SYNTHESIS OF SOME NEW HETEROCYCLIC COMPOUNDS FROM
2-AMINOBENZHYDRAZIDE

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Abstract
2-Aminobenzhydrazide (1) was used as a precursor for preparation of some new heterocyclic
compounds and Schiff bases (2-9). Also, derivatives containing thiadiazole, oxadiazole and triazole
rings were prepared by treating compound (1) with phenyl isothiocyanate (10-13). The structure of
these compounds were characterized from there melting point, FTIR spectroscopy and elemental
analysis.

Keywords: 2-Aminobenzhydrazide, pyrazole, Schiff bases, quinazoline.

Introduction
Heterocyclics bearing nitrogen, sulphur
and oxygen atoms constitute the core structure
of a number of pharmacologically and
biologically active interesting compounds. The
efficiency of azoles as chemotherapeutic
agents is well studied. For example pyrazole
and pyrazolone derivatives exhibit
antibacterial, antifungal [1,2] and Cox
inhibition activity [3] while oxadiazole,
thiadiazole and triazole derivatives are widely
used for medicinal [4-7] and industrial
purposes [8] like azoles, quinazoline
derivatives showed therapeutic effects because
of their antihistaminic [9], analgesic and anti-
inflammatory activities [10]

Recently, quinazoles and quinazolines
were tested as a good immune modulators
[11]. Schiff bases have also been widely
reported biologically active due to the
toxophoric C=N linkage in them [12].

Prompted by these observations, it was
decided to use 2-aminobenzhydrazide as a
starting material for the preparation of new
heterocyclic compounds and Schiff bases.
Scheme (1).
**Experimental Materials:**
All chemical used were supplied from Merk Chemical, Fluka AG, BDH Chemicals. Melting points were recorded using Electrothermal melting point apparatus. Infrared spectra were recorded with Pye – Unicam SP3-100 or Shimadzu FTIR – 8400. Elemental analysis (C,H,N) were carried out in Euro EA elemental analyzer.

**Preparation of 2-amino benzydrazide. (1):**
A mixture of methyl anthranilate (0.01 mole) and hydrazine hydrate 40% (10ml) in ethanol (30ml) was heated under reflux for 4hr.
The reaction mixture was concentrated and cooled. The solid was filtered, washed with water and recrystallized from ethanol [13].

**General procedure for preparation of (2-amino benzoyl)-3-methyl-1H-pyrazole-5-(4H)-one. (2) ,(2-aminobenzoyl) pyrazolidine-3,5-dione. (3) and (2-aminophenyl) (3,5-dimethyl-1H-pyrazole-1-yl) methanone. (4):**
To (0.01 mole) of compound (1) methyl acetoacetate, diethyl malonate and acetylacetone (0.01 mole) was added and reaction mixture was heated under reflux for half an hour then (10ml) of ethanol absolute was added and the mixture was refluxed for an additional 1hr, respectively. The products, which separated on cooling, were collected by filtration and recrystallized from ethanol [14].

**General procedure for preparation of Schiff bases. (5 a, b, c, d):**
A mixture of compound (1) (0.01 mole) and substituted aromatic aldehydes (0.02 mole) in absolute ethanol (25ml) was heated under reflux for 1hr. this mixture allowed to cool and poured into water. The solid product was collected and recrystallized from ethanol.

**Preparation of potassium 2-(2-amino benzoyl) hydrazine carbo dithioate. (6):**
Compound (1) (0.01 mole) was dissolved in absolute ethanol (25ml) and (0.01 mole) of potassium hydroxide was added to the stirred solution. Then CS₂ was added gradually with cooling. After 1hr of stirring, the salt was collected without further purification.

**Preparation of 5-(2-aminophenyl)-1,3,4-oxadiazole-2-thiol. (7):**
Compound (6) was dissolved in ethanol and heated under reflux for 4hr. The reaction mixture was cooled, filtrated and the filtrate was acidified with dilute hydrochloric acid. The solid product was collected and recrystallized from ethanol.

**Preparation of N-(2-methyl-4-oxoquinazoline-3-(4H)-yl) acetamide. (8):**
To (0.01 mole) of compound (1) (10ml) of acetic anhydride was added and the mixture was heated under reflux for 4hr. Then allowed to cool and poured over crushed ice and extracted with chloroform. The solvent was removed from the organic layer to give an oily residue [14].

**Preparation of N-(4-oxoquinazoline-3-(4H)-yl) fromamide. (9):**
(0.01 mole) of compound (1) was dissolved in (10ml) of formic acid and heated under reflux for 4hr. The mixture allowed to cool and poured into cold water. The solid product was collected and recrystallized from ethanol [14].

