Microwave-assisted facile synthesis of 2-substituted 2-imidazolines

Mohsin Y. Pathan, Vijaykumar V. Paike, Pandurang R. Pachmase, Sandeep P. More, Suresh S. Ardhapure, and Rajendra P. Pawar*

Organic Chemistry Synthesis Laboratory, Dnyanopasak College, Parbhani-431401, India
E-mail: rppawar@yahoo.com

Abstract
A novel method for the synthesis of 2-substituted 2-imidazolines under microwave irradiation is reported. The yields of product obtained using this protocol are significantly high and the reaction time is reduced.

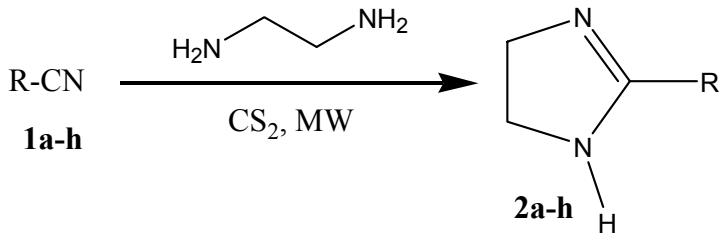
Keywords: 2-Imidazoline, aldehyde, nitrile, carbon disulphide, microwave irradiations

Introduction

Various types of 2-imidazolines are biologically and pharmaceutically very important, since many imidazoline derivatives possess antidiabetic, antihypertensive, and anti-inflammatory activity. Moreover 2-substituted imidazolines are synthetically important due to their use as a synthetic intermediates[1], catalysts[2], chiral auxiliaries[3], chiral catalysts[4] and ligands for asymmetric catalysis[5] in various synthetic reactions. To date, there are several synthetic methods for 2-imidazolines starting mainly from aldehydes and ethylenediamine with NBS.[6] Some methods includes synthesis from nitriles[7], carboxylic acids[8], esters[9], ortho-esters[10], hydroxy-amides[11] and mono or disubstituted chlorodicyanovinyl benzene[12]. Recently, the organic reactions under microwave irradiation are attracted attention of scientists due to their high reaction rate, mild reaction conditions and the formation of clean products[13]. Microwave-assisted reactions required short reaction times hence become more popular route for organic chemists[14]. A substantial improvement for the synthesis of indole-dihydropyridine derivatives has been obtained using microwaves in presence of carbon disulphide[15]. The microwave irradiation of benzonitriles, ethylenediamine and sulfur is also reported for the synthesis of 2-imidazolines[16]. Nevertheless, most of these methods suffer from unsatisfactory product yield, critical product isolation procedure and longer reaction time; hence there is still a scope to find potential methods for this transformation.

Result and Discussion

First time we are reporting the microwave irradiation of different nitriles with ethylenediamine in presence of the solvent carbon disulphide afforded the corresponding 2-substituted imidazolines (Scheme 1). The exact mechanism of the reaction is not clear to date. However, a plausible explanation is that carbon disulphide reacts with the nitrile and ethylenediamine to form an iminodithiocarbamate, which on elimination of carbon disulphide and ammonia produces the 2-imidazoline.



