# *Reactions of 2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene and 6-Amino-1,4-dihydro-1,4-diphenyl-5-cyano-3-methylpyrano[2,3-c]pyrazole with Arylidenemalononitriles, α,β-Acetylenic Esters and Ketones*

**Ahmed S. A. Youssef**

**Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, P.O. 11566, Cairo, Egypt.**

*Reacciones de 2-amino-3-ciano-4,5,6,7-tetrahidrobenzo[b]tiofeno y 6-amino-1,4-dihidro-1,4-difenil-5-ciano-3-metilpirano[2,3-c]pirazol con arilidenmalononitrilos, esteres α,β-acetilénicos y cetonas*

*Reaccions de 2-amino-3-ciano-4,5,6,7-tetrahidrobenzo[b]tiofè i 6-amino-1,4-dihidro-1,4-difenil-5-ciano-3-metilpirano[2,3-c]pirazole amb arilidenmalononitrils, èsters α,β-acetilènics i cetones*

*Recibido: 28 de octubre de 2008; aceptado: 4 de diciembre de 2008*

## RESUMEN

La reacción del 2-amino-3-ciano-4,5,6,7-tetrahidrobenzo[*b*]tiofeno **(1a)** con los arilidenmalononitrilos **2a-c** da los derivados de benzotieno[2,3-*d*]pirimidina **3a-c** como mezclas de los isómeros *E* y *Z*, así como los isómeros ***Z*-3c** y ***E*-3c** en el caso de **2c**. Un tratamiento similar del 6-amino-1,4-dihidro-1,4-difenil-5-ciano-3-metilpirano[2,3-*c*]pirazol **(4)** con **2b**,**d** rinde los derivados de pirazolopiranopirimidina **5a**,**b** como los estereoisómeros *Z* y *E*. El tratamiento de **4** con los esteres acetilénicos y cetonas **6a**-**d** proporciona los derivados de pirano[2,3-*c*]pirazol ***Z*-(7a-d**). Al hacer reaccionar **1a** con **6c**-**e** se obtienen los derivados de aroilmetilenbenzamidobenzo[*b*]tiofeno **8a**-**c.** Se confirman las estructuras de todos los productos mediante datos espectroscópicos y microanálisis.

**Palabras clave:** Derivados de 4,5,6,7-tetrahidrobenzo[*b*]tiofeno, derivados de pirano[2,3-*c*]pirazol, arilidenmalononitrilos, derivados de benzotieno[2,3-*d*]pirimidina, derivados de etenilaminopirano[2,3-*c*]pirazol, derivados de aroilmetilenbenzamidobenzo[*b*]tiofeno.

## SUMMARY

Reactions of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene **(1a)** with arylidenemalononitriles **2a-c** gave the benzothieno[2,3-*d*]pyrimidine derivatives **3a-c** as *E*,*Z*-mixtures as well as ***Z*-3c** and ***E*-3c** isomers in case of **2c**. Similar treatment of 6-amino-1,4-dihydro-1,4-diphenyl-5-cyano-3-methylpyrano[2,3-*c*]pyrazole **(4)** with **2b**,**d** yielded the pyrazolopyranopyrimidine derivatives **5a**,**b** as *Z*- and *E*- steroisomers. Treatment of **4** with acetylenic esters and ketones **6a**-**d** afforded the ethenylaminopyrano[2,3-*c*]pyrazole derivatives ***Z*-(7a-d)**. Reacting **1a** with **6c**-**e** gave the aroylmethylenebenzamidobenzo[*b*]thiophene derivatives **8a-c.** Structures of all products are evidenced by microanalytical and spectral data.

**Key words:** 4,5,6,7-Tetrahydrobenzo[*b*]thiophene derivatives, pyrano[2,3-*c*]pyrazole derivatives, arylidenemalononitriles, benzothieno[2,3-*d*]pyrimidine derivatives, ethenylaminopyrano[2,3-*c*]pyrazole derivatives, aroylmethylenebenzamidobenzo[*b*]thiophene derivatives.

