

Communication

Solvent Free, Microwave Assisted Conversion of Aldehydes into Nitriles and Oximes in the Presence of $\text{NH}_2\text{OH}\cdot\text{HCl}$ and TiO_2

Lucas Villas-Boas Hoelz, Biank Tomaz Gonçalves, José Celestino Barros and Joaquim Fernando Mendes da Silva *

Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro, Av. Athos da Silveira Ramos 149, CT Bloco A, Cidade Universitária, Rio de Janeiro, RJ 21941-909, RJ, Brazil

* Author to whom correspondence should be addressed; E-Mail: joaquim@iq.ufrj.br.

Received: 27 October 2009; in revised form: 22 December 2009 / Accepted: 23 December 2009 / Published: 29 December 2009

Abstract: Aromatic aldehydes bearing electron-donating groups are easily converted into their respective nitriles using $\text{NH}_2\text{OH}\cdot\text{HCl}$ and TiO_2 under microwave irradiation, while those bearing an electron-withdrawing group give the corresponding oximes.

Keywords: titanium dioxide; aldehydes; nitriles; oximes; microwave irradiation

1. Introduction

Titanium dioxide (TiO_2) has attracted the attention of synthetic organic chemists due to its application as a heterogeneous catalyst and as a photocatalyst. In addition, TiO_2 is inexpensive, non-toxic and safe [1]. TiO_2 may complex with the carbonyl oxygen atoms of aldehydes and ketones, thus activating them for nucleophilic attack [2]. Sharghi and Sarvari converted aldehydes and ketones into the respective amides in the presence of $\text{NH}_2\text{OH}\cdot\text{HCl}$ and TiO_2 in a one-pot, solvent free procedure, but with long reaction times [3]. Aldehydes may also be converted into their respective nitriles in good yields and short reaction times using $\text{NH}_2\text{OH}\cdot\text{HCl}$ under microwave irradiation using, however, the toxic *N*-methyl-2-pyrrolidinone (NMP) as solvent [4]. In the two cases, the mechanism involves oxime generation, but while the amides are obtained through Beckmann rearrangement, the nitriles are generated through dehydration.

The transformation of aldehydes into nitriles is a highly valued reaction, due to the versatility of the latter as starting materials in organic synthesis [8]. Although several methods are known for the transformation of aldehydes to their corresponding nitriles [4,6–13], many drawbacks such as low yields, harsh reaction conditions and tedious work-up procedures limit the use of some of these procedures. Furthermore, some of them use corrosive, toxic, expensive or commercially unavailable reagents [2,4].

Oximes, another important class of aldehyde derivatives, also have useful applications in organic synthesis and in analytical chemistry. These compounds, besides being intermediates for isoxazoline [14] and *N*-hydroxylamino nitrile synthesis [15], also have a potential use in perfumery industry due to their higher stability when compared to their corresponding aldehydes, while retaining a pleasant odour [16].

Based on these facts, we decided to evaluate the conversion of aldehydes into oximes and then into nitriles in the presence of $\text{NH}_2\text{OH}\cdot\text{HCl}$ and TiO_2 under microwave irradiation, in order to favor dehydration over Beckman rearrangement of the intermediate oxime. Product formation was followed by GC-MS and the spectroscopic data of products were compared to those available in the literature.

2. Results and Discussion

Since we have been interested in the synthetic and medicinal usefulness of vanillonitrile derivatives, we started our research studying the effects of time and irradiation potency on the conversion of vanillin to its oxime and nitrile under microwave irradiation. The results obtained are summarized in Table 1.

Table 1. Time and Potency Effects on the Conversion of Vanillin into Vanillonitrile and Vanillin Oxime.

Entry	Time (min)	Power (W)	% Nitrile	% Oxime	% Others
1	0,5	100	60	40	0
2	1	100	75	25	0
3	5	100	83	4	13
4	1	200	53	34	13
5	1	300	56	29	15
6	2	300	62	20	18

Conditions: 1 mmol vanillin, 5 mmol TiO_2 , 5 mmol $\text{NH}_2\text{OH}\cdot\text{HCl}$.

