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YTTRIUM TRIFLATE CATALYZED SYNTHESIS OF 1,4-DIHYDROPYRIDINES UNDER SOLVENT FREE CONDITIONS

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Abstract
An efficient one-step synthesis yttrium triflate catalyzed Hantzsch multi component synthesis of 1,4-dihydropyridines involving aromatic aldehyde, ethyl/methyl acetoacetate and ammonium acetate is described. The present method is an important supplement to the existing methods for the synthesis of 1,4-dihydropyridines under solvent-free, mild conditions with improved yields and it tolerates a wide variety of substituents.

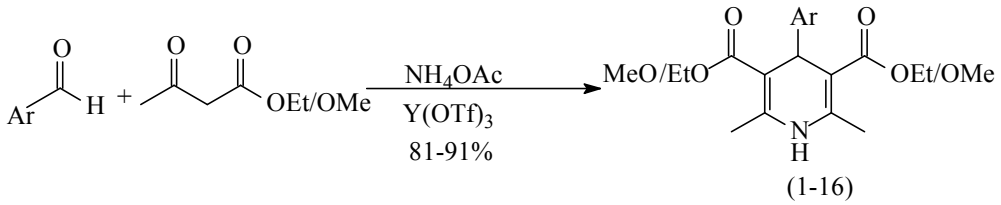
Keywords: Hantzsch reaction, 1,4-dihydropyridines, yttrium triflate.

Introduction

Synthesis of pyridine involving dihydropyridines (DHPs) as intermediates is Hantzsch discovery[i]. However in late 1980s when the four component Hantzsch reaction keeping aromatic aldehyde as one of the components resulting in 1,4-aryl-dihyropyridines led a new thrust in the area of DHP chemistry as these were acted as calcium channel blocking agents and therefore have become valuable drugs for heart diseases with useful effects on angina, hypertension and in biological systems, particularly in NADH led biological oxidation-reduction[ii]. Owing to their significant biological activity[iii], considerable attention has been paid to the synthesis of 1,4-dihydropyridines. The classical method of synthesis of DHP involves mixing of an aldehyde with ethyl acetoacetate and ammonia in acetic acid or refluxing in alcohol[iv]. We have chosen Yttrium triflate as a catalyst for the preparation of 1,4-dihydropyridines. Yttrium triflate is commercially available, water tolerable and reusable catalyst. In this paper we report a facile method of synthesis of 1,4-dihydropyridines employing $Y(OTf)_3$ as new catalyst under solvent free conditions.

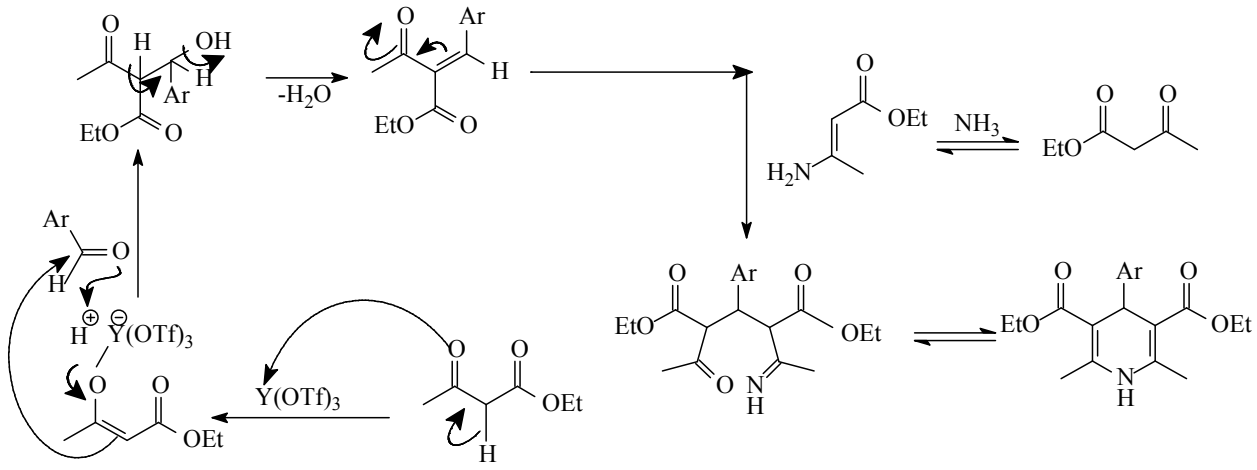
Results and discussion

The multi component cyclocondensation reaction involving aromatic aldehyde (1 mmol), ammonium acetate (1 mmol), ethyl acetoacetate (2 mmol) and yttrium triflate (0.01 mmol) under solvent free conditions was carried out at room temperature to afford the corresponding 1,4-dihydropyridines (Scheme-1).



