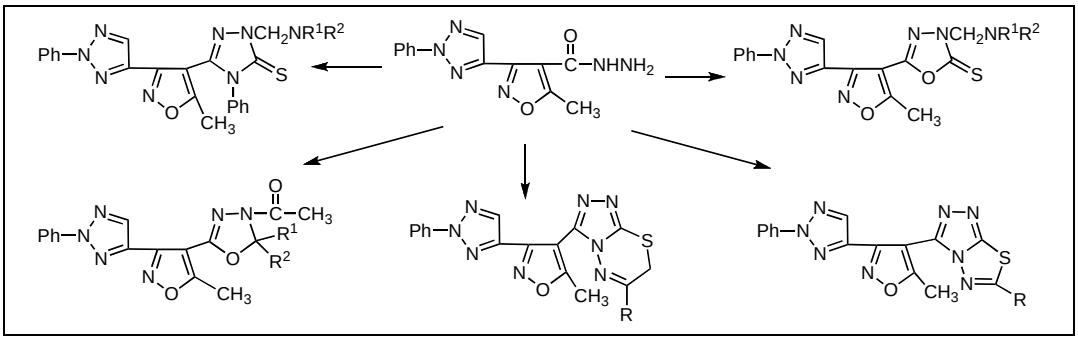
Synthesis of New Heterocyclic Compounds Having 1,2,3-Triazole and Isoxazole Rings in a Single Molecule

Qiu Chen, Fangming Liu*, Feng Xu, Chun Yang

Key Laboratory of Organosilicon Chemistry and Material Technology, Ministry of Education
Hangzhou Normal University, Hangzhou, 310012, China

Received October 13, 2006



Five series of new heterocyclic compounds of 1,2,4-triazole Mannich bases, 1,3,4-oxadiazole Mannich bases, 1,3,4-oxadiazolines, 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazines and 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles, in which 1,2,3-triazolyl and isoxazolyl have been united, were synthesized from the intermediate of 5-methyl-3-(2-phenyl-2*H*-1,2,3-triazol-4-yl)isoxazole-4-carbohydrazide, Their structures were established by spectroscopy.

J. Heterocyclic Chem., **45**, 77 (2008).

INTRODUCTION

Recent studies show that many sorts of heterocyclic compounds containing the rings system of triazole, isoxazole, oxadiazole, thiadiazole and thiadiazine, have a wide range of biological activities. Generally, triazole derivatives have been synthesized as possible antidepressants and plant growth regulators [1-3]. Some of the 1,2,4-triazole derivatives have anti-inflammatory activities and some are antifungal agents or herbicides [4-6]. Isoxazole derivatives form a part of many drugs used for antidepressant therapy and the treatment of osteoarthritis or rheumatoid arthritis [7,8]. On the other hand, 1,3,4-oxadiazoline-5-thiones, 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles have anticancer, antibacterial , antiseptic, anthelmintic and antimicrobial physiological activities [9-12]. Thus, it seemed of interest to combine various heterocyclic rings into a single molecule with the hope of finding activities and improving the function of some drugs.

Although the present literature revealed that a lot of compounds with 1,3,4-oxadiazoles, 1,3,4-oxadiazolines 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadizoles, containing a 1,2,3-triazole ring or isoxazole ring, have been synthesized [13-15], to our knowledge, not much have been mentioned in the synthesis of compounds containing the 1,2,3-triazole ring and isoxazole ring together in a single molecule. We designed 5-methyl-3-(2-phenyl-2*H*-1,2,3-triazol-4-yl)isoxazole-4-carbohydrazide as an intermediate **(5)**, and synthesized five new series of heterocyclic derivatives of 1,2,4-triazole Mannich bases, 1,3,4-oxadiazole Mannich bases, 1,3,4-oxadiazolines, 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazines and 1,2,4-triazolo[3,4-*b*]1,3,4-thiadizoles, in which 1,2,3-triazolyl and isoxazolyl have been united. The synthetic route is shown in Scheme 1.

RESULTS AND DISCUSSION

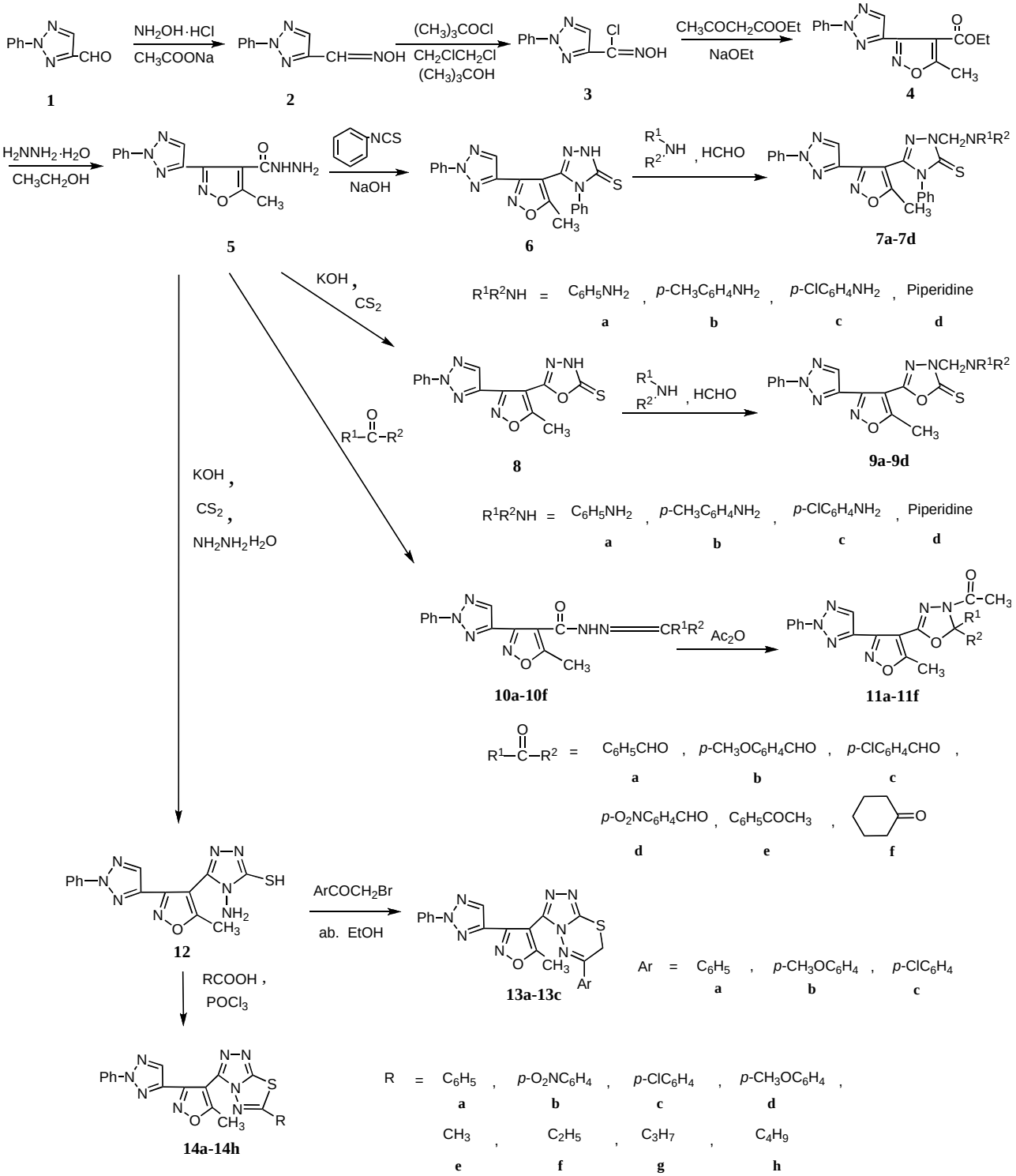
For preparation of the intermediate of **4**, the α-chloro-2-phenyl-1,2,3-triazole-4-formaldehyde oxime **(3)** can easily undergo auto-polymerization easily, if sodioacetoacetic ester was added into the solution of **3**. Therefore, **3** was added drop by drop into a stirring solution of sodioacetoacetic ester at low temperature to avoid polymerizing and obtain excellent yields of **4**.

