Asian Journal of Chemistry; Vol. 27, No. 12 (2015), 4358-4360

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.19127

Catalytic Hydrogenation of Substituted Pyridines with PtO_2 Catalyst

REDDYMASU SREENIVASULU[1], KALLURI VENKATA SRI RANGANATH[2] and RUDRARAJU RAMESH RAJU[1,*]

[1]Department of Chemistry, Acharya Nagarjuna University, Nagarjuna Nagar-522 510, India
[2]Department of Chemistry, Guru Ghasidas Viswavidyalaya (Central University), Bilasapur-495 009, India

*Corresponding author: Fax: +91 863 2293292; E-mail: rrraju1@gmail.com

Received: 24 February 2015; *Accepted*: 13 April 2015; *Published online*: 29 August 2015; AJC-17471

The challenging methodology for the hydrogenation of substituted pyridines with mild reducing catalyst PtO_2 in glacial acetic acid as a protic solvent using clean hydrogen under 50 to 70 bar atmospheric pressure leads to the synthesis of piperidine derivatives is reported. All the hydrogenated compounds were characterized by ^{1}H NMR and ESI-MS.

Keywords: Piperidines, Hydrogenation, PtO_2, Substituted pyridines.

INTRODUCTION

The most powerful catalytic hydrogenation was one of the ways to produce a wide array of important compounds in large quantities using inexpensive and clean hydrogen gas without forming any waste. The hydrogenation of nitrogen containing heterocyclic compounds has been investigated by different catalysts such as palladium, nickel, rhodium, ruthenium and platinum. The hydrogenation of substituted pyridines is of particular interest to scientists[1-8] as the resulting functionalized piperidines are most important intermediates in the synthesis of both natural products and pharmaceuticals[9-12]. Mono substituted piperidine derivatives were synthesized by the catalytic hydrogenation of the corresponding pyridines with ruthenium dioxide catalyst at high temperatures and larger atmospheric pressures[13]. Further the lower atmospheric pressures favour the catalytic hydrogenation of pyridines with rhodium on carbon catalyst[14]. The catalytic hydrogenation of pyridines with aryl substituent's leads to the selective reduction of the heterocyclic ring was desired[15,16] under acidic conditions.

The synthesis of pinacol derivative of pyridines has been achieved by the coupling of selective hydrogenated acetyl pyridines with adams catalyst, PtO_2[17]. Partial catalytic hydrogenation of catechol, 4-phenyl pyridine, 4-(3-phenyl propyl) pyridine and N,N-alkyl amino pyridines had done with the mild reducing catalyst PtO_2[18-20]. N-substituted pyridinium salts undergo catalytic hydrogenation with PtO_2 afforded piperidine derivatives[21]. The unexpected product piperidine hydrochloride was also obtained by the catalytic hydrogenation of nicotinic acid, 3-hydroxy pyridine hydrochloride, 3-pyridyl diphenyl acetate hydro chloride and 2-methoxy pyridine with PtO_2[22-24].

cis-Piperidine derivatives were also synthesized by the catalytic hydrogenation of certain pyridine derivatives with acidified PtO_2 catalyst[25,26].

Due to the aromatic nature of pyridine nucleus, the hydrogenation of these heterocyclic moieties often requires the elevated temperatures in combination with significant hydrogen pressures and the survey of literature reveals that most of the pyridine derivatives was not satisfactorily reduced with mild reducing catalyst PtO_2 at high temperatures. In this paper we reported one methodology to the synthesis of piperidine derivatives from the catalytic hydrogenation of pyridine substrates with mild reducing catalyst PtO_2 at room temperatures only. The catalytic hydrogenation of substituted pyridines by the absorption of three moles of clean hydrogen with PtO_2 as catalyst under 50 to 70 bar atmospheric pressure in glacial acetic acid at room temperature then afforded piperidine derivatives (Fig. 1).

