Cleavage of the N–O bond in substituted hydroxylamines under basic conditions

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The cleavage of the N–O bond in hydroxylamines $R^1NR–OR^2$ accompanied by oxidation of the adjacent carbon is directed by the CH acidity of R^1 and R^2 groups.

Oxidation by organic amine oxides has been effectively employed[1–3] to convert organic halides (Scheme 1) into corresponding aldehydes. In these methods, the aldehyde oxygen comes from the amine oxide used as an oxidant[1] so that, in the intermediate, the carbon atom adjacent to the oxygen atom is oxidised. Similarly, the oxidation at carbon atom in the 3-position of isoxazoles[4] and the oxidative rearrangement of isoxazol-3-ones[5] have been reported. To our knowledge, the tendencies for N–O cleavage in hydroxylamines $R^1NR–OR^2$ **1** have not been studied under basic conditions although similar N–O bond reductive cleavage can be expected *via* an intermediate carbanion.

Scheme 1

We studied the behaviour of **1** under basic conditions (Et_3N, NaOMe, NaH or LDA in THF). In a series of substrates we tried to arrange the substituents around the N–O moiety in order to favour the formation of a carbanion adjacent to oxygen or nitrogen. The results are summarised in Table 1.

We observed differences in the behaviour of mono- (**1a**), di- (**1b**) and tribenzylhydroxylamine (**1c**). While **1a** (Table 1, run 1) is apparently converted by sodium hydride to benzaldehyde (Scheme 2), and the latter is condensed with an excess of unreacted **1a** into the final product *O*-benzylbenzaldoxime, **1b** and **1c** unexpectedly do not undergo any transformations under the same conditions (runs 2 and 3). The difference may be accounted for by the lower CH acidity of methylene in **1b** and **1c**.

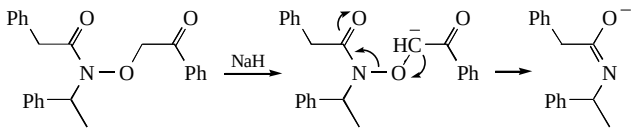
1a

Scheme 2

Benzoyloxyphthalimide **1d** does not react with weak bases such as triethylamine (Table 1, run 4) or strong bases (sodium hydride, run 5). With sodium ethoxide (run 7) or lithium diisopropylamide (run 6), ring opening takes place. Thus, the acidity of the benzylic methylene in **1b**–**d** is insufficient to provide a carbanion for further transformations though the nitrogen is involved into the electron-withdrawing phthalimide system.

N-Benzoyloxy-α-phenylethylamine **1e** benzoylated at the oxygen atom has only one possibility to form a carbanion capable of N–O cleavage. Under basic conditions, **1e** is slowly converted (Table 1, run 8) into acetophenone and acetophenone oxime (after treatment with water).

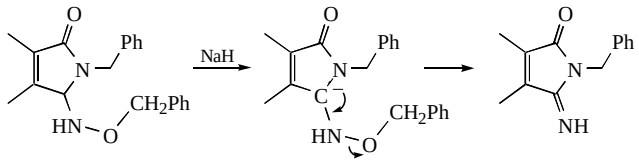
Since the introduction of a carbonyl group should increase drastically the acidity of the α-methylene adjacent to the oxygen atom, we tested the behaviour of *N*-benzoylmethoxyphthalimide **1f**. We found that **1f** can be easily converted into phthalimide with a catalytic amount of sodium hydride (Table 1, run 9); the products of benzoylmethoxy group degradation were not identified. Similarly, *N*-benzoylmethoxy-*N*-(1-phenylethyl)phenylacetamide **1g** and *N*-benzoylmethoxy-*N*-*tert*-butylphenylacetamide **1h** undergo transformations leading to the corresponding amides in high yields (runs 10 and 11). The possible base catalysed mechanism involves the formation of a methylene carbanion followed by N–O bond cleavage (Scheme 3).



1g

Scheme 3

In the last example, 1-benzyl-5-benzyloxyamino-3,4-dimethylpyrrolin-2-one **1i**, the carbon atom adjacent to the N atom of the N–O system is a member of a pyrrolin-2-one ring. Apparently, the CH acidity at this atom is enough to allow intermediate carbanion formation[6] (Scheme 4) leading quantitatively to N–O cleavage products (Table 1, run 12).



