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Synthesis of Oxo Benzotriazino Acetic, Benzimidizolyl Hydrazides and Some of Their Hydrazones

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Abstract

In view of their high reactivity, hydrazides are important starting materials and intermediates in synthesis of certain amines, aldehydes, and heterocyclic compounds that are otherwise difficult to prepare. Many hydrazides, and in particular variously modified aromatic carboxylic acid hydrazides, have been tested for physiological effects since isonicotinic hydrazide was found to be tuberculostic. So in this study hydrazides of oxo benzotriazine and benzimidazole (4)-(13) were synthesised from their corresponding esters (3)-(12). Those two types of hydrazide compounds were allowed to react with some substituted Benz aldehydes. The result of this reaction revealed into the formation of new series of hydrazone compounds (5-12)-(14-18) respectively. The structure of the studied compounds were confirmed using IR,^{1}H NMR,^{13}C NMR, Mass measurements. These compounds were discussed according to the well supported spectral data.

Keywords: *Benzotriazino, Benzimidzolyl, Hydrazides, Hydrazones*

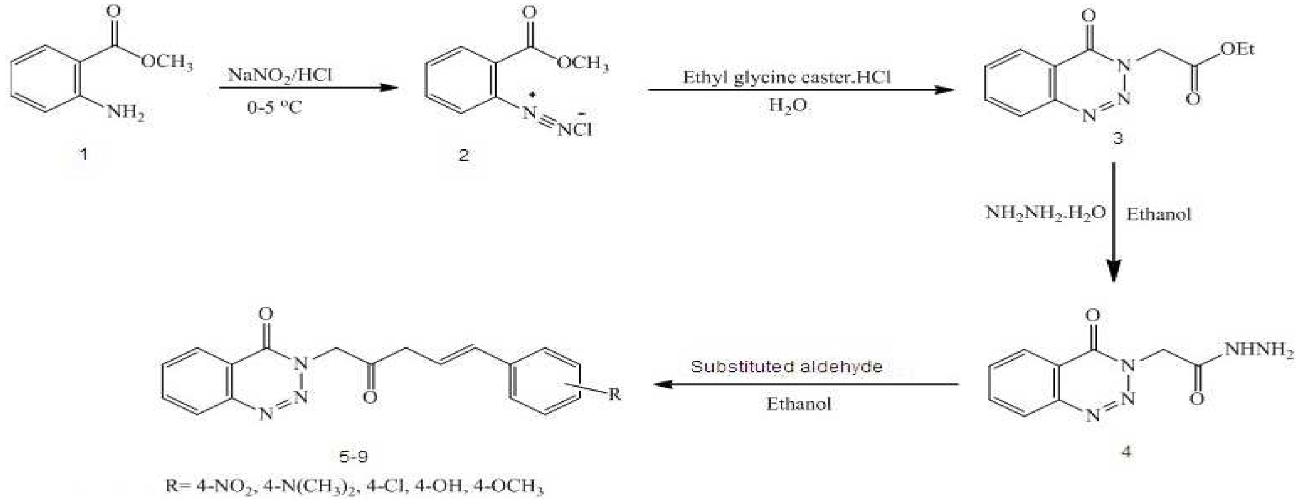
1. Introduction

There are numerous methods in the literature for the preparation of hydrazides such as carbodimide, N-Amination of amides, Nitrile hydrolysis and acylation of hydrazines (Pausen & Stoye 1970). The last one is the most popular methods for hydrazide synthesis. These hydrazide and their condensation products were stated to possess a wide range of biological activities (Rollas et al, 2002). Some of hydrazides and their analogous hydrazones are psychopharmacological agent, such as mono amino oxidase (MAO) inhibitor and serotonin antagonists (Pavan et al, 2010) hydrazides were also used to prepare diazoles and oxadiazoles compounds (Saundane & Manjunath, 2011 and Yassin & Seleim, 2012) and hydrazide (Hanumanagoud & Basavara-ja, 2013), most of them are biologically active and found many applications in medical area (Sriram et al, 2005). It is well known that hydrazides when allowed to react with aldehyde or ketones they transform into their corresponddding hydrazones (Freifelder, 1966). Hydrazone compounds due to their azomerhine group activity have drawn the atention of many researchers for the synthesis of numerous hydrazone compounds by the well-known hydrazinolysis method (Zabicky, 1970 and Govindasami, 2011). These hydrazones likewise corresponding hydrazides have proofed to have a wide range of pharmaceutical applications (Short 1921; Sheradsky, 1968, Smith et al, 1968 and Smith, 2004). In this work we tried to prepare two types of new hydrazide and some new derivatives of their hydrazones in an attempt to study their biological effect which will be our next work.

