Sodium nitrite (NaNO$_2$) catalysed iodo-cyclisation of alkenes and alkynes using molecular oxygen

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A B S T R A C T

We have developed a convenient iodo-cyclisation reaction using NaNO$_2$ as catalyst and molecular oxygen as the terminal oxidant. The reactive species, acetyl hypoiodite (IOAc), was generated in situ from TBAI and AcOH. The iodo-cyclisation reaction with a range of alkenes and alkynes gave good to excellent yields. Iodo-amination products can also be obtained using carbamates prepared from commercially available allylic alcohols and alkynic alcohols.

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The environmental and economic benefits of using molecular oxygen for the oxidation of organic molecules are clear. This oxidant is available at almost no cost and produces no environmentally hazardous by-products.[1] Catalysts such as *N*-hydroxyphthalimide (NHPI) were developed to carry the reactive oxygen.[1a] Alkanes were successfully oxidised with NHPI/O$_2$ to valuable oxygen-containing compounds such as alcohols and ketones.

Nitrogen monoxide (NO) is a highly reactive and unstable radical and can be oxidised easily to nitrogen dioxide (NO$_2$) by molecular oxygen (O$_2$). The unique redox property of NaNO$_2$ has allowed it to be exploited as a carrier for O$_2$. The NaNO$_2$/O$_2$ system has been reported recently for the oxidation of both primary and secondary alcohols.[2–5] These conditions were used in combination with catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and molecular bromine.[2a] Alternatively, the oxidation can also be carried out under a high pressure–air atmosphere with catalytic amounts of TEMPO and 1,3-dibromo-5,5-dimethylhydantoin.[2b] A catalytic amount of [bis(acetoxy)iodo]benzene (PIDA) and TEMPO/KNO$_2$ can be used for alcohol oxidation.[3] Solid supported PIDA is also useful in this reaction. The hypervalent iodine reagent, iodoxybenzene (PhIO$_2$), was exploited for the oxidation of alcohols in water and in combination with Br$_2$/NaNO$_2$.[4] Transition metals can also be included to promote the reaction. The FeCl$_3$–TEMPO–NaNO$_2$ system has been shown to be efficient for aerobic oxidation of a broad range of alcohols.[5]

Aerobic oxidative iodination activated by NaNO$_2$ has been shown to occur effectively and selectively with full iodine atom economy using air as the oxidant.[6] The NaNO$_2$/O$_2$ system can be modulated for environmental problems. For example, it can be used to efficiently oxidise persistent pollutants such as trichlorophenol into CO$_2$, CO and biodegradable organic products with high conversion rate. This system has displayed considerable promise for practical application in industry.[7]

A number of methods have been reported for the construction of lactones from olefinic carboxylic acids through halolactonisation.[8] We reported a new method for iodolactonisation based on diacetyloxyiodate(I). This hypervalent iodine reagent was generated in situ with tetra-*n*-butylammonium iodide (TBAI) and PIDA. PIDA, in turn, was generated in situ using a catalytic amount of iodobenzene with sodium perborate as the stoichiometric oxidant.[9] We are keen to develop a more efficient method for this iodolactonisation and in this Letter, we report the use of the NaNO$_2$/O$_2$ system for the cyclisation of alkenes and alkynes.

The iodolactonisation reaction of 2,2-dimethylpent-4-enoic acid **1a** was catalysed with NaNO$_2$ (20 mol %), TBAI (1.1 equiv) and acetic acid (1 equiv). Molecular oxygen was supplied through a balloon. Only a small amount of lactone **2a** (31%) was isolated (Table 1, entry 3). Acetic acid played an important role in this reaction. With only 0.5 equiv of acetic acid, the yield of **2a** was a disappointing 21% (entry 2) and no reaction was observed in the absence of acetic acid (entry 1). When 5 equiv of acetic acid were employed, the reaction was complete within 13 h in excellent yield. If oxygen was bubbled directly into the solvent, the reaction was complete within 7 h and the isolated yield was improved to 92% (entry 5). When 1% water (v/v) was added in CH$_2$Cl$_2$, only a 54% yield of **2a** was obtained after 36 h. The yield of the reaction was not affected when the amount of NaNO$_2$ was reduced to 10 mol % (entry 6). However, the efficiency of the reaction was greatly reduced when the catalyst loading was reduced to 5 or 2 mol % (entries 7 and 8). No reaction was observed in the absence of the catalyst. This reaction gives better yields and is complete within a shorter time compared to the more classical reaction conditions using I$_2$–Na$_2$CO$_3$–KI (64% yield after 25 h).[8h]

