Heteroatom Chemistry
Volume 9, Number 3, 1998

Synthesis of Oximes, Conversion to Nitrile Oxides and Their Subsequent 1,3-Dipolar Cycloaddition Reactions under Microwave Irradiation and Solvent-Free Reaction Conditions

Béatrice Touaux,[1] Françoise Texier-Boullet,[1] and Jack Hamelin[1]

[1]*Synthèse et Electrosynthèse Organiques 3, UMR 6510, Université de Rennes I, Campus de Beaulieu, 35042 Rennes, France*

Received 1 July 1997; revised 23 September 1997

ABSTRACT: *Aldoximes and ketoximes were readily synthesized from aldehydes and hydroxylamine hydrochloride on Al_2O_3 without solvent under microwave irradiation. At higher irradiation power, aldoximes dehydrated to nitriles and ketoximes rearranged to amides. Aldoximes reacted in a one-pot reaction with N-chlorosuccinimide and alkenes or alkynes over alumina under microwave irradiation to give isoxazolines or isoxazoles.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:351–354, 1998

INTRODUCTION

We have previously reported a simple fast and efficient procedure [1] either for the dehydrohalogenation of ethyl chlorooximidoacetate [2] or for the dehydration of methyl nitroacetate. In both cases, carboalkoxy formonitrile oxide was generated. We found it interesting to extend this type of dehydrohalogenation reaction to C-chlorooximes in order to provide an access to other nitrile oxides. The preliminary step in each case was the synthesis of the oxime and its α-chlorination. Most of the reported syntheses in solution require relatively long reaction times [3,4].

Owing to our studies related to syntheses in dry media under microwave irradiation, we found it worthwhile to try to modify the more classical syntheses by using Al_2O_3 (without solvent) during the condensation of the carbonyl derivative with the hydroxylamine hydrochloride to remove HCl.

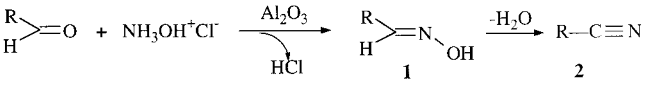
In the same way, we have developed a new procedure for the chlorination by means of N-chlorosuccinimide (NCS) without solvent under microwave irradiation. Then, the method previously reported for dehydrochlorination on Al_2O_3 was applied. Therefore, starting from the isolated oxime, chlorination by NCS, dehydrochlorination to the nitrile oxide, and trapping it by a dipolarophile were realized in a one-pot reaction.

ALDOXIME SYNTHESIS

Powdered hydroxylamine hydrochloride and aldehyde or ketone were adsorbed on Al_2O_3, and the mixture was submitted to microwave irradiation in a closed Teflon vessel in a domestic oven. After extraction with dichloromethane, the crude mixture was purified by recrystallization or column chromatography.

Correspondence to: Jack Hamelin

CCC 1042-7163/98/030351-04



The results are summarized in Table 1.

In all the cases, only the **E** isomer was formed. It has been shown that the **Z** isomer isomerizes to **E** in the presence of base [5]. The **Z** isomer was never observed, and this may be due to the basic character of Al_2O_3.

During the course of the various experiments designed to optimize the yields, we have seen that an elevation of the irradiation power led to the formation of a second product **2** together with **1.** We found that **2** was, in fact, the nitrile resulting from the dehydration of the oxime.

Accordingly, we have optimized the reaction conditions to obtain the nitrile as the major product. The results are reported in Table 2.

Nitriles have already been prepared in heterogeneous medium (KF/Al_2O_3) in the presence of CS_2 under microwave irradiation, but this method did not allow the synthesis of the intermediate oxime [6]. Meshram *et al.* [7], starting from the pure oxime, also reported the synthesis of nitrile over montmorillonite KSF. An analogous reaction was reported to occur over bentonite under microwave or ultrasound irradiation [8].

TABLE 1 Synthesis of Aldoximes **1**

1	R	*Power* (*W*)	*Ratio* *Ald/NH₂OH*	*Time* (*min*)	*% Yield*[a]
a	C_6H_5	400	1/1	15	66
b	4-Cl-C_6H_4	200	1/1.2	20	87
c	4-Me-C_6H_4	200	1/1.2	30	67
d	4-MeO-C_6H_4	100	1/2.2	20	70
e	isobutyl	100	1/1.2	20	60[b]
f	3-pyridyl	100	1/1.2	20	75

[a] Isolated yield.
[b] Yield estimated by ^1H NMR spectroscopy.

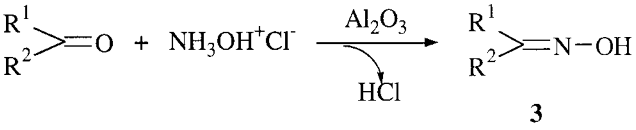
TABLE 2 Nitrile **2** Synthesis

2	R	*Power* (*W*)	*Ratio* *Ald/NH₂OH*	*Time* (*min*)	*% Yield*[b]
b	4-Cl-C_6H_4	750[a]	1/1.2	15	65
c	4-Me-C_6H_4	500[a]	1/1.4	20	48
d	4-MeO-C_6H_4	400	1/1	15	66
e	3-pyridyl	400	1/1	15	73

[a] Alumina previously dried for 5 minutes at 400 W.
[b] Isolated product.