The concentration of hydrazine affects the yield of **5** greatly. Higher yield of **5** was obtained, as volume proportion of ethanol/hydrazine is 1:0.4-0.5.

To avoid more subsidiary reactions, the synthesis of 1,3,4-oxadiazole Mannich bases **9a-9d** should be operated at room temperature.

If the reaction time is not long enough during the preparation of the derivatives of 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **13a-13c**, a mixture of product and intermediate is obtained, and must be purified through a difficult recrystallization. Prolonging the reaction time

Scheme 1: Synthetic Route



and recrystallization with ethyl acetate/ethanol were the key of synthesis.

At higher temperature partial charring occurred during the synthesis of the derivatives of 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **14a-14h**, therefore, lower temperature were used in the reaction of aliphatic acids than in the reaction of aromatic acid.

All compounds IR spectra showed absorption bands at 1520-1650cm^{-1}, 2900-2940cm^{-1}, which coincided with the vibration of C=N, C=C and the extension vibration of CH_3 or CH_2.

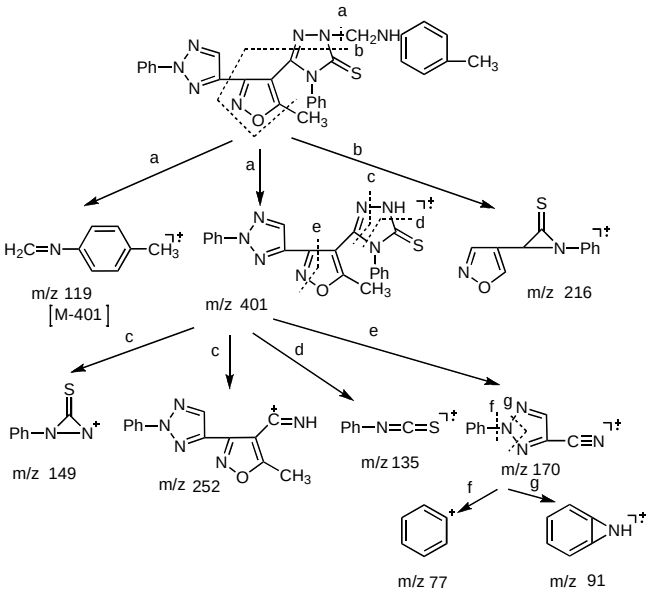
The compounds of **7a-7c**'s and **9a-9c**'s IR spectra displayed absorption bands of NH at 3300-3400 cm^{-1} except **7d** and **9d**, where the absorption bands of C=S at 1042cm^{-1} were observed. The compounds of **11a-11f**'s IR spectra showed characteristic absorption bands at 1660 cm^{-1} for carbonyl C=O. The compounds of **13a-13c**'s and **14a-14h**'s spectra displayed characteristic absorption bands at 1480 cm^{-1}, which coincided with the vibration of N=C–S [16].

The ^{1}H NMR spectra of N=C–H of 1,2,3-triazoles was δ 7.8-8.5, singlet. The chemical shift of Ar-H displayed multiplet at δ 6.5-8.0. The signal of CH_3 on isoxazole rings exhibited at δ 2.6-2.8, shifting to downfield, because of magnetic anisotropy of the ring. Inductive effect of N atom resulted in the shift of H of NCH_2N at δ 5.0-5.5, The weak broad peak at δ 5.0-5.7 corresponds to NH.

Total target molecules' MS Spectra displayed strong peaks at m/z 77, m/z 91, m/z 170 or 171, m/z 251 or 252. Those were characteristic peaks of the molecular ion fragment of 1,2,3-triazole containing phenyl and isoxazole ring.

