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A remarkably simple α-oximation of ketones to 1,2-dione monooximes using the chlorotrimethylsilane–isoamyl nitrite combination

Abdulkarim H. A. Mohammed[†] and Gopalpur Nagendrappa*

Department of Chemistry, Bangalore University (Central College Campus), Bangalore 560001, India

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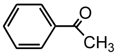
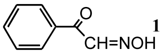
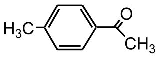
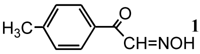
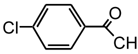
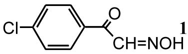
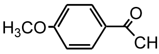
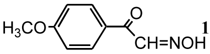
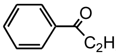
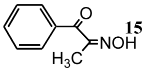
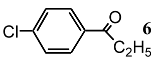
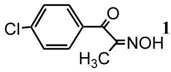
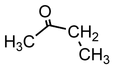
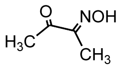
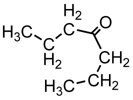
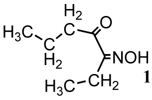
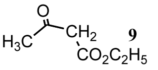
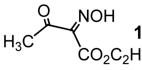
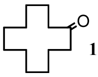
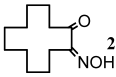
Abstract—Ketones undergo α-oximation by NOCl formed in situ from Me_3SiCl and isoamyl nitrite, either in solution or under solvent-free conditions, to produce 1,2-dione monooximes in excellent yields. The oximation is regiospecific in appropriate cases.

R_3SiX reagents, according to Fleming's analysis, react analogously to, but more selectively than HX.[1,2] Treating chlorotrimethylsilane (TMSCl) with isoamyl nitrite (AmONO) is an effective method for the in situ generation of NOCl in aprotic solvent media as well as under solvent free conditions. We have shown earlier that NOCl thus produced adds to vinylsilanes in a regiospecific and stereoselective manner.[3] This, to our knowledge, is the most convenient method for the generation and reaction of NOCl particularly for laboratory scale preparations. Conventional procedures for obtaining NOCl under anhydrous condition are rather cumbersome.[4]

The direct α-oximation of ketones, esters, and aldehydes by NOCl is known.[4a] Rasmussen and Hassner argue that the methods used are associated with many shortcomings and showed that silylenol ethers are superior for achieving better yields and selectivity.[5,6] However, the handling of silylenol ethers needs special care, and their preparation is an avoidable extra step. Therefore, earlier procedures are preferred even now for the preparation of α-oximino ketones.[7]

α-Oximino ketones find many applications. They are used as starting compounds for the synthesis of imidazoles,[7] oxazoles,[8] α-amino acids and esters,[4] α-amino alcohols,[9] pharmaceutically useful heterocycles[10] like luciferin analogues,[11] and other valuable products.[12] There is much patent literature describing the preparation of α-oximino ketones and their conversion to dioximes. α-Oximino ketones hydrolyze to synthetically

Table 1. α-Oxidation of ketones using TMSCl–AmONO

Entry	Ketone	Reaction time (h)	Product	M.P. (°C)	Yield[a] (%)
1	 **1**	1.0	 **11**	128-130	90
2	 **2**	1.0	 **12**	141-143	93
3	 **3**	1.0	 **13**	148-150	93
4	 **4**	0.7	 **14**	116-118	95
5	 **5**	0.5	 **15**	114-116	96
6	 **6**	0.5	 **16**	118-120	96
7	 **7**	2.0	 **17**	72-74	82
8	 **8**	3.5	 **18**[b]	167-169[b]	76
9	 **9**	2.5	 **19**	(liq)	73
10	 **10**	1.2	 **20**	54-56	79

[a] Isolated yields

[b] Isolated as dioxime after treating **18** with $NH_2OH.HCl$. M.P. is of the dioxime

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Keywords: oximation; TMSCl; amyl nitrite; 1,2-diketone monooxime; NOCl.

* Corresponding author. E-mail: nagendrappa@vsnl.net

[†] On leave from Sana'a University, Sana'a, Yemen.

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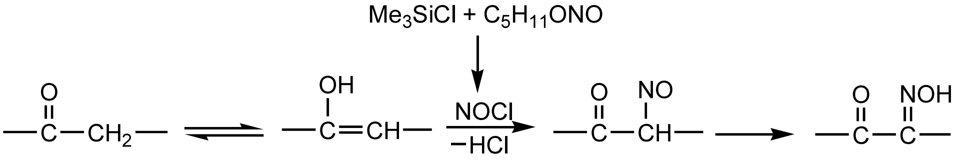

Scheme 1.

important α-diketones,[13] and serve as ligands for transition metal complexes.[14]

We have found that ketones undergo α-oximation readily on treatment with TMSCl and AmONO in solvents or under solvent-free conditions. The results are reported.

α-Oximation was carried out with aryl alkyl ketones **1**–**6**, alkyl ketones **7**–**9**, and the cyclic ketone **10**. One molar equivalent of TMSCl was added to the substrate (either neat or in CH_2Cl_2 solution) at −20°C, followed by the dropwise addition of an equivalent quantity of isoamyl nitrite. The reaction was found to be instantaneous, but the mixture was stirred for an additional period of 30 min before working up. The products were purified on a silica gel column using 5% ethyl acetate in petroleum ether (bp 45–55°C) as eluant, and identified by their mp, IR, ^{1}H and ^{13}C NMR spectra, which were compared with literature data. The α-ketooxime **18**, because of its reduced stability, was isolated as a dioxime by reacting with $NH_2OH{\cdot}HCl$. The results are given in Table 1.

The reactions run in the absence of solvent were found to give slightly better yields (about 2–5% more) than those from reactions run in solution. This observation makes the procedure particularly attractive because of its eco-friendly character.[15]

The oximation is brought about by NOCl formed in situ as shown previously by the reaction of Me_3SiCl with isoamyl nitrite.[3] It is to be noted that only one α-position of the ketones **7**–**10** is oximated, though both are susceptible, and that monooximation occurs regiospecifically in **7** and **9** on the more readily enolizable α-position. This indicates that the reaction starts with enolization (facilitated by TMSCl/HCl), and follows the route depicted in Scheme 1.

In conclusion, α-ketooximes can be prepared from ketones in a very simple manner. The reaction can be run on preparative scale.[16] No extra precaution was needed except to avoid the entry of moisture. This work discloses a new application of the organsilicon reagent, Me_3SiCl, for an important organic transformation.

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16. The reaction was run using 0.10–10.0 g of the ketone with no significant change either in yield or purity of the oximino ketone. Typical experimental procedure: Me_3SiCl (1.2 g, 11.0 mmol) was added slowly to the ketone in 5 mL of CH_2Cl_2 at −20°C in a 50 mL two-necked flask fitted with a $CaCl_2$ guard tube, followed by dry isoamyl nitrite (1.4 g, 12.0 mmol). The mixture turned blue and then yellow. After stirring for 30 min more, ether or CH_2Cl_2 (20 mL) was added and the reaction worked up in the usual way. The product was eluted on a silica gel column using pet. ether (bp 50–55°C) containing 5% ethyl acetate to get pure product.