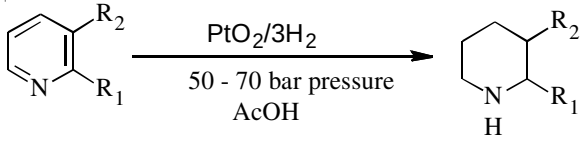


Fig. 1. Catalytic hydrogenation of substituted pyridines with PtO_2 catalyst

EXPERIMENTAL

All the starting materials and reagent (PtO_2) were purchased from Sigma Aldrich and TCI companies. Solvents were purchased from Merck and used without further purification. The Progress of the reactions were monitored by thin layer chromatography (TLC) with ninhydrin charring.

TABLE-1
CATALYTIC HYDROGENATION OF SUBSTITUTED PYRIDINE DERIVATIVES UNDER VARIOUS CONDITIONS

Entry	Catalyst	Solvent	Time (h)	Temp. (°C)	Pressure (bar)	Yield (%)
1	PtO_2	THF	12	50	50-70	–
2	PtO_2	MeOH	12	60	50-70	–
3	PtO_2	EtOH	16	70	50-70	–
4	PtO_2	THF/conc. HCl (0.1 equiv.)	16	50	50-70	–
5	PtO_2	MeOH/conc. HCl (0.1 equiv.)	16	60	50-70	–
6	PtO_2	EtOH/conc. HCl (0.1 equiv.)	16	70	50-70	–
7	PtO_2	THF/AcOH (0.1 equiv.)	18	50	50-70	10
8	PtO_2	MeOH/AcOH (0.1 equiv.)	10	60	50-70	15
9*	PtO_2	Glacial AcOH	6-10	rt	50-70	above 50

*9th entry is the optimization condition.

^{1}H NMR spectra were recorded on Bruker 300 MHz spectrometer with tetra methyl silane was internal standard. All the chemical shift values are reported in δ units. Mass spectra were performed on direct inlet system or LC by MSD trap SL.

General protocol for the catalytic hydrogenation of substituted pyridines with PtO_2: Stirred solution of substituted pyridines (1.0 g) in acetic acid (5 mL) was treated with 5 mol % catalytic amount of PtO_2 under H_2 gas pressure. After 6-10 h, it was quenched with $NaHCO_3$ then it was extracted with ethyl acetate (3 × 20 mL), filtered through celite and dried on Na_2SO_4. The solvent was evaporated under reduced to gave residue. Further the purification of residue was done by column chromatography (Silica gel, 60-120 mesh, 5 % EtOAc in pet. ether) to furnish the substituted piperidine derivatives. All the synthesized compounds are colourless liquids.

Spectral data of piperidine compounds

2-Bromopiperidine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.52-1.79 (m, 4H), 2.08-2.37 (m, 3H), 2.73-2.85 (m, 2H), 4.72 (t, *J* = 6.3 Hz, 1H). ESI-MS: *m/z* = 164 (100 %) (M^++H), 166 (98 %).

2-Fluoropiperidine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.42-1.57 (m, 4H), 1.61-1.78 (m, 2H), 2.69-2.78 (m, 2H), 4.03 (br.s, 1H), 4.89 (m, 1H). ESI-MS: *m/z* = 104 (M^++1).

2-Methylpiperidine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (d, *J* = 6.1 Hz, 3H), 1.52-1.94 (m, 6H), 2.09 (br.s, 1H), 2.89-2.68 (m, 3H). ESI-MS: *m/z* = 100 (M^++1).

2-Methoxypiperidine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.56-1.78 (m, 6H), 2.61-2.84 (m, 3H), 3.19 (s, 3H), 3.94 (t, *J* = 7.3 Hz, 1H). ESI-MS: *m/z* = 116 (M^++1).

3-Phenylpiperidine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.56-1.86 (m, 4H), 2.56-2.78 (m, 3H), 3.11 (dd, *J* = 5.2, 7.1 Hz, 2H), 7.11-7.21 (m, 5H). ESI-MS: *m/z* = 162 (M^++1).

3-Methylpiperidine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.02 (d, *J* = 6.3 Hz, 3H), 1.43-1.66 (m, 5H), 1.94 (br.s, 1H), 2.37-2.58 (m, 2H), 2.73-2.87 (m, 2H). ESI-MS: *m/z* = 100 (M^++1).

