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ECONOMICAL AND ECO-FRIENDLY METHOD FOR THE REDUCTION OF HETEROCYCLICS POSSESSING α, β - UNSATURATED ACID SYSTEMS USING NOVEL REDUCTION METHOD

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ABSTRACT

Reduction of hetero aryl acrylic acid to hetero aryl propionic acids was achieved using hydrazine hydrate and an oxidizing agent and yields were reported. Moreover, reduction of hetero aryl acrylic acids was also carried out using Palladium charcoal method and the yields of both the methods were compared. It was observed that though the yields were slightly less in hydrazine reduction method, the method appeared to be economical, eco-friendly with operational simplicity, reasonable yields and easy workup procedures which may be applied to large scale synthesis.

KEYWORDS: Diimide, Reduction, Arylacrylic acids, Eco-friendly.

INTRODUCTION

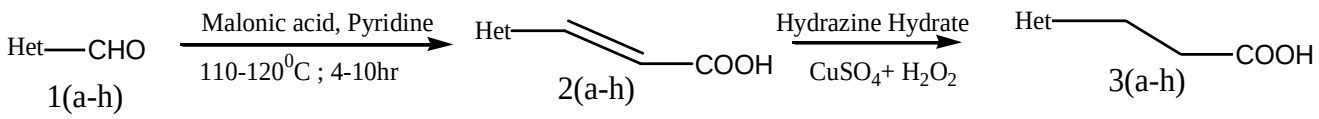
Reduction of carbon carbon double bonds is normally accomplished by using hydrogen and heterogeneous transition metal catalysts such as Rh/C, Pd/C, Raney Nickel, or Adams catalyst (PtO2).[1,2] Alternatively, homogeneous transition metal complexes such as Wilkinson's catalyst are also applied. Although these hydrogenations with transition metal catalysts often proceed efficiently, there are important limitations such as hydrogenolysis of benzylic, allylic and propargylic alcohols and amines is often inevitable.[3-5] In addition, several functional groups such as nitro groups, benzylic ketones and aryl halides are rapidly

reduced as well and moreover, these catalysts are highly expensive and in some cases disposal is the major problem. Reductions using hydrazine hydrate (diimide method) was a very old and establioshed method and has been in use for decades for the reduction of allylic double bonds, C=O, C=N and N=N bonds. In this method, the hydrogen is liberated *in situ* from imide(NH=NH), produced by the reaction of hydrazine hydrate and oxidizing agents such as hydrogen peroxide, sodium periodate, ferricyanide etc., in presence of metal catalysts such as copper sulphate, ferric oxide etc. This method could not be popularized because of low yields.

In our earlier study,[7] we reported synthesis of substituted pyrazole propionic acids from pyrazole acrylic acids using diimide reduction method. In continuation of this work, in the present study, we undertook the reduction of nine different heteroaryl acrylic acids namely, 2-furyl acrylic acid, Indole-3- acrylic acid, Imidazole-4-acrylic acid, Benzofuran-3- acrylic acid, Oxazole-4-acrylic acid, Pyridine-3-acrylic acid, Pyrazine-2- acrylic acid and quinoline-3-acrylic acid into corresponding propionic acids using both diimide reduction and palladium charcoal reduction method. We chose these heteroaryl acids as they are the core moieties in medicinally active compounds such as anti-inflammatory agents, cardiovascular agents, glucagon receptor modulators etc.

EXPERIMENTAL METHODS

Melting points were determined in open capillary tubes using Analab melting point apparatus and are uncorrected. Purity of the compounds was verified by a single spot in TLC using E-Merck silica Gel F254, 0.25 mm aluminum plates. Visualization was accomplished with UV light (254 nm) and iodine chamber. The IR spectra were recorded on Schimadzu FT-IR Spectrophotometer by using 1% potassium bromide discs. Mass spectra of the compounds were recorded on mass spectrometer (Agilent 1100series; EI/ESI-MS). All the 1H NMR spectra were recorded on Brucker 300 MHz Spectrometer using CDCl3/DMSO as solvent and tetramethylsilane as an internal Standard. Chemical shift values are listed in δ scale. Elemental analyses were carried out on a Carlo Erba 106 and Perkin Elmer model 240 analyzers.