## RESUM

La reacció del 2-amino-3-ciano-4,5,6,7-tetrahidrobenzo[*b*]tiofè **(1a)** amb els arilidenmalononitrils **2a-c** dóna els derivats de benzotieno[2,3-*d*]pirimidina **3a-c** com a barreges dels isòmers *E* i *Z*, així com els isòmers ***Z*-3c** i ***E*-3c** en el cas de **2c**. Un tractament similar del 6-amino-1,4-dihidro-1,4-difenil-5-ciano-3-metilpirano[2,3-*c*]pirazole **(4)** amb **2b**,**d** rendeix els derivats de pirazolepiranopirimidina **5a**,**b** com els estereoisòmers *Z* i *E*. El tractament de **4** amb els èsters acetilènics i cetones **6a**-**d** proporciona els derivats de pirano[2,3-*c*]pirazole ***Z*-(7a-d)**. En fer reaccionar **1a** amb **6c**-**e** s'obtenen els derivats d'aroïlmetilenbenzamidobenzo[*b*]tiofè **8a**-**c.** Es confirmen les estructures de tots els productes mitjançant dades espectroscòpiques i microanàlisi.

**Mots clau:** Derivats de 4,5,6,7-tetrahidrobenzo[*b*]tiofè, derivats de pirano[2,3-*c*]pirazole, arilidenmalononitrils, derivats de benzotieno[2,3-*d*]pirimidina, de-

*E-mail: ahmedy84@hotmail.com

rivats d'etenilaminopirano[2,3-*c*]pirazole, derivats d'aroïlmetilenbenzamidobenzo[*b*]tiofè.

## INTRODUCTION

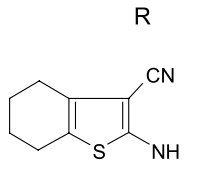
It has been reported[1] that the reaction of 2-amino-3-cyano-4, 5,6,7-tetrahydrobenzo [b] thiophene with methyl β-methoxyacrylate gave benzothienopyridine derivative. In continuation of our previous studies[2] on 2-amino-3-cyano-4, 5,6,7-tetrahydrobenzo[b]thiophene and 6-amino-1,4-dihydro-1,4-diphenyl-5-cyano-3-methylpyrano [2,3-*c*] pyrazole; the present work deals with their reactions with arylidene malononitriles, α , β-acetylenic ester and ketones . The reported biological activities [3-6] on the thienopyrimidines and the pyranopyrimidines prompted the author to study their reactions on the hope of getting new compounds of anticipated biological activities.

Treatment of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo [b] thiophene (**1a**) with arylidene malononitrile derivatives **2a-c** in refluxing n-butanol afforded the benzo thieno [2,3-*d*] pyrimidine derivatives **3a –c** as ***E***,***Z*** –mixtures as well as ***Z*-3** and ***E*-3** isomers in case of **2c** . Similar treatment of 6-amino-1,4-dihydro-1,4-diphenyl-5-cyano-3-methyl pyrano [2,3-*c*] pyrazole (**4**) with **2b**,**d** gave the pyrazolopyrano pyrimidine derivatives **5a**,**b** as ***Z***-(minor) and ***E***-(major) stereoisomers , respectively.

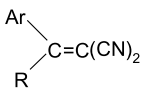
The structures of compounds **3** and **5** are substantiated from their microanalytical and spectral data. Their infared spectra show absorptions characteristic for NH and CN groups. Moreover, the $^1$H-NMR specta are in accord with the proposed structures. Analysis of the observed signals inferred that each compound of ***E***, ***Z*-3a-c** exists as a mixture of ***E***- and ***Z***-steroisomers in ratio of 2:3. Existence of the two stereoisomers has been evidenced from the location of two signals consistent with olefinic proton for compounds **3a**,**c** or methyl protons for compound **3b**. The higher ratio of ***Z***-isomers as compared with the ***E***-counterparts could be attributed to the existence of aryl moiety in the less hindered side. Configurational assignments to ***Z*-3**, ***E*-3**, ***Z*-5** and ***E*-5** are based on the assumption that the olefinic or methyl protons of the ***E***-configurated isomers are more deshielded by the aryl group as well as the hetero ring as compared with the ***Z***-counterparts. The EI-MS spectra of compounds 3 and 5 didn't show the molecular ion peaks probably due to their ease decomposition in the ionization chamber, but they showed some of abundant peaks.

The formation of compounds **3** and **5** can be explained as shown in scheme 1. A nucleophilic attack of the amino group of compound **1a** or **4** at one of the two cyano groups[7] of compounds **2** gave A. Cyclization with the ring cyano group gave **3** and **5.** (Scheme 1)

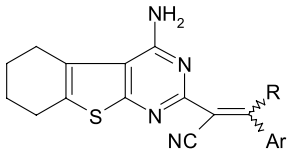
Treatment of **3a-c** with refluxing acetic anhydride on the hope of getting their N-acetyl derivatives was unsuccessful. However, 2-acetylamino -3-cyano benzo [b] thiophene **1b** was the only isolated product in each case.



