# Heterocyclic Synthesis Via Phosphine imino Intermediate

**Harith M. Al-Ajely**
*Chemistry Dept., College of Science, Mosul University, Mosul , Iraq*
(Received 10 / 12 / 2007 , Accepted 29 / 10 / 2008 )

## Abstract

In this work heterocyclic compounds were prepared by two path ways. The first one includes the preparation of 2-nitro, 2,4-dinitroazido benzene (1a,b) from the reaction of 2-chloro, 2,4-dinitrochloro benzene with sodium azide which are further reacted with triphenyl phosphene resulted into the formation of phosphene imine (2a,b), these compounds were allowed to react with some isocyanate compounds to afford compounds (3-6).

The second path includes the synthesis of ethyl azidoacetate and ethyl 2-propionate (7a,b) from the reaction of ethyl bromoacetate, ethyl 2-bromopropionate with sodium azide, these compounds were allowed to react with triphenyl phosphene forming phosphoimine compounds (9a,b), these compounds were reacted with butyl isocyanate resulted into the formation of carbodiimide compounds (10a,b), which were cyclized by their reaction with some primary amines and amino acid esters.

All synthesized compounds were identified by melting point and I.R spectroscopy and their results were discussed.

## Introduction

There are versatile methods in the literature for the preparation of carbodiimides[1-10]. The chemistry of carbodiimide has been investigated by three main reactions; The first one was the utility of carbodiimides as coupling agent in amide synthesis[11-14]. The second type of reactions include the addition reactions to the C=N bond[15-18], while the third type of reaction of carbodiimide is the utility as an intermediate in the synthesis of different types of heterocyclic compounds[19-25]. In our investigation carbodiimides were prepared and used as an intermediate part for the preparation of new set of heterocyclic compounds. The heterocyclic compound derived from carbodiimide reactions have shown numerous applications which include the following; Synthesis of polymeric precursors for the formation of nanocrystalline Ti-C-N composites, synthesis and antiplasmodial activity of a cysteine protein inhibiting bioting-lated aziridie-2,3-dicarboxylate monoclonal antibodies for the mycotoxius deovyrivalenol , 3-acetyl deoxyniralenol[28], the synthesis and the utility of benzoyl lecgonine hydrazide coupled to horseradish peroxidase[29].

According to the above important application of the carbodiimides products we start this investigation in a goal to find an application in medical area.

## experimental

All melting points were uncorrected using Electrothermal 9300 Apparatus. I.R spectra were performed using infrared spectrophotometer model Tensor 27 Bruker Co., Germany, as KBr disc or as thin film using sodium chloride disc. Amino acid isocyanate were prepared using the published procedure[30].

Amino acid esters free of HCl were prepared according to a well known procedure[31].

### Synthesis of 2-nitro, 2,4-dinitroazidobenzene[32] (1a,b)

Sodium azide (1.3 g, 0.0309 mole) was added to a solution of (0.026 mole) 2-nitro or 2,4-dinitrochlorobezene in (25 ml) of dry dimethyl formamide (DMF). The resulting mixture was refluxed with stirring for (2 hrs.). The solvent was evaporated under reduced pressure. The solid product (84%) yield was used in the next step without further purifications.

### Synthesis of triphenyl phosphine imino-2-nitrobenzene and triphenyl phosphene imino-2,4-dinitrobenzene[32] (2a,b)

Aizdo nitro and dinitrobenzene, compound (1), (0.004 mole) was dissolved in (10 ml) of dry 1,2-dimethoxy ethane and was added to a solution of (1 g, 0.006 mole) of triphenyl phosphine in (10 ml) of 1,2-dimethoxy ethane. The mixture was stirred for (30 min) at room temperature then it was refluxed at (60 °C) for one hr., cooled and filtered. The precipitated product was recrystallized from methylene chloride with yield of about (84,85%) and melting points of (100,102 °C) and (84 °C) (dec.) for 1a and b respectively.

