

Synthesis of Imidine Hydrochloride and Some Heterocyclic Compounds

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Abstract

Some heterocyclic compounds were prepared from the reaction of primary amine derivatives with imidate (which was prepared by the reaction of nitrile (1) with ethanol in presence of hydrogen chloride). Imidine was also prepared by the reaction of nitrile (1) with some primary amines in presence of aluminum chloride. The synthesized compounds were confirmed by IR spectra.

الخلاصة

تضمن البحث تحضير عدد من المركبات الحلقية غير المتجانسة من تفاعل مشتقات الامينات الاولى مع الاليميديت (المحضر من تفاعل النتريل (١) مع الايثانول بوجود كلوريد الهيدروجين) كما تم تحضير الاليميدين من تفاعل النتريل (١) مع بعض الامينات الاولى وبوجود كلوريد الالمنيوم.

Introduction

The imidines hydrochloride could be prepared by several methods. The most important method is the condensation reaction in which the nitrile react with amine in presence of Lewis acid catalysts such as AlCl_3 , BF_3 , ZnCl_2 , FeCl_3 , SnCl_4 ⁽¹⁾. Substitution reaction which involve the reaction of amines with imidate⁽²⁾, orthoesters⁽³⁾ and imidoyl chloride⁽⁴⁾, reduction of 1,3-disubstituted urea with sodium hydroborate⁽⁵⁾, amidoxime⁽⁶⁾, 3-amino benzoxazole⁽⁷⁾, self condensation of amide by phosphorous pentaoxide⁽⁸⁾, and addition of organomagnesium reagents to pyridinium salts derived from amide⁽⁹⁾.

The preparation of imidates (iminoesters) could be achieved by the addition of dry hydrogen chloride to a mixture of a nitrile and an alcohol^(10,11), the reaction of N-substituted imino chloride with alkoxide or phenoxide⁽¹²⁾, direct alkylation of amide with ethyl chloroformate⁽¹³⁾ and the reaction of ethyl orthoformate and primary amine⁽¹⁴⁾. While N-substituted imidate was prepared by the reaction of methyl imidate hydrochloride with methyl glycinate hydrochloride⁽¹⁵⁾.

Recently substituted imidate was synthesized from the reaction of ester with aryl azide⁽¹⁶⁾.

Some heterocyclic compounds can be prepared from imidate, such as

imidazole⁽¹⁷⁾, imidazoline⁽¹⁸⁾,
oxazole⁽¹⁵⁾, benzimidazole⁽¹⁹⁾,
benzoxazole, benzothiazole⁽²⁰⁾,
oxazoline⁽²¹⁾, indole⁽²²⁾, purine⁽²³⁾ and
pyrimidine⁽¹⁴⁾.

In this study preparation of new substituted imidines, imidates and some other heterocyclic compounds were achieved.

Experimental

Uncorrected melting point were determined using Electrothermal 9300 melting point apparatus. I.R. spectra was recorded by Infrared Spectrophotometer Model Tensor 27 Bruker Co. using KBr discs. β -(p-tolyl mercapto) propionitrile (comp. 1) was prepared according to the published procedure⁽²⁴⁾.

Synthesis of N-substituted β -(p-tolyl mercapto) propioamide hydrochloride (comp. 2a-e):

To a mixture of (0.02 mole) of comp. 1 and (0.02 mole) of amine was added slowly with stirring (0.02 mole) of anhydrous powdered aluminum chloride. The mixture is kept at 160 °C for 20 min and while still molten is poured slowly into a solution of 1 ml of concentration of hydrochloric acid in (100 ml) of water. Collected the solid and recrystallized from suitable solvent. The IR spectral data and melting point were showed in Table (1).

Synthesis of α -imino[β -(p-tolylmercapto) ethyl] oxo or mercapto acetic acid hydrochloride (3a-b):

A mixture of (0.01 mole) of comp. 1 dissolved in (10 ml) of dry chloroform and (0.01 mole) of glycolic or thioglycolic acid dissolved in dry chloroform, was cooled to 0 °C and saturated with dry hydrogen chloride gas. The mixture is kept at 0 °C for 24 hrs and added 30 ml of dry ether. The solid is filtrated and recrystallized from ethanol. The melting point and IR spectral data are indicated in Table (2).

Synthesis of 2-[4-tolyl mercaptoethyl] thiazoline-4-one (4):

Compound (3b) (1 gm) was refluxed in 20 ml of toluene for five hrs. Cooled the solution and evaporated the solvent to give the product and recrystallized from ethanol. The IR spectral data and the melting point were listed in Table (2).