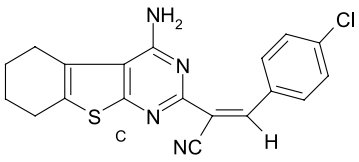

(**1**)
a, R= H
b, R= $COCH_3$



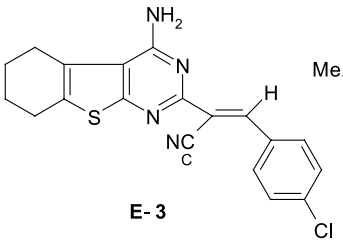

(**2**)
a, R= H; Ar= 4-$Me_2NC_6H_4$-
b, R= Me; Ar= 2,5-$(MeO)_2C_6H_3$-
c, R= H; Ar= 4-$ClC_6H_4$-
d, R= Me; Ar= 4-$BrC_6H_4$-



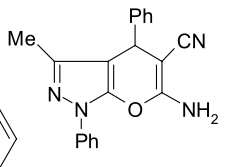

**E,Z- 3**
a, R= H; Ar= 4-$Me_2NC_6H_4$-
b, R= Me; Ar= 2,5-$(MeO)_2C_6H_3$-
c, R= H; Ar= 4-$ClC_6H_4$-



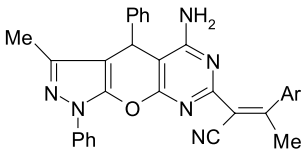

**Z- 3**



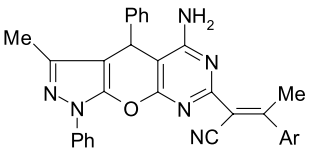

**E- 3**



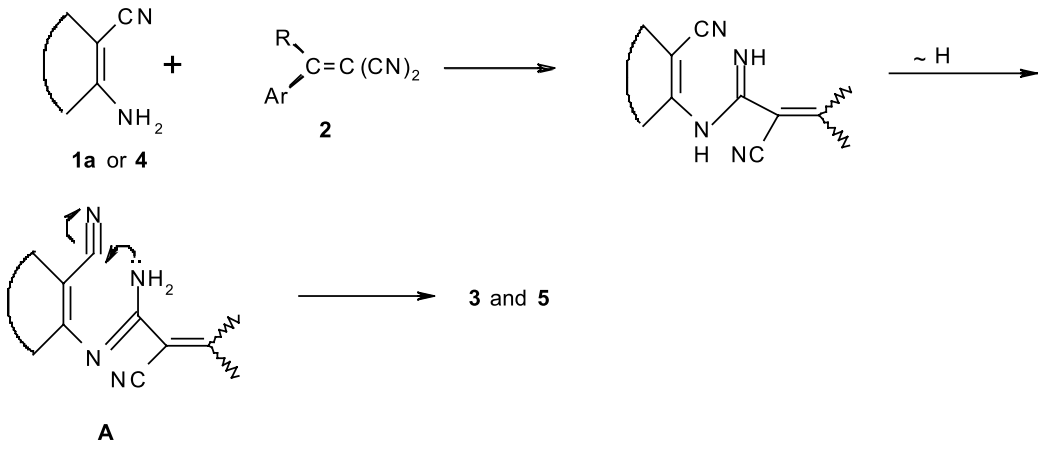

4




**Z-5**
a, Ar= 2,5- $(MeO)_2C_6H_3$-
b, Ar= 4-$BrC_6H_4$-




**E- 5**
a, Ar= 2,5- $(MeO)_2C_6H_3$-
b, Ar= 4-$BrC_6H_4$-




*Scheme 1*

The structure of **1b** is substantiated spectroscopically and chemically. The infrared and $^1$H-NMR spectra are devoid of any absorptions or signals correlated with aryl groups. The structure is rigidly confirmed by comparison with an authentic sample[8] prepared by refluxing **1a** with acetic anhydride.

