Tetrahedron Letters 55 (2014) 2442-2445

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

make this methodology very practical, simple and economical.

Fe₃O₄ nanoparticles/ethyl acetoacetate system for the efficient catalytic oxidation of aldehydes to carboxylic acids

Rosaria Villano^{a,*}, Maria Rosaria Acocella^b, Arrigo Scettri^b

^a Istituto di Chimica Biomolecolare—CNR, Trav. La Crucca 3, 07100 Sassari, Italy ^b Dipartimento di Chimica e Biologia—Università di Salerno, via Ponte Don Melillo, 84084 Fisciano (Salerno), Italy

ARTICLE INFO

ABSTRACT

Article history: Received 17 January 2014 Revised 19 February 2014 Accepted 28 February 2014 Available online 12 March 2014

Keywords: Oxidation Aldehydes Carboxylic acids Iron nanoparticles Catalysis

Introduction

In recent years, a great interest was paid to the development of more sustainable synthetic strategies, as greener alternatives to old traditional processes.¹

The oxidation of aldehydes² is a widely used reaction in organic chemistry, also for large scale applications. At present, some of these procedures require very expensive and rare transition metal catalysts (ruthenium,³ palladium,⁴ copper,⁵ iridium,⁶ rhodium,⁷ etc.) and the employment of solvents and so they are often characterized by production of toxic metal waste at the end of the reaction. All these aspects make many protocols environmentally polluting and so their application in the chemical industry is often difficult. Therefore, the possibility to realize alternative 'green' methodologies, also characterized by an easy separation and recycle of the catalyst seems to be desirable.

In this context, the application of magnetic iron oxide nanoparticles (Fe₃O₄ NPs) is a very promising area in the catalysis field.^{8,9} The emerging interest for this kind of nanoparticles, which are commercially available, is due to the possibility to modify their properties by simple protocols, involving the formation of covalent bonds with metal or organic ligands or, alternatively, simple coordination or adsorption of suitable activators.¹⁰ Notably, different from other nanoparticles, Fe₃O₄ NPs can be easily recovered at the end of the reaction by an external magnet and this opportunity is particularly advantageous for the separation of a catalyst characterized by much reduced particle size.

A new methodology for the oxidation of aldehydes promoted by commercially available Fe₃O₄ nanopar-

ticles (Fe₃O₄ NPs) activated by ethyl acetoacetate was developed. The use of ethyl acetoacetate as additive

was crucial to achieve high reactivities. All reactions were realized under solvent free conditions, using

air or tBuOOH as oxidants. Finally, the separation and reuse of the magnetically recoverable nanoparticles

However, it has to be noted that the employment of Fe_3O_4 NPs in oxidative processes has been poorly exploited in these last years.¹¹

In the course of an investigation targeted towards the achievement of new green protocols for the conversion of aldehydes into carboxylic acids, promoted by nanocatalysts, we have found that the catalytic properties of Fe_3O_4 NPs can be significantly increased by performing the oxidation in the presence of 1,3-dicarbonyl compounds, allowing the attainment of the final products with satisfactory yields and selectivities. In this protocol, involving solvent-free conditions, both air and *t*BuOOH were alternatively used as oxidants. Finally, the possibility to magnetically recover and reuse Fe_3O_4 NPs without any significant reduction in efficiency makes this procedure very competitive because of its simplicity, cheapness and environmental safety.

Results and discussion

In our study, *p*-anisaldehyde **1a** and ethyl acetoacetate were chosen respectively as the model substrate and the representative 1,3-dicarbonyl compound additive (Scheme 1).

However, a preliminary control experiment performed in the absence of ethyl acetoacetate (Table 1, entry 1), pointed out the very poor catalytic properties of Fe_3O_4 NPs. In fact, in the presence





© 2014 Elsevier Ltd. All rights reserved.



^{*} Corresponding author. Tel.: +39 079 2841204; fax: +39 079 2841298. *E-mail address:* rosaria.villano@icb.cnr.it (R. Villano).



Scheme 1. Oxidation of *p*-anisaldehyde.

of air as the oxidant and 20 mol % of Fe₃O₄ NPs, no reaction was found to take place at room temperature, while the final product **2a** could be isolated in only 8% yields after 24 h at 80 °C. Experiments in entries 2-4 revealed the beneficial effect of the presence of ethyl acetoacetate, although the formation of **2a** was found to occur in rather modest yield (up to 42%). Notably, the increase of air availability, as in entries 5 and 6, resulted in a more acceptable efficiency (up to 62% yield).