The results show that the best conversion rate was obtained by irradiating the solid mixture for five minutes at 100 W (entry 3). Increasing the power (entries 4-6) led to higher yields of undesired products (such as the amide and degradation products), while reduced reaction times furnished higher amounts of the oxime (entries 1-2).

It can also be observed that increasing reaction time from one to five minutes (entries 2 and 3) enhanced vanillonitrile yields, as well as the amounts of undesired products, and thus longer reaction times were not evaluated. For both reaction times no starting material could be detected.

We have also explored the effects of the amounts of TiO_2 and $\text{NH}_2\text{OH}\cdot\text{HCl}$ in the reaction mixture on the yield of the nitrile. Reducing the amounts of either of these reagents from 5 mmols to 2.5 mmols led to incomplete conversion of the aldehyde and, at the same time, to enhanced yields of undesired products (results not shown). Thus, after determining the best reaction conditions, we applied them to other aromatic aldehydes, as described in Table 2.

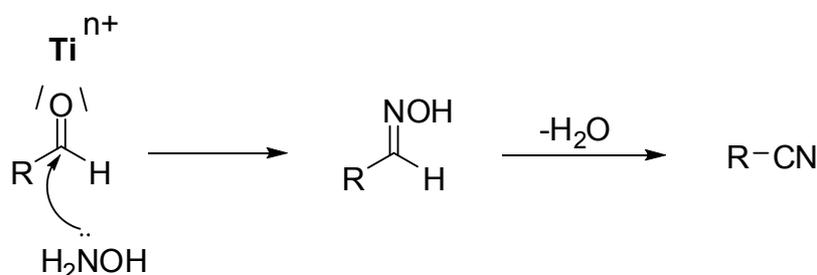
Table 2. Conversion of Aldehydes into Nitriles and Oximes in the Presence of $\text{NH}_2\text{OH}\cdot\text{HCl}$ and TiO_2 under Microwave Irradiation.

Entry	Aldehyde	% Aldehyde	% Nitrile	% Oxime	% Others
1	Ethylvanillin	0	83	5	12
2	4-Dimethylaminobenzaldehyde	0	84	4	12
3	4-Hydroxybenzaldehyde	0	81	10	9
4	2-Pyrrolicarboxaldehyde	0	77	22	0
5	4-Benzyloxyvanillin	0	82	7	11
6	2-Nitrobenzaldehyde	5	15	80	0
7	4-Nitrobenzaldehyde	2	17	81	0
8	4-Bromobenzaldehyde	0	20	80	0

Conditions: 1 mmol aldehyde, 5 mmol TiO_2 , 5 mmol $\text{NH}_2\text{OH}\cdot\text{HCl}$, 5 min, 100 W.

The aldehydes bearing electron donating groups were readily converted into the corresponding nitriles (entries 1-5, Table 2) in satisfactory conversion rates (77–84%), whereas substrates bearing electron withdrawing groups (entries 6-8, Table 2) afforded the respective oximes, along with significant amounts of the respective nitriles. In fact, it was previously observed that substrates bearing those groups require longer reaction times for total conversion into nitriles [17]. We further explored the effects of increasing power and reaction times in the conversion of 4-nitrobenzaldehyde to 4-nitrobenzonitrile, but no change in product ratios was observed. GC-MS monitoring supports a two step mechanistic proposal for these reactions (Scheme 1), where the conversion of the aldehyde into the respective nitrile occurs at the expense of the oxime through acid catalysed dehydration.