**Preparation of N-phenyl-2-(2-(3-phenyl thioureido)benzoyl) hydrazine carbothioamide. (10):**
A mixture of compound (1) (0.01 mole) and (0.02 mole) of phenyl isothiocyanate in ethanol absolute was heated under reflux. After 1hr the reaction mixture was cooled and the solid product was collected and recrystallized from ethanol [6, 7].

**Preparation of 1-phenyl -3-(2-(5-(phenyl amino)-1, 3, 4-thiadiazole-2-yl) phenyl) thiourea. (11):**
(0.01 mole) of compound (10) was dissolved in (10ml) of conc. H₂SO₄ and stirred for 1hr then poured onto crushed ice. The resulting solid was recrystallized from ethanol [6, 7].

**Preparation of 1-phenyl -3-(2-(5-(phenyl amino)-1, 3, 4-oxadiazole-2-yl) phenyl) thiourea. (12):**
To alcoholic solution of compound (10) (0.01 mole), (10ml) of 10% NaOH was added with cooling and stirring then iodine solution in 10% KI was added gradually, and the
stirring continued until the iodine color persisted. Heating was continued for 5 hr with reflux and the mixture was cooled and poured onto ice-cold water. The resulting solid was washed with water and recrystallized from ethanol [6, 7].

Preparation of 1-(2-(5-mercapto-4-phenyl-4H-1,2,4-triazole-3-yl) phenyl thiourea (13):

An aqueous solution of NaOH (10%, 10 ml) was added to (0.01 mole) of compound (10) and reaction mixture was refluxed for 4 hr. The resulting solution was cooled and acidified with 10% HCL adjusted PH to 6. The precipitate was collected, washed with cold water and recrystallized from ethanol [6, 7].

All physical constant for these compounds were reported in Table (1). Infrared data were reported in Table (2).

**Table (1)**

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Formula</th>
<th>Melting point °C</th>
<th>Elemental analysis calc. (found)%</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C %</td>
<td>H %</td>
</tr>
<tr>
<td>1</td>
<td>C₂H₇N₃O</td>
<td>121 - 123</td>
<td>55.62 (55.11)</td>
<td>5.96 (5.63)</td>
</tr>
<tr>
<td>2</td>
<td>C₁₃H₁₄N₅O₂</td>
<td>250 dec.</td>
<td>60.83 (60.47)</td>
<td>5.07 (4.91)</td>
</tr>
<tr>
<td>3</td>
<td>C₁₀H₁₂N₃O₃</td>
<td>230 dec.</td>
<td>54.79 (53.98)</td>
<td>9.11 (8.89)</td>
</tr>
<tr>
<td>4</td>
<td>C₁₂H₁₃N₅O</td>
<td>156 - 158</td>
<td>66.98 (66.01)</td>
<td>6.05 (5.83)</td>
</tr>
<tr>
<td>5a</td>
<td>C₂₁H₁₅N₅O₃</td>
<td>206 - 208</td>
<td>70.19 (69.96)</td>
<td>4.74 (4.52)</td>
</tr>
<tr>
<td>5b</td>
<td>C₂₁H₁₃N₅OCl₂</td>
<td>172 – 174</td>
<td>63.64 (62.98)</td>
<td>3.79 (3.11)</td>
</tr>
<tr>
<td>5c</td>
<td>C₂₁H₁₃N₅O₅</td>
<td>118 – 120</td>
<td>60.43 (59.98)</td>
<td>3.60 (3.21)</td>
</tr>
<tr>
<td>5d</td>
<td>C₂₁H₁₃N₅O₃</td>
<td>226 – 228</td>
<td>58.88 (58.43)</td>
<td>3.50 (3.21)</td>
</tr>
<tr>
<td>6</td>
<td>C₂₁H₁₅N₅OS</td>
<td>184 – 186</td>
<td>49.74 (47.11)</td>
<td>3.63 (3.43)</td>
</tr>
<tr>
<td>7</td>
<td>C₆H₅N₃OS</td>
<td>oily</td>
<td>59.11 (58.83)</td>
<td>4.43 (4.12)</td>
</tr>
<tr>
<td>8</td>
<td>C₁₃H₁₄N₅O₂</td>
<td>218 – 220</td>
<td>57.14 (55.38)</td>
<td>3.70 (3.11)</td>
</tr>
<tr>
<td>9</td>
<td>C₂₁H₁₅N₅O₃</td>
<td>148 – 150</td>
<td>59.90 (51.84)</td>
<td>4.51 (3.13)</td>
</tr>
<tr>
<td>10</td>
<td>C₂₁H₁₃N₅O₃</td>
<td>240 dec.</td>
<td>62.53 (62.12)</td>
<td>4.22 (3.95)</td>
</tr>
<tr>
<td>11</td>
<td>C₂₁H₁₅N₅S₂</td>
<td>210 dec.</td>
<td>65.12 (64.69)</td>
<td>4.39 (3.98)</td>
</tr>
<tr>
<td>13</td>
<td>C₂₁H₁₅N₅S₂</td>
<td>194 – 196</td>
<td>62.53 (62.31)</td>
<td>4.22 (3.92)</td>
</tr>
</tbody>
</table>
### Table (2)

