The Islamic University Journal (Series of Natural Studies and Engineering)
Vol.14, No.2, P.31-38, 2006, ISSN 1726-6807, http//www.iugaza.edu.ps/ara/research/

SYNTHESIS OF SOME NEW SUBSTITUTED IMIDAZO(1,2-*a*)PYRIDINES AND THEIR 2-ONE DERIVATIVES

Bassam A. Abu Thaher
Chemistry Department, Faculty of Science,
Islamic University of Gaza, P.O.Box 108, Gaza, Palestine.
E-mail: bthaher@iugaza.edu.ps
Tel.: +970-8-2860700;
Fax.: +970-8-2860800

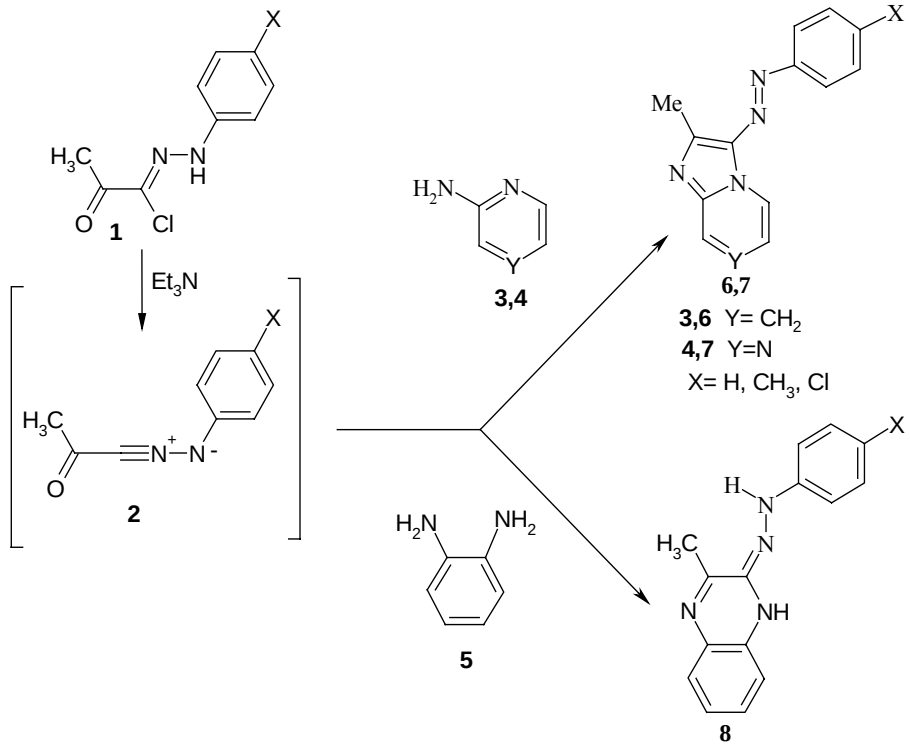
الملخص: يتفاعل 3،2-ثنائي أمينو البيريدين **(11)** (ذو ثلاث ذرات نيتروجين نيوكليوفيلية) بشكل انتقائي مع النيتريل إيمينات **(10،2)** بطريق التكثيف الحلقي لينتج إميدازو [1,2-*a*] بيردين **(12)** و إم ـيدازو [1,2-*a*] بيردين-2-ون **(13)** على الترتيب. وقد تم التحقق من التركيب البنائي للنواتج بتحليل بياناتها الطيفية مثل IR, MS, NMR.

ABSTRACT: 2,3-diaminopyridine **(11)** (a tri-nitrogen nucleophile) undergoes regioselective cyclocondensation reaction with nitrilimines **(2,10)** affording 8-aminoimidazo[1,2-a]pyridines **(12)** and 8-aminoimidazo[1,2-a]pyridine-2- ones **(13)**, respectively. The structures of the new compounds **(12,13)** were deduced from their IR, MS and NMR spectral data.

Key Words: 2,3-diaminopyridine; nitrilimines; 8-aminoimidazo[1,2-a]- pyridines; 8-aminoimidazo[1,2-a]pyridine-2-ones.