A rationalization for the conversion of compounds **3a**-**c** into **1b** is presented in scheme2. Protonation by a trace amount of acetic acid present in acetic anhydride at $N_1$ ring nitrogen followed by ring cleavage gave the arylidene malononitrile derivatives **2a**-**c** and **1a**. Acylation of **1a** with acetic anhydride gave **1b**. The suggested mechanism was supported by detection of the arylidene malononitrile derivatives **2a**-**c** by TLC in the reaction mixtures. (Scheme 2)

Reactions of 6-amino-1,4-dihydro-1,4-diphenyl-5-cyano-3-methylpyrano [2,3-c] pyrazole (**4**) with acetylenic esters and ketones **6a**-**d** in refluxing ethanol in presence of a catalytic amount of triethylamine as a base , gave ethenylamino pyrano [2,3-*c*] Pyrazole derivatives **Z**-(**7a**-**d**). (Scheme 3)

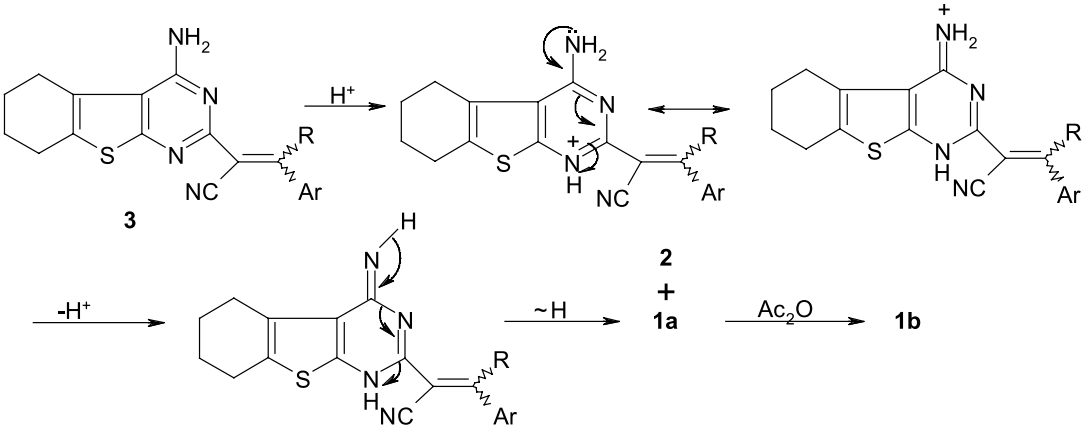
However, the treatment of 2–amino -3-cyano – 4,5,6,7-tetrahydro benzo [b] thiophene (**1a**) with acetylenic ketones **6c**-**e** in refluxing n-butanol in presence of piperidine as a base, yielded the aroylmethylene benzamido benzo [b] thiophene derivatives **Z**-**8a**-**c** as keto-enol tautomeric mixtures in ratios of 3:2. (Scheme 4)

Structures of compounds **7** and **8** are substantiated from their microanalytical and spectral data. Their infrared spectra exhibit absorptions corresponding to NH, CN and C=O groups. The $^1$H-NMR spectra of **7**, **8** are in accord with the proposed structures. The ***Z***-configuration has been assigned to **7** and **8** is based on the higher δ value observed for the olefinic proton, as it is more deshielded by the oxo group in case of **7a** as well as the aryl groups in case of compounds of **7b**-**d** and **8** as compared with the ***E***-counterpart.

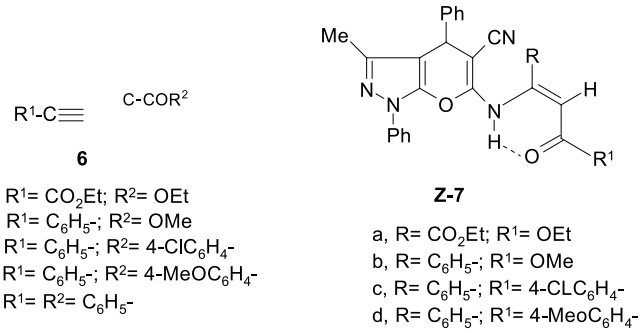
The lower absorption value of CO group is a good evidence for existence of **7** and **8** as their chelated forms shown. In chloroform solution the $^1$H-NMR spectra of compounds **8** show two broad singlet signals for NH and OH protons. This is in consistence with their existence as amino-imino dynamic equilibrium in a ratio of 3:2. The down field values of NH and OH protons are in harmony with their existence as their chelated forms shown. The higher ratios of the amino- tautomers as compared with the imino ones is due to their thermodynamic stabilities. Further support for the assigned structures of compounds **7** and **8** is gained from their mass spectra. Compounds **7a**,**c** and **8a-c** reveal the molecular ion peaks beside some of abundant peaks. However, the molecular ion peaks are missed in case of compounds **7b**,**d** but they show some of important peaks.