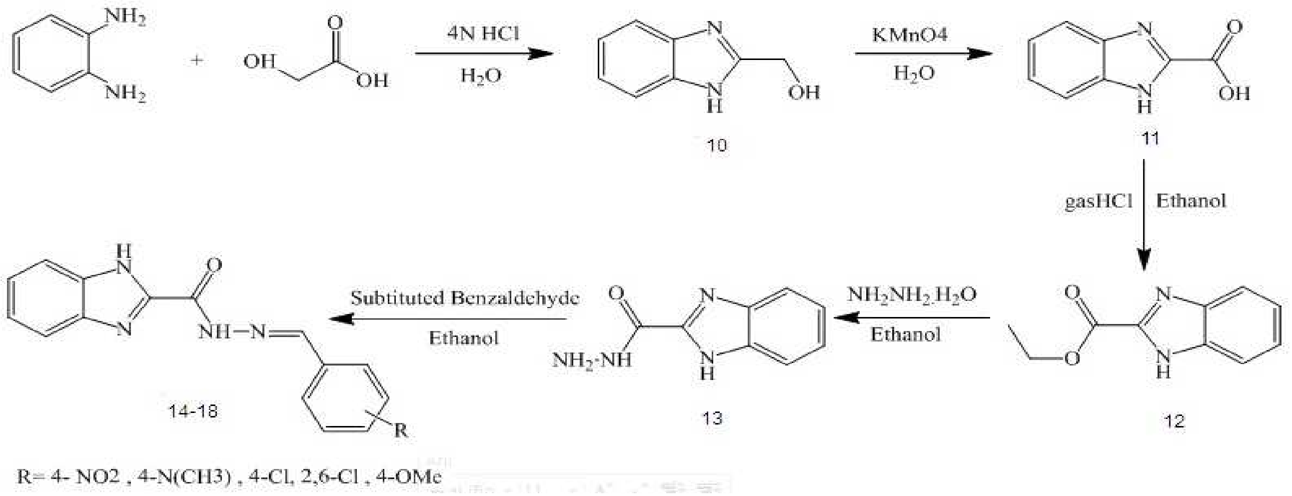
2. Materials and Methods

All reagents and chemicals were from BHD and Sigma-Aldrich companies and used without further purification. Melting points were determined with Electro thermal 9300 melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR. ^{1}H, ^{13}C NMR spectra were recorded at 250 or 400 MHz on a Bruker AV-1400 model or Bruker AV-1250 Model NMR instrument. Accurate masses were obtained using a Water-Micromass LCT electrospray mass spectrometer. All the measurements were performed at the Chemistry Department, University of Sheffield, Sheffield, United Kingdom. Methyl anthranilate (1), Scheme 1 was prepared according to the well-known procedure (Wiklund & Bergman, 2006) Compounds 10, 11 as shown in Scheme 1 were prepared following the published procedure (Thakurdesai et al, 2007) compound (12), Scheme 2 was also prepared following the published work of (Silvertein et al, 1974). Structures of these compounds were elucidated using IR, NMR and mass measurements.