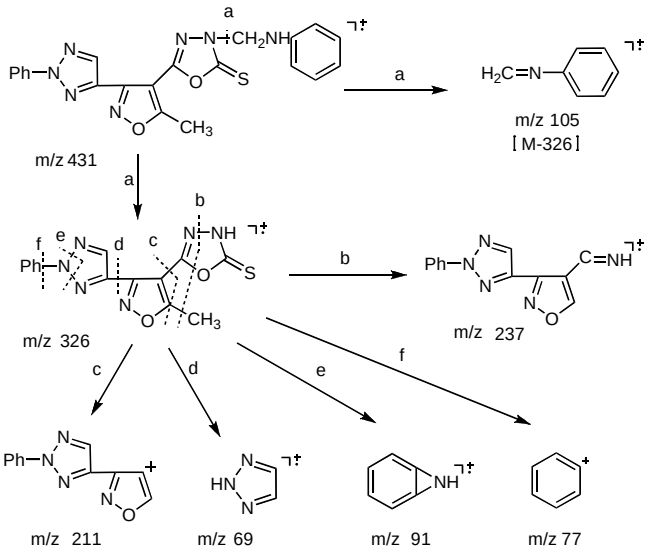
Because of poor molecular stability of 1,2,4-triazole Mannich bases of **7a-7d**, molecular ion peaks were not observed in their electron impact mass spectra, but showed characteristic peaks of m/z 401, m/z corresponding to [M-401], m/z 135, m/z 149, m/z 216. The fragmentation pattern of **7b** was shown in Scheme 2.

Scheme 2: Proposal Fragmentation Processes of **7b**



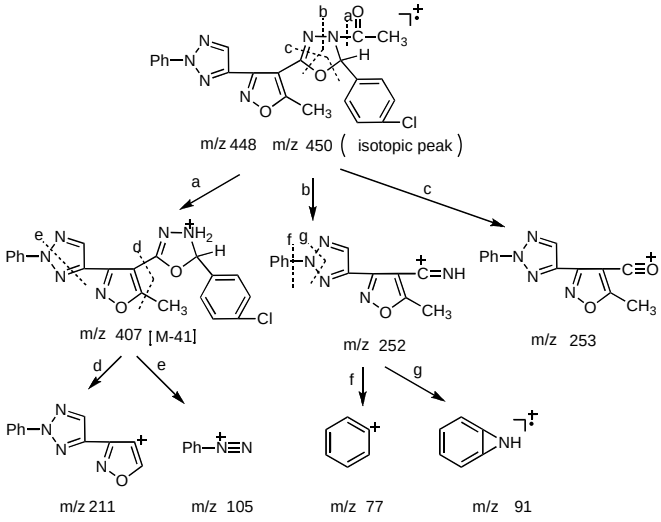
The molecular stability of 1,3,4-oxadiazole Mannich bases of **9a-9d** was poor as well, and only some of the compounds showed molecular ion peaks, but there were characteristic peaks at m/z 326, m/z corresponding to [M-326]. The fragmentation pattern of **9a** is shown in Scheme 3.

Scheme 3: Proposal Fragmentation Processes of **9a**



Molecular ion peaks are observed in all oxadiazolines (**11a-11f**) spectra, and showed characteristic peaks at m/z [M-42] or m/z [M-41]. The fragmentation pattern of **11c** is shown in Scheme 4.

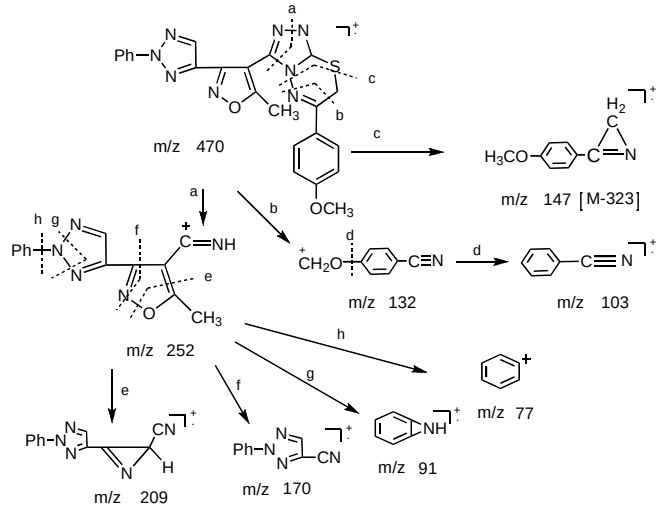
Scheme 4: Proposal Fragmentation Processes of **11c**



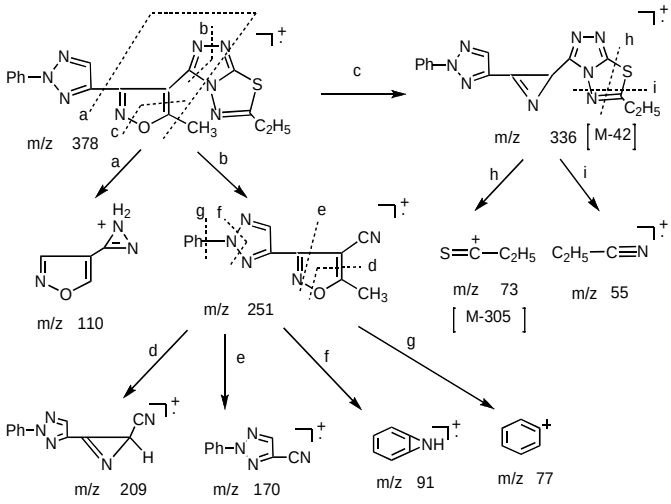
Molecular ion peak are observed for all 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazines (**13a-13c**), and showed characteristic peaks at m/z [M-337] or m/z [M-336] and m/z [M-323]. The fragmentation pattern of **13b** is shown in Scheme 5.

Molecular ion peaks are obsesrved for all 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**14a-14h**), and showed characteristic peaks at m/z [M-42], m/z [M-305] or m/z [M-336] . The fragmentation pattern of **14f** was shown in Scheme 6.

Scheme 5: Proposal Fragmentation Processes of **13b**



Scheme 6: Proposal Fragmentation Processes of **14f**



EXPERIMENTAL

Melting points were taken in an X-5 micro melting point apparatus and were uncorrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer (KBr pellets). Mass spectra were recorded on an Agilent 5975 spectrometer (EI, 70ev). ^{1}HNMR Spectra were obtained on a Bruker AV 400MHz instrument in $CDCl_3$ using TMS as an internal standard. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer.

