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Synthesis of aryl 2-oxazolines from aromatic nitriles and aminoalcohols using magnetically recoverable Pd/Fe_3O_4

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ABSTRACT

This paper describes the synthesis of aromatic 2-oxazolines from aromatic aldehydes and 2-aminoalcohols using magnetically recoverable Pd/Fe_3O_4. This method is found to be applicable for wide range of aromatic nitriles and amino alcohols. High catalytic activity and ease of recovery using an external magnetic field are additional eco-friendly attributes of this catalytic system. The catalyst was recycled for five times without significant loss of catalytic activity.

Key words: Oxazolines, aromatic nitriles, Magnetically recoverable Pd/Fe_3O_4, Amino alcohols.

INTRODUCTION

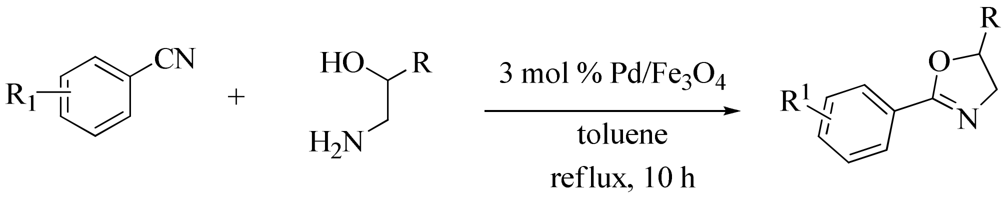
Construction of nitrogen containing five-member heterocycles is an important synthetic strategy for organic chemist due to their wide range of applicability in synthesis of various biologically active compounds and their scope as asymmetry ligand in catalysis. Among them, 2-oxazolines, (4,5-dihydrooxazoles) exist in variety of natural products and biologically active compounds and as enzyme inhibitors.[1] Few of the natural products having oxazoline frame work are : Bistratamide, acinetobactin, ascidiacyclamide, *trans*, *trans*- ceratospongamide, agrobactin, westiellamide .[2]

Oxazoline derivatives exhibit several pharmaceutical activities such as antidiabetic, antihypertensive, antidepressive, anticancer, anti HIV-1, antitumor and antialzheimer activities to name a few.[3] Optically active mono- and bis- oxazolines are used as chiral auxillaries and ligands in asymmetric synthesis.[4] Achiral oxazolines finds their use as an important protecting group, and a valuable intermediate in organic synthesis.[5]

Numerous methods for the construction of 2-oxazolines have been reported, from carboxylic acids, esters, nitriles, aldehydes, hydroxyamides and from olefins.[6] Adolfsson and co-workers prepared chiral 2-(aminoalkyl)oxazolines from α-amino acids and 1,2-amino alcohols by conventional method and later some of them have developed a synthesis of oxazolines by using carboxylic acids and amino alcohols.[7] Furthermore, Natale and co-workers and Mashima and co-workers were developed a one-pot direct synthesis of 2-oxazolines from ester and amino alcohols using $LnCl_3$ and Zinc triflate respectively.[8] Recently Bedekar and co-workers found that natural kaolinitic clay as an effective as catalyst for the conversion of aromatic and aliphatic nitriles with 1, 2-aminoalcohol to 2-oxazolines.[9]

Heterogeneous catalysis is particularly attractive as it allows the production and ready separation of large quantities of products with the use of a small amount of catalyst. Magnetic nanoparticles are a class of nanostructured materials of current interest, due largely to their advanced technological and medical applications, envisioned or realized.[10] Among the various magnetic nanoparticles under investigation, Fe_3O_4 nanoparticles are arguably the most extensively studied[11] and recently emerged as promising supports for immobilization metal nanoparticles. Fe_3O_4-supported metal catalysts can be separated from the reaction medium by an external permanent magnet. Pd/Fe_3O_4 was were prepared according to literature[12] and the amount of palladium in the catalyst was determined with an inductively coupled plasma, atomic emission spectroscopy (ICPAES) instrument and Palladium content was measured as 0.14 mmolg^{-1}.