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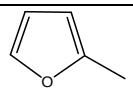
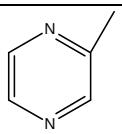
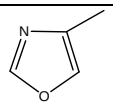
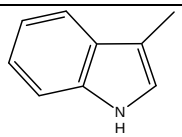
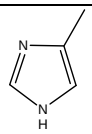
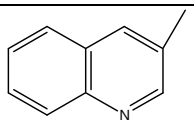
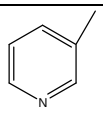
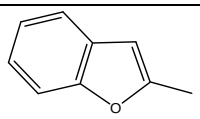
a		e	
b		f	
c		g	
d		h	

Scheme 1. General scheme of synthesis of hetero aryl propionic acids

General procedure for the preparation of heteroaryl acrylic acids[8]

Equimolar amounts of heteroaryl carbaldehyde and malonic acid was dissolved in pyridine (10 mL) containing a catalytic amount of piperidine (0.5 mL) and the reaction mixture was refluxed for 4-10 h on oil bath. The progress of the reaction was monitored by TLC and then the reaction mixture was poured into crushed ice with stirring and acidified with conc. HCl to remove any traces of pyridine. The resultant precipitate was filtered, washed with water and dilute HCl, dried and recrystallized from glacial acetic acid or any appropriate solvent.

General procedure for the reduction of heteroaryl acrylic acids into propanoic acids by Diimide method

Heteroaryl acrylic acid (0.01 mole) was dissolved in hydrazine hydrate (99%) in a 250 mL conical flask containing 20 mL of water. The flask was immersed in an ice bath and to which added few crystals of $CuSO_4$ with stirring. To the cold solution, hydrogen peroxide (30%) was added slowly such that the temperature remains below 30^0C. The reaction mixture was then allowed to stand in ice bath for 30 min to one hour followed by 10 min at room temperature. To the above mixture, concentrated HCl was added with stirring. An oily product was separated which on cooling gave crystalline compound.

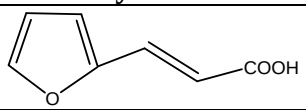
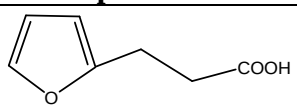
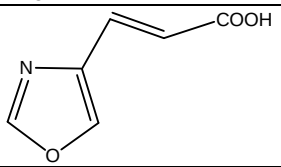
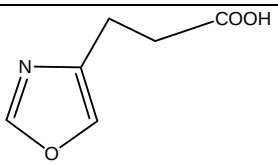
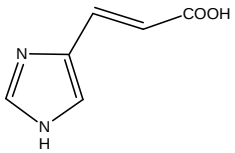
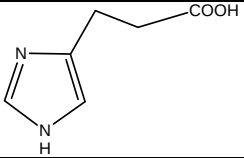
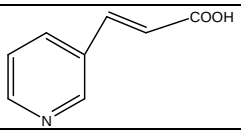
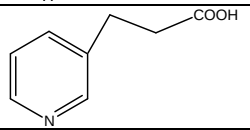
General procedure for the reduction of heteroaryl acrylic acids into propanoic acids by Palladium-charcoal method

To a solution of heteroaryl acrylic acid in ethyl acetate was added 20% palladium–charcoal, ammonium formate in ethyl acetate with constant stirring. The reaction mixture was stirred for overnight and the excess ethyl acetate was distilled off under reduced pressure. The precipitate was filtered, dried and recrystallized from appropriate solvent.

RESULTS AND DISCUSSION

The synthesis of different heteroaryl propionic acids (3a-h) was carried out as per the scheme-1. From different heteroaryl aldehydes (1a-h), hetero aryl acrylic acids (2a-h) were synthesized by condensing with malonic acid in pyridine under reflux for 4-10 hr. The structures of the acrylic acids were conformed on the basis of FTIR, Mass and proton NMR spectral data. Subsequently, the acrylic acids (2a-h) were converted into corresponding propionic acids by diimide and palladium charcoal reduction methods and structures were further confirmed by physical, spectral data and the yield and reaction times were compared (Table 1). It was observed that there was variation in reaction time from 0.5 hr to 1.0 hr in case of diimide method while the reaction times were 8-14 hr in case of palladium charcoal method. In six cases, we found that the yields were slightly less in diimide method when compared to palladium charcoal method. However, in case of **3d** and **3f** the yields were slightly more with diimide method.

Table 1. Comparison of yields and reaction times between diimide method and Pd-Charcoal method.