Equimolar quantities of hydrazide (4) Scheme 1 or hydrazide (13) Scheme 2 and substituted benz aldehyde in (25 ml) of absolute ethanol were refluxed for three hours. The reaction mixture was cooled and the solid precipitate was recrystallised from ethanol physical, spectral data is given in the discussion of individual compounds as below.



Scheme 1



Scheme 2

Synthesis of hydrazide Compounds (4) Scheme 1, (13) Scheme 2 (General Procedure)

A mixture of the ester (3) Scheme 1 or ester (12) Scheme 2 (0.05 mol.), and hydrazine hydrate (80%), (0.10 mol.) in ethanol (20 ml) were refluxed for 2 hours. Excess ethanol was evaporated under reduced pressure and the precipitate product was crystallised from ethanol.

Synthesis of Hydrazone Compounds (5-9), (14-18) (General Procedure)

3. Results and Discussion

Ethyl 2-(4-oxobenzo[d][1,2,3]triazin-3(4H)-yl)acetate(3)

Oilbp100-111 °C, IR spectrum, υ, cm^{-1}: 3004 (Ar-CH str.), 2988 (Aliphatic-CH str.), 2110 (N=N str.), 1747 (C=O str. easter), 1685 (C=O str. amide),1615, 1488 (C=C str.), 1436 (C-Hbend), 1275 (C-N str.). High resolution mass spectrum (EI): Found: m\z 234.08 $[M]^+$, Calculated 234.23.

2-(4-oxobenzo[d][1,2,3] triazin-3 (4H)-yl)acetic hydrazide

(4)

This compound (mp. 243-244 ^{o}C) was prepared by hydrazinolysis of compound (3) as shown in Scheme 1. The elucidation of its structure comes from IR, NMR and mass. IR spectrum, υ, cm^{-1}: 3309 (NH str.), 3038 (Ar-CH str.), 2958 (aliphatic-CH str.), 2163 (N=N str.), 1678, 1659 (C=O str.), 1633, 1446 (C=C str.), 1375 (C-H bend), 1336 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 4.3 (2H, s, NH$_2$), 5.0 (2H, s, CH$_2$), 7.9-8.3 (4H, m, Ar-CH), 11.4 (1H, s, NH). ^{13}C NMR (DMSO-d_6), δ, ppm: 51.13, 119.85, 124.96, 128.54, 133.51, 136.00, 144.27, 166.12, 170.13. High resolution mass spectrum (EI): Found: m/z 220.20 [M]$^{+}$, Calculated 220.21

Aryl-N-(4-oxo benzo[d][1,2,3]triazin-3-(4H-yl) acetic hydrazones (5-9)

These series of hydrazone compounds, were prepared from the reaction of compound (4) with some substituted benzaldehydes, Scheme 1. These compounds were characterised by a combination of spectral methods IR, NMR and mass. IR indicates the presence of azomethine group (-CH=N-) absorbed around 100-1640 cm^{-1}, ^{1}H NMR also support this finding through the signal resonated around 8.5-8.6 ppm while ^{13}C NMR showed signal resonating around 145.35-150.6 ppm related to the azomethine carbon for the studied compounds. The details of spectral data were illustrated below:

3-nitrophenyl-N(4-oxobenzo[d][1,2,3]triazino-3(4H)-yl) hydrazone (5)

White solid, mp. 278-280 ^{o}C, 85% yield. IR spectrum, υ, cm^{-1}: 3200 (NH str.), 3062 (Ar-CH str.), 2962 (aliphatic-CH str.), 1700, 1665 (C=O str.), 1605 (C=N str.), 1600, 1411 (C=C str.), 1388 (C-H bend), 1334 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 5.7 (2H, s, CH), 7.7-8.3 (8H, m, Ar-CH), 8.6 (1H, s, CH), 12.1 (1H, s, NH).^{13}C NMR (DMSO-d_6), δ, ppm: 51.89, 119.57, 121.67, 121.79, 124.78, 125.05, 128.64, 130.88, 133.59, 136.22, 142.80, 145.64, 148.74, 155.37, 163.77, 168.47. High resolution mass spectrum (EI): Found: m/z 353.10 [M]$^{+}$, Calculated 353.09. The above data supporting the presence of the aromatic rings through the proton chemical shifts indicated above together with the resonating protons of the triazole ring and the amide protons. ^{13}C spectral data also support the presence of aromatic carbons resonating between 124-136 ppm while the triazine carbons appeared at 148,163 ppm for ring carbon and the carbonyl carbon respectively.