KETOXIME SYNTHESIS

Although ketoximes do not form nitrile oxides, we have investigated some reactions to check the scope of our procedure toward ketones. According to the same experimental path, we have prepared the ketoximes **3** reported in Table 3.



In various attempts toward optimization, we have observed that, by raising the irradiation power, a second product was formed that was identified as the amide resulting from a Beckmann rearrangement. This reaction, under this type of operation, has already been mentioned in the literature [9,10].

NITRILE OXIDES AND 1,3-DIPOLAR CYCLOADDITIONS

Starting with some of the above-mentioned aldoximes, we have studied their chlorination and dehydrochlorination in dry medium. The usual chlorination methods consist of either bubbling dry Cl_2 into the oxime solution or addition of N-chlorosuccinimide to the solution. Then, addition of a base removes HCl, and the nitrile oxide generated in situ is trapped by a dipolarophile. In 1985, Torssell [11] reported the synthesis of 2-isoxazolines starting from an oxime, NCS, alumina or Florisil in $CHCl_3$ solution in the presence of a catalytic amount of pyridine. After having been stirred for one night, the 2-isoxazoline was formed.

According to our results [1] with respect to ethyl chlorooximidoacetate, we have adapted the method in the following way: oxime, NCS, Al_2O_3, and a dipolarophile were mixed together without solvent and then irradiated by microwaves in a single-mode apparatus [12]. The results are summarized in Table 4.

TABLE 3 Ketoximes **3**

3	*R¹*	*R²*	*Power* (*W*)	*Ratio* *Ket/NH₂OH*	*Time* (*min*)	*% Yield*[b]
a	Ph	Ph	100	1/1	20	71
b	Me	Me	200	2/1	20	82
c	-$(CH_2)_4$-		200	1/1	20	70
d	Me	Ph	100[a]	1/2	20	65

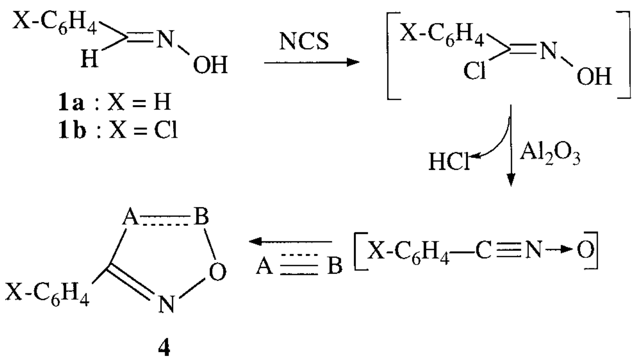
[a] Open vessel.
[b] Isolated product.

TABLE 4 Nitrile Oxides

Oxime	*Product*	*Dipolarophile* *A* = *B*	*Power* (*W*)	*Ratio Oxime/* (*A* = *B*)	*Time* (*min*)	*% Yield*[a]
1a	**4aa**	$CH_2{=}CHCO_2Me$	30	1/2	4	60
	4ab	N-phenyl maleimide	30	1.5/1	4	68
	4ac	$MeO_2CC{\equiv}CCO_2Me$	30	1/1	10	55
	4ad + **4′ad**	$H\text{-}C{\equiv}CCO_2Me$	30	1/1	5	77[b]
1b	**4ba**	$CH_2{=}CHCO_2Me$	30	1/2	4	55
	4bb	N-phenyl maleimide	60	1/1	5	61
	4bc	$MeO_2CC{\equiv}C\text{-}CO_2Me$	60	1/1	5	57
	4bd + **4′bd**	$H\text{-}C{\equiv}CCO_2Me$	60	1/1	5	68[b]

[a] Isolated product.

[b] In these cases, two regioisomers **4** and **4′** were formed in the ratio of 80/20 in agreement with the literature [13].



In all cases wherein the reaction has previously been reported in the literature, the present yields are either equivalent or slightly higher. In summary, we have developed a new procedure for an old reaction that is simple, fast, and more friendly for the environment.

EXPERIMENTAL

Thin-layer chromatography (TLC) procedures were carried out on 0.2 mm precoated plates of silica gel 60F-254 (Merck). Visualization was made with UV light (254 and 365 nm). Preparative column chromatography was carried out on silica gel 60 Merck (230–240 Mesh). Melting points were determined by use of a Kofler melting-point apparatus.

^{1}H NMR spectra were recorded on BRUKER WP 80 CW (80 MHz) and BRUKER AC 300 P (300 MHz) instruments. Chemical shifts are expressed in parts per million downfield from TMS as an internal standard. Mass spectra (MS) were taken on a VARIAN MAT 311 instrument at an ionizing potential of 70 eV in the “Centre de Mesures Physiques de l’Ouest” (CRMPO, Rennes).

OXIME SYNTHESIS

All reagents were purchased from Acros or Aldrich Chimie and were used without further purification.