S. N.	Heteroaryl acrylic acid	Heteroaryl Propionic acid	% Yield		Reaction time (hrs)	
			Diimide	Pd-Charcoal	Diimide	Pd-Charcoal
1			66	72	0.5	12
2			58	64	0.6	14
3			60	66	1.0	10
4			70	62	0.5	08

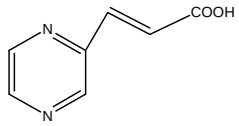
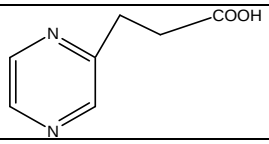
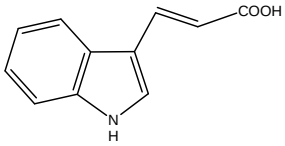
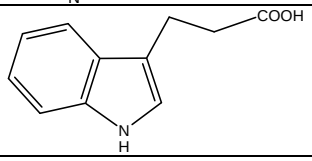
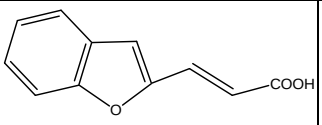
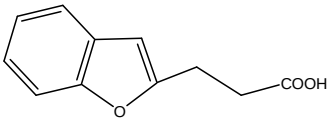
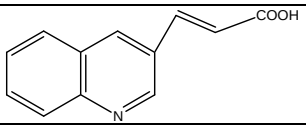
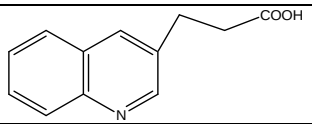
5			58	64	0.8	12
6			72	65	0.6	07
7			68	75	0.9	08
8			63	70	1.0	12

Table 2. Spectral data of heteroaryl propionic acids (3a-h)

Compound	Proton NMR(δ)	IR (cm^{-1}; KBR disc)	Mass (m/z)
3a	11.19(s, 1H, OH), 7.89(d, 1H, Ar-H), 7.66(d, 1H, Ar-H), 6.11(s, 1H, Ar-H), 2.89 (s, 2H, CH_2), 2.49 (s, 2H, CH_2)	3350 cm^{-1} (-O-H), 2900 cm^{-1} (-C-H),1726 cm^{-1}(C-C)	140(M^+)
3b	11.05(s, 1H, OH), 7.85(d, 1H, Ar-H), 7.56(d, 1H, Ar-H), 2.81 (s, 2H, CH_2), 2.59 (s, 2H, CH_2)	3351 cm^{-1} (-O-H), 2902 cm^{-1} (-C-H),1725 cm^{-1}(C-C)	142(M+1)
3c	13.04(s, 1H, NH of imidazole), 11.05(s, 1H, OH), 7.78(d, 1H, Ar-H), 7.54(d, 1H, Ar-H), 2.78 (s, 2H, CH_2), 2.58 (s, 2H, CH_2)	3366 cm^{-1} (-O-H), 2900 cm^{-1} (-C-H),1728 cm^{-1}(C-C)	140(M^+)
3d	11.15(s, 1H, OH), 8.49-7.96(m, 3H, Ar-H), 7.34(d, 1H, Ar-H), 2.82 (s, 2H, CH_2), 2.57 (s, 2H, CH_2)	3363 cm^{-1} (-O-H), 2910 cm^{-1} (-C-H),1724 cm^{-1}(C-C)	152 (M+1)
3e	11.01(s, 1H, OH), 8.57-8.25(m, 3H, Ar-H), 7.69-7.42(m, 4H, Ar-H), 2.81(s, 2H, CH_2), 2.59 (s, 2H, CH_2)	3357 cm^{-1} (-O-H), 2903 cm^{-1} (-C-H),1725 cm^{-1}(C-C)	152(M^+)
3f	13.02(s, 1H, NH of benzimidazole), 11.05(s, 1H, OH), 7.89-7.46(m, 4H, Ar-H), 7.31(d, 1H, Ar-H), 2.79 (s, 2H, CH_2), 2.69(s, 2H, CH_2)	3364 cm^{-1} (-O-H), 2920 cm^{-1} (-C-H),1725 cm^{-1}(C-C)	190(M+1)
3g	11.02(s, 1H, OH), 8.15-8.01(d, 2H, Ar-H), 7.69-7.42(m, 4H, Ar-H), 2.79(s, 2H, CH_2), 2.56 (s, 2H, CH_2)	3354 cm^{-1} (-O-H), 2910 cm^{-1} (-C-H),1725 cm^{-1}(C-C)	201 (M^+)
3h	11.00(s, 1H, OH), 7.51-7.43(d, 2H, Ar-H), 7.20-7.11(m, 2H, Ar-H), 6.69(d, 1H, Ar-H), 2.87(s, 2H, CH_2), 2.64(s, 2H, CH_2)	3350 cm^{-1} (-O-H), 2900 cm^{-1} (-C-H),1731 cm^{-1}(C-C)	190(M^+)

CONCLUSION

The present study involved in the conversion of heteroaryl acrylic acids to propionic acids using hydrazine hydrate reduction was found to have some advantages like cost affordability, operational simplicity and environmental friendly even when applied to large scale synthesis. The procedures that we have followed can be applied in the synthesis of drugs like oxaprozin, eprosartan and indole-3-propionic acid and in many other anti-inflammatory, antidiabetic and cardiovascular drugs.

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