In the present work, we report our investigations on the application of Fe_3O_4 supported Pd(0) nanoparticles (Pd/Fe_3O_4) for the synthesis of practical and atom-economic aromatic 2-oxazolines from the reaction of aromatic nitriles and 2-aminoalcohols (Scheme 1).



Scheme 1

MATERIALS AND METHODS

4. Experimental Section

4.1. General

All chemicals were purchased from Sigma-Aldrich and S.D Fine Chemicals, Pvt. Ltd. India and used as received. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F_{254} plates. All the other chemicals and solvents were obtained from commercial sources and purified using standard methods. The IR spectra of all compounds were recorded on a Perkin-Elmer, Spectrum GX FTIR spectrometer. The IR values are reported in reciprocal centimeters (cm^{-1}). The ^{1}H, ^{13}C NMR spectra were recorded on a Varian- 400 MHz, Bruker-Avance 300 MHz Spectrometer. Chemical shifts (δ) are reported in ppm, using TMS (δ =0) as an internal standard in $CDCl_3$. ESI mass spectra were recorded on a Finnigan LCQ Advantagemax spectrometer.

4.2. Typical experimental procedure:

To a solution of benzonitrile (1 mmol), amino alcohol (1.2 mmol) in toluene (3 ml), Pd/Fe_3O_4 (1.5 mol %) was added. The reaction mixture was stirred at 100 ^oC and monitored by TLC. After completion of the reaction, the reaction mixture was quenched with $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organics were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel to afford the pure product. All products were characterized by IR, ^1H NMR, ^{13}C NMR and mass spectroscopic techniques.

Reuse of Catalyst. After completion of the reaction the catalyst was recovered by filtration and washed several times with ethyl acetate and then ether and dried for further reuse. The catalyst showed consistent activity for five cycles.

Spectroscopic data for the representative compounds:

4.2.1. 5-methyl-2-phenyl-4,5-dihydrooxazole (Table 2, Entry 1): ^1H NMR δ(300 MHz, $CDCl_3$) 7.86 (d, *J* = 8.5 Hz, Ar, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, Ar, 2H), 4.70 – 4.85 (m, 1H), 4.05 (dd, *J* = 9.3 Hz, 9.3 Hz, 1H), 3.52 (dd, *J* = 7.4 Hz, 7.4 Hz), 1.37 (d, *J* =6.1Hz, $-CH_3$, 3H). EI MS (m/z): 161 (M^+).

4.2.2. 5-methyl-2-p-tolyl-4,5-dihydrooxazole (Table 2, entry 2): ^1H NMR δ(300 MHz, $CDCl_3$) 7.80 (d, *J* = 7.9 Hz, Ar, 2H), 7.18 (d, *J* = 7.9 Hz, Ar, 2H), 4.77 – 4.87 (m, 1H), 4.11 (dd, *J* = 9.3 Hz, 9.2 Hz, 1H), 3.57 (dd, *J* = 7.4 Hz, 7.2 Hz), 2.4 (s, $-CH_3$, 3H), 1.43 (d, *J* = 6.0Hz, $-CH_3$, 3H). EI MS (m/z): 175 (M^+).

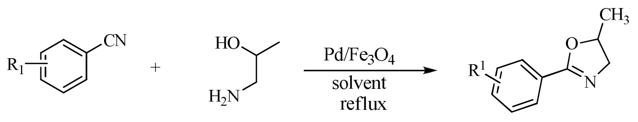
4.2.3. 4-ethyl-2-p-tolyl-4,5-dihydrooxazole (Table 2, Entry 7): ^1H NMR δ(300 MHz, $CDCl_3$) 7.82 (d, *J* = 8.1 Hz, Ar, 2H), 7.20 (d, *J* = 7.9 Hz, Ar, 2H), 4.46 (t, *J* = 7.9 Hz, 1H), 4.17- 4.43 (m, 1H), 4.02 (t, *J* = 7.9 Hz, 1H), 2.42 (s, $-CH_3$, 3H), 1.57 – 1.82 (m, 2H), 1.3 (t, *J* = 7.4 Hz, 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 157.4, 137.1, 134.1, 131.7, 130.2, 120.6, 111.8, 56.1, 11.6. EI MS m/z 189 (M^+).