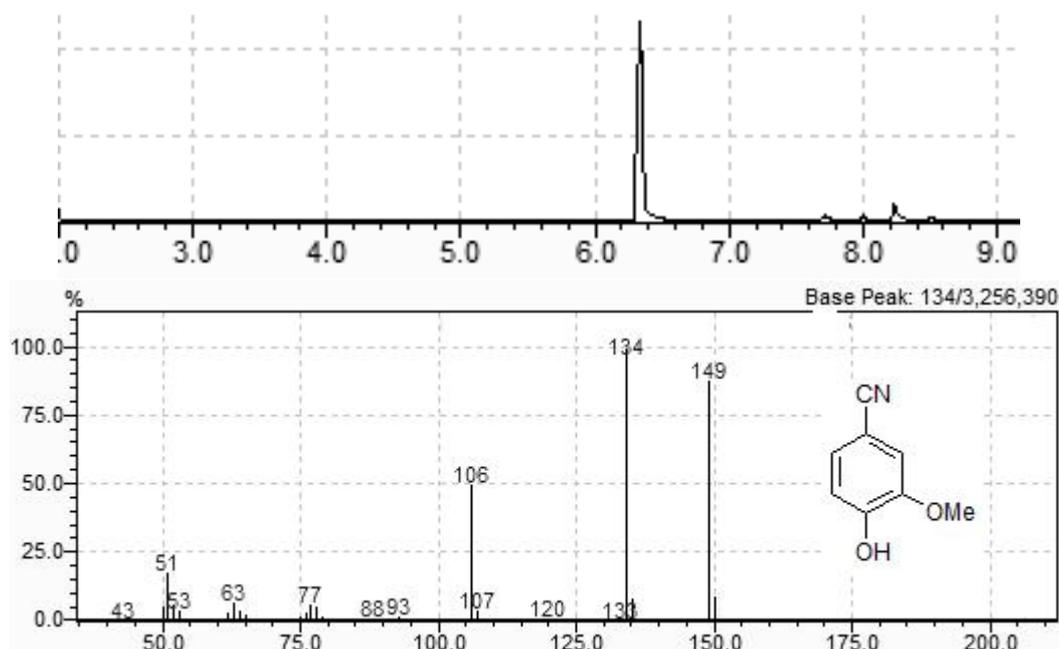
Scheme 1. Proposed sequence of transformations during TiO_2 promoted conversion of aldehydes into nitriles.



In order to test this hypothesis, we performed the reaction between vanillin and hydroxylamine hydrochloride in the absence of TiO_2 (100 W, 5 min). The HCl liberated during oxime formation promoted dehydration, but with reduced efficiency when compared to titanium oxide (44% vanillonitrile, 27% oxime, 29% other products). Addition of *p*-toluenesulfonic acid led to a complex

mixture of products, while the addition of NaOH or Na₂CO₃, either in the presence or absence of TiO₂ yielded exclusively the oxime with 100% conversion rate. The same occurred with the other aldehydes, what makes this procedure a useful method for rapid, solvent free, microwave assisted synthesis of aldoximes. The reaction can be easily scaled-up, and the synthesis of vanillonitrile using a 4-fold amount of all the reagents led to a 92% conversion to vanillonitrile, which could be purified by flash column chromatography, yielding pure product in 85% isolated yield (Figure 2).

Figure 2. GC chromatogram of scaled up conversion of vanillin into vanillonitrile and MS of the major compound ($t_R = 6.33$ min).



3. Experimental

3.1. General

The HRGC/MS analyses were carried out on a Shimadzu QP-2010 operating in electron ionization mode at 70 eV. Helium was used as carrier gas and the injection split ratio was 1:100. Separation was achieved on DB-5 capillary column (30 m × 0.25 mm × 0.25 μm) using the following temperature program: 1 min at 60 °C, 20 °C/min until 260°C, then 10 min at 260 °C. Ion source and injection temperature were at 260 °C. ¹H-NMR spectrum of vanillonitrile was recorded on a Bruker HC200 spectrometer, using CDCl₃ as solvent. The FTIR spectrum was recorded on a Nicolet 550 spectrometer (KBr pellets).

