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Preparation, Investigation and Theoretical Study of α-chloroacetamide-*N*-(*p*-substituted) Phenyl

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Abstract

Six new compounds of α-chloroacetamide-*N*-(*p*-substituted) phenyl of general formula $ClCH_2CONHPhX$; where X = H, Me, OMe, Br, Cl and NO_2 have been prepared and investigated spectroscopically and theoretically. AM1 and PM3 semi empirical methods were confirmed that compounds existed as amide form.

Keywords: IR; ^{13}CNMR; α-chloroacetamide-(N-P-X) phenyl; Correlation analysis; AM1 semi-empirical calculation.

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1. Introduction

Acetamide-*N*-phenyl compounds were very important materials for medicinal, dyes and stabilizers [1, 2]. These amides compounds are difficult to prepare by direct reaction of carboxylic acids with amines because amines are bases that convert acidic carboxyl group to their carboxylate anion [3].

$$RCO_2H + R'NH_2 \longleftrightarrow RCO^-_2 + R'N^+H_3 \quad (1)$$

Therefore, the carboxylic acid was converted to acyl halide, which is highly reactive as acylating agent and reacts very rapidly with the amine [4].

Many methods exist for converting carboxylic acid to acyl halide, for example, molecules devoid of acid sensitive functional group can be converted to acyl halide with thionyl chloride and phosphorous pentachloride [5].

Therefore other activation procedures, which generate a halide in situ in the presence of nucleophile are required. Refluxing carboxylic acid, triphenyl phosphine, bromo tri-

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chloro methane, and an amine give rise to the corresponding amide [6], as shown below:

$$RCOOH + R'NH_2 \xrightarrow[BrCCl_3]{PPh_3} RCONHR' \quad (2)$$

This reaction presumably proceeds via acyl chloride, because it is known that triphenyl phosphine and CCl_4 converts the carboxylic acid to the corresponding acyl chloride [7] PPh_3 and N-bromosuccinimide generate acyl bromide [8].

The aim of this paper is to prepare α-chloroacetamide-*N*-(*p*-substituted) phenyl which has important role as intermediate to synthesize *p*-acetylacetphenole which was used for headache [9]. These new compounds were prepared by condensation using PPh_3 /CCl_4 with *p*-x-aniline as shown below:

$$PPh_3+CCl_4 \rightarrow Ph_3P^+CCl_3Cl^- \quad (3)$$

$$Ph_3P^+CCl_3Cl^- + ClCH_2COOH \rightarrow ClCH_2COOP^+Ph_3 + HCCl_3 \quad +Cl^- \quad (4)$$

$$ClCH_2COOP^+Ph_3 + Cl^- \rightarrow O{=}PPh_3 + ClCH_2COCl \quad (5)$$

$$ClCH_2COCl + p\text{-}X\text{-}C_6H_5NH_2 \rightarrow p\text{-}X\text{-}C_6H_5NHCOCH_2Cl + p\text{-}X\text{-}C_6H_5NH_3^+Cl^- \quad (6)$$

Physical properties, IR, ^{13}CNMR spectra, and theoretical study were also reported.

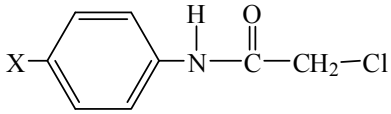
2. Experiment

2.1. *Preparation*

Six compounds of α-Cl-acetamide-N-(*p*-X-) phenyl were prepared in this study based on literatures [10-13].

A mixture of α-chloroacetic acid (0.94 gm; 0.01 moles) and triphenyl phosphine (2.6 gm; 0.01 mole) was dissolved in 25ml CCl_4 in round bottom flask and was refluxed with stirring for 1 hour in water bath. Then the mixture was cooled in ice water bath for 15 minutes. Two layers (organic and aqueous) were formed from which the organic layer (acyl chloride) was separated and cooled in ice water bath and magnetic stirrer. *p*-X-aniline [0.01 mole] was added slowly to cooled acyl chloride. The mixture was left for 1/2 hour. During the reaction period, colorless crystals were precipitated out of the solution. The colorless crystals were collected, and washed with 1:1 (ethanol-H_2O) to obtain the six compounds as described in Table 1.

Table 1. Characteristics of compounds.