Furthermore, an increase of catalyst up to 40 mol % did not result in a significant improvement of the process (entries 7 and 8), as well as the use of an excess of ethyl acetoacetate (entry 10).

On the other hand, the structure of the employed 1,3-dicarbonyl compound seemed to influence notably the preparative outcome, as confirmed in entry 11 where methyl acetoacetate was used under the optimized conditions (compare entries 6 and 11). Of course, product **2a** was isolated in only low yield by performing the oxidation in the absence of Fe₃O₄ NPs (entry 12) or in the presence of a catalytic amount of ethyl acetoacetate (entry 13). Moreover, the background oxidation of aldehyde **1a** after 24 h at 80 °C, in the absence of Fe₃O₄ NPs and ethyl acetoacetate, was very modest (entry 14).

Finally, scale-up experiments were realized to evaluate the applicability of the optimized conditions of entry 6: in these cases, the model aldehyde (0.625 mmol and 1.0 mmol) reacted without a significant reduction in efficiency (59% and 61% isolated yields respectively).

At the end of each experiment, a very viscous mixture was observed (Fig. 1a). So, in order to make an easy magnetic separation of the catalyst, a small amount of ethyl acetate (1.0 ml) was added during work-up (Fig. 1b) and the nanoparticles were recovered by using an external magnet (Fig. 1c).

Then, the performance of other oxidants was investigated (Scheme 2, Table 2). Model aldehyde **1a** could be smoothly transformed into the desired carboxylic acid **2a** by using a stoichiometric amount of *t*BuOOH. This result was particularly intriguing

Table 1 Optimization of reaction conditions for the oxidation of *p*-anisaldehyde 1a



Figure 1. Work-up: (a) mixture at the end of the reaction; (b) mixture after addition of EtOAc; (c) easy magnetic separation of the catalyst.



Scheme 2. Model reaction.

Table 2	
Oxidant screening for the oxidation of <i>p</i> -anisaldehyde 1a	

Entry	Fe ₃ O ₄ NPs (%)	Oxidant	t (h)/ T (°C)	2a Yield ^a (%)
1	20	Air (1 atm)	24/80	62
2	20	<i>t</i> BuOOH ^b (1 equiv)	1/80	55
3	20	<i>t</i> BuOOH ^b (1 equiv)	4/80	72
4	20	<i>t</i> BuOOH ^b (1 equiv)	24/80	84
5	-	<i>t</i> BuOOH ^b (1 equiv)	24/80	27
6	20	$H_2O_2^c$ (1 equiv)	24/80	20

^a Isolated yields.

^b 5.5 M solution in decane.

^c 30% hydrogen peroxide solution.

because in the oxidation of aldehydes with *t*BuOOH catalyzed by $Bi_2O_3^{12}$, Mohr's salt¹³ or $CuBr_2^{5b}$ an excess of oxidant (up to 5 equiv) and the presence of solvent were required in order to have good conversions. On the contrary, in this case, when a stoichiometric amount of *t*BuOOH was used as the oxidant, the corresponding acid **2a** was obtained in 72% isolated yield after only 4 h (Table 2, entry 3) and 84% after 24 h (entry 4). Moreover, a control experiment performed in the absence of iron nanoparticles

Entry ^a	Fe ₃ O ₄ NPs (%)	Ethyl acetoacetate (equiv)	<i>t</i> (h)/ <i>T</i> (°C)	2a Yield ^b (%)
1	20	_	24/80	8
2	20	1	1/80	15
3	20	1	24/80	35
4	20	1	48/80	42
5 ^c	20	1	24/80	49
6^d	20	1	24/80	62
7	40	1	24/80	28
8 ^d	40	1	24/80	39
9 ^d	10	1	24/80	46
10 ^d	20	2	24/80	63
11 ^{d,e}	20	1	24/80	43
12 ^d	_	1	24/80	19
13 ^d	20	0.20	24/80	23
14 ^d	_	_	24/80	19

^a All reactions were carried out under solvent-free conditions in a closed vial (size 4 ml) with 0.0625 mmol of aldehyde at 80 °C (oil bath) for the indicated time, using air (1 atm) as the oxidant. The carboxylic acid **2a** was the exclusive product.

^b Yields refer to isolated compounds **2a**.

^c In this entry the reaction was performed in a closed vial (size 15 ml).

^d The reaction was realized in an open system.

