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Lithium perchlorate as a new catalyst for efficient, mild and one-pot synthesis of 2,2-disubstituted imidazolidine derivatives from various aromatic ketones and ethylene diamine

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A new strategy for the preparation of imidazolidine derivatives from reaction of different aromatic ketones with 1,2-ethane diamine in the presence of $LiClO_4$ under the solution phase conditions is described. The products have been obtained in high to excellent yields and appropriate reaction times. The structure of resulting heterocycles has been determined by physical and spectroscopic data.

Key words: synthesis, one-pot, lithium perchlorate, imidazolidine, ketones, diamine

INTRODUCTION

A number of naturally occurring substances have been found to contain the imidazole nucleus. Some of these compounds and their synthetic derivatives possess therapeutic value [1]. Imidazolidines are important building blocks in biologically active compounds [2–5] and carriers of pharmacologically active carbonyl compounds [6–7]. Imidazolidine ring formation and its cleavage are important in various fields: (i) in organic synthesis, imidazolidines can act as protective groups since they are particularly easy to hydrolyze in acidic solutions and are stable in basic solutions, (ii) nitroalkanes can be acylated with imidazolidines, and (iii) imidazolidines can act as intermediates in the biosynthesis of nucleotides [8–11].

The derivatives of imidazolidine-2-thione such as azolothiazines and benzimidazolidine-2-thiones have an important role in medicinal chemistry owing to their wide application as drugs and drug-intermediates [12–14]. Many different pharmacological activities such as antimicrobial, antirheumatic, antidepressant, immunomodulator, anti-inflammatory, analgesic and various other activities are associated with functionalized benzimidazolidine-2-thione [15–22].

As pointed out by Lambert, relatively few papers have been published on the preparation of unsymmetrical N,N'-disubstituted imidazolidines. Symmetrical imidazolidines were also prepared early by different researchers such as Bisscoff, Scholtz, Donia, etc. The treatment of organic compounds under solution phase conditions enables rapid synthetic transformation at ambient pressure. The ability of imidazolidine-2-thione and its alkyl derivatives to act as ligands with different metal ions has also been established [23]. Imidazolidines are intermediates in the biosynthesis of nucleotides, and some of their metal complexes are found to be active as cytotoxic metallopharmaceuticals [24–28].

In recent years, the use of lithium perchlorate has attracted attention due to the enhanced rate, chemo- and stereoselectivity and selectivity to various organic transformations [29]. Lithium perchlorate is found to retain its activity even in the presence of amines and has also been found to activate effectively nitrogen-containing compounds such as imines [30]. Recently, $LiClO_4$ has emerged as a powerful promoter in many chemical processes and in different organic reaction such as the Michael addition of amines to α, β-unsaturated olefins, regioselective ring-opening of

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epoxides, diastereoselective synthesis of *cis*-aziridine carboxylates, etc. [31–33].

With attention to wide application of imidazolidine derivatives in organic synthesis, biochemistry and medicine chemistry and ongoing to our research [34], we now report a simple and efficient procedure to prepare 2,2-disubstituted imidazolidines from aromatic ketones catalyzed by lithium perchlorate in high to excellent yields. Our prime objective is to develop an innovative route for the synthesis of these heterocyclic compounds.

RESULTS AND DISCUSSION

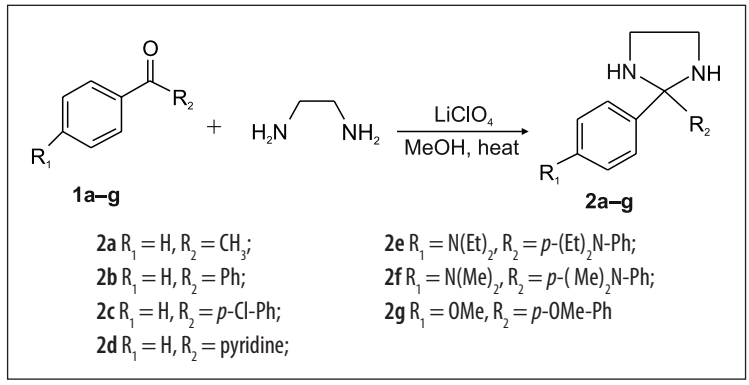
In this research, we hope to report a convenient and mild method for preparation of imidazolidine derivatives from reaction of various aromatic ketones with ethylene diamine catalyzed by $LiClO_4$ under the solution phase conditions (Scheme).

In order to investigate the catalyst effect, the reaction of benzophenone with ethylenediamine without a catalyst was not a considerable product after 10 h (Table 1, entry 1). Also, the reaction in the presence of various catalysts was performed and the obtained results show that the lithium perchlorate (5 mol%) can be the best catalyst in this reaction (Table 1, entry 4).

In this reaction, 2,2-disubstituted imidazolidines were obtained as products in good to excellent yields by refluxing in a methanol solution. The obtained products were confirmed by physical and spectroscopic methods.