### Synthesis of 2-substituted (or disubstituted)-2H-1,2,3-benzotriazole compounds[32] (3-6)

A mixture of compound (2) (0.002 mole) in (30 ml) of dry acetonitrile was added to the isocyanate (0.002 mole) or (0.001 mole) dissolved in (5 ml) of acetonitrile. The final mixture was stirred at r.t. for (30 min), then refluxed at (60 °C) for (6 hrs). The solvent was evaporated under reduced pressure. The yield product was recrystallized from ethanol. The yield amount and the physical properties were indicated in Table (1).

### Synthesis of ethyl azido acetate and ethyl 2-azido propionate compounds[33] (7a,b)

Ethyl bromoacetate or ethyl 2-bromopropionate (0.1 mole) was added to (100 ml) of methanol containing (29 g, 0.2 mole) of glacial acetic acid. The mixture was allowed to cool to (0-5 °C), then it was added to a cooled mixture of (13 g, 0.2 mole) sodium azide dissolved in (35 ml) of chilled water. The total mixture was allowed to stirred in a cooled water bath (0-5 °C) for (24 hrs). The solvent (methanol) was evaporated under reduced pressure using rotary evaporator. Water (15 ml) was added to the final mixture and (50 ml) of ether. The organic layer was separated and washed with water twice time (5 ml), then it was dried on anhydrous sodium sulphate, filtered and the filtrate was evaporated under reduced pressure. The yield of the synthesized compounds (7a,b) was (73%, 71%) as an oily liquids with b.p. of (171°C, 58°C) respectively.

### Synthesis of triphenyl phosphine imino ethyl esters[32] (9a,b)

Using the same previous procedure for the preparation of compounds (2a,b) by reacting equimolar amounts of sodium azide and the corresponding ester resulted into the formation of oil compounds with boiling points (144 °C, 163 °C) and total yield of about (63%).

**Synthesis of 1-n-butyl-3-(□-ethyl carboxylato) carbodiimide[34] (9a,b)**

Butyl isocyanate (0.9 g, 0.01 mole) was dissolved in (25 ml) of dry THF. This solution was added to a stirred solution made by dissolving (0.01 mole) of the corresponding phosphine imino ethyl ester in (25 ml) THF. The final solution was allowed to stir for 24 hrs. at R.T. The solvent was evaporated under reduced pressure. Oily product was obtained with b.p. (128 °C, 117 °C) respectively, and with an overall yield of about (51%).