**Characteristic IR absorption bands.**

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Infrared data ($\nu_{max}$ cm$^{-1}$) (KBr disc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(NH, 2NH$_2$) 3450 – 3200; (CO amide) 1620.</td>
</tr>
<tr>
<td>2</td>
<td>(NH$_2$) 3280 – 3200; (C-H methyl) 2985; (CO amide) 1689, 1643; (C=N) 1580; (CH$_3$ bend) 1370.</td>
</tr>
<tr>
<td>3</td>
<td>(NH, NH$_3$) 3440 – 3325; (C-H arm) 3186; (CO amide) 1620, 1600.</td>
</tr>
<tr>
<td>4</td>
<td>(NH$_2$) 3400 – 3280; (C-H methyl) 2990; (CO amide) 1660; (C=N) 1580; (C=C) 1525; (CH$_3$ bend) 1460.</td>
</tr>
<tr>
<td>5a</td>
<td>(OH), (NH) 3400 – 3300; (CO amide) 1620; (C=N) 1510.</td>
</tr>
<tr>
<td>5b</td>
<td>(NH) 3325; (CO amide) 1635; (C=N) 1488; (C-Cl) 825.</td>
</tr>
<tr>
<td>5c</td>
<td>(NH) 3350; (CO amide) 1650; (C=N) 1590; (NO$_2$) 1520 asy. and 1340 sym.</td>
</tr>
<tr>
<td>5d</td>
<td>(OH), (NH) 3400 – 3250; (CO amide) 1630; (C=N) 1475; (C-Cl) 820.</td>
</tr>
<tr>
<td>7</td>
<td>(NH amide) 3471 – 3371; (S-H weak) 2761; (C=N) 1627; (C=S) 1272; (C-O-C oxadiazole ring) 1188.</td>
</tr>
<tr>
<td>8</td>
<td>(NH amide) 3142; (C-H arm) 3016; (C-H methyl) 2929; (CO amide) 1697, 1610; (C=N) 1525; (CH$_3$ bend) 1367.</td>
</tr>
<tr>
<td>9</td>
<td>(NH amide) 3433; (CH arm) 3062; (CO-H) 2923 (CO amide) 1697, 1604; (C=N) 1566.</td>
</tr>
<tr>
<td>10</td>
<td>(NH) 3355 – 3200; (C-H arm) 3116, 3031; (CO amide) 1674; (C=S) 1334, 1195.</td>
</tr>
<tr>
<td>11</td>
<td>(NH) 3247– 3217; (C-H arm) 3132; (C=N) 1658; (C=S-C thiadiazole ring) 1640.</td>
</tr>
<tr>
<td>12</td>
<td>(NH) 3300 – 3100; (C=N) 1670; (C=S) 1230 (C-O-C oxadiazole ring) 1190.</td>
</tr>
<tr>
<td>13</td>
<td>(NH) 3278; (C-H arm) 3132; (S-H) 278; (C=N triazole ring) 1650; (C=S) 1240.</td>
</tr>
</tbody>
</table>

### Results and Discussion

Acid hydrazides can be considered as useful intermediates leading to the formation of some heterocyclic compounds. So compound (1) has been chosen as a starting material for synthesis of new heterocyclic compounds and Schiff bases. In the first part of this work compound (1) was treated with different carbonyl compounds such as methyl acetoacetate, diethylmalonate and acetylacetone to give the corresponding pyrazole derivatives (2-4), respectively[14] (Scheme 1).

The IR spectra of compounds (2), (3) and (4) showed the stretching bands of (NH$_2$) group at 3200-3440 cm$^{-1}$ and appearance of (C =N) stretching band at 1580 cm$^{-1}$ for compound (2) and (4) while it appears at 1525 cm$^{-1}$ for compound (3). The stretching band of (CO amide) appears at 1689 cm$^{-1}$ for compound (2), 1600 cm$^{-1}$ for compound (3) and 1660 cm$^{-1}$ for compound (4). Moreover, the IR spectra for compound (2) and (4) showed stretching bands for (C – H of CH$_3$) at 2985 cm$^{-1}$ for compound (2) and at 2990 cm$^{-1}$ for compound (4) in addition to the bands at 1370 cm$^{-1}$ for compound (2) and 1460 cm$^{-1}$ for compound (4) due to (C – H bending in CH$_3$). The mechanism for the formation of pyrazole ring includes nucleophilic attack of NH - NH$_2$ electrons of compound (1) at the carbonyl carbons of methyl acetoacetate, diethylmalonate and acetylacetone with ring closing and elimination of two molecules consists of H$_2$O and CH$_3$OH for compound (2), two C$_2$H$_5$OH for compound (3) or two molecule of H$_2$O for compound (4) (Scheme 3).
The Schiff bases (5 a, b, c, d) were synthesized from the reaction of compound (1) with two moles of different substituted benzaldehydes. The IR spectra of Schiff bases showed the stretching bands of (NH) groups of the derivatives at 3250 – 3400 cm\(^{-1}\) bands at 1470 -1590 cm\(^{-1}\) for two (C = N) groups.