4.2.4. 4-methyl-2-p-tolyl-4,5-dihydrooxazole (Table 2, Entry 12): ^1H NMR δ(300 MHz, $CDCl_3$) 7.81 (d, *J* = 7.9 Hz,Ar, 2H), 7.20 (d, *J* = 7.9 Hz, Ar, 2H), 4.51 (t, *J* = 9.0 Hz, 8.1 Hz, 1H), 4.31- 4.43 (m, 1H), 3.94 (t, J = 7.5 Hz, 7.7 Hz, 1H), 2.42(s, $-CH_3$, 3H), 1.38 (d, J = 6.6 $-CH_3$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 151.8, 149.3, 135.6, 124.9, 123.1, 74.2, 62.0, 29.6, 21.3. EI MS (m/z): 175 (M^+).

RESULTS AND DISCUSSION

In our initial studies, various solvents were investigated using benzonitrile and 1-aminopropan-2-ol as model substrates to know solvent effect on the synthesis of oxazolines (Table 1). The reaction conditions were optimized and the best conditions were found to be 1.5 mol % of Pd/Fe_3O_4 and toluene as the solvent as shown in Table 1, entry 1. By virtue of these optimized conditions, the reaction afforded the desired product in 85 % yield. Subsequently, the reaction condition was optimized by employing different solvents, wherein various polar and non polar solvents were examined and it was found that all of them had negative influence on the reaction to different degrees (Table 1, entries 2 - 8).

Table 1. Optimization of reaction conditions for the synthesis of oxazolinies.[a]



Entry	Solvent	Time (h)	Yield (%)[b]
1	Toluene	10	85
2	Benzene	10	60
3	CH_2Cl_2	10	20
6	DMF	24	0
7	DMSO	24	0
8	1,4 dioxane	24	35
9	CH_3CN	24	15
10	CH_3NO_2	10	48

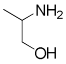
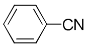
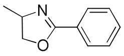
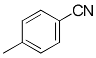
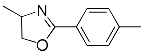
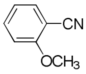
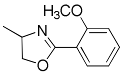
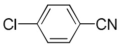
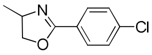
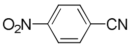
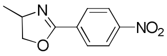
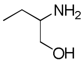
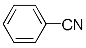
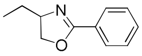
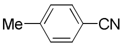
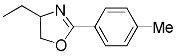
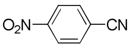
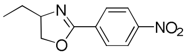
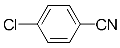
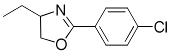
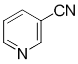
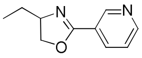
[a] *Reaction conditions: benzonitrile (1 mmol), 1-aminopropan-2-ol (1.2 mmol), Pd/Fe_3O_4 (1.5 mol%) and solvent (3 mL) at their reflux temperature.*

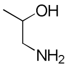
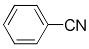
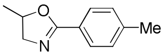
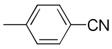
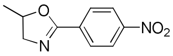
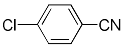
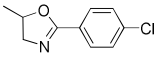
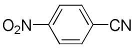
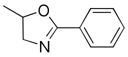
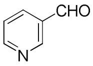
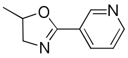
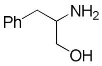
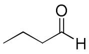
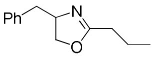
The general applicability of this reaction was evaluated with diverse aldehydes and amino alcohols. In case of 1-amino-propan-2-ol as the amino-alcohol variant, it was observed that the reaction yielded better results for electron releasing substrates (Table 2, entries 1-5). When 2-aminobutan-1-ol was taken the substrate, electron withdrawing aldehydes yielded better results than electron releasing one (Table 2, entries 6-10). Overall the yields are better compared to 1-amino-propan-2-ol. When the reaction was carried out with a hetero-aromatic aldehyde, pyridine-3-aldehyde and the yield was moderate (Table 2, entry 10).