Introduction

Nitrilimines are generated *in situ* from their hydrazonoyl chloride precursors **(1)** in presence of triethylamine. They undergo cyclo-condensation reaction yielding various heterocyclic systems [1-3]. In previously reported works, 2-aminopyridine **(3)** as well as aminopyrazine **(4)** were reported to react with nitrilimines **(2)** to produce the corresponding imidazo[1,2-a]pyridines **(6)** [4,5] and imidazo[1,2-a]pyrazines **(7)** [6], respectively. The importance and the biological activity of similar heterocyclic systems were reported in the literature [7,8]. In another work, *o*-phenylenediamine **(5)** (a dinitrogen nucleophile) was reported to react with nitrilimines giving the benzoquinoxaline derivatives **(8)**, scheme (1) [9]



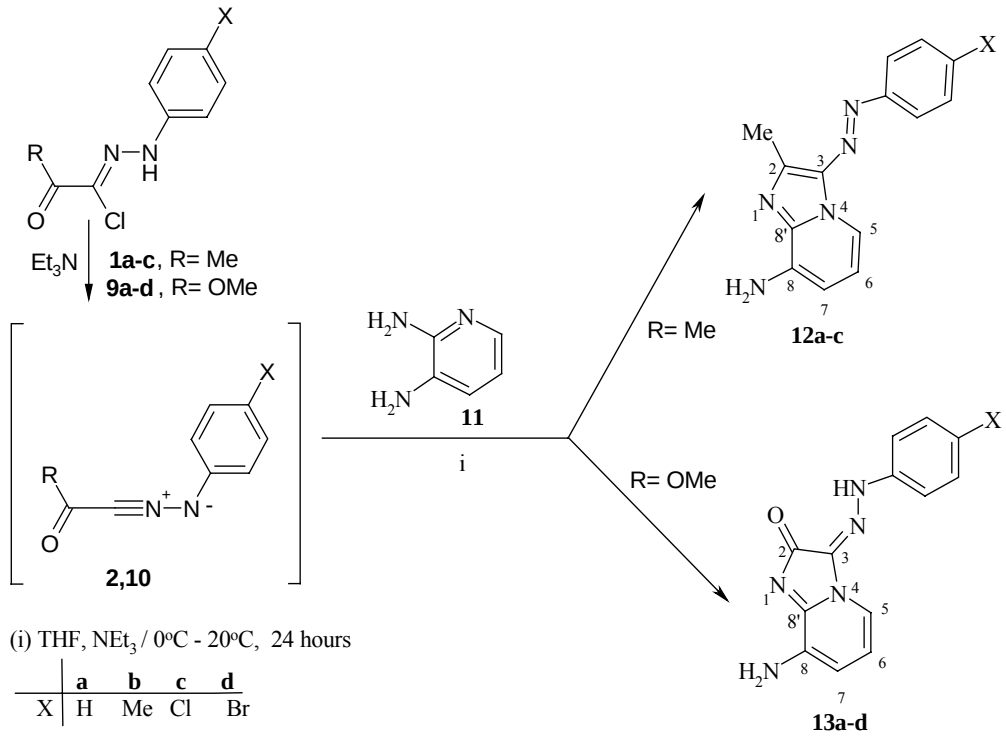
Scheme (1)

2,3-Diaminopyridine (a tri-nitrogen nucleophile) **(11)** can react with nitrilimines through the diamino groups like *o*-phenylenediamine or through the pyridine's nitrogen and the 2-amino group. In the present work, the reaction between 2,3-Diaminopyridine and differently substituted nitrilimines **(2,10)** will be investigated.