Scheme 1. Synthesis of 1,4-Dihydropyridines.

The sixteen 1,4-dihydropyridines obtained following the Scheme -1 are given in Table-1. Tentative mechanism of the $Y(OTf)_3$ catalysis for the synthesis of 1,4-dihydropyridines is shown in Scheme-2.



Scheme 2. Tentative mechanism for $Y(OTf)_3$ catalyzed Hantzsch synthesis of 1,4-dihydropyridines.

This method was not only afforded the products in excellent yields but also avoids the problems associated with handling, safety and pollution. Yttrium triflate is eco-friendly for a variety of organic transformations, non-volatile, non-explosive, easy to handle. As the reaction was carried out under solvent-free conditions, clean products were obtained. However, traces of impurities associated with the catalytic modification were removed either by recrystalisation from ethyl acetate and pet.ether mixture (1:2V/V) or by column chromatography of the resulting crude material over silica gel (Merck 60 – 120 mesh) using ethyl acetate and pet. ether (2.5:7.5V/V) as the mobile phase. The yields presented in Table-1 are the best results obtained with a 1:1:2:0.01 molar ratio of aromatic aldehyde:ammonium acetate:ethyl acetoacetate:yttrium triflate. All the products were characterized by melting points, ^{1}H NMR, and mass spectral analysis. In Table-2 a comparative account of different Lewis acid catalyzed synthesis of dihydropyridines is presented. From the table it can be noticed that $Y(OTf)_3$ is not an efficient catalyst like that of mineral acid activated silica gel with respect to yield and reaction time. However, among the other catalysts compared, $Y(OTf)_3$ affords very good yields and in a aldehyde dependent reaction time.

Experimental

Melting points are uncorrected. ^{1}HNMR spectra were recorded at 400 MHz in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on VG Micromass 7070 H spectrometer operating at 70 ev.

General procedure for the synthesis of 1,4-dihydropyridines

A mixture of aromatic aldehyde (1 mmol), ethyl acetoacetate/ methyl acetoacetate (2 mmol), ammonium acetate (1 mmol), was taken in a 50 ml R.B flask and stirred at room temperature. To this, yttrium triflate (0.01 mmol) was added and reaction mixture was stirred at room temperature for appropriate time (Table-1). After completion of the reaction as indicated by TLC, it was poured in to ice cold water and extracted with ethyl acetate. The organic layer was washed with sodium thiosulfate and then water, dried and concentrated in vacuo. The crude product was purified by column chromatography using silica gel (60-120 mesh) and eluted with ethyl acetate: pet.ether (2.5:7.5) to afford the pure 1,4-dihydropyridine product.

Spectral data for selected compounds

2,6-Dimethyl-4-(4-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylicacid diethyl ester.(c): m.p (°C): 130 (litt-128(11)), ^{1}HNMR ($CDCl_3$) (δ): 1.20 (t, 6H, J = 8.5Hz), 2.31 (s, 6H), 4.09 (q, 4H, J = 8.2Hz), 5.03 (s, 1H), 5.11 (brs, 1H), 7.40 (d, 2H), 8.10 (d, 2H), MS (EI): m/z (%) 375 (56) $[M+H]^+$.

2,6-Dimethyl-4-(4-methoxy-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylicacid diethyl ester. (d): m.p (°C): 160 (litt-159(11)), ^{1}HNMR ($CDCl_3$) (δ): 1.23 (t, 6H, J = 7.9Hz), 2.30 (s, 6H), 3.78 (s, 3H), 4.06 (q, 4H, J = 8.4Hz), 5.01 (s, 1H), 5.23 (br, 1H), 7.55 (m, 4H). MS (EI): m/z (%) 360 (77) $[M+H]^+$.

Conclusion

Yttrium triflate is an efficient catalyst for the synthesis of a variety of substituted 1,4-dihydropyridines. The present method is an important supplement to the existing methods for the synthesis of 1,4-dihydropyridines under solvent free mild conditions with improved yields.