**General procedure for the reaction of amines and amino acid esters with carbodiimide[34]**

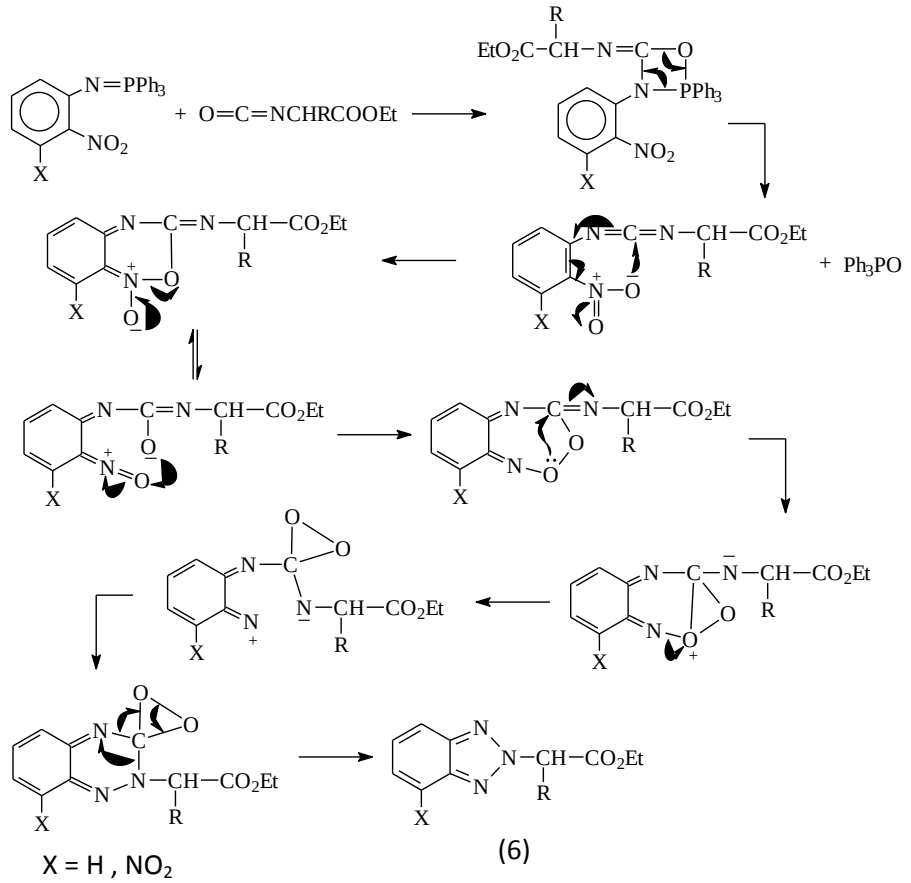
Carbodiimide (one of compounds 10a,b) (0.01 mole) in (25 ml) of dry THF was added to a solution of (0.01 mole) amine or amino acid ester dissolved in (25 ml) dry THF. The resulting mixture was stirred at r.t for 24 hrs. Evaporation of the solvent by rotary evaporator resulted into the formation of solid compound which was recrystallized from suitable solvent as indicated in Table (2).

**Results And Discussion**

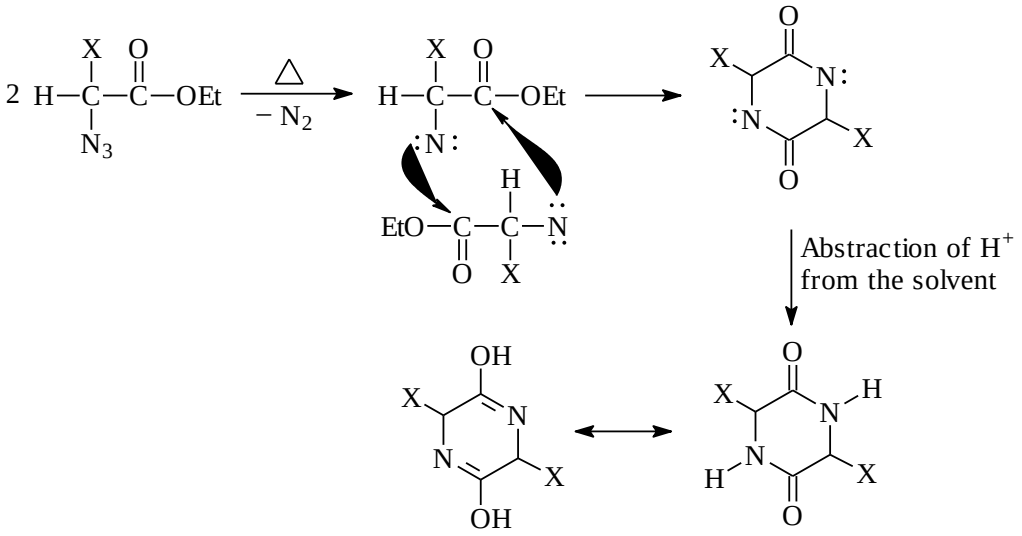
Azido nitrobenzene (compounds 1a,b) were characterized by the azido group absorbed at (2150, 2121 $cm^{-1}$) respectively. The formation of phosphineimino nitro compounds (2a,b) (Scheme 1) were also characterized by the N=P bond which absorbed at (693,744 $cm^{-1}$) respectively (Table 1).