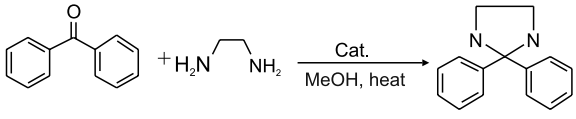
In continuation of our studies on the synthesis of Schiff bases [35–39], we decided to prepare the Schiff base ligands by treatment of ethylendiamine with some aromatic ketones in the presence of $LiClO_4$ in the methanol solution. In this study, there was not any Schiff base and the spectroscopic data of products were consistent with the structure of disubstituted imidazolidines. Due to the steric hindrance of the ketones in comparison with aldehydes, the reaction of ketones with ethylenediamine resulted in the formation of imidazolidines; while 3-nitrobenzaldehyde resulted in the related Schiff base (Table 2, entry 8). The corresponding results are summarized in Table 1. As it can be seen from this Table, the presence of an electron donating group on the aromatic rings of ketones (Table 1, entries 5, 6 and 7) resulted in low product yields after long reaction times. It seems related to high conjugation of the carbonyl group which results in low activity to the reaction.

In conclusion, this efficient, mild and new method for preparation of imidazolidine derivatives from aryl ketones with ethylenediamine in the presence of lithium perchlorate as a catalyst has some advantages such as availability of carbonyl compounds, simplicity of the reaction, good to excellent yields of the reaction products, appropriate reaction times, simple work-up and environment-friendly mild reaction conditions. These reactions occurred by refluxing under media solution. The products have been confirmed by physical and spectroscopic data.



Scheme

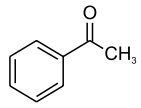
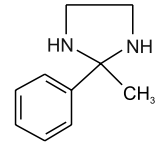
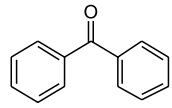
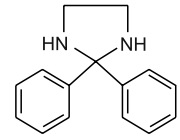
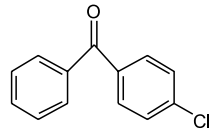
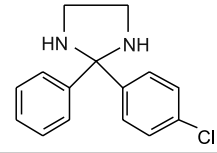
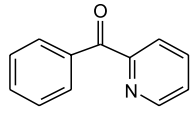
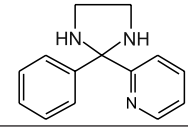
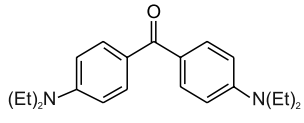
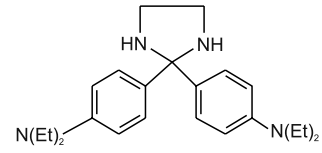
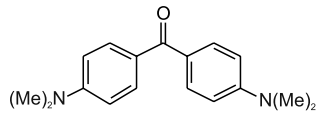
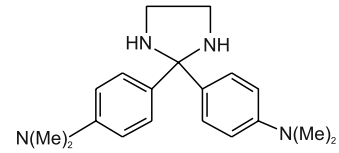
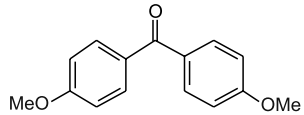
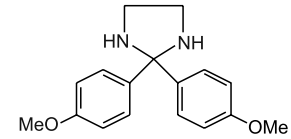
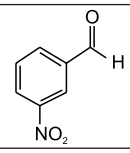
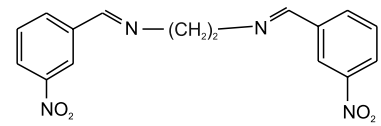
Table 1. **Optimization of the reaction conditions**



Entry	Catalyst	Catalyst amount, mol%	Time, h	Yield[a], %
1.	None	–	10	12
2.	$LiClO_4$	1	5	26
3.	$LiClO_4$	2	3	53
4.	$LiClO_4$	5	1.2	78
5.	$LiClO_4$	10	1	77
6.	$NaClO_4$	10	8	48
7.	$KClO_4$	10	8	42
8.	$NaIO_3$	10	15	25

[a] Isolated yields.

Table 2. **Preparation of imidazolidine derivatives from aromatic ketones with ethylene diamine catalyzed by $LiClO_4$**

Entry	Substrate	Product	Time, h	Yield[a], %
1.			1.5	82
2.			1.2	78
3.			10.5	80
4.				96
5.			Overnight	10[b]
6.			Overnight	<10[b]
7.			Overnight	<10[b]
8.			1	90

[a] Isolated yields; [b] TLC yields. These reactions were refluxed in the presence of 30 mol% of catalyst overnight as harsh reaction conditions.

EXPERIMENTAL SECTION

The chemicals were purchased from the Fluka and Merck chemical companies. The ketones and solvent were purified by standard methods and dried before use by conventional methods. IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nicolet FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in d_6-DMSO on a Bruker DRX-400 spectrometer for sample as indicated with tetramethylsilane as an internal reference. Mass spectra were recorded on a Finnigan MAT 44S by Electron Ionization (EI) mode with an ionization voltage of 70 eV. Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. The purity determination of the substrates and reactions monitoring by the solvent system were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

General procedure for preparation of disubstituted imidazolidines

A solution of ethylenediamine (0.24 g, 4 mmol) in absolute methanol (15 ml) was added to a solution of ketone (4 mmol) and 0.034 g (0.2 mmol) lithium perchlorate in methanol by stirring and refluxing. The reaction mixture was stirred for 0.5 h overnight. The progress of reaction was monitored by TLC. After the reaction, the white solid remained. The reaction mixture was filtered off, the solid product was washed with a solvent and recrystallized from methanol pure 2,2-disubstituted imidazolidine was obtained in 78–96% yields. The structure of products was identified by spectroscopic data.