Sub. (X)	Comp. No.	Colors	Mol. formula	Mol. Weight	Melting point (°C)
H	1	white	C_8H_8ClNO	169.61	132-134
CH_3	2	yellow	$C_9H_{10}ClNO$	183.63	160-162
OCH_3	3	white	$C_9H_{10}ClNO_2$	199.63	120-121
Cl	4	white	$C_8H_7Cl_2NO$	204.05	175-177
Br	5	yellow	$C_8H_7ClBrNO$	248.5	173-174
NO_2	6	yellow	$C_8H_7ClN_2O_3$	214.61	163-164

2.2. *Physical measurements*

IR spectra were recorded on a SHMADZU 8400 FT-IR spectrophotometer. Melting points were measured on a Gallenkamp melting point apparatus and were uncorrected.

3. Theoretical Calculations

All theoretical computations were performed in a Pentium IV PC. The AM1 and PM3 semi-empirical methods in the program Hyperchem 6.01 were utilized to compute the properties of compounds (Mulliken charge (q_M) and heat of formation (ΔH)). CS Chem Draw Prog 4.5 was used to compute theoretical ^{13}C chemical shifts.

A correlation analysis was done using the software program Minitab for windows release 11.11.

4. Results and Discussion

^{13}CNMR

The prepared compounds (1 to 6) are characterized depending on the additive method by using CS-Chem Drow Program. The available table for chemical shifts of ^{13}CNMR [14, 15, 16], are also utilized in the characterization. The values of peaks position are shown in Table 2.

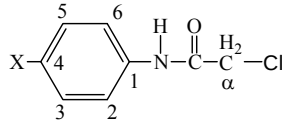
FTIR spectra

In the examination of IR spectra for these compounds, references [17-19] were utilized. The spectra of these compounds show that all compounds have common peaks such as a variable intensity of aromatic C-H stretching (3100-3000 cm^{-1}). Two strong peaks of aromatic double bond C=C stretching emerged at 1570-1520 cm^{-1} and 1470-1480 cm^{-1}. Also strong peak owing to C-N stretching is found near 1480 cm^{-1} and another strong peak at 1680-1750 cm^{-1} is attributed to C=O stretching .

Absorption bands exist near 3300-3260 cm^{-1} which belongs to the υ_{N-H} stretching as shown in Table 3.

In addition to these absorption peaks, there is a number of characterized absorption bands of substituted benzene such as C-Br and C-Cl stretching at 750 and 850 cm^{-1}, respectively, C-H bending of CH_3 at 1615 cm^{-1}, and asymmetrical and symmetrical C-H stretching for methyl group at 2960 and 2870 cm^{-1}, respectively.

Table 2. Band of ^{13}CNMR spectra of these compounds.



x	C_1	$C_{2,6}$	$C_{3,5}$	C_4	C(=O)	C_α	Others
H	136.0	120.1	128.2	125.1	169.5	42.2	
Me	134.2	120.5	129.2	134.5	169.3	42.1	21.7
OMe	136.0	124.1	120.5	147.1	169.1	42.0	45.5
Cl	134.1	123.1	130.1	139.2	169.5	42.3	
Br	135.4	121.2	133.3	123.8	169.6	42.3	
NO_2	144.1	120.1	125.1	145.0	169.9	42.5	

The compound α-chloroamide-*N*-(*p*-substituted) phenyl was found to exist in amide ↔ imidic acid equilibrium due to the mobility of NH proton to oxygen of carbonyl group (Fig. 1).

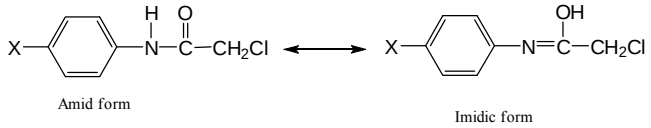


Fig. 1. Equilibrium between amide form and imidic form.

Table 3. Carbonyl and NH stretching vibration in cm^{-1} for the products.

X	C=O	N-H
H	1614	3267
CH_3	1700	3280
OMe	1720	3260
Cl	1740	3300
Br	1735	3300
NO_2	1750	3290

AM1 and PM3 semi-empirical calculation methods have shown that the amide is more stable than imidic acid form and the heat of formation of amide form are smaller than imidic acid Table 4.

IR spectra agreed with these results although the peak of absorption C=N group does not reveal in all spectra of these compounds.

Table 4. Calculated AM1 and PM3, Heat of formation (ΔH) (Kcal. Mol) and Mulliken charge for para carbon q_{MCP} and for nitrogen q_{MN}.