2-nitrophenyl-N(4-oxobenzo[d][1,2,3]triazin-3(4H)-yl) hydrazone (6)

Pale yellow solid, mp. 142-143 ^{o}C, 70% yield. IR spectrum, υ, cm^{-1}:3225 (NH str.), 3080 (Ar-CH str.), 3000 (aliphatic-CH str.), 1714, 1677 (C=O str.), 1600 (C=N str.), 1567, 1441 (C=C str.), 1356 (C-H bend), 1339 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 5.6 (2H, s, CH), 7.7-8.4, (8H, m, Ar-CH), 8.5 (1H, s, CH), 12.2 (1H, s, NH). ^{13}C NMR (DMSO-d_6), δ, ppm: 51.11, 119.20, 119.58, 125.06, 128.53, 128.66, 128.98, 131.20, 133.73, 134.07, 136.24, 140.67, 144.30, 148.55, 155.38, 168.44. High resolution mass spectrum (EI): Found: m/z 353.10 [M]$^{+}$, Calculated 353.09. This hydrazine also indicate the presence of both the aromatic rings and the triazine ring and the hydrazone moiety. IR, measurements revealed this finding through the above data proton and ^{13}C NMR also supports their existence as indicated above. Aromatic protons were resonating at 1600 ppm. while ^{13}C NMR showed resonating carbon ring between 123-134 ppm. The triazine ring carbons also resonating at 148,119 and 155 ppm. The azomethine group of hydrazone appeared at 168 ppm, for its carbonyl carbon.

4-chlorophenyl-N(4-oxobenzo[d][1,2,3]triazino-3(4H)-yl) hydrazone (7)

Yellow solid, mp. 132-133 ^{o}C 67% yield. IR spectrum, υ, cm^{-1}:3219 (NH str.), 3064 (Ar-CH str.), 2957 (aliphatic-CH str.), 1715, 1673 (C=O str.), 1611 (C=N str.), 1597, 1448 (C=C str.), 1353 (C-H bend), 1333 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 5.6 (2H, s, CH$_2$), 7.5-8.3 (8H, m, Ar-CH), (1H, s, CH), 12.0 (1H, s, NH).^{13}C NMR (DMSO-d_6), δ, ppm: 54.99, 118.66, 119.28, 124.88, 125.66, 127.06, 129.88, 131.05, 133.21, 137.55, 143.41, 151.67, 161.25, 172.56. High resolution mass spectrum (EI): Found: m/z 342.07 [M]$^{+}$, Calculated 342.07. The spectral data above support the presence of benzene rings as well as triazole ring and the methane moiety through IR showing C=C stretching at 1557, C=N at 1611 cm^{-1}. ^{13}C NMR showed aromatic carbons resonating between 124-137 ppm. While triazine ring carbons found at 118,161 ppm. While C=N appeared at 143 ppm and amide carbonyl at 172 ppm. Proton NMR also support this finding through the aromatic protons resonating at 7-8 ppm and the amide proton of azomethine appeared at 1611 ppm.