Results and Discussion

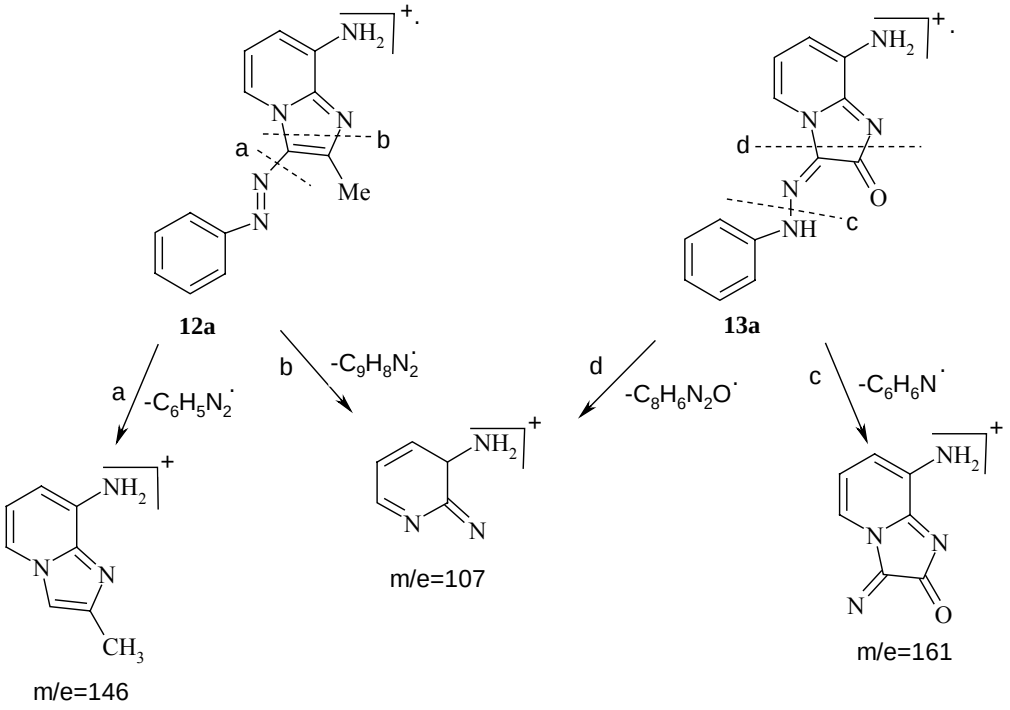
Synthesis

The reaction of 2,3-diaminopyridine **(11)** with hydrazonoyl halides **(1,9)** in the presence of triethylamine was carried out by mixing equivalent amounts of them in THF, and the reaction mixture was stirred overnight. The organic solvent was evaporated under reduced pressure. The crude product was washed with water, filtered and crystallized from hot ethanol. The strutcural assignment of the products (**12,13**) was mainly based on IR, MS and NMR spectra (scheme 2).



Scheme (2)

The IR spectra of compounds **12** exhibit medium bands in the region 3300-3200 cm^{-1} (NH_2 stretching), and medium bands in the range 1620-1500 cm^{-1} (C=N, and aromatic carbons, stretching). Compounds **13** exhibit three bands between 3300-3200 cm^{-1} for NH_2 and NH, also C=O streching bands appear around 1660 cm^{-1}. The EI-MS spectra of compounds **12a** and **13a** show their correct molecular ions. Fragments in their spectra support the structure of these compounds. Thus fragments 146 and 107 give an evidence for the structure of compound **12a**, whereas, the fragments 161 and 107 support the suggested structure of compound **13a**.



The ^{1}H-NMR spectra of compounds **12** show a singlet for the methyl protons around 2.7 ppm. The peak of the methyl protons of the acetyl heterocycles derived from nitrilimines appears usually at 2.4 ppm [3]. In addition, a singlet appears about 4.5 ppm for the amino group.

^{13}C-NMR data of compounds **12** shows no peak for the carbonyl carbon of the acetyl group around 193 ppm [2,3], but only the signals of the aromatic and olefinic carbons in the range 114-152, in addition to the CH_3 signal around 14 ppm. This is a strong evidence that the carbonyl carbon of nitrilimines is converted to alkene carbon as it appeared in structures **12** (scheme 2).

The ^{1}H-NMR spectra of compounds **13a-d** display two signals about 5.6 and 12.3 ppm which are assigned to the amino groups and the hydrazone NH groups, respectively. ^{13}C-NMR data of these compounds shows the ring C=O signal at 168 ppm. No OCH_3 signal appears around 53 ppm. These results clarify that the reaction between nitrilimines and 2,3-diaminopyridine is a one step cyclocondesation reaction leading to 8-amino-imidazopyridines (**12**) or 8-aminoimidazopyridine-2-ones (**13**) depending on the type of the nitrilimine used. Apparently, the presence of the 3-amino group in compound **11** has no influence on the mode of this reaction.

Experimental

2,3-Diaminopyridine **(11)** was purchased from Acros. Melting points (uncorrected) were determined on an electrothermal Mel-Temp. apparatus. ^{1}H- and ^{13}C NMR spectra were measured on a Bruker DPX-300 instrument with TMS as an internal reference. EI - MS spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV; ion source temperature = 200 ^{0}C. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer.

Hydrazonoyl chlorides **(1a-c,9a-d)** were prepared *via* direct coupling of the appropriate arenediazonium chloride with 3-chloro-2,4-pentanedione or methyl chloroacetylacetate, recpectively, in an aqueous pyridine solution following standard procedures [10-12].