Synthesis of 2-phenyl-1,2,3-triazole-4-formaldehyde (1). Compound of **1** was prepared according to literature [17], mp 67-68 °C.

Synthesis of 2-phenyl-1,2,3-triazole-4-formaldehyde oxime (2). Compound of **2** was prepared according to literature [18], mp 135-137 °C.

Synthesis of α-chloro-2-phenyl-1,2,3-triazole-4-formaldehyde oxime (3). Compound of **3** was prepared according to literature [19], mp 143-145 °C.

Synthesis of 3-(2-phenyl-1,2,3-triazol-4-yl)-5-methylisoxazole-4-ethyl formate (4). To a solution of ethanol of 0.08 mol sodio-acetoacetic ester, 0.08 mol of chloroformaldehyde oxime (**3**), dissolved in 100 ml of absolute ethanol, was added gradually at –5~0 °C under stirring condition. The solution was stirred at low temperature for 1 h again, then stirred at room temperature for 2 h. Cold water was added into the solution. The resulting solid was filtered, washed with water, and finally recrystallized from ethanol to give white crystal of **4**, yield 78%, mp 83-84 °C.

5-Methyl-3-(2-phenyl-2*H*-1,2,3-triazol-4-yl)isoxazole-4-carbohydrazide (5). A solution of 0.04 mol of isoxazole ethyl formate (**4**), dissolved in 30 ml of ethanol, was treated to 15 ml 85% of hydrazine and refluxed for 5 h. A white solid separated out after the mixture had cooled. The solid was collected by filtration, washed and recrystallized from ethanol to get white crystal of **5**, yield 77%, mp 176-178 °C.

Synthesis of 1-substituted-aminomethyl-3-(3-(2-phenyl-1,2,3-triazol-4-yl)-5-methylisoxazol-4-yl)-4-phenyl-1,2,4-triazole-5-thiones (Mannich bases 7a-7d). A mixture of 8 mmol of carbohydrazide (**5**) and 8.8 mmol of phenylisosulfocyanate was dissolved in ethanol, and heated under reflux for 4 h to give a white solid. The resulting solid was treated to 160 ml 5% of NaOH, and refluxed for 1.5 h. The pH of the mixture was brought to 5 by adding 1:1 of hydrochloric acid to give white solid. A white crystal of **6** was obtained after recrystallization from ethanol. Yield 80%, mp 247-248°C.

Compound **6** (1 mmol) and 0.5 ml 36% of formaldehyde were refluxed in 20 ml of ethanol for 1 h, and 1.1 mmol substituted amine was added at room temperature under stirring condition, then refluxed for 2 h, and stirred again at room temperature until a white solid was separated. The resulting solid was recrystallized from ethanol/benzene to give Mannich bases **7a-7d**.

7a, Yield 62%, mp 154-155 °C, white crystal. ^{1}H NMR δH: 7.81 (s, 1H, triazole-H), 7.82-6.96 (m, 15H, ArH), 5.75 (d, 2H, NCH_2N), 5.47 (t, 1H, NH), 2.41 (s, 3H, isoxazole-CH_3).IR. νmax: 3405 (NH), 3061 (PhH), 2941 (CH_3 or CH_2), 1651, 1603, 1557, 1498 (Ar, C=N), 1252 (N-N=C), 1170, 1075, 1042 (C=S). MS. m/z: 401, 216, 149, 135, 105, 91, 77. *Anal.* Calcd. for $C_{27}H_{22}N_8OS$: C, 64.02; H, 4.38; N, 22.12, Found: C, 63.89; H, 4.27; N, 22.06.

7b, Yield 69%, mp 145-146 °C, white crystal. ^{1}H NMR δH: 7.83(s, 1H, triazole-H), 7.88-6.88 (m, 14H, ArH), 5.73(s, 2H, NCH_2N), 5.44 (s, 1H, NH), 2.42 (s, 3H, isoxazole-CH_3), 2.18 (s, 3H, $PhCH_3$). IR. νmax: 3406 (NH), 3015 (PhH), 2920 (CH_3 or CH_2), 1619, 1589, 1551, 1498 (Ar, C=N), 1256 (N-N=C), 1168, 1075, 1040 (C=S). MS. m/z: 401, 252, 216, 149, 135, 119, 91, 77. *Anal.* Calcd. for $C_{28}H_{24}N_8OS$: C, 64.60; H, 4.65; N, 21.52, Found: C, 64.49; H, 4.57; N, 21.46.

7c, Yield 79%, mp 236-238 °C, pale yellow crystal. ^{1}H NMR δH: 7.88 (s, 1H, triazole-H), 7.82-6.88 (m, 14H, ArH), 6.40 (s, 2H, NCH_2N), 5.71 (s, 1H, NH), 2.42 (s, 3H, isoxazole-CH_3). IR. νmax: 3428 (NH), 3132 (PhH), 2963 (CH_3 or CH_2), 1666, 1596, 1542, 1500 (Ar, C=N), 1264 (N-N=C), 1202, 1155, 1042 (C=S). MS. m/z: 401, 252, 171, 149, 139, 135, 91, 77. *Anal.* Calcd. for $C_{27}H_{21}N_8OSCl$: C, 59.99; H, 3.92; N, 20.74, Found: C, 59.78; H, 3.87; N, 20.67.

7d, Yield 80%, mp 199-201 °C, white crystal. ^{1}H NMR δH: 7.98 (s, 1H, triazole-H), 7.99-7.08 (m, 10H, ArH), 5.30 (s, 2H, NCH_2N), 2.50 (s, 3H, isoxazole -CH_3), 2.82, 1.52, 1.23 (m, 10H, piperidine-H). IR. νmax: 3100 (PhH), 2938 (CH_3), 2853(CH_2),

1648, 1585, 1556, 1499 (Ar, C=N), 1225 (N-N=C), 1156, 1118, 1041 (C=S). MS. m/z: 401, 252, 216, 170, 149, 135, 91, 77. *Anal.* Calcd. for $C_{26}H_{26}N_8OS$: C, 62.63; H, 5.26; N, 22.49, Found : C, 62.59; H, 5.27; N, 22.31.