4-hydroxyphenyl-N(4-oxobenzo[d][1,2,3]triazino-3(4H)-yl) hydrazone (8)

White solid, mp. 194-196 ^{o}C, 72% yield. IR spectrum, υ, cm^{-1}: 3220 (OH str.), 3156 (NH str.), 3050 (Ar-CH str.), 2980 (aliphatic-CH str.), 1702, 1672 (C=O str.), 1654 (C=N str.), 1604, 1446 (C=C str.), 1350 (C-H bend), 1332 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 5.6 (2H, s, CH$_2$), 6.8-8.3 (8H, m, Ar-CH), (1H, s, CH), 10.0 (1H, s, OH), 11.8 (1H, s, NH).^{13}C NMR (DMSO-d_6), δ, ppm: 53.68, 121.13, 122.06, 124.88, 125.87, 128.86, 131.06, 136.00, 143.24, 145.76, 149.27, 161.87, 170.01. High resolution mass spectrum (EI): Found: m/z 324.108 [M]$^{+}$, Calculated 324.109. This hydrazone was also confirmed its structure according to the above spectral data in which IR provide evidence of existing both aromatic 1604 cm^{-1}, azomethane moiety as well as the absorption of triazine ring at 1654 cm^{-1}. ^{1}H NMR is also provide evidence for the presence aromatic ring protons resonating around 6.8-8.3 ppm, NH of azomethine at 11.8 ppm. ^{13}C NMR provides the following evidences; 122-136 ppm for aromatic carbons, 149 ppm for hydroxylic aromatic carbon and 143, 170 ppm for azomethine and carbonyl carbons respectively. Triazine ring carbons appeared at 148.99 and 161.8 ppm for its carbonyl group.

4-methylphenyl-N(4-oxobenzo[d][1,2,3]triazino-3(4H)-yl) hydrazone (9)

Pale yellow solid, mp. 210-211 °C. IR spectrum, υ, cm^{-1}: 3182 (NH str.), 3063 (Ar-CH str.), 2959 (aliphatic-CH str.), 1701, 1667 (C=O str.),1614 (C=N str.), 1582, 1416 (C=C str.),1392 (C-H bend),1332 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 5.6 (2H, s, CH), 7.3-8.3 (8H, m, Ar-CH),(1H, s, CH), 11.9 (1H, s, NH).^{13}C NMR (DMSO-d_6), δ, ppm: 21.51, 51.85, 119.58, 125.05, 127.61, 128.62, 129.90, 131.64, 133.67, 136.18, 140.40, 144.31, 145.05, 155.36, 167.99. High resolution mass spectrum (EI): Found: m/z 322.12 $[M]^+$, Calculated 322.13. This hydrazone likewise the above discussion but here the methyl carbon appeared at 21.51 while the aromatic carbon attached to this group appeared at 155.37. The carbon of azomethine resonated here at 140.40 (lower value due to donate on effect of the methyl group).

Ethyl ^{1}H-benzo[d]imidazole-2-carboxylate (12)

This compound was prepared by the esterification of compound (11) with ethanol, mp. 220-222 °C, 80% yield. The IR spectrum, υ, cm^{-1}: 3233 (NH str.), 3054 (Ar-CH str.), 2992 (aliphatic-CH str.), 1718 (C=O str.), 1622 (C=N str.), 1488 (C=C str.), 1315 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 1.3 (3H, t, CH_3), 4.4 (2H, q, CH_2), 7.4-7.7 (4H, m, Ar-CH), 13.5 (1H, s, NH). ^{13}C NMR (DMSO-d_6), δ, ppm: 21.51, 51.15, 125.05, 127.44, 127.61, 128.62, 131.64, 133.67, 140.40, 167.99. High resolution mass spectrum (EI): Found: m/z 191.082 $[M]^+$, Calculated 191.082.

1H-benzo[d]imidazole-2-carbohydrazide (13)

This hydrazide was also prepared by hydrazinolysis of compound (12). Melting point of this yellow solid compound 242-243 °C. The spectral data support its formation, IR sp-ectrum, υ, cm^{-1}: 3321, 3256 (NH str.), 3064 (Ar-CH str.), 2967 (aliphatic-CH str.), 1658 (C=O str.), 1606 (C=N str.), 1596, 1474 (C=C str.), 1323 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 4.7 (1H, s, NH), 6.9 (1H, s, NH), 7.4-7.7 (4H, m, Ar-CH), 12.3 (1H, s, NH), 13.5 (1H, s, NH). ^{13}C NMR (DMSO-d_6), δ, ppm: 124.96, 128.54, 133.51, 136.00, 141.00, 144.28, 149.72. High resolution mass spectrum (EI): Found: m/z 177.07 $[M]^+$, Calculated 177.08.