This phosphineimino intermediate (compound 2) was subjected to further reaction with either hexamethylene diisocyanate or butyl isocyanate resulted into the formation of compounds 3 and 4 respectively. Their I.R data were indicated in Table (1), which confirm their formation through the absorption bands at(1617-1638$cm^{-1}$) assigned to (C=N). The other absorption bands were shown in Table (1). Compounds (5a,b) were formed as a result of the reaction of toluene diisocyanate with the phosphineimino intermediate (2). Their I.R data (Table 1) showed the triazole ring formation through the -C=N- absorption bands at (1638 $cm^{-1}$) for both (2a,b), other bands are indicated in this Table. Compounds (6a,b) were obtained by the reaction of valine, systeine ethyl esters with the phosphineimino compound (2b). These 5-nitro-□-substituted ethyl benzotriazole carboxylate compounds were characterized by the (C=O) ester moieties absorption at (1711, 1778 $cm^{-1}$) and the (C=N) of the triazole ring appeared at (1637, 1619 $cm^{-1}$) respectively. The other absorptions bands for ($NO_2$ , C=C aromatic) were indicated in Table (1).

The proposed mechanism for the cyclization process could be outlined as follows:




The published paper of preparing azido ester[35,36] was unavailable in our library nor in an online internet search. However, the procedure for the preparation of tert-butyl azido ester[37] was used but instead of obtaining a liquid as it was indicated elsewhere[38], solid compound was obtained with melting point as indicated in Table (2). Using the published procedure which was published by Boyer and Straw[39] no product was obtained due to immiscibility of the bromoesters in water-alcohol mixture, therefore we modify the Tennent et al. procedure as it was indicated in the experimental part. The solid product which was obtained by the first procedure could be summarized by the following Scheme.




This postulated mechanism was supported by the work of Smolinsky and Pryde on similar compounds[40].

The abstraction of hydrogen from the solvent may occur after the nitrene formation (before cyclization) then –⁻NH will attack the carbonyl of the second ester molecule resulted into the formation of final piprazine 3,6-dione compounds. The formation of NH by abstraction of hydrogen radical from the solvent was also supported by the work on the thermal decomposition of mesitylene-2-sulfonyl azide[41]. The formation of piprazine 3,6-dion was resulted from both inter and intra molecular attack of the nitrogen atom of the azido group after the loss of $N_2$ gas. The IR data of these compounds were in a good agreement with the proposed mechanism above through the following bands (1638 $cm^{-1}$) for (C=N) of both compounds (8a,b) and the carbonyl of the amide (I) band and (NH) amide II band absorbed at (1617 $cm^{-1}$) for both (a,b), and (1560-1564 $cm^{-1}$) respectively. Moreover, the ester group was absent in the IR absorption spectra, which supports the postulated mechanism as mentioned above. The evidence of nitrene formation was coming from certain aspect of decomposition which have reviewed[42,43]. It is important to note here that the stored azido ester for more than 3 days in refrigerator cause to dimerize. This was in agreement with Toho University Team, finding which mentioned that ethyl azidoacetate was unstable compound[44].