1i

Scheme 4

Thus, the cleavage of the N–O bond in **1** under basic conditions is directed by the formation of a carbanion centre adjacent to either nitrogen or oxygen atom. The structures in which a carbanion can be formed near nitrogen undergo reduction of the N–O with the release of $R_2O^–$ as a leaving group and formation of an imine. Similarly, if a carbanion is situated near oxygen, the cleavage leads to $RR^1N^–$ and an aldehyde.

References

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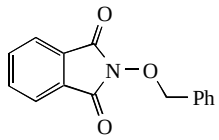
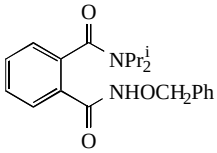
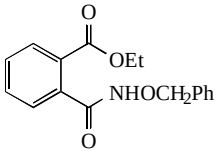
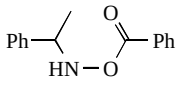
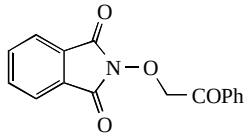
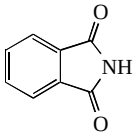
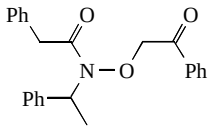
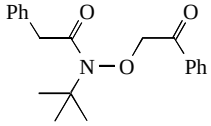
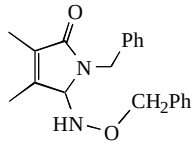
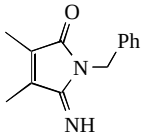
Table 1 The cleavage of **1** by bases in THF (20 °C, 0.1 M substrate solution, 2 equiv. of the base).

Run	Substrate	Base	Time/h	Product	^{1}H NMR ($CDCl_3$), δ/ppm	Yield (%)
1	$PhCH_2ONH_2$ **1a**	NaH	40	$PhCH{=}NOCH_2Ph$	5.21 (s, 2H), 7.3–7.6 (m, 10H), 8.13 (s, 1H)	70
2	$PhCH_2ONHCH_2Ph$ **1b**	NaH	60	—		—
3	$PhCH_2ONH(CH_2Ph)_2$ **1c**	NaH	60	—		—
4	 **1d**	Et_3N[a]	16	—		—
5	**1d**	NaH	96	—		—
6	**1d**	LDA	2		1.06 (d, 6H, *J* 6.1 Hz), 1.49 (d, 6H, *J* 7 Hz), 3.5 (m, 2H), 4.97 (s, 2H), 7.2–7.7 (m, 9H)	32
7	**1d**	NaOEt	48		1.35 (t, 3H, *J* 7.1 Hz), 4.32 (q, 2H, *J* 7.1 Hz), 5.07 (s, 2H), 7.2–7.5 (m, 9H), 8.63 (br. s, 1H)	20
8	 **1e**	NaH^b	72	PhCOMe		56
				PhC(Me)NOH	2.22 (s, 3H), 7.3 (m, 3H), 7.5 (m, 2H), 9.03 (s, 1H)	25
9	 **1f**	NaH^b	16			95
10	 **1g**	$NaOEt^b$	1	$PhCH_2CONHCHPhMe$	1.62 (d, 3H, *J* 7 Hz), 3.83 (d, 1H, *J* 16 Hz), 3.94 (d, 1H, *J* 16 Hz), 5.6 (br. s, 1H), 6.55 (q, 1H, *J* 7 Hz), 7.1–7.5 (m, 10H, Ph)	93
11	 **1h**	$NaOEt^b$	1	$PhCH_2CONHBu^t$	1.27 (s, 9H), 3.46 (s, 2H), 5.3 (br. s, 1H, NH), 7.2–7.4 (m, 5H)	97
12[c]	 **1i**	NaH^b	12		1.94 (s, 3H), 1.95 (s, 3H), 4.80 (s, 2H), 7.2–7.4 (m, 5H), 8.2 (br. s, 1H)	98
				$PhCH_2OH$		95

[a]88 °C. [b]10 mol%. [c]*Procedure*: to **1i** (0.200 g, 0.62 mmol) in THF (5 ml), NaH (0.004 g dispersion in oil, 0.1 mmol) was added. The mixture was stirred for 24 h, quenched with 1 M HCl, evaporated and extracted with ethyl acetate. Column chromatography (40% ethyl acetate–hexane) afforded benzyl alcohol (61 mg, 95% yield) and 1-benzyl-3,4-dimethyl-5-imino-1,5-dihydro-2*H*-pyrrol-2-one (0.130 g, 98% yield) as a solid, mp 83 °C. MS, *m*/z: 215 (M + 1). FTIR (KBr, ν/cm^{-1}): 3282 , 1710, 1640, 1446, 1072.