Syntheses of Aryl - N- 1Hbenz [d] imidazole -2-yl-hydrazone (14-18)

The condensation of some substituted benzaldehydes with compound (13) resulted into the formation of the above compounds (Scheme 2). The formation of azomethine group (-CH=N) comes from the study of IR, NMR and mass spectra. These studies supports its formation through IR which revealed the absence of the original C=O group absorption in amide. NMR showed **–**CH-of azomethine group resonating at 8.5-8.8 ppm and ^{13}C NMR of the carbon of this group at 145.35-148.6 ppm. Details of their spectral data where illustrated below:

4-nitrophenyl -N- 1H-benzo [d] imidazole-2-yl hydrazone (14)

White solid, mp. 300-302 °C, 80% yield. IR spectrum, υ, cm^{-1}: 3233-3147 (NH str.), 3090 (Ar-CH str.), 2967 (aliphatic-CH str.), 1667 (C=O str.), 1600 (C=N str.), 1548 (asym. N-O), 1446 (C=C str.), 1344 (sym. N-O), 1323 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 7.3-8.3 (8H, m, Ar-CH), 8.8 (1H, s, CH), 12.9 (1H, s, NH) 13.6 (1H, s, NH). ^{13}C NMR (DMSO-d_6), δ, ppm: 113.26, 121.72, 124.21, 125.54, 128.57, 131.28, 132.47, 141.78, 144.99, 145.11, 145.22, 149.51, 157.11. High resolution mass spectrum (EI): Found: m/z 310.093 $[M]^+$, Calculated 310.094. The above spectral data confirmed the formation of hydrazone through IR which indicate the presence of hydrazone group stretching at 3233,1667 cm^{-1} for NH and carbonyl. The presence of aromatic rings and imidazole moiety also supported by the above spectral data. ^{1}H, ^{13}C NMR data all provide evidences for hydrazone formation. Evidence of aromatic protons resonating at 7-7,8 ppm., two types of NH, one for hydrazone and the other for imidazole ring proton. ^{13}C NMR also provides another support through the aromatic protons of both types. The ring attached to the nitro group showed 128-132 ppm. while the benzoxazoyl ring carbons resonating around 113-125 ppm and finally the azomethine carbon at 141.78 ppm and the carbonyl of this group appeared at 157.11 ppm.

4-dimethylaminophenyl-N-1H-benzo[d]imidazole-2-yl hydrazone (15)

Yellow solid, mp. 283-285 °C 75% yield. IR spectrum, υ, cm^{-1}: 3193 (NH str.), 3022 (Ar-CH str.), 2886 (aliphatic-CH str.), 1654 (C=O str.), 1611 (C=N str.), 1442 (C=C str.), 1309 (C-N str.). ^{1}H NMR (DMSO-d_6), δ, ppm: 3.0 (6H, s, $(CH_3)_2$), 6.8-7.7 (8H, m, Ar-CH), 8.5 (1H, s, CH) , 12.2 (1H, s, NH) , 13.5 (1H, s, NH). ^{13}C NMR (DMSO-d_6), δ, ppm: 48.55, 114.25, 120.77, 123.54, 125.89, 131.77, 132.42, 133.41, 141.24, 142.01, 143.91, 144.71, 145.05, 157.47. High resolution mass spectrum (EI): Found: m/z

308.15 $[M]^+$, Calculated 308.14. Spectral discussion of this hydrazone is similar to the previous one.