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References

i. Hantzsch, A.; Justus, Liebigs. Ann. Chem. 1, 215 (1882**).**

ii. (a) Coghlan, M. J.; Carroll, W. A.; Gopalakrishnan, M. J. Med. Chem. 44, 627 (2001). (b) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P., Organic Chemistry, Oxford University Press New York, (2001).

iii. Shan, R.; Velazquez, C.; Knaus, E. E. J. Med. Chem. 47, 254 (2004**).**

iv. Love, B.; Sander, K. M. J. Org. Chem. 30, 1914 (1965).

iv. Xicum, W.; Haipeng, G.; Zhengjum, Q.; Lei, L.; Helin, Y. Synth. Commun. 41, 3251 (2011).

v. Adharvana, C. M.; Syamasundar, K. Catal. Commun. 6, 624 (2005).

vii. Sabita, G.; Kiran, K. R. G. S.; Srinivas, R. C.; Yadav, J. S. Tetrahedron Lett. 44, 4129 (2003**).**

viii. Abdelmadjid, D.; Wassima, G.; Raouf, B.; Ali, B.; Salah, R.; Bertrand, C. Tetrahedron Lett. 50, 5248 **(**2009).

ix. Abdelmadjid, D.; Raouf, B.; Ali, B.; Salah, R.; Bertrand, C. Synlett 4, 509 **(**2008**).**
x. Maheswara, M.; Siddaiah, V.; Koteswara, R. Y.; Yew-Min, T.; Sridhar, C. J. Mole. Cata. A Chemical. 260, 179 **(**2006).
xi. Sabitha, G.; Arundhathi, K.; Sudhakar, K.; Sastry, B. S.; Yadav, J. S. Synth. Commun. 39, 2843 (2009**).**
xii. Nayak, A. S. Indian J. Het. Chem. 18, 2843 **(**2009**).**
xiii. Suresh, D. K.; Jagir, S. S. Synth. Commun. 39, 1957 (2009**).**
xiv. Che-Chien, C.; Song, C.; Soosung, K.; Li, K.; Xinyong, T.; Prativa, P.; Sara, F. D.; Chi-Hao, L.; James, D. S.; Richard, B. S. Bioorg. Med. Chem. 18, 3147 (2010**).**
xv. Katy, L. B.; Gemma, E. V.; Steven, V. L. Org. Lett. 10, 3627 (2008**).**

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Table 1. Yttrium triflate catalyzed Hantzsch condensation of 1,4-dihydropyridine derivatives under solvent-free conditions[#].

S.No	R	X	Time (hrs)	Yield (%)[@]	MP (°C) Obs. (Lit.)	References
A	H	OEt	3.0	91	156(158)	xi
B	4-Cl	OEt	4.0	90	141(144)	xi
C	4-NO_2	OEt	5.0	82	130(128)	xi
D	4-OCH_3	OEt	5.5	86	160(159)	xi
E	4-F	OEt	6.5	88	135(139)	xi
F	3-Cl	OEt	5.0	89	141(140)	viii
G	3-NO_2	OEt	5.5	84	164(163)	xi
H	2-NO_2	OEt	5.5	83	171(169)	xi
I	3,4,5,-Tri OMe	OEt	7.0	84	139(142)	xii
J	H	OMe	3.5	90	200(197)	xiii
K	4-Cl	OMe	5.0	88	195(198)	xiii
L	4-NO_2	OMe	5.5	83	195(197)	xiv
M	4-OCH_3	OMe	3.5	85	184(186)	xiii
N	2-NO_2	OMe	4.0	89	187(190)	xv
O	3-Cl	OMe	4.5	88	165(-)	-
P	3-NO_2	OMe	6.0	81	210(210)	xiii

The NMR and MASS data of the pure products were identical to those of the authentic samples.
@ Isolated yield.

Table 2. Comparative account of synthesis of dihydropyridines with different catalysts.

Compound	$Y(OTf)_3$		PEG-400[v]		Silicagel/ $NaHSO_4$[vi]		TMSI/NaI[vii]		PPh_3[viii]		$PhB(OH)_2$[ix]		$HClO_4$-SiO2[x]		$CeCl_3.7H_2O$[xi]	
	Time; Yield		Time; Yield		Time; Yield		Time; Yield		Time; Yield		Time; Yield		Time; Yield		Time; Yield	
	(h.)	(%)	(h.)	(%)	(h.)	(%)	(h.)	(%)	(h.)	(%)	(h.)	(%)	(h.)	(%)	(h.)	(%)
H	3	91	7	85	6	85	6	80	5	72	4	90	0.20	95	3	80
4-Cl	4	90	5	89	6	80	6	78	2	81	5	82	0.20	89	4	91
4-NO_2	5	82	6	75	8	75	-		2	92	4	92	0.33	92	3.5	82
4-OCH_3	5.5	86	7	85	6	80	6	76	3	75	5	82	0.28	92	4	82
4-F	6.5	88	-		7.5	75	8	74	-		-		-		3.5	86
3-Cl	5	89	-		-		-		3	85	4	90	-		-	
3-NO_2	5.5	84	6	90	7.5	75	-		4.5	94	4	91			5	71
2-NO_2	5.5	83	-		8	75	8	73	-		-		0.35	92	5.6	65
3,4,5,-Tri OMe	7	84	-		8	78	-		-		-		-		-	