Synthesis of 2-(3-(2-phenyl-1,2,3-triazol-4-yl)-5-methyl-isoxazol-4-yl)-4-substituted-amino methyl-1,3,4-oxadiazoline-5-thiones (Mannich bases 9a-9d). 10 mmol of carbohydrazide **(5)** was dissolved in 100 ml of ethanol containing 15 mmol of KOH, and 50 ml of ethanol solution of 15 mmol CS_2 was added gradually at room temperature. The reaction mixture was heated on water-bath for 6 h then the solvent was removed by distillation. The residue was stirred with 200 ml of water, and the solution was brought to a pH of 7-5 to give a large amount of white solid. The precipitated product was collected by filtration, washed thoroughly with water, dried and recrystallized from ethanol/DMF to give white needle crystal of **8**. Yield 75%, mp 229-231 °C.

A solution of 1 mmol of **8** in 10 ml of ethanol containing 0.5 ml 36% of formaldehyde was refluxed for 1 h, and 1 mmol of substituted amine in 5 ml of ethanol was added at room temperature under stirring condition. After a moment, a white solid was separated, and continued to stir for 2 h. The mixture allowed to stand overnight, filtered and recrystallized from ethanol to give white or pale yellow crystals of **9a-9d.**

9a, Yield 77%, mp 154-156 °C, pale yellow crystal. ^{1}H NMR δH: 8.29 (s,1H, triazole-H), 8.14-6.88 (m, 10H, ArH), 5.56 (s, 2H, NCH_2N), 5.13 (s, 1H, NH), 2.69 (s, 3H, isoxazole-CH_3). IR. νmax: 3338 (NH), 3034 (PhH), 2968 (CH_3 or CH_2), 1662, 1603, 1527, 1499 (Ar, C=N), 1260 (N-N=C), 1089, 1044 (C=S). MS. m/z: 431 (M^+), 326, 237, 211, 105, 91, 77, 69. *Anal.* Calcd. for $C_{21}H_{17}N_7O_2S$: C, 58.45; H, 3.97; N, 22.74, Found: C, 58.21; H, 3.90; N, 22.69.

9b, Yield 74%, mp 143-145 °C, pale yellow crystal. ^{1}H NMR δH: 8.27 (s, 1H, triazole-H), 8.15-6.77 (m, 9H, ArH), 5.52 (s, 2H, NCH_2N), 5.04 (s, 1H, NH), 2.70 (s, 3H, isoxazole-CH_3), 2.21 (s, 3H, PhCH_3). IR. νmax: 3366 (NH), 3049 (PhH), 2921 (CH_3 or CH_2), 1616, 1597, 1519, 1497 (Ar, C=N), 1250 (N-N=C), 1095, 1042 (C=S). MS. m/z: 326, 237, 251, 211, 170, 119, 91, 77. *Anal.* Calcd. for $C_{22}H_{19}N_7O_2S$: C, 59.31; H, 4.30; N, 22.02, Found: C, 59.15; H, 4.24; N, 22.00.

9c, Yield 76%, mp 139-141 °C, pale yellow crystal. ^{1}H NMR δH: 8.26 (s, 1H, triazole-H), 8.13-6.79 (m, 9H, ArH), 5.50 (d, 2H, NCH_2N), 5.14 (t, 1H, NH), 2.73 (s, 3H, isoxazole-CH_3). IR. νmax: 3398 (NH), 3118, 3060 (PhH), 2940 (CH_3 or CH_2), 1621, 1601, 1520, 1494 (Ar, C=N), 1248 (N-N=C), 1089, 1042 (C=S). MS. m/z: 326, 237, 251, 211, 170, 91, 77, 69. *Anal.* Calcd. for $C_{21}H_{16}N_7O_2SCl$: C, 54.18; H, 3.47; N, 21.08, Found: C, 54.01; H, 3.39; N, 20.95.

9d, Yield 79%, mp 132-134 °C, white crystal. ^{1}H NMR δH: 8.35 (s, 1H, triazole-H), 8.15-7.26 (m, 5H, ArH), 5.07 (s, 2H, NCH_2N), 2.79 (s, 3H, isoxazole-CH_3), 1.31-2.78 (m, 10H, piperidine-H). IR. νmax: 3154 (PhH), 2936 (CH_3 or CH_2), 1596, 1494 (Ar, C=N), 1248 (N-N=C), 1087, 1042 (C=S). MS.m/z: 326, 251, 211, 171, 91, 77, 69. *Anal.* Calcd. for $C_{20}H_{21}N_7O_2S$: C, 56.72; H, 5.00; N, 23.16, Found: C, 57.64; H, 4.87; N, 23.08.

Synthesis of 2-substituted-3-acetyl-5-(3-(2-phenyl-1,2,3-triazol-4-yl)-5-methylisoxazol-4-yl)-1,3,4-oxadiazolines (11a-11f). 1 mmol of carbohydrazide **(5)** was dissolved in 15 ml of ethanol with 2-3 D glacial acetic acid, and 1.1 mmol of substituted aldehydes or ketones was added. The mixture was heated under reflux for 3 h, and a yellow or white crystal separated after the mixture had cooled, which was collected by filtration and washed with ethanol to give **10a-10f**. The crude products were used without further purification. **10a**, Yield 88%, mp 145-146 °C, pale yellow crystal. **10b**, Yield 89%, mp 177-178 °C, pale yellow crystal. **10c**, Yield 81%, mp 225-226 °C, pale yellow crystal. **10d**, Yield 91%, mp 253-255 °C, white crystal. **10e**, Yield 74%, mp 132-134 °C, white crystal. **10f**, Yield 82%, mp 170-171 °C, white crystal.

A mixture of **6** and 5 ml of acetic anhydride was refluxed for 1.5 h. The product was poured into cold water, and allowed to stand overnight to turn the oily matter into solid. The separated solid was washed, dried and recrystallized from ethanol to give crystals of **11a-11f**.