The treatment of compound (1) with CS\(_2\) in the presence of alcoholic KOH gives xanthate salt 6 which was heated for 4hr. to produce the oxadiazole derivative (7). The IR spectrum of this compound displayed two stretching bands of NH and NH\(_2\) at 3471 cm\(^{-1}\) and at 3371 cm\(^{-1}\). The other observed bands were at 2761 cm\(^{-1}\) for (S-H weak), 1627 cm\(^{-1}\) for (C = N), 1272 cm\(^{-1}\) for (C = S) and 1188 cm\(^{-1}\) which was characteristic for (C–O–C) of oxadiazole ring. See Table (2).

One the other hand, the reaction of compound (1) with other carbonyl compounds such as formic acid and acetic anhydride resulted in the formation of quinazoline derivatives (8) and (9) respectively[14]. By nucleophilic attack of the electros of two (NH\(_2\)) groups of compound (1) on the carbonyl group of two molecules of formic acid or acetic anhydride with elimination two H\(_2\)O molecules in the first step followed by another nucleophilic attack of NH electrons on the inner carbonyl group resulting intermolecular cyclization with elimination of another H\(_2\)O molecule (Scheme 4).
The IR spectra of these compounds revealed the absence of the stretching bands of (NH₂) groups and appearance of stretching bands of (N–H amide) at 3142 cm⁻¹ for compound (8) and at 3433 cm⁻¹ for compound (9). The IR showed also the appearance of two stretching bands at 1697 cm⁻¹ and 1610 cm⁻¹ for compound (8) and at 1697 cm⁻¹ and 1604 cm⁻¹ for compound (9) due to the two carbonyl amide groups of the quinazoline ring in addition to the appearance of (C = N) stretching band at 1525 cm⁻¹ for compound (8) and at 1566 cm⁻¹ for compound (9).

The second part of this work involves reacting compound (1) with two moles of phenyl isothiocyanate to give thiosemicarbazide derivative (10) [7,8] which showed IR stretching bands at 3355 – 3200 cm⁻¹ of (N – H) groups, 3116 cm⁻¹, 3031 cm⁻¹ of (C – H aromatic) of the benzene rings, 1674 cm⁻¹ of (C = O amide) and two bands at 1334 cm⁻¹ and at 1195 cm⁻¹ of the two groups of (C = S).

The cyclization of compound (10) with H₂SO₄, I₂ in KI in presence of 10% NaOH or 10% NaOH produce thiadiazole (11), oxadiazole (12) and triazole (13) derivatives respectively [6,7] (Scheme 2). Thiadiazole derivatives (11) gave diagnostic IR stretching bands at 3247 cm⁻¹, 3217 cm⁻¹ for (N – H) groups, 1658 cm⁻¹ for (C = N) and at 640 cm⁻¹ (C – S – C) of thiadiazole ring, while oxadiazole derivative (12). IR spectrum displayed the following stretching bands at 3300 – 3100 cm⁻¹ for (N – H) groups, 1670 cm⁻¹ for (C = N), 1230 cm⁻¹ for (C = S) and 1190 cm⁻¹ for (C – O – C) of oxadiazole ring. Also triazole derivative (13) showed characteristic IR stretching bands at 3278 cm⁻¹ for (N-H) group, 2785 cm⁻¹ weak for (S – H) group, 1650 cm⁻¹ for (C = N) of triazole ring and 1240 cm⁻¹ for (C = S).

These products included Scheme 1 and 2 are useful intermediate heterocyclic compounds for further investigations such as the physiological effects, good chelating reagents for organometallic cyclo compounds using deferent central ions, this work may be continued for investigating the NMR – spectra for those heterocyclic compounds.
References


الخاصة

تم في هذا البحث استخدام 2-امينو بنزهيدرازيون (1) كمادة أولية لتحضير بعض المركبات الحلقية غير المتجمدة الجديدة وقواعد شف (2 – 9). كما تم تحضير مركبات تحتوي حلقات ثنائيلازول والأوكثيدرازيون والتروابازول بتفاعل مركب (1) مع فنيل ايزوثياوسيانات (10 – 13) . شُخصت هذه المركبات من خلال درجات الأنصهار وتقلية FTIR وتحليل الخاصر...

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