A bromine-catalysed free-radical oxidation of acetamides from primary and secondary alkylamines by H_2O_2

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Published on 26 February 2001. Downloaded by Ohio Link Offices on 01/09/2013 22:47:37.

Received (in Liverpool, UK) 7th November 2000, Accepted 8th February 2001 First published as an Advance Article on the web 26th February 2001

New procedures based on the oxidation by brominecatalysed hydrogen peroxide in a two-phase system provide simple and cheap transformations of alkylamines to carbonyl derivatives (aldehydes, ketones, carboxylic acid, imides, lactams) through the corresponding acetamides.

Classical rearrangement reactions, such as the Hofmann^{1,2} and Curtius^{1,3} rearrangements, allow the transformation of carboxylic acids to amines through the corresponding amides or acyl azides [eqn. (1)], while the Beckmann^{4,5} rearrangement involves the formation of amides from ketones through the oximes [eqn. (2)].

$$R-COOH \longrightarrow R-CO-NH_2 (R-CON_3) \longrightarrow R-NH_2 (1)$$

In this Communication we report a new simple oxidation procedure, which allows the reverse transformation of alkylamines to carboxylic acids, aldehydes, ketones and imides through the intermediates acetamides [eqn. (3)].

$$R^{1} \xrightarrow{\text{NH}_{2}} R^{2} \xrightarrow{\text{R}^{2}} R^{2} \xrightarrow{\text{CH}_{3}} R^{1} \xrightarrow{\text{CH}_{3}} R^{1} \xrightarrow{\text{COOH}, R^{1} \text{CONHCOCH}_{3}} (R^{1} = \text{alkyl}, R^{2} = H)$$

$$R^{1} \xrightarrow{\text{COOR}^{2}} (R^{1} \text{ and } R^{2} = \text{alkyl}, \text{aryl})$$

$$R^{1} \xrightarrow{\text{CHO}} (R^{1} = \text{aryl}, R^{2} = H)$$
(3)

Recently we have reported^{6,7} simple and highly selective methods for the oxidation of primary alcohols to either aldehydes or esters, depending on the benzylic or aliphatic nature of the alcohol, by bromine-catalysed H_2O_2 [eqns. (4) and (5)].

Ar-CH₂OH + H₂O₂
$$\xrightarrow{Br_2}$$
 ArCHO + 2 H₂O (4)

$$2 \text{ R-CH}_2\text{OH} + 2 \text{ H}_2\text{O}_2 \xrightarrow{\text{Br}_2} \text{RCOOCH}_2\text{R} + 4 \text{ H}_2\text{O} \qquad (5)$$

The selectivity of these reactions is determined by the relative rates of hydrogen abstraction by bromine atom from the alcohol (k_4) and from the corresponding aldehyde (k_5) . For benzylic alcohols $k_4 > k_5$ and the reaction gives high selectivity in aldehyde with complete conversion, whereas for non-benzylic alcohols $k_4 << k_5$ and the oxidation gives high selectivity in esters even at very low conversion, without formation of a significant amount of aldehydes.

Aliphatic amines, in principle, should be more reactive, both for enthalpic and polar reasons, than the corresponding alcohols towards hydrogen abstraction by Br. The acidic medium, however, deactivates the amines by protonation, which reverses the polar effect and increases the strength of the C–H bonds in

DOI: 10.1039/b008965f

the α -position. To avoid this limitation we have investigated the bromine-catalysed H_2O_2 oxidation of the corresponding acetamides.

With primary alkyl groups, the carboxylic acid was easily obtained, but when the primary alkyl group was benzylic the corresponding aldehyde was formed instead, with good selectivity at complete conversion. A free-radical chain is involved according to Scheme 1.

R-CH₂-NHCO-CH₃ + Br•
$$\frac{k_a}{-HBr}$$
 R-ĊH-NHCHO-CH₃
 $\xrightarrow{Br_2}$ R-CHBr-NHCO-CH₃ $\xrightarrow{H_2O}$ R-CHOH-NHCOCH₃
→ CH₃CONH₂ + R-CHO $\xrightarrow{Br• k'_a}$ R-ĊHO $\xrightarrow{Br_2}$ R-COOH
 \xrightarrow{HBr} R-ĊOH-NHCO-CH₃ $\xrightarrow{Br_2}$ R-CO-NHCO-CH₃
Scheme 1

Also in this case, as for alcohol oxidation, the selectivity was determined by the relative rates of hydrogen abstraction by Brfrom the amide (k_a) or from the aldehyde (k'_a). Since $k_a > k'_a$ for R = aryl, while $k_a << k'_a$ for R = alkyl, an opposite behaviour is observed in the two cases. Polar and enthalpic effects, due to the different electronic configurations of the alkyl (π -type) and acyl (σ -type) radicals,⁸ determine this different reactivity, as previously^{6,7} discussed for the oxidation of alcohols.

With secondary alkyl groups the corresponding ketones were obtained, but under the reaction conditions a partial bromination of the ketones occurs; conversion and selectivity are low with cyclohexyl derivatives, due to the particular ease of bromination of cyclohexanone, compared to acyclic ketones.⁹

By-products of the oxidation according to Scheme 1 are the imides, formed by further oxidation of α -hydroxyamides before cleavage. In any case, imides can be easily hydrolysed, so that high overall yields of carboxylic acids can be obtained by refluxing the acidic reaction mixture; under the reaction conditions (room temperature) the imides are not substantially hydrolysed, supporting the mechanism of Scheme 1 for the formation of carboxylic acids.