11a, Yield 76%, mp 159-160 °C, white crystal. ^{1}H NMR δH: 8.38 (s, 1H, triazole-H), 7.90-7.41 (m, 10H, ArH), 7.26 (s, 1H, oxadiazoline-H), 2.86 (s, 3H, $COCH_3$), 2.15 (s, 3H, isoxazole-CH_3). IR. νmax: 3170, 3061 (PhH), 2922 (CH_3), 1660 (C=O), 1249 (N-N=C), 1075 (C-O-C). MS. m/z: 414 (M^+), 253, 252, 211, 172, 105, 91, 77. *Anal.* Calcd. for $C_{22}H_{18}N_6O_3$: C, 63.75; H, 4.38; N, 20.29, Found: C, 63.69; H, 4.29; N, 20.19.

11b, Yield 71%, mp 189-191 °C, white crystal. ^{1}H NMR δH: 8.39 (s, 1H, triazole-H), 8.23-7.00 (m, 9H, ArH), 7.01 (s, 1H, oxadiazoline-H), 3.90 (s, 3H, OCH_3), 2.86 (s, 3H, $COCH_3$), 2.15 (s, 3H, isoxazole-CH_3). IR. νmax: 3159, 3078 (PhH), 2929 (CH_3), 1672(C=O), 1250 (N-N=C). 1081 (C-O-C). MS. m/z: 444 (M^+), 403, 252, 211, 171, 105, 91, 77. *Anal.* Calcd. for $C_{23}H_{20}N_6O_4$: C, 62.14; H, 4.54; N, 18.92, Found: C, 61.98; H, 4.47; N, 18.89.

11c, Yield 71%, mp 134-136 °C, white crystal. ^{1}H NMR δH: 8.32 (s, 1H, triazole-H), 8.23-7.36 (m, 9H, ArH), 7.01 (s, 1H, oxadiazoline-H), 2.85 (s, 3H, $COCH_3$), 2.15 (s, 3H, isoxazole-CH_3). IR. νmax: 3172, 3083 (PhH), 2921(CH_3), 1681 (C=O), 1248 (N-N=C), 1072 (C-O-C). MS. m/z: 448 (M^+), 450 (M^++2), 407, 253, 252, 211, 171, 105, 91, 77. *Anal.* Calcd. for $C_{22}H_{17}N_6O_3Cl$: C, 58.91; H, 3.82; N, 18.75, Found: C, 58.70; H, 3.78; N, 18.61.

11d, Yield 90%, mp 140-142 °C, yellow crystal. ^{1}H NMR δH: 8.31(s, 1H, triazole-H), 8.22-7.27 (m, 9H, ArH), 7.11 (s, 1H, oxadiazoline-H), 2.77 (s, 3H, $COCH_3$), 2.33 (s, 3H, isoxazole-CH_3). IR. νmax: 3117, 3059 (PhH), 2927 (CH_3), 1663 (C=O), 1249 (N-N=C), 1081 (C-O-C). MS. m/z: 459 (M^+), 418, 253, 252, 211, 105, 91, 77. *Anal.* Calcd. for $C_{22}H_{17}N_7O_5$: C, 57.50; H, 3.73; N, 21.35, Found: C, 57.38; H, 3.66; N, 21.20.

11e, Yield 70%, mp 103-105 °C, white crystal. ^{1}H NMR δH: 8.33 (s, 1H, triazole-H), 8.23-7.26 (m, 10H, ArH), 2.73 (s, 3H, $COCH_3$), 2.28 (s, 3H, oxadiazoline-CH_3), 2.28 (s, 3H, isoxazole-CH_3). IR. νmax: 3178, 3070 (PhH), 2949 (CH_3), 1658 (C=O), 1253 (N-N=C), 1084 (C-O-C). MS. m/z: 428 (M^+), 371, 253, 252, 211, 105, 91, 77. *Anal.* Calcd. for $C_{23}H_{20}N_6O_3$: C, 64.46; H, 4.71; N, 19.62, Found: C, 64.39; H, 4.67; N, 19.57.

11f, Yield 70%, mp 134-135 °C, white crystal. ^{1}H NMR δH: 8.38(s, 1H, triazole-H), 8.15-7.26 (m, 5H, ArH), 2.76(s, 3H, $COCH_3$), 2.65-1.36 (m, 10H, cyclohexanyl-H), 2.24(s, 3H, isoxazole-CH_3). IR. νmax: 3024 (PhH), 2946, 2854 (CH_3, CH_2), 1661 (C=O), 1246 (N-N=C), 1078(C-O-C). MS. m/z: 406 (M^+), 364, 321, 253, 211, 171, 105, 91, 77. *Anal.* Calcd. for $C_{21}H_{22}N_6O_3$: C, 62.04; H, 5.46; N, 20.69, Found: C, 61.97; H, 5.40; N, 20.51.

Synthesis of 3-(3-(2-phenyl-1,2,3-triazol-4-yl)-5-methylis-oxazol-4-yl)-6-substituted-7*H*-1,2,4-triazolo[3,4-*b*]1,3,4-thia-diazines (13a-13c). 10 mmol of carbohydrazide **(5)** and 15 mmol of KOH were dissolved in 25 ml of ethanol. 5 ml of ethanol solution of

15 mmol of CS_2 was added slowly at room temperature under stirring condition, stirred for 15 h then the mixture was diluted with 10 ml of dry ether, and kept stirring for 0.5 h. The solid was collected by filtration, washed with ether to give the white potassium salt, and was employed without further purification.

The salt, prepared as described above, was refluxed for 6 h in 4 ml of water containing 4 ml 85% of hydrazine. Dilution with 100 ml of cold water and acidification with 1:1 of hydrochloric acid resulting in a large amount of pale yellow solid. This product was collected by filtration, recrystallized from ethanol/DMF to give crystal of **12**. Yield 73%, mp 243-246 °C.

A mixture of **12** and α-substitued-bromoacetophenone was dissolved in 25 ml of absolute ethanol, and refluxed for 6-10 h. The 1:1 of aqueous ammonia brought pH of the solution to 9 after the mixture had cooled. Having stood overnight, the product was collected by filtration and recrystallized from ethanol/ethyl acetate to give the crystals of **13a-13c**.