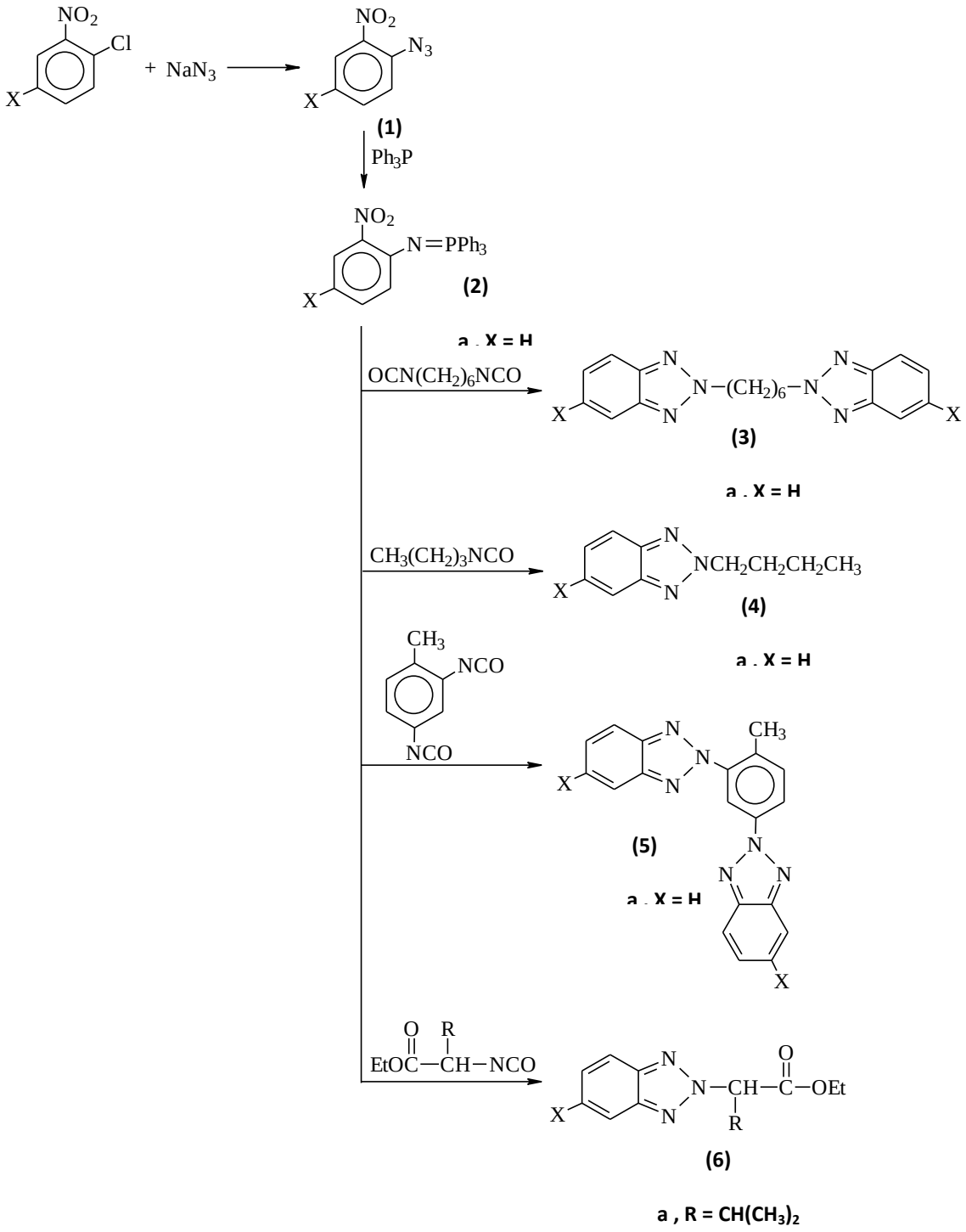
Compounds (9a,b) were prepared according to the procedure mentioned in the experimental part and Scheme (2). The IR data (Table 2) showed the presence of (N=P) absorption band at (698, 791 $cm^{-1}$), (C=O) ester absorbed at (1744, 1739 $cm^{-1}$) for the compounds (a,b) respectively.

The carbodiimide (compounds 10a,b) were prepared by the reaction of butyl isocyanate with compound (9) (Scheme 2).

The IR data (Table 2) also support the formation of the carbodiimide through the absorption bands at (2117, 2123 $cm^{-1}$) for (10a,b) respectively together with the ester carbonyl group through its absorption at (1739, 1742 $cm^{-1}$) for (a,b) respectively.