A series of δ-pentenoic acids **1b–g** (Fig. 1) were subjected to the optimised conditions for iodolactonisation using 10 mol % of NaNO$_2$ and 5 equiv of acetic acid (Table 2, entries 1–6). The

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Table 1
Iodolactonisation of 2,2-dimethylpent-4-enoic acid **1a**
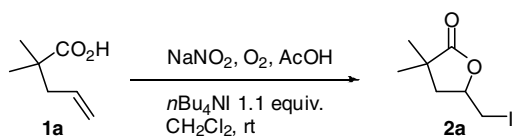
Entry	NaNO$_2$ (equiv)	AcOH (equiv)	Time (h)	Yield[a] (%)
1	0.2	0	36	0
2	0.2	0.5	36	21
3	0.2	1	36	31
4	0.2	2	36	43
5	0.2	5	7	92[b]
6	0.1	5	15	90
7	0.05	5	36	48
8	0.02	5	36	36
9	0	5	36	0

[a] Isolated yield.
[b] Oxygen was bubbled directly into the reaction.
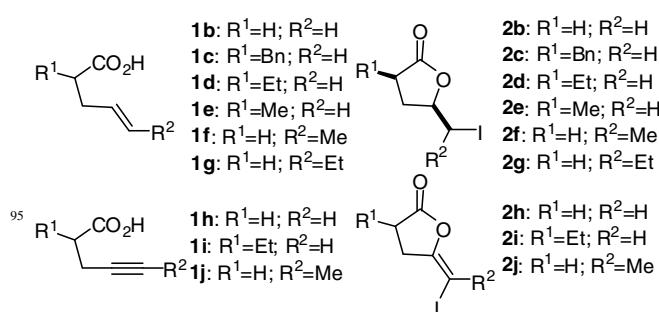
Figure 1. Substrates and products of iodolactonisation.

Table 2
Iodolactonisation of various alkenes and alkynes

| Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	**1b**	24	**2b**	87
2	**1c**	16	**2c**	84 (dr = 1.7:1)
3	**1d**	13	**2d**	61 (dr = 1.7:1)
4	**1e**	16	**2e**	84 (dr = 2:1)
5	**1f**	18	**2f**	80 (dr = 5:1)
6	**1g**	20	**2g**	94 (dr = 2.3:1)
7	**1h**	18	**2h**	64
8	**1i**	22	**2i**	84
9	**1j**	22	**2j**	74

[a] Isolated yield, no side products observed for all the substrates.

reactions were complete within 24 h and good yields were obtained. Only the 5-*exo*-trig ring-closed lactones **2b–g** were isolated. NMR studies of the lactones **2c–g** showed that the *syn* isomers were the major products.

This protocol was also employed with alkynes **1h–j** to prepare iodoenol lactones **2h–j** (Table 2, entries 7–9) which were reported as potential inhibitors of serine proteases and glutathione *S*-transferases.[10] The reaction was highly diastereoselective and only the *E* olefins were formed.

We replaced TBAI with the more common iodide source, sodium iodide (NaI). We found that acetic acid was required as solvent for the reaction to proceed well. Lactone **2a** was isolated in 74% yield (Scheme 1).