13a, Yield 56%, mp 202-204 °C, yellow crystal. ^{1}H NMR δH: 8.16 (s, 1H, triazole-H), 7.76-7.27 (m, 10H, ArH), 3.68 (s, 2H, thiadiazine-H), 2.73 (s, 3H, isoxazole-CH_3). IR. νmax: 3110, 3073 (PhH), 2902 (CH_3), 1646, 1592, 1562, 1492 (Ar, C=N, C=N-S), 1226 (N-N=C), 685 (C-S-C). MS. m/z: 440 (M^+), 252, 170, 117, 103, 91, 77. *Anal*. Calcd. for $C_{22}H_{16}N_8OS$: C, 59.98; H, 3.66; N, 25.45, Found: C, 59.79; H, 3.59; N, 25.33.

13b, Yield 73%, mp 170-171 °C, white crystal. ^{1}H NMR δH: 8.15 (s, 1H, triazole-H), 7.74-6.79 (m, 9H, ArH), 3.81 (s, 3H, OCH_3), 3.62 (s, 2H, thiadiazine-H), 2.74 (s, 3H, isoxazole-CH_3). IR. νmax: 3101 (PhH), 2903 (CH_3), 1608, 1551, 1519, 1457 (Ar, C=N, C=N-S), 1261 (N-N=C), 688 (C-S-C). MS. m/z: 470, 252, 209, 170, 147, 132, 103, 91, 77. *Anal.* Calcd. for $C_{23}H_{18}N_8O_2S$: C, 58.71; H, 3.86; N, 23.83, Found: C, 58.68; H, 3.79; N, 23.74.

13c, Yield 56%, mp 182-183 °C, white crystal. ^{1}H NMR δH: 8.14 (s, 1H,triazole-H), 7.75-7.24 (m, 9H, ArH), 3.63 (s, 2H, thiadiazine-H), 2.74 (s, 3H, isoxazole-CH_3). IR. νmax: 3112 (PhH), 2911 (CH_3), 1633, 1593, 1522, 1493 (Ar, C=N , C=N-S), 1229 (N-N=C), 698 (C-S-C). MS. m/z: 474 (M^+), 476 (M^++2), 251, 209, 170, 151, 137, 103, 91, 77. *Anal.* Calcd. for $C_{22}H_{15}N_8OSCl$: C, 55.69; H, 3.19; N, 23.63, Found: C, 55.47; H, 3.13; N, 23.51.

Synthesis of 3-(3-(2-phenyl-1,2,3-triazol-4-yl)-5-methylisoxazol-4-yl)-6-substituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles (14a-14c). A mixture of 1.47 mmol of **12** and 1.62 mmol of carboxylic acid in 5.0 ml of $POCl_3$, was heated under reflux at 90-115 ℃ for 5 h. After removed of the excess of $POCl_3$ under reduced pressure, 50 ml of cold water was added into the residue. The resulting solid was filtered, washed with 10% NaOH and water, then dried, recrystallized from ethanol/DMF to give products of **14a-14h**.

14a, Yield 77%, mp 183-184 °C, pale yellow crystal. ^{1}H NMR δH: 8.25 (s, 1H, triazole-H), 7.80-7.24 (m, 10H, ArH), 2.75 (s, 3H, isoxazole-CH_3). IR. νmax: 3138, 3074 (PhH), 1648, 1596, 1457 (Ar, C=N ,C=N-S), 1234 (N-N=C), 682 (C-S-C). MS. m/z: 426 (M^+), 384, 252, 209, 170, 121, 110, 91, 77. *Anal.* Calcd. for $C_{21}H_{14}N_8OS$: C, 59.14; H, 3.31; N, 26.29, Found: C, 59.01; H, 3.27; N, 26.15.

14b, Yield 80%, mp 256-257 °C, pale yellow crystal. ^{1}H NMR δH: 8.32 (s, 1H, triazole-H), 8.26-7.25 (m, 9H, ArH), 2.76 (s, 3H, isoxazole-CH_3). IR. νmax: 3110, 3034 (PhH), 1638, 1603, 1455 (Ar, C=N, C=N-S), 1244 (N-N=C), 687 (C-S-C). MS. m/z: 471 (M^+), 429, 251, 209, 166, 136, 120, 110, 91, 77. *Anal.* Calcd. for $C_{21}H_{13}N_9O_3S$: C, 53.49; H, 2.78; N, 26.75, Found: C, 53.30; H, 2.70; N, 26.67.

14c, Yield 75%, mp 195-197 °C, pale yellow crystal. ^{1}H NMR δH: 8.14 (s, 1H, triazole-H), 7.75-7.24 (m, 9H, ArH), 2.74 (s, 3H, isoxazole-CH_3). IR. νmax: 3143, 3049 (PhH), 1670, 1595, 1461 (Ar, C=N, C=N-S), 1245 (N-N=C), 693 (C-S-C). MS. m/z: 460 (M^+), 462 (M^++2), 418, 251, 209, 170, 155, 137, 110, 91, 77. *Anal.* Calcd. for $C_{21}H_{13}N_8OSCl$: C, 54.78; H, 2.85; N, 24.35, Found: C, 54.61; H, 2.79; N, 24.21.

14d, Yield 65%, mp 208-209 °C, pale yellow crystal. ^{1}H NMR δH: 8.30 (s, 1H, triazole-H), 7.74-6.87 (m, 9H, ArH), 3.83 (s, 3H, OCH_3), 2.73 (s, 3H, isoxazole-CH_3). IR. νmax: 3152, 3049 (PhH), 2933 (CH_3), 1686, 1608, 1459 (Ar, C=N, C=N-S), 1265(N-N=C), 702 (C-S-C). MS. m/z: 456 (M^+), 251, 209, 171, 151, 136, 110, 108, 91, 77. *Anal.* Calcd. for $C_{22}H_{16}N_8O_2S$: C, 57.89; H, 3.53; N, 24.55, Found: C, 57.71; H, 3.47; N, 24.43.

14e, Yield 60%, mp 191-192 °C, brown crystal. ^{1}H NMR δH: 8.29 (s, 1H, triazole-H), 7.74-7.26 (m, 5H, ArH), 2.68 (s, 3H, isoxazole-CH_3), 2.50 (s, 3H, thiadiazole-CH_3). IR. νmax: 3132 (PhH), 2922 (CH_3), 1651, 1596, 1455 (Ar, C=N, C=N-S), 1244 (N-N=C), 700 (C-S-C). MS. m/z: 364 (M^+), 322, 252, 209, 170, 110, 91, 77, 59. *Anal.* Calcd. for $C_{16}H_{12}N_8OS$: C, 52.74; H, 3.32; N, 30.75, Found: C, 52.57; H, 3.27; N, 30.69.