Compound (11) was prepared by bubbling ethyl amine gas (FLuka company) through the solution of compound (10) in THF for (1.5 hr). The IR spectrum of this compound indicates the presence of (C=N) bond absorbed at (1618 $cm^{-1}$) together with the (C=O) amide band absorbed at (1640 $cm^{-1}$) which supports the presence of this compound in the keto-enol form.

Compounds (12,13), (Scheme 2) were resulted from the reaction of valine ethyl ester and n-hexylamine with compound (10). The IR data (Table 2) indicate that cyclic compound and not bicyclic compounds were formed through the presence of the ester group absorbed at (1734, 1730 $cm^{-1}$) for compounds (12a,b) together with the (C=N) appeared at (1617-1639 $cm^{-1}$). The (C=O) amide bands absorbed between (1638-1639 $cm^{-1}$) for the compounds (12a,b; 13a,b) respectively. So, compounds (12a,b) did not show the bicyclic formation through the attack of the amine moiety toward the carbonyl of ester which may be due to the steric effect of the isopropyl group (the residue of systein amino acid ester).


NO2
Cl
X
+ NaN3
NO2
N3
X
(1)
Ph3P
NO2
N=PPh3
X
(2)
a , X = H
OCN(CH2)6NCO
N
N
N
N
N
N
X
X
(3)
a , X = H
CH3(CH2)3NCO
N
N
X
NCH2CH2CH2CH3
(4)
a , X = H
CH3
NCO
NCO
N
N
N
X
CH3
N
N
N
N
X
(5)
a , X = H
O
R
EtOC
CH
NCO
N
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CH
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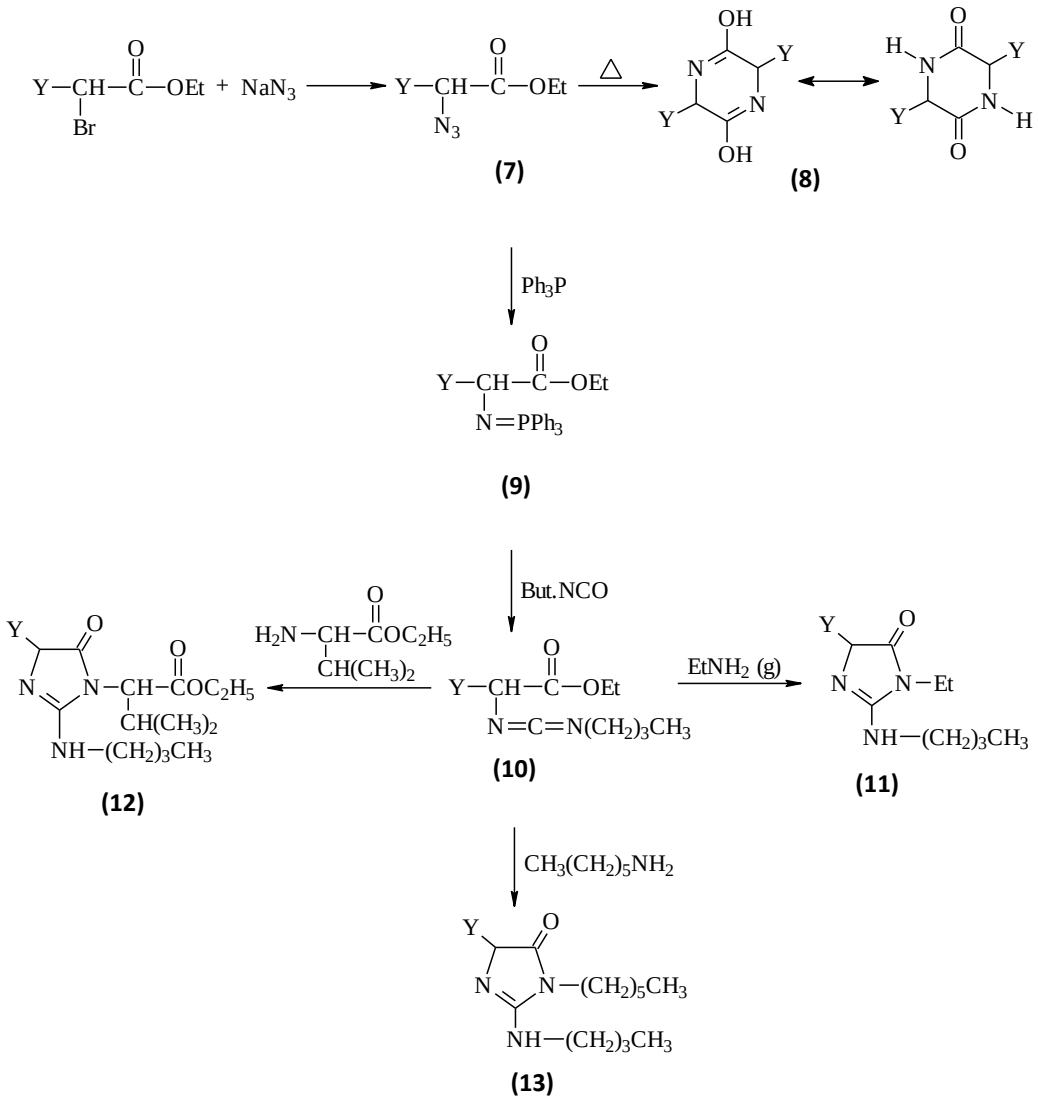
OEt
O
R
(6)
a , R = CH(CH3)2