^e The reaction was realized in the presence of methyl acetoacetate instead of ethyl acetoacetate.

$$\begin{array}{c} & & \\ R & \\ H & \\ \hline \\ 1 & \\ 1 & \\ 1 & \\ 1 & \\ \hline \\ 1 &$$

Scheme 3. Application of the methodology to different aldehydes.

confirmed their determining role for a successful oxidative process even though, in this last case, no negligible yield was observed (entry 5). Furthermore, H_2O_2 was less efficient than *t*BuOOH (entry 6).

The success of this methodology was further demonstrated by applying the optimized conditions (air or tBuOOH as the oxidant) to different aldehydes (Scheme 3).

As shown in Table 3, our experiments revealed that Fe₃O₄ NPs/ ethyl acetoacetate was able to catalyze the oxidation of different classes of aldehydes (aromatic, aliphatic and α , β -unsaturated). Moreover, for aromatic aldehydes, both substrates bearing either electron-withdrawing or electron-donating groups reacted well at 80 °C, except for nitro-derivatives: in these cases, modest (entry 6) or poor (entry 7) yields were observed. Good results were observed also with low molecular weight aldehydes (entries 11 and 13), by performing the reaction in a closed vial (size 15 ml).

On the other hand, the same catalytic system Fe_3O_4 NPs/ethyl acetoacetate was also tested in the oxidation of benzyl alcohol, but no oxidation product was observed so that starting material could be recovered completely unchanged. This result confirms that the methodology is suitable for the selective oxidation of aldehydes to carboxylic acids.

Finally, the reusability of the nanoparticles was examined in the model reaction (Scheme 4). Even though the catalyst loading seems to be quite high (20 mol %), it could be recovered easily and reused. In fact after the reaction, the metal catalyst was recovered magnetically (as shown in Fig. 1), washed with EtOAc and dried in vacuum at 80 °C for 2 h. Afterwards, a new reaction was performed by adding aldehyde and ethyl acetoacetate under the optimized conditions. The results in Table 4 showed that the nanoparticles could be used at least four times without a significant change in activity.

Table 3

Application	of	the	methodolo	ogv t	0	different	aldehvdes	1
ppmcation	~		meenouore			annerence	anachyaco	-

Entry	Aldehyde 1	Oxid. ^a	Prod.	2 Yield ^b (%)
1	4-Methoxybenzaldehyde (1a)	А	2a	62
		В	2a	84
2	Biphenyl-4-carboxaldehyde (1b)	Α	2b	85
		В	2b	91
3	4-Cyanobenzaldehyde (1c)	А	2c	85
		В	2c	80
4	4-Methylbenzaldehyde (1d)	А	2d	71
		В	2d	99
5	2-Fluorobenzaldehyde (1e)	А	2e	26
		В	2e	67
6	4-Nitrobenzaldehyde (1f)	А	2f	23
		В	2f	45
7	2-Nitrobenzaldehyde (1g)	А	2g	ND
		В	2g	ND
8	Dodecanal (1h)	А	2h	99
9	trans-Cinnamaldehyde (1i)	А	2i	54
		В	2i	33
10	trans-2-Hexen-1-al (1j)	А	2j	63
11 ^c	trans-2-Hexen-1-al (1j)	А	2j	87
12	2-Methylpentanal (1k)	А	2k	30
13 ^c	2-Methylpentanal (1k)	А	2k	80

^a Oxidant A: air; oxidant B: *t*BuOOH.

^b Isolated yields.



Scheme 4. Model reaction.

Table 4 Recycling of the Fe₃O₄ NPs

Entry	Cycle	Yield ^a (%)
1	1	62
2	2	66
3	3	59
4	4	61

^a Isolated yields.

Conclusions

In this Letter we propose a competitive methodology for the oxidation of aldehydes to carboxylic acids, catalyzed by commercially available Fe_3O_4 nanoparticles activated by ethyl acetoacetate. The catalytic system was able to promote the reaction by using tBuOOH as the oxidant as well as by using air. This last alternative makes this strategy particularly intriguing; moreover, other advantages such as the solvent-free approach and the possibility to recover easily (by an external magnetic field) and reuse the iron oxide nanoparticles are very important from the view point of 'green chemistry'.

Experimental

General

TLC was performed on Merck Kiesegel 60 F_{254} plates and visualized by a 254 nm UV lamp. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). All reagents (Aldrich and Fluka) were used without further purification. Fe₃O₄ NPs were purchased from Sigma–Aldrich. NMR spectra were recorded on a Varian 400 (400.135 MHz for ¹H and 100.03 MHz for ¹³C) spectrometer.