Synthesis of ethyl β -(p-tolyl mercapto) propioimide hydrochloride (5):

A mixture of (0.1 mole) of (comp. 1) dissolved in (40 ml) of dry chloroform and (0.1 mole) of absolute ethanol is cooled to 0 °C and saturated with dry hydrogen chloride gas. The flask is stoppered and place in refrigerator for 7 days and then equal volume of dry ether is added. The imide hydrochloride precipitate and filtered. The melting point and IR spectral data is listed in Table (2).

Synthesis of 2-[2-p-tolyl mercaptoethyl] imidazoline (6a):

A mixture of (0.01 mole) of comp. 5 and (0.01 mole) of redistilled ethylene diamine in 15 ml of absolute ethanol. The mixture is refluxed for 6 hrs and then kept at 0 °C overnight. A small amount of salt was filtered. The filtrate evaporate and the residual recrystallized from water to produce a prism needles. The IR data and the physical constant were showed in Table (2).

Synthesis of 2-[2-tolyl mercaptoethyl] oxazoline (6b):

A mixture of (1.3 gm, 0.005 mole) comp. 5 and (0.61 gm, 0.01 mole) of ethanolamine in 20 ml of absolute ethanol was refluxed for 4 hrs., filtered the salt and evaporated the solvent to produce the product. Recrystallized from water. The IR spectral data and the melting point were showed in Table (2).

Synthesis of ethyl N-carboethoxy methyl β -(p-tolyl mercapto) propioimide (7)⁽²⁵⁾:

At first prepare the free imide by shaken the (0.01 mole) imide hydrochloride in ether with a strong solution of potassium carbonate at 0 °C. The ethereal solution was shaken with (0.01 mole) glycine ethyl ester hydrochloride in 2 ml of water for 1 hr. The ether layer was separated, washed with water, dried over sodium sulphate and the solvent evaporated to afford the crude product. The product was recrystallized from ethanol. The melting point and IR spectral data were showed in Table (2).

Synthesis of 4-carboethoxy methylene-2-[2-tolyl mercaptoethyl] oxazoline (comp. 8)⁽²⁶⁾:

A mixture of (0.01 mole) of comp. 5 in 20 ml of ether was shaken with 10 ml of 50% sodium hydroxide, the ether layer was separated and mixed with (0.01 mole) of ethyl serine ester hydrochloride in 3 ml of water. The two layers vigorously shaken together for 8 hrs. After that a sufficient water is added to dissolve the ammonium chloride. The ether layer separated, washed three times with water, dried and evaporated to give the product. The melting point and IR spectral data were showed in Table(2).

Synthesis of 2-[2-tolyl mercapto ethyl] benzimidazole (9a)⁽¹⁾:

To a suspension of (0.005 mole) of comp. 5 in 10 ml of methanol was added with stirring, a solution of (0.005 mole) of o-phenylene diamine in 10 ml methanol. After stirring for 30 min at 20-25 °C a thick mass of crystals separates. The mixture was refluxed for 1 hr. Cooled and the precipitate filtered and washed with water to give the product. The melting point and IR spectral data were showed in Table (2).

Synthesis of 2-[2-tolyl mercaptoethyl] benzoxazole (9b)⁽¹⁾:

A mixture of (0.005 mole) of comp. 5 and (0.005 mole) of o-aminophenol in 10 ml of dry methanol were heated on a steam bath for 30 min. After that cooled, water containing a little sodium carbonate was added to neutralize the solution. Evaporating the solvent afford the product. The melting point and IR spectral data were listed in Table (2).

Synthesis of 5[-2-tolyl mercaptoethyl] tetrazole (10):

A mixture of (0.01 mole) of comp. 5 and (0.015 mole) of sodium azide in 25 ml of acetic acid was refluxed for 24 hrs. The salt of sodium chloride was filtered, evaporated the solvent to give a colorless needles of product. The melting point and IR spectral data were showed in Table (2).

Synthesis of β -(p-tolyl mercapto) propioamide hydrochloride (11):