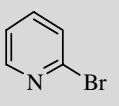
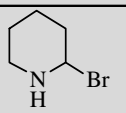
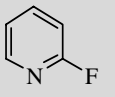
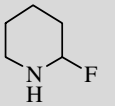
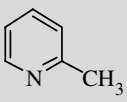
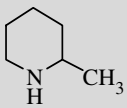
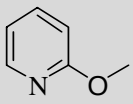
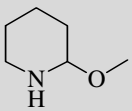
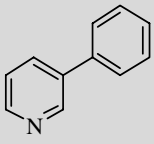
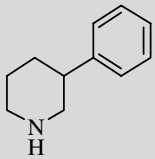
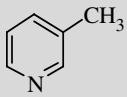
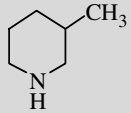
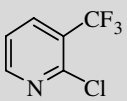
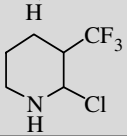
2-Chloro-3-(trifluoromethyl)piperidine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.51-1.79 (m, 4H), 2.05-2.38 (m, 1H), 2.74 (t, *J* = 5.8 Hz, 2H), 4.51 (br.s, 1H), 4.94 (d, *J* = 9.1 Hz, 1H).ESI-MS: *m/z* = 188 (M^++1).

RESULTS AND DISCUSSION

To optimize the reaction conditions, we had investigated the catalytic hydrogenation of substituted pyridine derivatives with platinum oxide in different solvents like tetrahydrofuran, methanol and ethanol, but this hydrogenation was not preceded. After a small quantity of acetic acid was added to the reaction mixture to enhance the activity of catalyst. At this condition the progress of reaction appears to a small extent, but not significantly. Further the significant progress of the reaction would achieved in better yields with glacial acetic acid was used as a protic solvent. Here the optimized results were given in Table-1.

The catalytic hydrogenation of 2-methoxy pyridine and 2-chloro pyridine in absolute methanolic hydrochloride with PtO_2 then 2-methoxy piperidine and 2-chloro piperidines were almost susceptible products, but they cannot be detected in the reduction product. Apparently the unexpected product piperidine was obtained. The expected products such as methoxy piperidine and chloro piperidine derivatives were obtained by the catalytic hydrogenation of 2-methoxy pyridine

TABLE-2
CATALYTIC HYDROGENATION OF SUBSTITUTED PYRIDINE DERIVATIVES UNDER ACETIC ACID AS A PROTIC SOLVENT AT ROOM TEMPERATURE

Entry	Reactant	Product	Time (h)	Yield (%)
1			6	53
2			6	51
3			4	68
4			8	54
5			8	55
6			6	62
7			10	58

and 2-chloro-3-trifluoro methyl pyridines with PtO_2 in glacial acetic under 50 bar atmospheric pressure at room temperature from 6-8 h. Further the hydrogenation of 2-methyl pyridine and 3-methyl pyridine with PtO_2 in glacial acetic acid under 70 bar atmospheric pressure afforded the corresponding 2-methyl and 3-methyl piperidine derivatives from 4-6 h. Under similar experimental conditions, the catalytic hydrogenation of 2-bromo and 2-fluoro pyridines gave the 2-bromo and 2-fluoro piperidine derivatives with 50 bar atmospheric pressure at 6 h. A similar protocol was applied for 3-phenyl pyridine with 60 bar atmospheric pressure yielded the 3-phenyl piperidine at 8 h (Table-2).

Conclusion

In conclusion, the catalytic hydrogenation of pyridine derivatives with PtO_2 catalyst still remains challenging methodology. The decreasing poisonous character of pyridine derivatives and enhancing the catalytic activity towards PtO_2 catalyst then the selection of glacial acetic acid was suitable protic solvent. Further our research work should be concentrated on the catalytic hydrogenation of indoles and pyrroles by the mild reducing catalyst PtO_2.

ACKNOWLEDGEMENTS

The authors are thankful to Department of Science & Technology, New Delhi, India for financial assistance in the form of Young Scientist major research project F. No. SR/FT/CS-095/2009.

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