Typical procedure for the oxidation of aldehydes to carboxylic acids

To a vial with the catalyst (20 mol %) under air, aldehyde (0.0625 mmol) and ethyl acetoacetate (1 equiv) were added. The mixture was heated at 75–80 °C for 24 h. After cooling at rt, ethyl acetate (1.0 ml) was added and the catalyst was separated by simple magnetic decantation. Then, the combined solvent was removed in vacuo and the mixture was purified via trituration or flash column. Spectroscopic data of products 2 were consistent with those reported in the literature (2a, ¹⁴ 2b, ¹⁵ 2c, ¹⁶ 2d, ¹⁴ 2e, ¹⁷ 2f, ¹⁴ 2h, ¹⁸ 2i, ¹⁹ $2j^{20}$ and $2k^{21}$).

4-*Methoxybenzoic acid* (**2a**):¹⁴ 5.9 mg, 62% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, 2H, *J* = 8.8 Hz), 6.95 (d, 2H, *J* = 8.8 Hz), 3.88 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 164.0, 132.3, 121.6, 113.7, 55.5.

Biphenyl-4-carboxylic acid (**2b**):¹⁵ 10.5 mg, 85% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.20–8.18 (m, 2H), 7.72–7.69 (m, 2H), 7.66–7.63 (m, 2H), 7.50–7.39 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 170.6, 146.5, 139.9, 130.7, 129.0, 128.3, 127.5, 127.3, 127.2.

4-*Cyanobenzoic* acid (**2c**):¹⁶ 7.8 mg, 85% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, 2H, *J* = 8.4 Hz), 7.79 (d, 2H, *J* = 8.4 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 169.2, 132.9, 132.3, 130.7, 117.8, 117.2.

 $^{^{\}rm c}$ In this entry the reaction was performed in a closed vial (size 15 ml) and the metal catalyst was washed with $\rm CH_2Cl_2$ instead of EtOAc.

4-*Methylbenzoic acid* (**2d**):¹⁴ 6.0 mg, 71% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 2.43 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 144.7, 130.3, 129.2, 126.5, 21.8.

2-Fluorobenzoic acid (**2e**):¹⁷ 2.3 mg, 26% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.06–8.01 (m, 1H), 7.62–7.56 (m, 1H), 7.26–7.15 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 168.8, 161.3, 135.5 (d, *J* = 9.1 Hz), 132.8, 124.1 (d, *J* = 3.8 Hz), 120.0, 117.1 (d, *J* = 22.1 Hz).

4-Nitrobenzoic acid (**2f**):¹⁴ 2.4 mg, 23% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.33 (d, 2H, *J* = 8.8 Hz), 8.28 (d, 2H, *J* = 8.8 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 173.1, 153.4, 138.9, 131.7, 122.2.

Dodecanoic acid (**2h**):¹⁸ 12.4 mg, 99% yield. ¹H NMR (400 MHz, CDCl₃) δ 2.35 (t, 2H, *J* = 7.6 Hz), 1.68–1.58 (m, 2H), 1.55–1.20 (m, 16H), 0.89 (t, 3H, *J* = 6.7 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 179.7, 34.0, 31.9, 29.6, 29.4, 29.3, 29.2, 29.0, 24.7 22.7, 14.1.

trans-Cinnamic acid (**2i**):¹⁹ 5.0 mg, 54% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, 1H, *J* = 15.9 Hz), 7.60–7.50 (m, 2H), 7.43–7.37 (m, 3H), 6.46 (d, 1H, *J* = 15.9 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 172.0, 147.7, 133.6, 130.7, 129.0, 128.3, 117.1.

trans-Hex-2-enoic acid (**2j**):²⁰ 6.2 mg, 87% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.06 (dt, 1H, *J* = 15.6, 6.8 Hz), 5.83 (d, 1H, *J* = 15.6 Hz), 2.25–2.19 (m, 2H), 1.54–1.46 (m, 2H), 0.95 (t, 3H, *J* = 7.6 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 171.5, 152.4, 120.5, 34.3, 21.1, 13.6.

2-*Methylpentanoic acid* (**2k**):²¹ 5.8 mg, 80% yield. ¹H NMR (400 MHz, CDCl₃) δ 2.51–2.45 (m, 1H), 1.70–1.63 (m, 1H), 1.46–1.30 (m, 3H), 1.18 (d, 3H, *J* = 7.2 Hz), 0.92 (t, 3H, *J* = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 182.5, 39.0, 35.6, 20.3, 16.8, 13.9.

Acknowledgment

We are grateful to MIUR and University of Salerno for financial support.