Elemental analyses were carried out at the “Laboratoire Central de Microanalyses du CNRS” (Lyon).

The domestic microwave oven (PHILIPS AVM 602) operates at seven powers from 90 to 900 W. The closed Teflon vessels were purchased from SAVILLEX, Minnesota, USA. The single-mode apparatus was a microwave digester, Maxidigest MX350 from PROLABO [12], operating continuously from 30 to 300 W and fitted with a stirring device and an open Pyrex reactor having a diameter of 3 cm.

General Procedure. Aldehyde or ketone (2.5 mmol) and finely ground hydroxylamine hydrochloride in various ratios (see tables) were mixed with 3 g of Al_2O_3 dried or not. After irradiation for the time and at the power given in the tables, the mixture was extracted with CH_2Cl_2. After filtration and removal of the solvent, the resulting oxime was purified by column chromatography, recrystallization or sublimation.

Oximes **1a** to **1f** and **3a** to **3d** were identified by comparison with literature data [5].

NITRILE SYNTHESIS

Nitriles **2b** to **2d** were identified in agreement with literature data.

ISOXAZOLINES AND ISOXAZOLES

General Procedure. One to 1.5 eq. of aldoxime (5 to 7.5 mmol), the same amount of NCS, and 1 to 2 eq. of dipolarophile (5 to 10 mmol) were adsorbed on 5 g of Al_2O_3. The mixture was then irradiated in the single-mode apparatus for a given time and power (see tables). Then the mixture was extracted with CH_2Cl_2, and, after removal of the solvent, the mixture was distilled or recrystallized or sublimated after washing with CCl_4 to remove the succinimide.

The isoxazolines and isoxazoles were characterized according to the literature data [13–19], except for **4bb.**

5-(4-chlorophenyl)-3-phenyl-3a,6a-dihydro-4H-Pyrrolo[3,4-d]isoxazole-4,6(5H)-dione. Mp: 176°C (sublimation to remove succinimide, then washing with CCl_4). ^1H NMR ($CDCl_3$): 4.90 (d, 1H, ^3J = 16 Hz); 5.50 (d, 1H, ^3J = 16 Hz); 7.10–8.10 (m, 9H, Ar$\underline{H}$).

REFERENCES

[1] B. Touaux, B. Klein, F. Texier-Boullet, J. Hamelin, *J. Chem. Res. (S),* 1994, 116, and reference cited.
[2] A. K. Kozikowski, M. Adamzyk, *J. Org. Chem., 48,* 1983, 366.
[3] S. R. Sandler, W. Karo: *Organic Functional Group Preparations,* Vol III, pp. 365–405. Academic Press, New York, 1972.
[4] D. E. Pearson, O. D. Keaton, *J. Org. Chem., 28,* 1963, 1557–1558.
[5] C. Berrier, R. Brahmi, H. Carreyre, J. M. Coustard, J. C. Jacquesy, B. Violeau, *Bull. Soc. Chim. Fr., 128,* 1991, 730–737.
[6] D. Villemin, M. Lalaoui, A. Ben Alloum, *Chem. Ind. (London),* 1991, 176.
[7] H. M. Meshram, *Synthesis,* 1992, 943–944.
[8] F. Delgado, A. C. Cano, O. Garcia, J. Alvarado, L. Velasco, C. Alvarez, H. Rudler, *Synthetic. Commun., 22,* 1992, 2125–2128.
[9] A. I. Bosch, P. De La Cruz, E. Diez Barka, A. Loupy, F. Langa, *Synlett,* 1995, 1259.
[10] A. Laurent, P. Jacquault, J. L. Di-Martino, J. Hamelin, *J. Chem. Soc. Chem. Commun.,* 1995, 1101.
[11] K. G. B. Torssell, A. C. Hazell, R. C. Hazell, *Tetrahedron, 41,* 1985, 5569–5575.
[12] R. Commarnot, R. Didenot, J. F. Gardais, *Fr. Demande, 2,* 560, 259 (ClBO1J19/12). 06 Sept. 1985, Appl. 84/3, 496, 02 mar. 1984; *Chem. Abstr., 105,* 1986, 17442e.
[13] M. Christl, R. Huisgen, *Tetrahedron Lett., 50,* 1968, 5209–5213.
[14] K. Harada, E. Kaji, S. Zen, *Chem. Pharm. Bull., 28,* 1980, 3296–3303.
[15] T. Shimizu, Y. Hayashi, K. Teramura, *Bull. Chem. Soc. Jpn., 57,* 1984, 2531–2534.
[16] W. I. Awad, S. Omran, M. Sobhy, *J. Chem. U. A. R., 10,* 1967, 1–8.
[17] T. Wei, Z. Zhang, T. Li, H. Hu, *Heteroatom Chem., 3* (5–6), 1992, 603–609.
[18] A. Nagajaran, M. Pillay, Krishna, *Indian J. Chem., Sect. B., 32* B(4), 1993, 471–474.
[19] A. Battaglia, A. Dondoni, F. Taddei, *J. Heterocyclic Chem., 7* (3), 1970, 721–724.