The halocyclisation reaction of olefinic compounds has been shown to work with ambident nucleophiles such as carbamates, ureas and amides.[11] Preference for the O-cyclised or N-cyclised
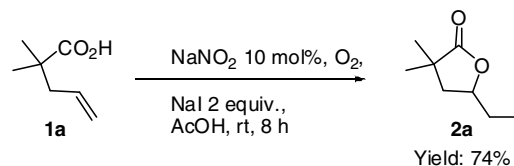
Scheme 1. Iodolactonisation using sodium iodide.
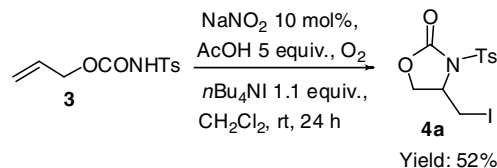
Scheme 2. Iodo-amination of *O*-allylic carbamates.
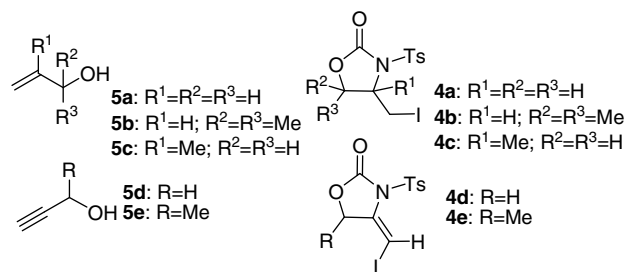
**Figure 2.** Substrates and products of the iodo-amination reaction.

products is highly dependent on the reaction conditions. To test the substrate scope of the NaNO$_2$/O$_2$ system, *O*-allylic carbamate **3** was subjected to our optimised conditions affording the iodo-amination product **4a** in 52% isolated yield (Scheme 2). The O-cyclised product and the 6-*endo* product were not observed. It is noteworthy that this iodo-amination reaction can be carried out in one pot. Allylic alcohols **5a–c** (Fig. 2) can be converted to the corresponding carbamates in situ (Table 3), however, only moderate yields were obtained (Table 3, entries 1–3). Further optimisations to improve the isolated yields were not successful which included the reaction time and the ratio of reagents. We also found that the alkynic alcohols **5d–e** could give interesting amino-alkenes **4d–e**. However, they were obtained in relatively low yields. NOE experiments showed that only *E* olefins **4d–e** were formed.

Based on these preliminary data, we have proposed a possible pathway for the reaction (Scheme 3). NO acts as a catalyst to carry O$_2$ by conversion into NO$_2$. NO$_2$ oxidises iodide from TBAI in the

Table 3
Iodo-amination of various alkenes and alkynes

Entry	**5**	Time (h)	**4**	Yield[a] (%)
1	**5a**	24	**4a**	70
2	**5b**	24	**4b**	42
3	**5c**	24	**4c**	78
4	**5d**	28	**4d**	36
5	**5e**	28	**4e**	40

[a] Isolated yield.

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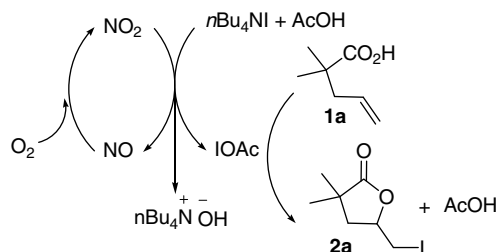
Scheme 3. Proposed reaction pathway.

presence of acetic acid to generate the reactive species, acetyl hypoiodite (IOAc)[12], which promotes the iodo-cyclisation reactions. The possibility of the formation of molecular iodine in this system was excluded by a simple starch solution test.

In conclusion, we have developed a convenient iodo-cyclisation reaction using $NaNO_2$ as catalyst and molecular oxygen as the terminal oxidant. The reactive species, acetyl hypoiodite (IOAc), was generated in situ from TBAI and AcOH. The iodo-cyclisation reaction with a range of alkenes and alkynes gave good to excellent yields of products. Iodo-amination products can also be obtained using carbamates prepared from commercially available allylic alcohols and alkynic alcohols.

Acknowledgements

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.013.

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