14f, Yield 65%, mp 137-138 °C, brown crystal. ^{1}H NMR δH: 8.29 (s, 1H, triazole-H), 7.73-7.27 (m, 5H, ArH), 2.70 (s, 3H, isoxazole-CH_3), 2.79 (q, 2H, thiadiazole-CH_2R), 1.11 (t, 3H, RCH_3). IR. νmax: 3134(PhH), 2981, 2925 (CH_3, CH_2), 1650, 1596, 1454 (Ar, C=N, C=N-S), 1243 (N-N=C), 700 (C-S-C). MS. m/z: 378 (M^+), 336, 251, 209, 170, 110, 91, 77, 73, 55. *Anal.* Calcd. for $C_{17}H_{14}N_8OS$: C, 53.96; H, 3.73; N, 29.61, Found: C, 53.73; H, 3.67; N, 29.50.

14g, Yield 63%, mp 125-127 °C, brown crystal. ^{1}H NMR δH: 8.28 (s, 1H, triazole-H), 7.73-7.28 (m, 5H, ArH), 2.71 (t, 3H, isoxazole-CH_3), 2.71 (s, 2H, thiadiazole-CH_2R), 1.54 (m, 2H, $R^1CH_2R^2$), 0.84 (t, 3H, RCH_3). IR. νmax: 3132 (PhH), 2965, 2928 (CH_3, CH_2), 1643, 1599, 1455 (Ar, C=N, C=N-S), 1245 (N-N=C), 686 (C-S-C). MS. m/z: 392 (M^+), 350, 251, 209, 172, 110, 91, 77. *Anal.* Calcd. for $C_{18}H_{16}N_8OS$: C, 55.09; H, 4.11; N, 28.55, Found: C, 54.89; H, 4.07; N, 28.48.

14h, Yield 67%, mp 118-119°C, brown crystal.^{1}H NMR δH: 8.28 (s, 1H, triazole-H), 7.73-7.28 (m, 10H, ArH), 2.70 (s, 3H, isoxazole-CH_3), 2.71 (s, 2H, thiadiazole -CH_2R), 1.49-1.13 (m, 4H, $R^1(CH_2)_2R^2$), 0.74 (t, 3H, CH_3R). IR. νmax: 3052 (PhH), 2963, 2934 (CH_3, CH_2), 1637, 1599, 1456 (Ar, C=N, C=N-S), 1244 (N-N=C), 687 (C-S-C). MS. m/z: 406 (M^+), 364, 251, 209, 170, 110, 105, 89, 91, 77, 57. *Anal.* Calcd. for $C_{19}H_{18}N_8OS$: C, 56.14; H, 4.46; N, 27.57, Found: C, 55.92; H, 4.37; N, 27.42.

REFERENCES

[1] Bradbury, R. H.; Rivett, J. E. *J. Med. Chem.,* **1991**, *34*, 151.

[2] Hirota, T.; Sasaki, K.; Yamamoto, T.; Nskayama, T. *J. Heterocycl. Chem.,* **1991**, *28*, 257.

[3] Walser, A.; Flynn, T.; Mason, C. *J. Heterocycl. Chem.,* **1991**, *28*, 1121.

[4] Mazzone, G.; Bonina, F.; Panico, A. M.; Amico-Roxas, M.; Caruso, A.; Blandino, G.; Vanella, A. *Farmaco. Ed. Sci.,* **1987**, *42*, 525.

[5] Massa, S.; Di Santo, R.; Retico, A.; Artico, M.; Simonetti, N.; Fabrizi, G.; Lamba, D. *Eur. J. Med. Chem.,* **1992**, *27*, 495.

[6] Er-Rhaimini, A.; Mornet, R. *J. Heterocycl. Chem.,* **1992,** *29*, 1561.

[7] Skolnick, P. *J. Clin. Psychiaty,* **2002**, *63*, 19.

[8] Scheen, A. J.; Malaise, M. *Rev. Med. Liege.,***2004**, *59*, 251.

[9] Aboraia, A. S.; Abdel-Rahman, H. M.; Mahfouz, N. M.; EL-Gendy, M. A. *Bio. Med. Chem.,* **2006**, *14*, 1236.

[10] Qiao, R. Z.; Hui, X. P.; Xu, P. F.; Zhang, Z. Y.; Cheng, D. L. *Chin. J. Chem.,* **2001**, *19*, 800.

[11] Eweiss, N. F.; Bahajaj, A. A.; Elsherbini, E. A. *J. Heterocycl. Chem.,* **1987**, *24*, 1173.

[12] Chanda, M. S.; Kaknikv, B. M.; Ganguly, N. *J. Indian Chem. Soc.,* **1990**, *67*, 695.

[13] Liu, F. M.; Yu, J. X.; Lu, W. J.; Liu, G.; Liu, Y.T. ; Chen, Y.Z. *Chin. J. Org. Chem.* (in Chinese), **1999**, *19*, 157.

[14] Liu, F. M.; Yu, J. X.; Liu, Y.T.; Chen, Y.Z. *Acta Chimica Sinica,* (in Chinese), **1998**, *56*, 618.

[15] Liu, F. M.; Keyume, A. *Chem. J. Chin. Univ.*(in Chinese), **2004**, *9*, 1673.

[16] Chairstos, D. A.; Vagenas, G. V.; Tzavellas, L. C. *J. Heterocycl. Chem.,* **1994,** *31*, 1593.

[17] Liu, F. M.; Cao, L.H. *J. Xinjiang Univ.*(in Chinese), **1993**□*10*, 70.

[18] Doyle, F .P.; Hanson, J. C.; Longe, A.A.W.; Nayler, J.H.C.; Stove, E. R. *J. Chem. Soc.,* **1963**, *85*, 5838.

[19] Huang, R.Q.; Sun, J.Y.; Ma, J.A.; Li, H.Y. *Chin. J. Appl. Chem.* (in Chinese), **1998,** *15* , 9.