4-chlorophenyl-N-1H-benzo[d] imidazole- 2-yl hydrazone (16)

Red solid, mp. 270-272 ^{o}C, 70% yield. IR spectrum, υ, cm^{-1}: 3230-3140 (NH str.), 3090 (Ar-CH str.), 2967 (aliphatic-CH str.), 1667 (C=O str.), 1600 (C=N str.), 1548 (asym. N-O), 1446 (C=C str.), 1344 (sym. N-O), 1323 (C-N str.). ^{1}H NMR (DMSO-d$_6$), δ, ppm: 7.3-8.3 (8H, m, Ar-CH), 8.8 (1H, s, CH), 12.9 (1H, s, NH), 13.6 (1H, s, NH). ^{13}C NMR (DMSO-d$_6$), δ, ppm: 115.57, 121.44, 125.87, 127.47, 133.45, 133.54, 136.89, 143.56, 144.97, 145.03, 146.87 159.02. High resolution mass spectrum (EI): Found: m/z 310.09 $[M]^+$, Calculated 310.09. The above spectral data of this compound also support its formation. ^{13}C NMR showed higher value of azomethane carbon resonating at 143.56, its carbonyl at 159 ppm due to the resonance and inductive effects of chlorine toward this group.

2,6-dichlorophenyl-N-1H-benzo[d]imidazole-2-yl hydrazone (17)

White solid, mp. 265-266 ^{o}C, 85% yield. IR spectrum, υ, cm^{-1}: 3225-3303 (NH str.), 3057 (Ar-CH str.), 2920 (aliphatic-CH str.), 1684 (C=O str.), 1619 (C=N str.), 1442 (C=C str.), 1314 (C-N str.), 852-785 (C-Cl str.). ^{1}H NMR (DMSO-d$_6$), δ, ppm: 7.4-7.8 (7H, m, Ar-CH), 8.8 (1H, s, CH), 12.9 (1H, s, NH), 13.6 (1H, s, NH). ^{13}C NMR (DMSO-d$_6$), δ, ppm: 113.17, 120.54, 123.37, 125.09, 129.54, 131.15, 131.85, 134.42, 135.04, 142.99, 144.89, 145.35, 156.01. High resolution mass spectrum (EI): Found: m/z 333.030 $[M]^+$, Calculated 333.031. The spectral data also supports its formation. It was nearly the same as compound (16) with little differences especially for ^{13}C assignments in which ortho substituents of chlorine affects the chemical shift of azomethane group and appeared at 142.99 ppm and its carbonyl at 156 ppm.

4-methoxyphenyl-N-1H-benzo[d]imidazole- 2-yl hydrazone(18)

White solid, mp. 280-281 ^{o}C 65% yield. IR spectrum, υ, cm^{-1}: 3200 (NH str.), 3097 (Ar-CH str.), 2980 (aliphatic-CH str.), 1664 (C=O str.), 1601 (C=N str.), 1446 (C=C str.), 1323 (C-N str.), 1248 (asym. O-CH$_3$), 1026 (sym. O-CH$_3$).^{1}H NMR (DMSO-d$_6$), δ, ppm: 3.8 (3H, s, CH$_3$), 7.0-7.8 (8H, m, Ar-CH), 8.6 (1H, s, CH), 12.4 (1H, s, NH), 13.5 (1H, s, NH). ^{13}C NMR (DMSO-d$_6$), δ, ppm: 55.7, 113.08, 114.84, 120.41, 123.24, 124.87, 127.22, 129.37, 134.99, 143.00, 145.31, 149.72, 155.60, 161.48. High resolution mass spectrum (EI): Found: m/z 295.119 $[M]^+$, Calculated 295.119. The spectral data above all support the formation of hydrazone as mentioned above for similar compounds. The effect of e-donating group of p-methyl group cause to the azomethine C=N to resonate at 143, while the carbonyl carbon was resonated at 161.48 ppm.

4. Conclusion

We conclude from the above study that the new hydrazides were successfully prepared by hydrazenolysis of the corresponding esters. The final hydrazone compounds were important heterocyclic Schiff bases. They might find medical applications such as drug discovery beginning from in vitro studies which will be investigated in our next work. All compound structures were well confirmed by spectral methods.

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