Scheme 1

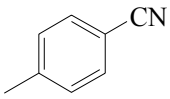
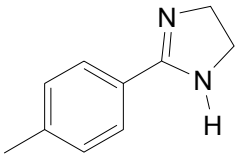
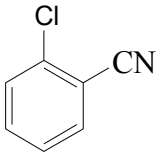
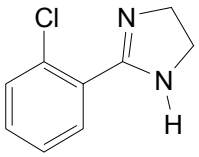
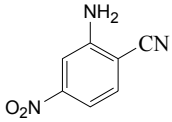
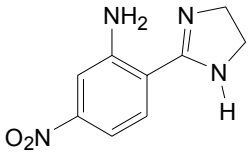
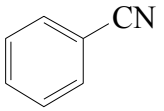
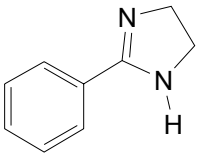
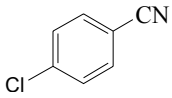
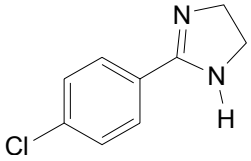
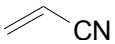
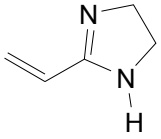
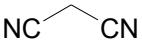
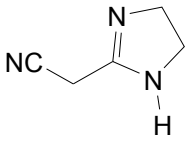
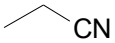
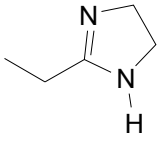
In a typical method benzonitrile (1d) and ethylenediamine (1:4 proportion) were mixed with solvent carbon disulphide in a 50 ml. Erlenmeyer flask. The Erlenmeyer flask was placed in the microwave oven and irradiated for 1 minute in a domestic microwave oven (Samsung) at low power (operating at 100 W, After irradiation, the temperature of the mixture was 45 ^{O}C). The reaction mixture was allowed to cool at room temperature. The cold water was added and the mixture was extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. The crude 2-imidazoline (**2d**) was crystallized from cyclohexane in 70-80% yield. Under the same reaction conditions, a variety of nitriles are converted to corresponding 2-imidazolines in 70-80% yields within 1 minute (Table 1).

The effect of microwave irradiation in this reaction without solvent carbon disulphide was also investigated. The results show that the reaction does not took place in 1 h microwave irradiation at same power. Similarly by conventional thermal heating also the reaction do not complete in 15 h in absence of solvent carbon disulphide. But the reaction has been completed by conventional thermal heating in presence of solvent carbon disulfide within half an hour (Entry 2b, 2c, 2d).

This study describes a successful approach for the synthesis of 2-imidazolines using a domestic microwave oven. This microwave technology does not require linking-cleaving chemistry and afford the products immediately.

In conclusion, a simple and efficient method for the synthesis of 2-imidazolines has been explored. Mild reaction conditions, shorter reaction time, easy and quick isolation of the products, low power consumption and excellent yields are main advantages of this method, which makes it an attractive and useful contribution to the present methodologies.

Table 1. Synthesis of 4,5-Dihydro-1*H*-imidazole derivatives (**2a-h**) under microwave and conventional conditions

Entry	Substrate **1**	Product **2**	MW Condition		Conventional conditions	
			Time (Sec.)	Yield[a] (%) (M. P.^{O}C)	Time (Min.)	Yield[a] (%)
a.			15	76 (178)[16]	-	-
b.			45	75 (Oil)	30	70
c.			43	78 (161)	25	72
d.			150	80 (102)[16]	35	75
e.			40	77 (185)[16]	-	-
f.			43	76 (49)	-	-
g.			68	75 (113)	-	-
h.			35	80 (50)	-	-

[a]Isolated yield after column chromatography.

– Indicates the reactions are not studied conventionally.

Experimental Section

General Procedures. Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer-1420 spectrophotometer. ^{1}H NMR spectra ($CDCl_3$) were recorded on Gemini-200 MHz spectrophotometer with TMS as internal standard.

General procedure for the preparation of 2-imidazolines under reflux conditions (2b-d). A mixture of nitrile (0.04 mol) and ethylenediamine (0.16 mol) and carbon disulphide solvent (0.01 mol) was refluxed on an oil bath (120 °C) for 35 minutes. The progress of the reaction was monitored by TLC (Ethyl acetate/Methanol; 4:1). The reaction mixture was cooled at room temperature. Cold water was added to it and then extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Crystallization of the crude product from cyclohexane gave the pure product in 70-80% yields (Table 1).

General procedure for the preparation of 2-imidazolines under microwave irradiation (2a-h). Microwave assisted reactions were carried out in a domestic microwave oven (Samsung-LCE 2733 GXTL) for realistic control of the microwaves operating at 850 W generating 2450 MHz frequency through out the required time.

A mixture of nitrile (0.01 mol), ethylenediamine (0.04 mol) and carbon disulphide solvent (0.001 mol) was taken in a Erlenmeyer flask. The Erlenmeyer flask was placed in a microwave oven and irradiated under at low power (100 W) for 30-150 seconds. The completion of the reaction was monitored by TLC using ethyl acetate: methanol (4:1) as eluent. The reaction mixture was cooled at room temperature. Cold water (20 mL) was added to it and then extracted with chloroform (3 x 25 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Crystallization of the crude product from cyclohexane gave the pure product in 70-80% yields (Table 1).