## CONCLUSION

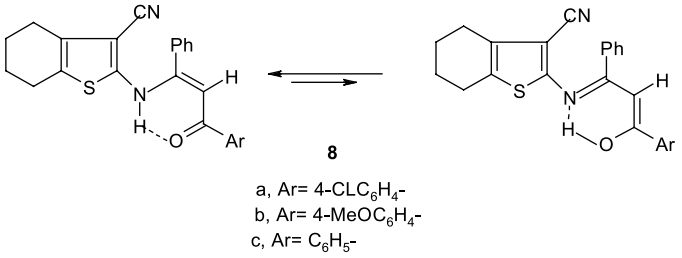
It is inferred that reactions of amino, cyano benzothiophene and amino, cyano pyranopyrazole derivatives with arylidene malono- nitriles proceed through attack of amino group at one of the two cyano groups and not at the β-




*Scheme 2*




*Scheme 3*




*Scheme 4*

carbon of the α,β-unsaturated system[7,13]. On the other hand their reactions with acetylenic esters and ketons proceed through attack at the β- carbon of the acetylenic system[14-16] and not at the carbonyl function.

## EXPERIMENTAL

Melting points were measured on an electrothermal melting point apparatus. Elemental analyses were carried out at the Microanalytical Unit, Cairo University. Infrared spectra were measured on a unicam SP1200 spectrometer using KBr Wafer technique. $^1$H-NMR spectra were measured on a varian Gemini 200 MHZ instrument with chemical shifts (δ) expressed in ppm down field from $Me_4Si$. Mass spectra were recorded on a shimadzu GC-MS-QP 1000 EX instrument operating at 70 ev. Column chromatography and TLC were runned on silica Gel Voeim, activity Ш / 30 mm according to Brockmann & Schodder and TLC aluminium sheets silica Gel 60 $F_{254}$ (Merck).

2-Amino-3-Cyano-4, 5,6,7-tetrahydrobenzo [b] thiophene[8] (**1a**), 6-amino-1,4-dihydro-1,4-diphenyl-5-cyano-3-methylpyrano [2,3-c] pyrazole[9] (**4**) , arylidene malononitriles[10] **2** , acetylenic esters [11] and ketones [12] **6** were prepared according to literature methods .

**Reactions of 1a with Arylidene malononitriles 2a-c**

A mixture of **1a** (3 mmole) and each of arylidene mononitriles **2a-c** (3 mmole) in n-butanol (20 ml) is refluxed for 20 hrs. The reaction mixture is concentrated and left to stand at room temperature overnight to give a solid. Crystallization from proper solvents gives the title compounds ***E***, ***Z***-(**3a-c**). The n-butanol mother liquor in case of reaction **1a** with **2c** was evaporated and chromatographed over silica gel. Successive elution with Petroleum ether (b.p.60-80) / ether (9:1 V/V) afforded ***E*-3c**, and then with petroleum ether (b.p. 60-80 /ether) (1:1 v/v) gave ***Z*-3c**.

***E*,*Z*-3-(4-N,N-Dimethylaminophenyl)-2-(4-amino-5,6,7,8-tetrahydro- benzo[b] thieno [2,3-d] pyrimidin-2-y1) propenonitrile (*E*,*Z*-3a)** , 0.7 g (62% yield) , m.p. 120-122°C (light petroleum b.p 40-60°C). IR: 3447,3329,3207 (NH), 3060 (aryl-H), 2933,2911,2838 (alkyl-H), 2196 (C≡N),1620(C=N) , 1588 , 1522 (C=C) , 854,765 ($\delta_{2\text{-H}}$) cm$^{-1}$; $^1$H-NMR ($CDCL_3$) δ: 1.77 (m,4H, 2$CH_2$) , 2.49 (m,4H, 2$CH_2$),3.08(s, 6H, $NMe_2$ for *E*-isomer) , 3.14 (s, 6H, $NMe_2$ for *Z*-isomer) , 4.59 (broad s, $NH_2$ exchangeable), 6.77 (dd, 2H, ArH, $J_o$-=7.88 Hz , $J_{m-}$ =2.54 Hz), 7.48 (s, 1H, CH=, for *Z*- isomer), 7.81 (dd, 2H, ArH, $J_o$-= 7.26 Hz, $J_m$-= 2.64 Hz),8.26(s, 1H, CH=, for *E*-isomer); MS m/z(%): 375 ($M^{+\cdot}$,missed),197 ($M^{+\cdot}$ of 2a ,3) , 180 ($M^{+\cdot}$+ 2 of 1a ,3) , 178 ($M^{+\cdot}$ of 1a , 41) , 177 (15) , 150 (base) . Anal. Calcd for $C_{21}H_{21}N_5S$: C, 67.17; H, 5.64; N, 18.65. Found: C, 66.95; H, 5.89; N, 18.86 %.