X	ΔH (amide form)		Δ*H* (imidic acid form)		amide form	
	AM1	PM3	AM1	PM3	q_{MCP}	q_{MN}
H	80.013	78.11	85.212	79.1	-0.138	-0.33
Me	103.104	100.1	114.111	103.210	-0.146	-0.38
OMe	104.712	102.71	107.122	108.191	-0.133	-0.322
Br	122.010	124.213	123.00	125.92	-0.164	-0.320
Cl	123.122	123.96	125.717	126.121	-0.153	-0.301
NO_2	130.212	131.11	131.73	132.001	-0.068	-0.302

Correlation analysis

Mulliken charge of nitrogen (q_{MN}) for these compounds with σp of Hammett equation was carried out and compared with correlation analysis of q_{MN} of *p*-x-aniline. It was found that the nitrogen of amides is considerably less sensitive to electron withdrawal and donation than q_{MN} of amine (*p*-x-aniline) as shown below:

$$q_{MN} = \rho \sigma_p \ldots \text{Hammett equation}$$

$r = 0.97 \quad \rho = 0.09 \quad n = 6 \quad \ldots$ [for *p*-x-aniline]

$r = 0.92 \quad \rho = 0.06 \quad n = 6 \quad \ldots$ [for these amide]

This is because the strong conjugation of amide nitrogen pair electrons with the carbonyl group, which complete for conjugation with π system of phenyl.

Plotting Mullikan charge of para carbon atoms against ^{13}C SCS of para carbon atoms gives a straight line (Fig. 2). The linearity of plots confirms that the nature of substituent effect on q_M could be related to that of ^{13}C SCS of para carbon. The equation for linearity was represented below:

$q_{MN} = -1.34 + 0.00885 \ ^{13}C \text{ SCS}$

$SD = 0.0085 \quad r = 0.97 \quad F = 85.13 \quad n = 6$

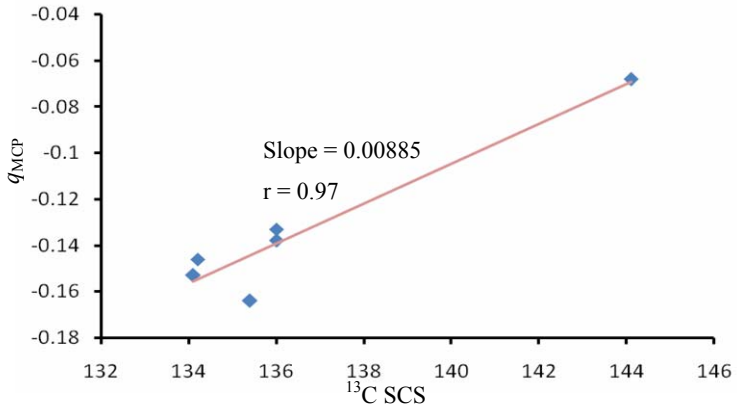


Fig. 2. The relationship between q_{MCP} of Cp and ^{13}C SCS.

Electronic properties

Some molecular information about the system considered is given in Table 5. The AM1 geometry optimization yields a planar structure as the stable form of the studied molecules. The ball and stick models of some molecules are shown in Fig. 3.

Table 5. Some of the molecular information about the molecules studied.

Compounds	Substituent	No. of electrons	No. of doubly occupied levels	No. of total orbital
1	H	58	29	52
2	CH_3	64	32	58
3	OMe	70	35	62
4	Cl	64	32	55
5	Br	64	32	55
6	NO_2	74	37	63

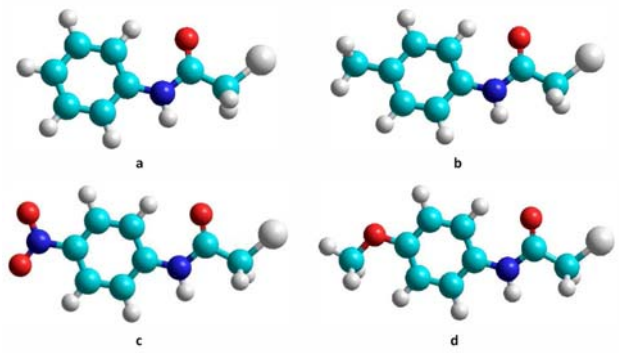


Fig. 3. The ball and stick models of some molecule. (a) H, (b) CH_3, (c) NO_2, (d) OCH_3.

5. Conclusion

Six compounds of α-Cl-acetamide N-(*p*-X-) phenyl were prepared (X= H, Me, OMe, Cl, Br and NO_2). These compounds were found to exist as amide not imidic acid form through analysis using IR spectra and AM1 semi-empierical method.

Correlation analysis between Mulliken charges of nitrogen (q_{MN}) and σp of Hammett equation shows that the nitrogen for these compounds is less sensitive to the substituent as compared with the nitrogen of *p*-X-aniline.

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