2-*p*-Tolyl-4,5-dihydro-1*H*-imidazole (2a). IR (cm^{-1}): 3350, 1630, 1540, 1480; ^{1}H NMR ($CDCl_3$) δ: 2.35(S, 3H**,** CH_3)**,** 3.01 (t, *J*=7.6Hz, 2H, CH_2), 3.81 (t, *J*=7.6Hz, 2H, CH_2), 4.11 (s, 1H, NH), 7. 01 (dd, 2H, Ar-CH), 7.50 (dd, 2H, Ar-CH). ^{13}CNMR δ: 21.1, 37.7, 50.6, 129, 130.2, 131.6, 140.8 and 164.9.

2-(2-Chloro phenyl)-4,5-dihydro-1*H*-imidazole (2b). *(Oil)* IR (cm^{-1}): 3320, 1625, 1560, 1410; ^{1}H NMR ($CDCl_3$) δ: 3.2 (t, *J*= 7.5Hz, 2H, CH_2), 3.81 (t, *J* =7.6Hz, 2H, CH_2), 4.15 (s, 1H, NH), 7.2-7.6 (m, 4H, Ar-CH).

2-(4,5-dihydro-1*H*-imidazole-2-yl)-5-nitro phenylamine (2c). IR (cm^{-1}): 3350-3210, 1620, 1555, 1440; ^{1}H NMR ($CDCl_3$) δ: 3.12 (t, *J* = 7.6Hz, 2H, CH_2), 3.79 (t, *J* = 7.7Hz, 2H, CH_2), 4.0 (s, 1H, NH_2), 4.19 (s, 1H, NH), 7.4-7.7 (m, 3H, Ar-CH).

2-Phenyl-4, 5-dihydro-1*H*-imidazole (2d). IR (cm^{-1}): 3280, 3060, 1615, 1556, 1430; ^{1}H NMR ($CDCl_3$) δ: 3.04 (t, *J* = 7.6Hz, 2H, CH_2), 3.79 (t, *J* = 7.5Hz, 2H, CH_2), 4.13 (s, 1H, NH), 7.2-7.7 (m, 4H, Ar-CH).

2-(4-Chloro phenyl)-4,5-dihydro-1*H*-imidazole (2e). IR (cm^{-1}): 3325, 1630, 1560, 1415; ^{1}H NMR ($CDCl_3$) δ: 3.21**,** (t, *J* = 7.5Hz, 2H, CH_2), 3.81 (t, *J* = 7.6Hz, 2H, CH_2), 4.14 (s, 1H, NH),

7.3-7.6 (m, 4H, Ar-CH).

2-Vinyl-4, 5-dihydro-1*H*-imidazole (2f). IR (cm^{-1}): 3330, 3075, 1625, 1270; ^1H NMR ($CDCl_3$) δ: 1.6 (t, *J* = 7.6Hz, 2H, CH_2), 2.7 (t, *J* = 7.6Hz, 2H, CH_2), 4.14 (s, 1H, NH), 5.3 (dd, 2H, CH_2)**,** 5.3 (dd, 1H, CH).

(4, 5-dihydro-1*H*-imidazole-2-yl) acetonitrile (2g). IR (cm^{-1}): 3350, 2350, 1631; ^1H NMR ($CDCl_3$) δ: 1.6 (t, *J* = 7.6Hz, 2H**,** CH_2)**,** 2.7 (t, *J* = 7.7Hz, 2H, CH_2), 2.53 (s, 2H, CH_2). 4.15 (s, 1H, NH).

2-methyl-4,5-dihydro-1*H*-imidazole (2h). IR (cm^{-1}): 3335, 2975, 1625, 1465; ^1H NMR ($CDCl_3$) δ: 0.9 (s, 3H, CH_3), 1.3 (q, 2H, CH_2), 1.6 (t, *J* = 7.6Hz, 2H, CH_2), 2.7 (t, *J* = 7.6Hz, 2H, CH_2) 4.15 (s,1H, NH).

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