**Scheme (1)**



**Scheme (2)**

**Table (1): Physical and IR spectral data for compounds (1-6)**

| Comp. No. | m.p. (°C) | Yield (%) | Rec. solvent | I.R □ $cm^{-1}$ , KBr | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | $NO_2$ asm. sym. | C-N | C=N | C⋯⋯C Aromatic | C=C Aromatic | C=O Ester | N=P | N=N=N |
| 1a | 200-202 dec. | 84 | Ethanol | 1525<br>1349 | 1279 | - | 1421 | 1525 | - | - | 2150 |
| 1b | - | 69 | Ethanol | 1546<br>1343 | 1262 | - | 1416 | 1496 | - | - | 2121 |
| 2a | 100-102 | 85 | $CH_2Cl_2$ | 1581<br>1307 | - | - | 1433 | 1474 | - | 693 | - |
| 2b | 61-62 | 72 | $CH_2Cl_2$ | 1510<br>1341 | - | - | 1432 | 1474 | - | 744 | - |
| 3a | 176-177 | 52 | Ethanol | - | 1268 | 1638 | 1473 | 1568 | - | - | - |
| 3b | 96-98 | 67 | Ethanol | 1475<br>1252 | 1182 | 1617 | 1434 | 1475 | - | - | - |
| 4a | 71-74 | 71 | Ethanol | - | 1279 | 1638 | 1475 | 1575 | - | - | - |
| 4b | 106-108 | 69 | Ethanol-$H_2O$ | 1474<br>1339 | 1189 | 1638 | 1414 | 1574 | - | - | - |
| 5a | 253-255 | 76 | Ethanol | - | 1218 | 1638 | 1474 | 1559 | - | - | - |
| 5b | 219-223 | 78 | Ethanol-$H_2O$ | 1557<br>1319 | 1199 | 1638 | 1415 | 1557 | - | - | - |
| 6a | 136-138 | 48 | Ethanol-$H_2O$ | 1559<br>1360 | 1119 | 1637 | 1416 | 1559 | 1711 | - | - |
| 6b | 158-159 | 47 | Ethanol | 1468<br>1345 | 1309 | 1637 | 1436 | 1568 | 1778 | - | - |

