of NBS was performed on 5-methoxyindanone (**1a**), and also in this case only the side chain dibromo derivative was formed in 98% yield.

Typical procedures: *Bromination in water*: To a suspension of ketone **1a** (1 mmol) in water (10 mL), *N*-bromosuccinimide (NBS, 1 mmol) was added and the reaction mixture heated to 60 °C while stirring. H_2SO_4 (40% aq solution, 2 mmol) was then added and stirring continued for 5 h. The crude product isolated from the reaction mixture using *tert*-butyl methyl ether/water extraction contained **3a** (72%), which was additionally purified by crystallisation from ethanol to give pure **3a**, mp 120 °C (Found: C, 49.85; H, 3.91. $C_{10}H_9BrO_2$ requires C, 49.82; H, 3.76), IR ν_{max}(KBr)/cm^{-1} 3051, 2934, 1724, 1591, 1327, 1277, 1250, 1111, 1057, 806, 584; ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 2.69–2.73 (m, 2H, CH_2), 3.02–3.07 (m, 2H, CH_2), 4.00 (s, 3H, CH_3O), 6.94 (d, $J = 8.4$ Hz, 1H, ArH) 7.69 (d, $J = 8.4$ Hz, 1H, ArH); ^{13}C NMR (76 MHz; $CDCl_3$) δ_C 27.1 (CH_2), 36.3 (CH_2), 56.8 (CH_3O), 110.0 (ArC), 11.2 (ArCH), 124.0 (ArCH), 131.8 (ArC), 156.9 (ArC), 160.9 (ArC), 204.8 (CO); MS (EI, 70 eV) *m*/*z* 239.97902 (100%, M^+. $C_{10}H_9BrO_2$ requires 239.97859). *Neat bromination:* Ketone **1a** (1 mmol), *N*-bromosuccinimide (NBS, 1 mmol) and *p*-toluenesulfonic acid (PTSA, 0.1 mmol) were ground in a porcelain mortar and then heated to 60 °C for 10 min. This turned the reaction mixture into a paste. When the reaction mixture was cooled to room temperature, isolation using *tert*-butyl methyl ether/water extraction gave a crude product containing **2a** (87%), which was additionally purified by crystallisation from ethanol. *Dibromination* was achieved using a similar procedure with 2 mmol of NBS by heating at 80 °C for 1 h. The crude product contained 2,2-dibromo-5-methoxyindanone (99%), which was additionally crystallised from ethanol to give the pure compound, mp 109–110 °C (Found: C, 37.23; H, 2.66. $C_{10}H_8Br_2O_2$

Table 4. Bromination of various ketones, diketones and keto esters under solvent-free conditions[a]

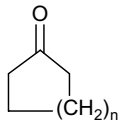
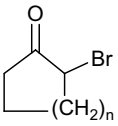
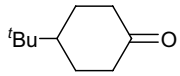
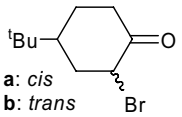
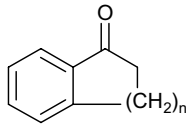
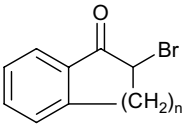


9 **10**

Substrate	R^1	R^2	Catalyst	Temperature (°C)	Time (min)	Product[b] (%)
9a	Ph	Me	PTSA	20	180	**10a** (75)
9b	Ph	Ph	PTSA	80	10	**10b** (95)
9c	Ph	COPh	/	20	180	**10c** (98)
9d	Ph	COOEt	/	20	180	**10d** (97)
9e	*n*-C_4H_9	*n*-C_3H_7	PTSA	20	180	**10e** (93)
9f	Adamantyl	H	PTSA	80	10	**10f** (80)

[a] Reaction conditions: ketone (1 mmol), NBS (1 mmol) and PTSA (0.1 mmol) when noted.
[b] Yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture with internal standard (1,4-di-*tert*-butyl-benzene for **9a**, **9b** and **9c**, *o*-xylene for **9d** and naphthalene for **9e** and **9f**).

Table 5. Solvent-free bromination[a] of cyclic ketones with NBS

Substrate		Product		Yield[b] (%)
	**11a** $n=1$ **b** $n=2$ **c** $n=3$		**12a** **b** **c**	84 93 84
	**13d**	 **a**: *cis* **b**: *trans*	**14**	83 **14a**:**14b** = 1:1
	**15a** $n=1$ **b** $n=2$		**16a** **b**	87 86

[a] Reaction conditions: ketone (1 mmol), NBS (1 mmol), PTSA (0.1 mmol), 20 °C, 2 h.
[b] Yield after column chromatography.

requires C, 37.54; H, 2.52), IR ν_{max}(KBr)/cm^{-1} 1710, 1595, 1490, 1300, 1260, 1095, 1015; ^{1}H NMR (300 MHz; $CDCl_3$) 3.93 (s, 3H, CH_3O), 4.25 (s, 2H, CH_2), 6.81–6.83 (m, 1H, ArH), 7.00 (dd, $J = 2.2$ Hz and 8.6 Hz, 1H, ArH), 7.86 (d, $J = 8.6$ Hz, 1H, ArH); ^{13}C NMR (76 MHz; $CDCl_3$) δ_C 52.3, 55.9, 57.4, 109.1 (ArCH), 117.0 (ArCH), 121.6 (ArC), 128.4 (ArCH), 150.1 (ArC), 167.0 (ArC), 191.1 (CO); MS (EI, 70 eV) m/z 317.89025 (50%, M^+. $C_{10}H_8Br_2O_2$ requires 317.88910), 239 and 241 (100%), 160 (85%), 132 (40%), 89 (45%), 69 (55%), 63 (40%).

Acknowledgements

This research was supported by the Ministry of Higher Education, Science and Technology of the Republic of Slovenia and the Young Researcher program (I.P.) of the Republic of Slovenia. We are thankful to the staff of the National NMR Centre at the National Institute of Chemistry in Ljubljana.

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