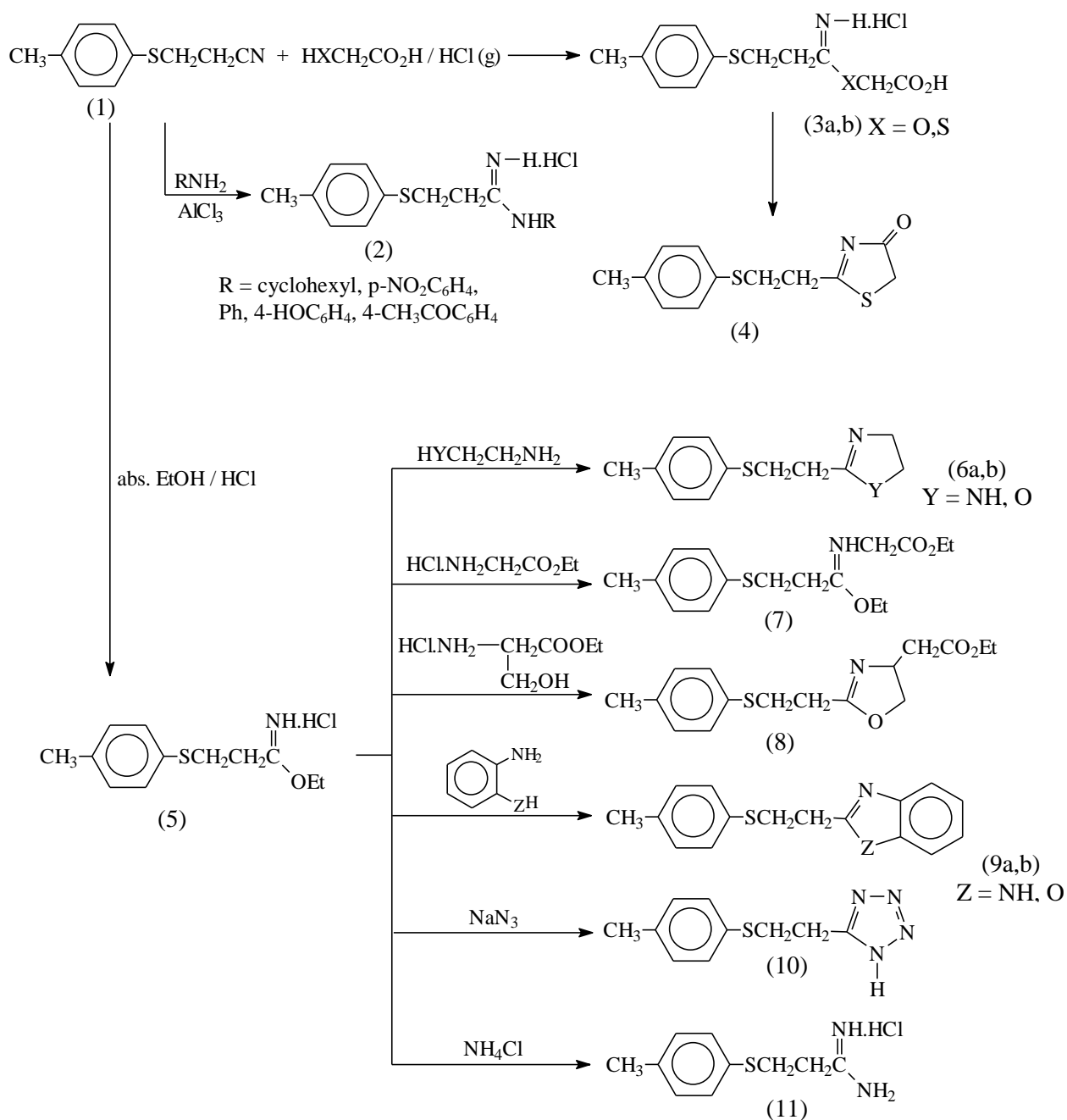
(0.01 mole) of comp. 5 is poured into separating funnel containing enough of an ice-cold 50% sodium hydroxide solution to give an alkaline solution. 20 ml of ether is added, the mixture is shaken vigorously, the organic layer separated, washed with water until neutral, dried over sodium sulphate, and concentrated to give the crude imide. The latter is dissolved in (10 ml) of (75%) aqueous ethanol containing (0.02 mole) of ammonium chloride and heated at 70 °C for four hrs., cooled and diluted with 2-3 volume of acetone. The unreacted ammonium chloride that separated was filtered and the filtrate is concentrated. After standing overnight at 0 °C, to produce a colorless needles. The melting point and IR spectral data is showed in Table (2).

Table 1: Melting point, yield and IR spectral data for compounds (2a-e)

Comp. No.	m.p. °C	Yield %	Recrys. solvent	IR ν cm ⁻¹					
				C-S	C=C	C=N	C=O	N-H	O-H
2a	139-141	83	Water	796	1605	1635	-	3386	-
2b	163-165	71	Ethanol	839	1587	1632	-	3361	-
2c	45-47	56	50% Ethanol	800	1593	1641	-	3370	-
2d	98-100	76	Ethanol	809	1620	1650	-	3302	3349
2e	132-134	70	Ethanol	831	1606	1634	1702	3321	-

Table 2: Melting point, yield and IR spectral data for compounds (3-11)

Comp. No.	m.p. °C	Yield %	IR ν cm ⁻¹				
			C-S	C-O	C=N	C=O	N-H
3	86-87	62	796	1090	1635	-	3160
3a	100-102	71	792	1102	1614	1718	3172
4	201-203	59	803	-	1641	1683	3146
5	78-80	72	806	1090	1631	-	3145
6a	248-250	84	801	-	1639	-	3276
6b	112-114	58	802	1092	1642	-	-
7	56-58	64	795	1121	1632	1772	3566
8	97-100	89	795	1201	1635	1761	-
9a	202d.	82	755	1144	1589	-	3298
9b	135-137	85	802	1084	1639	-	-
10	191-193	78	793	-	1587	-	3443
11	108-110	87	789	-	1644	-	3306

