Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Scandium(III) Triflate-Catalyzed Efficient Synthesis of Substituted 1-Pyridylimidazo-[1,5-a]-pyridines

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Published online: 04 Sep 2009.

To cite this article: Shrinivas S. Kottawar , Shaphi A. Siddiqui , Vishal P. Chavan , Wamanrao N. Jadhav & Sudhakar R. Bhusare (2009): Scandium(III) Triflate-Catalyzed Efficient Synthesis of Substituted 1-Pyridylimidazo-[1,5-a]-pyridines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:19, 3546-3549

To link to this article: http://dx.doi.org/10.1080/00397910902788158

Synthetic Communications®, 39: 3546–3549, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902788158

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Scandium(III) Triflate–Catalyzed Efficient Synthesis of Substituted 1-Pyridylimidazo-[1,5-a]-pyridines

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Abstract: An efficient synthesis of substituted 1-pyridylimidazo-[1,5-a]-pyridines has been accomplished using scandium(III) triflate as catalyst under mild conditions in excellent yields.

Keywords: Ammonium chloride, 1,2-dipyridyl ketone, Lewis acid, 1-pyridylimidazo-[1,5-a]-pyridines, scandium(III) triflate

INTRODUCTION

The synthesis of imidazo-[1,5-a]-pyridines mainly involves the acylation reaction of 2-aminomethylpyridine, followed by cyclization with phosphorus oxychloride or polyphosphoric acid[1] or thioacylation followed by ring closure using dicyclohexylcarbodiimide (DCC) or mercuric salts.[2] Other approaches include use of 2-cyanopyridine by the Vilsmeier reaction[3] or by oxidization reaction of Schiff bases in the presence of molecular sieves or metal ions, requiring two to three steps from the dipyridyl ketone.[4–8] The synthetic protocols for 1-pyridylimidazo-[1,5-a]-pyridines reported so far suffer from one or more disadvantages, such as harsh reaction conditions, poor yields, longer reaction times, and the use of hazardous reagents and often expensive acid catalysts. In addition,

Received November 3, 2008.
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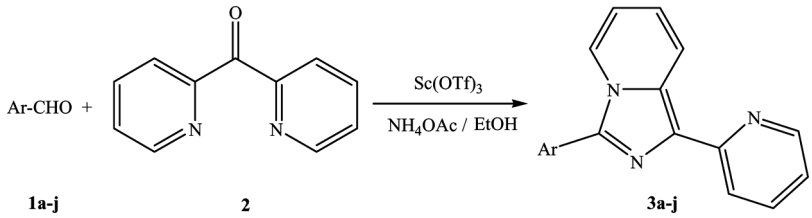

Scheme 1. Synthesis of 1-pyridylimidazo-[1,5-a]-pyridines catalyzed by scandium(III) triflate.

a method based on a reaction strategy using room temperature acidic ionic liquid [HBIM]-BF_4 has been reported.[9] Moreover, the synthesis of these heterocycles has been carried out in dimethylformamide (DMF), dimethylsulfoxide (DMSO), and acetic acid, leading to complex isolation and recovery procedures. Therefore, the development of facile and environmentally friendly methods for the synthesis of 1-pyridylimidazo-[1,5-a]-pyridines is a necessary part of organic synthesis.

The present protocol is not only simple and high-yielding but also decreases environmental pollution. At the onset of this work, we have investigated a variety of reaction conditions with the model reaction using metal triflates as catalyst (Table 1).

Initially, a systematic study was carried out to find the best molar concentration of catalyst scandium(III) triflate for the synthesis of 1-pyridylimidazo-[1,5-a]-pyridine derivatives; the reaction of 1,2-dipyridyl ketone, benzaldehyde, and ammonium acetate was carried out in either in the absence of catalyst or in the presence of various solvents under different conditions (Table 1). As shown, the best yield was achieved when 5 mol% catalyst used in ethanol as solvent (Table 1, entry 6).

Table 1. Synthesis of **3a** under different reaction conditions

Entry	Solvent	$Sc(OTf)_3$ (mol%)	Time (h)	Temp. (°C)	Isolated yield (%)
1	Dichloromethane	5	12	30	20
2	Acetonitrile	5	12	RT	15
3	Acetonitrile	5	1	Reflux	80
4	Methanol	5	12	RT	Traces
5	Methanol	5	1.5	Reflux	85
6	Ethanol	5	0.5	Reflux	93
7	Ethanol	0	12	Reflux	00
8	Ethanol	1	12	Reflux	20
9	Ethanol	2	12	Reflux	55

Table 2. Synthesis of 1-pyridylimidazo-[1,5-a]-pyridines

Entry	Ar-CHO	Reaction time (min)	Isolated yield (%)[a]
a	C_6H_5-CHO	30	93
b	4-OCH_3-C_6H_4-CHO	30	91
c	2-OH-C_6H_4-CHO	40	90
d	4-OH-C_6H_4-CHO	40	87
e	3-OH-C_6H_4-CHO	35	91
f	2-Cl-C_6H_4-CHO	50	89
g	4-CH_3-C_6H_4-CHO	35	88
h	3-OCH_3-4-OH-C_6H_3-CHO	50	92
i	4-NO_2-C_6H_4-CHO	60	80
j	4-OH-3,5-di-tert-but-C_6H_2-CHO	40	94

[a]All of the products were characterized by spectral and physical data.

Encouraged by this success, we extended the methodology to a variety of aromatic aldehydes, which are summarized in Table 2. This method is effective for the preparation of 1-pyridylimidazo-[1,5-a]-pyridines **3a–j** from both electron-rich as well as electron-deficient aromatic aldehydes. The aryl groups substituted with different groups and also the same groups located at different positions of the aromatic ring did not show any marginal effect on the formation of 1-pyridylimidazo-[1,5-a]-pyridines **3**. Another advantage of this methodology is a nearly stiochiometric amount of ammonium acetate was used in the course of the reaction, whereas previously many-fold ammonium acetate was required. This is an additional advantage of the novel methodology.

In conclusion, we describe a mild and efficient method for the synthesis of 1-pyridylimidazo-[1,5-a]-pyridines using scandium(III) triflate as a novel Lewis acid catalyst. This method is not only provides an excellent complement to 1-pyridylimidazo-[1,5-a]-pyridines synthesis but also avoids the use of hazardous acids or bases and harsh reaction conditions. The advantages of this method include good substrate generality, the use of inexpensive reagents and catalyst, mild conditions, and operational ease.

GENERAL EXPERIMENTAL PROCEDURE

A mixture of 1,2-dipyridyl ketone (10 mmol), aromatic aldehyde (10 mmol), ammonium acetate (20 mmol), and scandium(III) triflate (5 mol%) in ethanol (10 ml) was stirred at 75 °C for the appropriate time (Table 2), and the completion of reaction was monitored by thin-layer

chromatography (TLC). After completion, the reaction mixture was treated with aqueous sodium bisulfate. The separated solids were filtered, washed with water, and dried. The crude products obtained were purified by column chromatography on silica gel (60–120 mesh size) using 25% ethyl acetate in petroleum ether as eluent.

ACKNOWLEDGMENTS

We acknowledge Dr. P. L. More, Principal. Dnyanopasak College, Parbhani, for providing necessary facilities and UGC, New Delhi, for financial support (MRP-47-125/06).

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