Synthesis of 8-aminoimidazo[1,2-*a*]pyridines (12,13)

General Procedure

To stirred and cooled solutions (0^{o}C) of hydrazonoylchlorides **(1,9)** (11 mmol) in THF (30 mL) was portionwise added a solution of 2,3-diaminopyridine **(11)** (12 mmol) in THF (20 mL) , and triethylamine (3 mL) in THF (5 mL). The reaction mixture was stirred at 0 ^{o}C for 10-15 min., and then at room temperature overnight. The solvent was evaporated under reduced pressure. The crude precipitated solid product was washed with water, collected, dried, crystallized from hot ethanol and if necessary purified by preparative TLC using $CHCl_3$ / CH_3OH (95:5 v/v) solvent pair as an eluent. The following compounds were prepared using this procedure.

8-amino-2-methyl-3-phenylazoimidazo[1,2-*a*]pyridine (12a)

Yield of pure **12a** = 1.1g (44%) m.p. =130-131 ^{o}C. IR (KBr): ν_{max} 3299, 3196 (NH_2), 3050 (aromatic hydrogens), 2920, 2842 (aliphatic hydrogens), 1615 (C=N), 1555, 1525 (aromatic carbons) cm^{-1}, MS: *m/z* ($C_{14}H_{13}N_5$) = 251 ($M^{+\cdot}$,base beak), 146 (M^{+}-PhN_2); 107 (M^{+}- $PhN_2C{=}CCH_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.8 (s, 3H, CH_3); 4.6 (s, 2H, NH_2), 6.6 (d,1H, J = 7.1 Hz), 6.8 (t,1H, J = 7.1 Hz), 7.3 (t, 1H, J = 7.1 Hz), 7.4 (t, 2H, J = 7.2 Hz), 7.8 (d, 2H, J = 7.2 Hz), 9.15 (d, 1H, J = 7.1 Hz) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3); 108.36, 115.7, 118.5, 121.7, 124.4, 128.9, 129.1, 134.0, 135.1, 138.7, 153.8 (aromatic carbons) ppm.

8-amino-2-methyl-3-(4-methylphenylazo)imidazo[1,2-*a*]pyridine (12b)

Yield of pure **12b** =1.2 g (45%); m.p. = 128-129 ^{o}C. IR (KBr): ν_{max} = 3333, 3286 (NH_2), 3016 (aromatic hydrogens), 2958, 2917 (aliphatic hydrogens), 1618 (C=N), 1600, 1558, 1530 (aromatic carbons), cm^{-1}, MS: *m/z*

($C_{15}H_{15}N_5$) = 265 ($M^{+\cdot}$, base beak), 146 [M^+- PhN_2], 107 (M^+- ArN_2C=CCH3); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.4 (s, 3H, *p*-CH_3-Ph), 2.8 (s, 3H, CH_3), 4.5 (s, 2H, NH_2), 6.6 (d,1H, J = 7.2 Hz), 6.8 (t,1H, J = 7.2 Hz), 7.3 (d, 2H, J = 8.1 Hz), 7.7 (d, 2H, J = 8.1 Hz), 9.2 (d, 1H, J = 7.2 Hz) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 21.4 (*p*-CH_3-Ph), 108.0, 115.5, 118.5, 121.6, 129.7, 130.1, 133.8, 134.9, 138.7, 139.3, 151.9 (aromatic carbons) ppm.

8-amino-3-(4-chlorophenylazo)-2-methylimidazo[1,2-*a*]pyridine (12c)
Yield of pure **12c** =1.3g (46%); m.p. = 169-170 ^{o}C. IR (KBr): ν_{max} = 3376, 3312 (NH_2), 3060 (aromatic hydrogens), 2952, 2913 (aliphatic hydrogens), 1609, 1562, 1525 (aromatic carbons) cm^{-1}; MS: *m/z* ($C_{14}H_{12}N_5Cl$) = 285 ($M^{+\cdot}$, base beak), 146 [M^+- ArN_2], 107 (M^+- ArN_2C=CCH3); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.8 (s, 3H, CH_3), 4.5 (s, 2H, NH_2), 6.6 (d,1H, J = 7.4 Hz), 6.8 (t,1H, J = 7.4 Hz), 7.4 (d, 2H, J = 8.6 Hz), 7.7 (d, 2H, J = 8.6 Hz), 7.8 (d, 2H, J = 8.6 Hz), 9.2 (d, 1H, J = 7.4 Hz) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 108.7, 115.9, 118.7, 122.8, 129.2, 129.8, 134.0, 134.4, 135.1, 138.9, 152.3 (aromatic carbons) ppm.