With 2-aminopropan-1-ol, electron withdrawing groups gave better yield compared to electron donating substrate. (Table 2, entry 11-15). Aliphatic aldehyde, *n*-butyraldehyde with 3-amino-4-phenylbutan-2-ol gave the desired oxazoline in reasonable amount (Table 2, entry 16).

To check the recyclability of the catalyst, as can be seen from Table 3, the reaction was performed with benzonitrile and amino alcohol. The catalyst was separated from the reaction mixture by applying external magnetic field and reused without significant loss of catalytic activity.

Table 2: Synthesis of aromatic 2-oxazolines from different benzonitriles and amino alcohols[a]

Entry	Amino alcohol	arylnitrile	Product	Yield(%)
1				77
2				73
3				78
4				55
5				59
6				84
7				62
8				74
9				83
10				66

Entry	Amino alcohol	Aldehyde	Product	Yield(%)
11				61
12				96
13				78
14				82
15				61
16				58

[a] *Reaction conditions: benzonitrile (1 mmol), amino alcohol (1.2 mmol), Pd/Fe_3O_4 (1.5 mol %) and toluene (3 mL) at 100 °C for 10 h.*

Table 3. Recovery and reuse of Pd/Fe_3O_4 nanoparticles for the synthesis of phenyl-2-oxazoline [a]

Entry	Yield (%)[b]					Average yield (%)
	First	Second	Third	Fourth	Fifth	
1	77	75	75	73	70	74

[a]Reaction conditions: benzonitrile (1 mmol), amino alcohol (1.2 mmol), Pd/Fe_3O_4 (1.5 mol %) and toluene (3 mL) at 100 °C for 10 h.

CONCLUSION

It can be concluded that a simple and straightforward method for the synthesis of the oxazoline from benzonitrile and an amino alcohol using magnetically recoverable Pd/Fe_3O_4 as the catalyst have been described. The reaction was carried out under milder condition and no other side products are obtained. The new catalytic reactions presented in this letter could be a meaningful addition to the existing methods

REFERENCES

[1] J. V. Greenhill, L. Lue, in: G.P. Ellis, D.K. Luscombe (Eds.), *Progress in Medicinal Chemistry*, vol. 3, Elsevier, NY, **1993**.

[2] (a) S. V. Downing, E. Aguilar, A. I. Meyers, *J. Org. Chem.* **1999,** *64*, 826; (b) W. M. Wuest, E. S. Sattely, C. T. Walsh *J. Am Chem Soc*. **2009**, *131*, 5056; (c) Y. Hamamoto, M. Endo, M. Nakagawa, T. Nakanishi, K. Mizukawa, *Chem. Commun.* 1983, 323; (d) Z. Chen, J. Deng, T. Ye, ARKIVOC, **2003**, 268; (e) T. Peterson, J. B. Neilands, *Tetrahedron Lett.* **1979**, *20*, 4805; (f) G. Haberhauer, E. Drosdow, T. Oeser, F. Rominger, *Tetrahedron*, **2008**, *64*, 1853.