With cyclic amines, such as 1 and 2, the higher stability of α -hydroxyamides leads to the corresponding imides 3 and 4 with high yields and to the corresponding lactams 5 and 6 by hydrolysis [eqns. (6) and (7)].



Table 1 Oxidation of R^1R^2NCOMe (1 mmol) by H_2O_2 and Br_2 in a two-phase system (H_2O-DCE^a)

#	R ¹	R ²	Br ² /mmol	H ₂ O ₂ / mmol	Solvent ml H ₂ O–DCE	Conv. %	Reaction products (%)
1^b	<i>n</i> -C ₄ H ₉	Н	0.4	1.8	1/4	>99	Carboxylic acid (68) Imide (26)
2^b	<i>n</i> -C ₆ H ₁₃	Н	0.4	1.8	1/4	97	Carboxylic acid (72) Imide (24)
3^b	Me ₂ CH-CH ₂	Н	0.4	1.8	1/4	95	Carboxylic acid (63) Imide (25)
4^b	<i>n</i> -C ₁₂ H ₂₃	Н	0.4	1.8	1/4	98	Carboxylic acid (72) Imide (23)
5^b	n-C ₄ H ₉	n-C ₄ H ₉	0.8	3.6	1/4	98	Carboxylic acid (66) Imide (28)
6^b	n-C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	0.8	3.6	1/4	92	Carboxylic acid (61) Imide (23)
7 ^c	n-C ₄ H ₉	Н	2.2	—	4/8	>99	Carboxylic acid (48) Imide (45)
80	<i>n</i> -C ₆ H ₁₃	Н	2.2	—	4/8	>99	Carboxylic acid (47) Imide (48)
9c	<i>n</i> -C ₁₂ H ₂₃	Н	2.2	—	4/8	96	Carboxylic acid (44) Imide (43)
10 ^d	n-C ₄ H ₉	Н	HBr 4.4	H_2O_2 2.2	4/8	93	Carboxylic acid (46) Imide (44)
11 ^c	Me ₂ CH-n-C ₅ H ₁₁	Н	1.3	_	4/8	95	Ketone (70) α -Br-ketone (12)
12 ^c	(n-Bu) ₂ CH	Н	1.3	—	4/8	93	Ketone (69) α -Br-ketone (13)
13 ^c	Ph-CH-Me	Н	1.3	_	4/8	>99	Ketone (73) α -Br-ketone (13)
14 ^c	Cyclohexyl	Н	1.3	_	4/8	26	α -Br-cyclohexanone (49) α -Br-cyclohexanone (51)
15 ^c	Cyclohexyl	Н	2.2	—	4/8	35	α -Br-cyclohexanone (53)
16 ^b	(n-Bu) ₂ CH	Н	0.3 HBr	1	1/4	41	α -Br-ketone (41) Ketone (71)
17d	(<i>n</i> -Bu) ₂ CH	H 1	2.6	1.3	4/8 4/8	89 98	α -Br-ketone (12) 3 (96)
10	1	1	2.2		4/0	100	J (05)
190	2	2	2.2		4/0	100	4 (93)
20^{o}	2	2	1.2	0.8	1/1	100	4 (98)
21 ^c	PhCH ₂	Н	0.5	—	2/2	49	Aldehyde (95) Imide (5)
22 ^c	<i>p</i> -Me-C ₆ H ₄ -CH ₂	Н	1.0	_	4/4	83	Aldehyde (81) Imide (12)
23 ^b	<i>p</i> -Me-C ₆ H ₄ -CH ₂	Н	0.3	1.2	1/6	96	Aldehyde (73) Imide (4)
24 ^d	p-Me-C ₆ H ₄ -CH ₂	Н	HBr 2.4	1.2	4/4	85	Aldehyde (82) Imide (6)
25 ^b	p-Cl-C ₆ H ₄ -CH ₂	Н	0.4	0.8	0.6/3	100	Aldehyde (89) Imide (4)

^{*a*} DCE = 1,2-dichloroethane. ^{*b*} Procedure: the aqueous solution of H_2O_2 was added dropwise to the mixture of the other reagents and solvents reported in the Table, at rt and under effective stirring for 3 h. ^{*c*} Procedure: the mixture of the reagents and solvents reported in the Table 1 was effectively stirred for 3 h at rt. ^{*d*} Procedure: as in *c* but 2 mol of HBr and 1 mol H_2O_2 were used instead of 1 mol Br_2 . All the reaction products were known and characterised by comparison with authentic samples (GLC-MS and NMR); quantitative yields were determined by GLC using as internal standards *n*-C₇H₁₅COOH for carboxylic acids, *p*-MeO-C₆H₄-CHO for aromatic aldehydes, *n*-Pr-CO-Pr-*n* for ketones and *n*-C₆H₁₃CONHCOMe for imides.



The reactions, carried out in a two-phase system (H₂O– ClCH₂CH₂Cl), are initiated by ambient light and the active oxidant is Br₂, which acts in the organic phase; the formed HBr is extracted by the aqueous phase and oxidised to Br₂ by H₂O₂ making the process catalytic in Br₂. Two procedures were utilised as reported in Table 1. In both cases the overall process is catalytic in Br₂, but a higher concentration of Br₂ makes the overall process faster; an aqueous solution of HBr and H₂O₂ can be utilised instead of Br₂ in a two-phase system. Procedure a) gives better results for the synthesis of carboxylic acids because a higher concentration of Br₂ accelerates the oxidation of ahydroxyamides to imides, while procedure b) is more suitable for the synthesis of ketones, which consumes the catalytic amount of Br_2 by electrophilic bromination and inhibits the free-radical oxidation.

Notes and references

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