3.2. Microwave assisted conversion of aldehydes into nitriles and oximes

A 25 mL reaction flask was charged with a ground mixture of an aldehyde (1 mmol), TiO₂ (5 mmol, 0.4 g) and hydroxylamine hydrochloride (5 mmol, 0.35 g). The reaction mixture was placed at a CEM Discovery microwave reactor (power-time method) and irradiated at the power settings and reaction times specified in Tables 1 and 2, with air-cooling and magnetic stirring for the duration of the reaction. After cooling to room temperature, the reaction mixture was resuspended in CH₂Cl₂ (10 mL),

filtered and a sample submitted to CG/MS analysis with the following results: *3-Ethoxy-4-hydroxybenzotrile*: $t_R = 6.92$ min. $M^+ = 33.7$ (71%). *4-Dimethylaminobenzotrile*: $t_R = 7.69$ min. $M^+ = 146$ (67%). *4-Hydroxybenzotrile*: $t_R = 5.94$ min. $M^+ = 119$ (100%). *2-Pyrrolicarbonitrile*: $t_R = 3.12$ min. $M^+ = 92$ (100%). *4-Benzyloxy-3-methoxybenzotrile*: $t_R = 7.52$ min. $M^+ = 239$ (100%). *2-Nitrobenzotrile*: $t_R = 6.09$ min. $M^+ = 148$ (31%). *4-Nitrobenzotrile*: $t_R = 5.39$ min. $M^+ = 148$ (31%). *4-Bromobenzotrile*: $t_R = 6.23$ min. $M^+ = 181$ (90%), 183 (86%).

3.3. Scale-up preparation of vanillonitrile

Vanillin (0.6 g, 4 mmol), TiO_2 (1.6 g, 20 mmol) and $NH_2OH \cdot HCl$ (1.4 g, 20 mmol) were ground in a mortar and the mixture was transferred to a 125 mL reaction flask. The reaction mixture was placed at a CEM Discovery microwave reactor (power-time method) and irradiated at 100 W for 5 minutes, with air-cooling and magnetic stirring for the duration of the experiment. After cooling to room temperature, the reaction mixture was resuspended in ethanol (10 mL), filtered and then purified by flash column chromatography using silica gel as adsorbent and hexane-ethyl acetate (7:3) as eluant, yielding pure vanillonitrile in 85% yield, m.p. = 84–87 °C (lit. 85–87 °C); ^1H-NMR δ ppm 3,93 (s, 3H, OCH_3), 6,20 (bs, 1H, OH), 6,94 (d, 1H, C_5-H), 7,02 (s, 1H, C_2-H), 7,35 (d, 1 H, C_6-H); FTIR ν cm^{-1} : 3373, 3076, 2229

3.4. Microwave assisted conversion of aldehydes into oximes under basic conditions

A 25 mL reaction flask was charged with a ground mixture of an aldehyde (1 mmol), Na_2CO_3 (5 mmol, 0.51 g) and hydroxylamine hydrochloride (5 mmol, 0.35g). The reaction mixture was placed at a CEM Discovery microwave reactor (power-time method) and irradiated at 100 W for 5 minutes, with air-cooling and magnetic stirring for the duration. After cooling to room temperature, the reaction mixture was resuspended in CH_2Cl_2 (10 mL), filtered and a sample submitted to CG/MS analysis.

4. Conclusions

Titanium oxide is a useful reagent for the acid promoted conversion of EDG-substituted aldehydes to nitriles through a solvent free, microwave assisted procedure. On the other hand, neutralization of the reaction mixture by addition of NaOH or Na_2CO_3 proved to be an efficient method for obtaining the corresponding aldoximes in quantitative conversion rates.

Acknowledgements

The authors wish to thanks CNPq, CAPES and FAPERJ for financial support.

References and Notes

1. Diebold, E. The surface science of titanium dioxide. *Surf. Sci. Rep.* **2003**, *48*, 53–229.
2. Lu, G.; Linsebliger, A.; Yates, J.T., Jr. Ti^{3+} defect sites on $TiO_2(110)$ - production and chemical-detection of active-sites. *J. Phys. Chem.* **1994**, *98*, 11733–11738.