[3] (a) F. Rondu, G. Lr Bihan, X. Wang, A. Lamouri, E. Touboul, G. Dive, T. Bellahsene, B. Pfeiffer, P. Renard, B. Guardiola-Lemaı ˆtre, D. Mane´chez, L. Pe´nicaud, A. Ktorza, J. J. Godfroid, *J. Med. Chem*. **1997**, *40*, 3793; (b) P. Bousquet, J. Feldman, *Drugs* **1999**, *58*, 799; (c) E. S. Vizi, *Med. Res. Rev*. **1986**, *6* , 431; (d) P. Wipf, P.C. Fritch, *Tetrahedron Lett.* **1994**, *35*, 5397; (e) R. J. Boyce, G. C. Mulqueen, G. Pattenden, *Tetrahedron Lett*. **1994**, *35*, 5705; (f) P. Wipf, S. Venkatraman, *Synlett* **1997**, 1; (g) M. Tomizawa, A. Cowan, J.E. Casida, *Toxicol. Appl. Pharmacol*. **2001**,*177*, 77.

[4] (a) G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2006**, *106*, 3561; (b) H. A. McManus, P. J. Guiry, *Chem. Rev*., **2004**, 104 (9), 4151.

[5] (a) J. A. Frump, *Chem. Rev*. **1971**, *71*, 483; (b) T. W. Greene, P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, 2nd ed. J. wiley: New York, **1991**.

[6] (a) P.J. Kocienski, *Protecting Groups;* Enders, D.; Noyori, R.; Trost, B.M., Eds.; George Thieme Verlag: Stuttgart, New York, **1994**.

[7] From Acids: (a) P. Vastila, I. M. Pastor, H. Adolfsson, *J. Org. Chem*. **2005**, *70*, 2921; (b) S. Rajaram, M. S. Sigman, *Org. Lett.*, **2002**, *4*, 3399; (c) C. O. Kangani, D. E. Kelley, *Tetrahedron Lett*. **2005**, *46*, 8917; (d) A. Cwik, Z. Hell, A. Hegedus, Z. Finta, Z. Horvath, *Tetrahedron Lett.* **2002**, *43*, 3985.

[8] (a) P. Zhou, J. E. Blubaum, C.T. Bums, N. R. Natale, *Tetrahedron Lett.* **1997**, *38*, 7019; (b) T. Ohshima, T. Iwasaki, K. Mashima, *Chem. Commun.* **2006**, 2711.

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[9] (a) I. M. Baltork, V. Mirkhani, M. Moghadam, S. Tangestaninejad, M. A. Zolfigol, M. Abdollahi-Alibeik, A. R. Khosropour, H. Kargar, S. F. Hojati, *Catal. Commun.* **2008**, *9*, 894; (b) I. M. Baltork, M. Moghadam, S. Tangestaninejad, V. Mirkhani, S. F. Hojati, *Catal. Commun.* **2008**, *9*, 1153; (c) G.K. Jnaneshwara, V.H. Deshpande, M. Lalithambika, T. Ravindranathan, A.V. Bedekar, *Tetrahedron Lett.* **1998**, *39,* 459.
[10] (a) C. T. Yavuz, J. T. Mayo, W. W. Yu, A. Prakash, J. C. Falkner, S. Yean, L. L. Cong, H. J. Shipley, A. Kan, M. Tomson, D. Natelson, V. L. Colvin, *Science* **2006**, *314*, 964; (b) S. H. Sun, C. B. Murray, D. Weller, L. Folks, A. Moser, *Science* **2000**, *287*, 1989; (c) M. K. Yu, Y. Y. Jeong, J. Park, S. Park, J. W. Kim, J. J. Min, K. Kim, S. Jon, *Angew. Chem., Int. Ed.* **2008**, *47*, 5362.
[11] (a) A. G. Roca, M. P. Morales, K. O'Grady, C. J. Serna, *Nanotechnology* **2006**, *17*, 783; (b) Y. H. Zheng, Y. Cheng, F. Bao, Y. S. Wang, *Mater. Res. Bull.* **2006**, *41*, 525; (c) C. Lang, D. Schueler, D. Faivre, *Macromol. Biosci.* **2007**, *7*, 144; (c) P. Majewski, B. Thierry, *Crit. Rev. Solid State Mater. Sci.* **2007**, *32*, 203.
[12] D. Guin, B. Baruwati, S. V. Manorama, *Org. Lett.* **2007**, *9*, 1419.