2-Methyl-2-phenyl imidazolidine (a): white solid; m. p. = 80–82 °C; IR (KBr)/ υ (cm^{-1}): 3 310–3 420 (s, NH), 2 960 (CH_2), 1 460, 1 600 (Ar); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.20–7.79 (m, 5H), 3.31 (dt, 4H, J_1 = 5.5 Hz, J_2 = 2.2 Hz), 1.76(2H, NH); 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 136.59, 128.23, 127.48, 126.60, 84.63, 43.38, 27.21; MS: *m/z* = 163 (M^++1, 5), 162 (M^+, 20), 147 (45), 77 (90), 70 (60); Anal. calcd. for C. H. N: 74.07 (C), 8.64 (H), 17.28 (N); Found: 74.28 (C), 8.70 (H), 17.02 (N).

2,2-Diphenyl imidazolidine (b): white solid: m. p. = 90–92 °C; IR (KBr) / υ (cm^{-1}): 3 300–3 400 (s, NH), 2 950 (CH_2), 1 450, 1 580 (Ar); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.25–7.84 (m, 10H), 3.39 (s, 4H), 2.28 (s, 2H) ^{13}C NMR ($CDCl_3$,100 MHz) δ ppm: 128.14, 128.07, 127.92, 127.90, 90.79, 42.89; MS: *m/z* = 225 (M^++1, 10), 224 (M^+, 25), 77 (95), 70 (60); Anal. calcd. for C. H. N: 80.35 (C), 7.14 (H), 12.5 (N); Found: 80.50 (C), 7.15 (H), 12.34 (N).

2-(4-Chlorophenyl)-2-phenyl imidazolidine (c): white solid; m. p. = 94–96 °C; IR (KBr)/ υ (cm^{-1}): 3 350–3 480 (s, NH), 2 940 (CH_2), 1 470, 1 590 (Ar); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.25–7.76 (m, 9H), 3.54 (dt, 4H, J_1 = 5.5 Hz, J_2 = 2.2 Hz), 1.55 (s, 2H) ^{13}C NMR ($CDCl_3$,100 MHz) δ ppm 135.9, 130.30, 128.28, 128.07, 128.14, 127.90, 127.69, 125.46, 85.40, 43. 14; MS: *m/z* = 259.5 (M^++1, 5), 258.5 (M^+, 30), 223 (70), 77 (90), 70 (65); Anal. calcd. for C. H. N: 68.15 (C), 6.08 (H), 11.35 (N); Found: 68.25 (C), 6.12 (H), 11.25 (N).

2-Phenyl-2(2-pyridyl)imidazolidine (d): white solid; m. p. = 83–85 °C; IR (KBr)/ υ (cm^{-1}): 3 320 (m), 3 250 (s), 3 041 (s), 2 981 (s), 2 880 (s), 1 585 (s), 1 446 (s), 1 382 (s), 1 042 (s), 1 016 (s), 965 (s), 748 (s), 610 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.51 (d, 1 H, *J* = 4.5 Hz), 7.35–7.70 (m, 8H), 3.11 (dt, 4H, J_1 = 5.5 Hz, J_2 = 2.2 Hz), 2.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm: 163.75, 149.60, 146.25, 136.05, 127.75, 126.87, 123.35, 121.62, 96.06, 85.55, 45.87; MS: *m/z* = 227 (M^++2, 0.7), 226 (M+1, 4.6), 225 (M^+, 9.5), 197 (30.1), 196 (26.9), 195 (70.6), 168 (23.8), 167(24.5), 147 (100), 118 (11.1), 91 (6.3), 78 (7.8), 44 (44.1) 77 (95), 70 (60); Anal. calcd. for C. H. N: 74.66 (C), 6.66 (H), 18.66 (N); Found: 75.05 (C), 7.01 (H), 18.01 (N).

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LIČIO PERCHLORATAS KAIP NAUJAS KATALIZATORIUS EFEKTYVIAI, ŠVELNIAI IR PAPRASTAI 2,2-DIPAKEISTŲ IMIDAZOLIDINO DARINIŲ SINTEZEI IŠ ĮVAIRIŲ AROMATINIŲ KETONŲ IR ETILENDIAMINO

S a n t r a u k a

Aprašyta nauja imidazolidino darinių sintezė, vykdyta panaudojus įvairių aromatinių ketonų reakciją 1,2-etandiaminu, dalyvaujant ličio perchloratui kaip katalizatoriui. Sintezės produktai gauti didelėmis išeigomis, o jų struktūra patvirtinta fizikiniais ir spektriniais duomenimis.