**Table (2): Physical and IR spectral data for compounds (7-13)**

| Comp. No. | m.p. (°C) | Yield (%) | Rec. solvent | I.R □ $cm^{-1}$ , KBr | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C-N | C=N | C⋯⋯C Aromatic | C=C Aromatic | C=O Ester | N=P | C-O-C | N=N=N N=C=N | N-H O-H |
| 7a | 171 | 89 | - | 1335 | - | - | - | 1739 | - | 1225 | 2121<br>- | - |
| 7b | 58 | 81 | - | 1299 | - | - | - | 1743 | - | 1196 | 2117<br>- | - |
| 8a | 204-207 | 78 | Ethanol | 1338 | 1638 | 1413 | 1564 | - | - | - | - | 3474 |
| 8b | 197-198 | 79 | Ethanol | 1340 | 1638 | 1413 | 1560 | - | - | - | - | 3417 |
| 9a | b.p. 179 | 93 | - | 1261 | - | - | - | 1744 | 698 | 1122 | - | - |
| 9b | b.p. 144 | 65 | - | 1283 | - | - | - | 1739 | 791 | 1175 | - | - |
| 10a | 163 | 91 | - | 1341 | 1651 | - | - | 1742 | - | 1196 | -<br>2117 | - |
| 10b | 128 | 78 | - | 1327 | 1637 | - | - | 1725 | - | 1217 | - | - |

| | | | | | | | | | | | 2123 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11 | 147-150 | 61 | Ethanol-$H_2O$ | 1267 | 1640 | - | - | - | - | - | - | 3413 |
| 12a | 183-185 | 52 | Ethanol | 1338 | 1638 | - | - | 1734 | - | 118 | - | 3415 |
| 12b | 122-125 | 56 | Ethanol | 1120 | 1638 | - | - | 1730 | - | 1120 | - | 3417 |
| 13a | 136-137 | 43 | Ethanol | 1267 | 1639 | - | - | - | - | - | - | 3415 |
| 13b | 169-174 | 53 | Ethanol-$H_2O$ | 1277 | 1639 | - | - | - | - | - | - | 3414 |

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# تحضير بعض الحلقات غير المتجانسة عن طريق الفوسفين ايمينو الوسطي

**حارث محمد العجيلي**

*قسم الكيمياء ، كلية العلوم ، جامعة الموصل ، الموصل ، العراق*

( تاريخ الاستلام: ١٠ / ١٢ / ٢٠٠٧ ، تاريخ القبول:٢٩ / ١٠ / ٢٠٠٨ )

**الملخص**

تم في هذا البحث تحضير عدد من المركبات الحلقية غير المتجانسة وذلك من خلال مسارين، حيث يتضمن المسار الاول تحضير مركبات ٢-نايترو، ٤،٢-ثنائي نايترو ازيدو بنزين (1a,b) من خلال تفاعل ٢-كلورو، ٤،٢-ثنائي نايترو كلوروبنزين مع ازيد الصوديوم. بعدها تم تحويل مركبات الازايد الى الفوسفين ايمين (2a,b) وذلك من خلال تفاعلها مع ثلاثي فنيل فوسفين ثم تمت حولقة هذه المركبات عن طريق تفاعلها مع بعض مركبات الايزوسيانات لينتج المركبات (٣-٦).

اما المسار الثاني فيتضمن تحضير مركبات اثيل ازيدو اسيتيت واثيل ٢-ازيدو بروبيونيت وذلك بتفاعل اثيل برومو اسيتيت واثيل ٢-بروبيونيت مع ازيد الصوديوم لينتج المركبات (7a,b) ومن ثم مفاعة هذه المركبات مع ثلاثي فنيل فوسفين لينتج مركبات الفوسفو ايمين (9a,b) ومن ثم مفاعلة هذه المركبات مع بيوتيل ايزوسيانات لينتج مركبات الكاربو ثنائي ايمايد (10a,b). تم حولقة هذه المركبات عن طريق تفاعلها مع بعض الامينات الاولية وبعض استرات الاحماض الامينية.

تم تشخيص هذه المركبات من خلال درجات الانصهار وطيف الاشعة تحت الحمراء (I.R) وتمت مناقشتها.