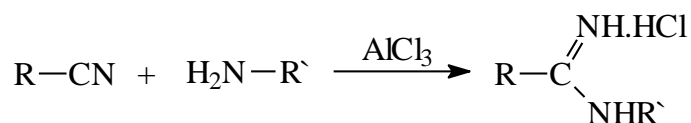


Scheme (1)

Results and Discussion

The imidine hydrochloride compounds (2a-e) could be prepared

by the reaction of nitrile with amines in present of anhydrous aluminum chloride as catalyst.



The IR spectral data showed the major absorption bands occurred at (1632-1650 cm^{-1}), (3302-3386 cm^{-1}) for C=N and N-H group respectively.

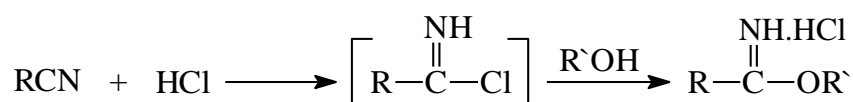
Compounds (3a,b) were prepared by the reaction of nitrile with an equimolar amount of glycolic or thioglycolic acid under dry condition at (0 °C) in the presence of hydrogen chloride gas. This compounds showed sharp absorption bands in IR spectra at (1614-1635 cm^{-1}) due to C=N, (1718- cm^{-1}) for C=O and (3160-3172 cm^{-1}) for NH.

Compound (4) was also prepared by the refluxing the compound (3b) in toluene. In the IR spectrum of

compound (4) showed absorption band at (1641 cm^{-1}) and (1683 cm^{-1}) related to C=N and C=O.

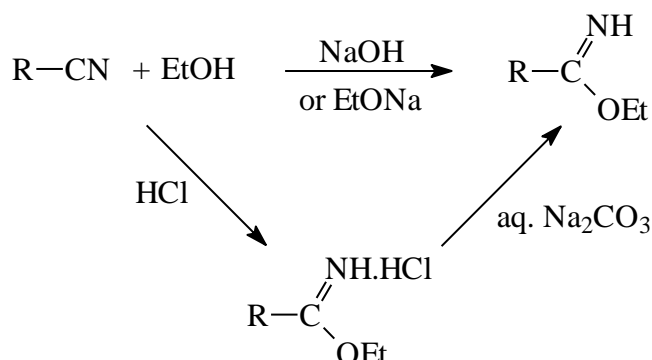
The ethyl- β -(p-tolyl mercapto) propioimide hydrochloride (5) was prepared by the similar condition applied in compound (3) preparation. The IR showed bands at (1090 cm^{-1}) for C-O, (1631 cm^{-1}) for C=N and (3145 cm^{-1}) for N-H.

The Pinner synthesis may involve the intermediate formation of imino chloride which subsequently reacts with alcohols.



Free imidates is obtained by treatment of the salt with an aqueous potassium carbonate. In addition to that, the free imide is prepared from

the reaction of nitrile with an alcohol in the presence of base, such as sodium hydroxide or sodium ethoxide.



Most unsubstituted aromatic and aliphatic nitriles are ineffective in the base-catalyzed process, but can be

used in Pinner methods to give imidates.

Compound (5) is considered as intermediate key to prepare some heterocyclic compounds.

The reaction of (5) with glycine ethyl ester hydrochloride gave the N-substituted imidate hydrochloride (7) by the substitution reaction. The IR spectrum showed bands at (1632 cm^{-1}), (1772 cm^{-1}) related to the, C=N and C=O, while compound (8) was prepared by the reaction of imidate with serine ester hydrochloride. This compound showed a sharp absorption bands in IR spectra at (1635 cm^{-1}), (1761 cm^{-1}) related to C=N, C=O ester groups respectively.

When compound (5) react with ethylenediamine, ethanolamine, o-phenylenediamine and o-aminophenol in alcohol under reflux it gave substituted imidazole, oxazole, benzimidazole and benzoxazole (6a,b, 9a,b) respectively. The IR spectral data support the above finding through the main stretching vibration absorption bands of (C=N) at ($1589\text{-}1642\text{ cm}^{-1}$) (see Table 2 for the other).

Imidate (5) was converted into tetrazole when treated with sodium azide. Several absorption bands appear in the (1587 cm^{-1}) and (3443 cm^{-1}) regions which are characteristic for the C=N and N-H groups.

Imidine hydrochloride (11) were prepared by the nucleophilic substitution reaction of imidate with ammonium chloride. The infrared structure of (11) was based on the absence of C-O (imidate) absorption in the IR spectrum.

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