8-amino-2-oxo-3-phenylazoimidazo[1,2-*a*]pyridine (13a)
Yield of pure **13a** = 1.5 g (59%); m.p. = 239-240 ^{o}C. IR (KBr): ν_{max} = 3304, 3190, 3164 (NH_2, NH), 3061 (aromatic hydrogens), 2958, (aliphatic hydrogens), 1660 (CO), 1620 (C=N), 1592,1579, 1558 (aromatic carbons) cm^{-1}; MS: *m/z* ($C_{13}H_{11}N_5O$) = 253 ($M^{+\cdot}$, base beak), 161 (M^+- PhNH), 135 (M^+- PhNHNC), 107 (M^+-PhNHNCCO); ^{1}H-NMR (300 MHz, DMSO-D_6):δ 5.6 (s, 2H, NH_2), 6.7-6.8 [m,2H, (H-6 and H-7, overlaped)], 7.0 (t,1H, J = 7.3 Hz), 7.3 (d, 2H, J = 7.8 Hz), 7.5 (d, 2H, J = 7.8 Hz), 7.7 (dd, 1H, J^3 = 7.3 Hz, J^4 = 1.1 Hz), 12.45 (br.s, 1H, NH) ppm; ^{13}C-NMR (75 MHz, DMSO-D_6): δ 114.3, 114.9, 115.3, 123.7, 128.9, 130.0, 130.2, 136.0, 142.7, 152.8 (aromatic carbons), 168.5 (CO) ppm.

8-amino-3-(4-methylphenylazo)-2-oxo-imidazo[1,2-*a*]pyridine (13b)
Yield of pure **13b** = 1.4g (52.4%); m.p. = 212-213 ^{o}C; IR (KBr): ν_{max} =3273, 3198, 3190 (NH_2, NH), 3030 (aromatic hydrogens), 2922, 2849 (aliphatic hydrogens), 1650 (CO), 1620 (C=N), 1559, 1521 (aromatic carbons) cm^{-1}; MS: *m/z* ($C_{14}H_{13}N_5O$) = 267 ($M^{+\cdot}$, base beak), 161 (M^+- ArNH), 135 (M^+- ArNHNC), 107 (M^+-ArNHNCCO); ^{1}H-NMR (300 MHz, $CDCl_3$):δ 2.3 (s, 3H, *p*-CH_3-Ph), 4.5 (s, 2H, NH_2), 6.6 (t, 1H, J = 6.4 Hz), 6.7 (dd, 1H, J^3 = 7.4 Hz, J^4 =1.0 Hz), 7.1 (d, 2H, J = 8.1 Hz), 7.2 (d, 2H, J = 8.1Hz), 7.6 (dd, 1H, J^3 = 7.4 Hz, J^4 = 1.0 Hz), 12.4 (br.s, 1H, NH) ppm; ^{13}C-

NMR (75 MHz, $CDCl_3$): δ 20.9 (*p*-CH_3-Ph), 113.3, 114.8, 115.3, 121.6, 124.6, 130.2, 134.0, 134.4, 139.5, 151.6 (aromatic carbons), 168.8 (CO) ppm.

8-amino-3-(4-chlorophenylazo)-2-oxo-imidazo[1,2-*a*]pyridine (13c)
Yield of pure **13c** = 1.6 g (55.7%); m.p. = 254-255 ^oC; IR (KBr): ν_{max} = 3278, 3198, 3188 (NH_2, NH), 3080 (aromatic hydrogens), 2958, 2958 (aliphatic hydrogens), 1657 (CO), 1620 (C=N), 1588, 1558 (aromatic carbons) cm^{-1}; MS: *m/z* ($C_{13}H_{10}ClN_5O$) = 287/289 ($M^{+\cdot}$, base beak), 161 (M^+- ArNH), 135 (M^+- ArNHNC), 107 (M^+-ArNHNCCO); ^{1}H-NMR (300 MHz, DMSO-D_6):δ 5.6 (s, 2H, NH_2), 6.7-6.8 [m,2H, (H-6 and H-7, overlaped)], 7.4 (d, 2H, J = 9.0 Hz), 7.5 (d, 2H, J = 9.0 Hz), 7.7 (dd, 1H, J^3 = 6.1 Hz, J^4 = 1.0 Hz), 12.3 (br.s, 1H, NH) ppm; ^{13}C-NMR (75 MHz, DMSO-D_6): δ 114.3, 115.1, 115.5, 116.6, 127.2, 129.3, 129.7, 136.0, 141.9, 153.3 (aromatic carbons), 168.5 (CO) ppm.