References and notes

 (a)Green Chemistry and Catalysis; Sheldon, R. A., Arends, I., Hanefeld, U., Eds.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, 2007; (b)Methods and Reagents for Green Chemistry: An Introduction; Tundo, P., Perosa, A., Zecchini, F., Eds.; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2007; (c) Dunn, P. J. Chem. Soc. Rev. **2012**, 41, 1452–1461.

- (a) Backvall, J. E. Modern Oxidation Methods; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, 2004; (b) Carey, F. A.; Sundberg, R. J. Advanced Organic Chemistry Part B; Springer, 2007.
- 3. Murahashi, S.-I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. J. Org. Chem. 1987, 52, 4319–4327.
- 4. Lerebours, R.; Wolf, C. J. Am. Chem. Soc. 2006, 128, 13052–13053.
- (a) Yoo, W.-J.; Li, C.-J. Tetrahedron Lett. 2007, 48, 1033–1035; (b) Das, R.; Chakraborty, D. Appl. Organometal. Chem. 2011, 25, 437–442; (c) Zhang, C.; Zong, X.; Zhang, L.; Jiao, N. Org. Lett. 2012, 14, 3280–3283.
- (a) Kiyooka, S.-I.; Wada, Y.; Ueno, M.; Yokoyama, T.; Yokoyama, R. Tetrahedron 2007, 63, 12695–12701; (b) Suzuki, T. Chem. Rev. 2011, 111, 1825–1845.
- 7. Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S. *Tetrahedron* **1981**, *37*, 4313–4319.
- For some examples: (a) Polshettiwar, V.; Baruwati, B.; Varma, R. S. Green Chem. 2009, 11, 127–131; (b) Zeng, T.; Yang, L.; Hudson, R.; Song, G.; Moores, A. R.; Li, C.-J. Org. Lett. 2011, 13, 442–445; (c) Cano, R.; Ramon, D. J.; Yus, M. J. Org. Chem. 2011, 76, 5547–5557; (d) Abu-Reziq, R.; Wang, D.; Post, M.; Alper, H. Adv. Synth. Catal. 2007, 349, 2145–2150; (e) Polshettiwar, V.; Varma, R. S. Chem. Eur. J. 2009, 15, 1582–1586.
- (a) Zeng, T.; Chen, W.-W.; Cirtiu, C. M.; Moores, A.; Song, G.; Li, C.-J. Green Chem. 2010, 12, 570–573; (b) Mojtahedi, M. M.; Abaee, M. S.; Alishiri, T. Tetrahedron Lett. 2009, 50, 2322–2325.
- 10. For a review, see Lim, C. W.; Lee, I. S. Nano Today 2010, 5, 412-434.
- (a) Polshettiwar, V.; Varma, R. S. Org. Biomol. Chem. 2009, 7, 37–40; (b) Chen, H. W.; Murugadoss, A.; Hor, T. S. A.; Sakurai, H. Molecules 2011, 16, 149–161.
- 12. Chakraborty, D.; Malik, P. Tetrahedron Lett. 2010, 51, 3521–3523.
- Chakraborty, D.; Majumder, C.; Malik, P. Appl. Organometal. Chem. 2011, 25, 487–490.
 Nicker M. Marchene, M. Barl, P. D. Lee, A. Sing, C. P. Marcen, P. S. Org. Lett.
- 14. Nair, V.; Varghese, V.; Paul, R. R.; Jose, A.; Sinu, C. R.; Menon, R. S. Org. Lett. 2010, 12, 2653–2655.
- Kumar, V. K. R.; Krishnakumar, S.; Gopidas, K. R. Eur. J. Org. Chem. 2012, 3447– 3458.
- 16. Cui, L.-Q.; Liu, K.; Zhang, C. Org. Biomol. Chem. 2011, 9, 2258–2265.
- Dobele, M.; Vanderheiden, S.; Jung, N.; Brase, S. Angew. Chem., Int. Ed. 2010, 49, 5986–5988.
- Leggio, A.; De Marco, R.; Perri, F.; Spinella, M.; Liguori, A. Eur. J. Org. Chem. 2012, 114–118.
- 19. Fujihara, T.; Xu, T.; Semba, K.; Terao, J.; Tsuji, Y. Angew. Chem., Int. Ed. 2011, 50, 523–527.
- 20. Chiang, P.-C.; Bode, J. W. Org. Lett. 2011, 13, 2422–2425.
- Qiu, J. C.; Pradhan, P. P.; Blanck, N. B.; Bobbitt, J. M.; Bailey, W. F. Org. Lett. 2012, 14, 350–353.