- Sharghi, H.; Sarvari, M.H. Titanium oxide (TiO₂) catalysed one-Step Beckmann rearrangement of aldehydes and ketones in solvent free conditions. *J. Chem Res. (S)* **2003**, *3*, 176–178.
- Chakraborti, A.K.; Kaur, G. One-pot synthesis of nitriles from aldehydes under microwave irradiation: Influence of the medium and mode of microwave irradiation on product formation. *Tetrahedron* **1999**, *55*, 13265–13268.
- North, M. *Comprehensive Organic Functional Group Transformation*; Katritzky, A.R., Meth-Cohn, O., Rees, C.W., Eds.; Pergamon: Oxford, UK, 1995; p. 617.
- Wang, E.C.; Lin, G.J. A new one pot method for the conversion of aldehydes into nitriles using hydroxyamine and phthalic anhydride. *Tetrahedron Lett.* **1998**, *39*, 4047–4050.
- Elmorsy, S.S.; El-Ahl, A.A.S.; Soliman, H.; Amer, F.A. Synthesis of triazidochlorosilane (TACS) - a novel silicon mediated one-pot conversion of aldehydes to nitriles. *Tetrahedron Lett.* **1995**, *36*, 2639–2640.
- Arote, N.D.; Bhalerao, D.S.; Akamanchi, K.G. Direct oxidative conversion of aldehydes to nitriles using IBX in aqueous ammonia. *Tetrahedron Lett.* **2007**, *48*, 3651–3653.
- Meshram, H.M. Dehydration of aldoximes to nitriles with clay. *Synthesis* **1992**, *10*, 943–944.
- Bajpai, A.; Deshpande, A.B.; Samant, S.D. An efficient one-pot synthesis of aromatic nitriles from aldehydes using Fe modified K10. *Synth. Commun.* **2000**, *30*, 2785–2791.
- Hegedüs, A.; Cwik, A.; Hell, Z.; Horváth, Z.; Esek, A.; Uzsoki, M. Microwave-assisted conversion of oximes into nitriles in the presence of a zeolite. *Green Chem.* **2002**, *4*, 618–620.
- Khezri, S.H.; Azimi, N.; Mohammed-Vali, M.; Eftekhari-Sis, B.; Hashemi, M.M.; Baniasadi, M.H.; Teimouri, F. Red mud catalyzed one-pot synthesis of nitriles from aldehydes and hydroxylamine hydrochloride under microwave irradiation. *ARKIVOK* **2007**, *xv*, 162–170.
- Sharghi, H.; Sarvari, M.H. An efficient solvent free and one-pot conversion of aldehydes into nitriles using NH₂OH.HCl/CH₃COCl/charcoal system. *J. Iran. Chem. Soc.* **2004**, *1*, 28–32.
- Morita, N.; Fukui, K.; Irikuchi, J.; Sato, H.; Takano, Y.; Okamoto, Y.; Ishibashi, H.; Tamura, O. Intermolecular cycloaddition of *N*-boranonitrone with alkenes. *J. Org. Chem.* **2008**, *18*, 7164–7174.
- Kürti, L., Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, MA, USA, 2005; p. 446.
- Ouédraogo, I.W.; Boulvin, M.; Flammang, R.; Gerbaux, P.; Bonzi-Coulibaly, Y.L. Conversion of natural aldehydes from *Eucalyptus citriodora*, *Cymbopogon citratus*, and *Lippia multiflora* into oximes: GC-MS and FT-IR analysis. *Molecules* **2009**, *14*, 3275–3285.
- Cho, B.R.; Chung, H.S.; Cho, N.S. Elimination reactions of (*E*)- and (*Z*)-benzaldehyde *O*-benzoyloximes. Transition state differences for the syn- and anti-eliminations forming nitriles. *J. Org. Chem.* **1998**, *63*, 4685–4690.

Sample Availability: Samples of the compounds are available from the authors.