8-amino-3-(4-bromophenylazo)-2-oxo-imidazo[1,2-*a*]pyridine (13d)
Yield of pure **13d** = 1.4 g (42.3%); m.p. = 215 ^oC (decomp.); IR (KBr): ν_{max} = 3370, 3299, 3183 (NH_2, NH), 3087 (aromatic hydrogens), 2950, (aliphatic hydrogens), 1677 (CO), 1615 (C=N), 1591, 1556 (aromatic carbons) cm^{-1}; MS: *m/z* ($C_{13}H_{10}BrN_5O$) = 331/333 ($M^{+\cdot}$, base beak), 161 (M^+- ArHNH), 135 (M^+- ArNHNC), 107 (M^+-ArNHNCCO); ^{1}H-NMR (300 MHz, DMSO-D_6):δ 5.6 (s, 2H, NH_2), 6.7-6.8 [m,2H, (H-6 and H-7, overlaped)], 7.4 (d, 2H, J = 9.0 Hz), 7.5 (d, 2H, J = 9.0 Hz), 7.7 (dd, 1H, J^3 = 6.1 Hz, J^4 = 1.0 Hz), 12.4 (br.s, 1H, NH) ppm; ^{13}C-NMR (75 MHz, DMSO-D_6): δ 114.2, 115.1, 115.5, 117.0, 125.7, 129.3, 132.1, 133.4, 142.3, 153.3 (aromatic carbons), 168.5 (CO) ppm.

ACKNOWLEDGEMENTS
The author thanks Dr. Jalal Zahra, Department of Chemistry, Jordan University, for measuring NMR and Mass spectra, and the Islamic University of Gaza, Gaza, Palestine, for financial support.

References

[1] M. M. El-Abadelah, S. Saleh, A. M. Awadallah, *Asian J.Chem*. **9**, 695 (1997), M. R. El-Haddad, A. R. S. Ferwanah, A. M. Awadallah, *J.Prakt.Chem*. **340**, 623 (1998).

[2] B. A. Abu Thaher, H.–H. Otto, *Monatsh. Chem*. **133**, 1011 (2002).

[3] B. A. Abu Thaher, J. A. Zahra, M. M. El-Abadelah, *J. Heterocycl. Chem.* **39**, 901 (2002).

[4] B. A. Abu Thaher, *Abhath Al-Yarmouk J*., *Basic Sciences and Engineering*. ***12(2B)***, 555-561 (2003).

[5] A. S. Shawali, M. Sami, M. S. Sherif and C. Parkanyi, *J. Heterocycl. Chem*. **17**, 877 (1980).

[6] B. A. Abu Thaher, *The Islamic University Journal (Sieres of Natural Studies and Engineering)* ***13, No.2***, 109 -115 (2005).

[7] Z. Cesur, N. Cesur, G. Otuk, S. Derbentil, *Arch. Pharm. turc.* **31**, 135 (1989), K. C. Joshi, V. N. Pathak, S. Sharma, *Indian J.Chem.* ***24B,*** 124 (1985).

[8] C. Sablayrolles, P. A. Bonnet, G. Cros, J. P. Chapat, M. Boucard, PCT Int. Appl. (1988), 41pp. CAN 109:231072, AN 1988:631072

[9] C. Parkanyi, A. O. Abdelhamid, A. S. Shawali, *J. Heterocycl. Chem*. ***21(2),*** 521-524 (1984).

[10] M. M. El-Abadelah, A. Q. Hussein, and B. A. Abu Thaher, *Heterocycles* **32**, 1879 (1991), N. F. Eweiss and A. Osman, *J. Heterocycl. Chem*. **17**, 1713 (1980).

[11] R. Fusco and R. Romani, *Gazz. Chim. Ital*. **76**, 419 (1946), R. R. Phillips, Org. Reactions Vol.**10**, P.143, 1959; H. C. Yao and P. Resnick, *J. Am. Chem. Soc*. **84**, 3514 (1962).

[12] G. C. Barrett, M. M. El-Abadelah, and M. K. Hargreaves, *J. Chem. Soc. (C)*, 1986 (1970).