***E*,*Z*-3- (2,5-Dimethoxyphenyl)-2- (4-amino-5,6,7,8-tetrahydrobenzo [b] thieno [2,3-*d*] pyrimidin-2-yl)-but-2-enonitrile (*E*,*Z*-3b)**, 0.8 g (65% yield), m.p. 158-160 C° (light petroleum b.p. 80-100). IR: 3446, 3329, 3207 (NH), 3030 (aryl-H), 2933, 2911, 2837 (alkyl-H), 2196 (C≡N), 1620 (C=N), 1521 (C=C) cm$^{-1}$; $^1$HNMR ($CDCL_3$) δ: 1.74 (m, 4H, 2 $CH_2$), 2.42 (m, 4H, 2 $CH_2$), 2.56 (s, 3H, $CH_3$, for *Z*- isomer), 2.58 (s, 3H, $CH_3$, for *E*- isomer), 3.77, 3.82 (two singlets, 6H, 2 $OCH_3$), 4.65 (broad s, $NH_2$ exchageable), 6.73- 7.72 (m, 3H, ArH). Anal. Calcd for $C_{22}H_{22}N_4O_2S$: C, 65.00; H, 5.46; N, 13.78. Found: C, 64.79; H, 5.53; N, 13.85 %.

***E*,*Z*-3-(4-Chlorophenyl) -2- (4-amino-5,6,7,8-tetrahydrobenzo [b] thieno [2,3-*d*] pyrimidin-2-yl) propenonitrile (*E*,*Z*-3c)**, 0.55 g (50 % yield), m.p. 123-125 C° (dilute ethanol). IR: 3440, 3332, 3208 (NH), 3035 (aryl-H), 2929, 2863 (alkyl-H), 2220 (C≡N), 1656 (C=N), 1595, 1560 (C=C), 824 ($\delta_{2\text{-H}}$) cm$^{-1}$; $^1$HNMR ($CDCL_3$) δ: 1.87 (m, 4H, 2 $CH_2$), 2.71 (m, 4H, 2 $CH_2$), 4.73 (broad s, $NH_2$ exchangeable). For *Z*-isomer: δ 7.44 (dd, 2H, ArH, $J_{o-}$= 8.6 Hz, $J_{m-}$=1.6 Hz), 7.73 (s, 1H, CH=), 7.86 (dd, 2H, ArH, $J_{o-}$= 8.6 Hz, $J_{m-}$= 1.86 Hz), For *E*- isomer δ: 7.52 (dd, 2H, ArH, $J_{o-}$= 8.6 Hz, $J_{m-}$=1.8 Hz), 7.88 (dd, 2H, ArH, $J_{o-}$= 8.4 Hz, $J_{m-}$=1.9 Hz), 8.38 (s, 1H, CH=); MS m/z (%): 366 ($M^{+\cdot}$, missed), 302 (28), 300 (base), 272 (77), 190 ($M^{+\cdot}$+2 of 2c, 25), 188 ($M^{+\cdot}$ of 2c, 75), 153 ($M^{+\cdot}$ of 2c-CL, base), 134 (15), 126 (25), 102 (12), 101 (10), 100 (17), 89 (40), 80 (30), 77 (13), 63 (26), 62 (27), 51 (24), 50 (55). Anal. Calcd for $C_{19}H_{15}CLN_4S$: C, 62.20; H, 4.12; N, 15.27. Found; C, 62,32; H, 4.27; N, 14.99 %.

***Z*-3-(4- Chlorophenyl)-2-(4-amino-5,6,7,8-tetrahydrobenzo [b] thieno [2,3-*d*] pyrimidin-2-yl) propenonitrile (*Z*-3c)**, 0.25 g (23 % yield), m.p. 108-110 C° (light petroleum b.p. 40-60). IR: 3446, 3329, 3207 (NH), 3033 (aryl-H), 2934, 2911, 2837 (alkyl-H), 2196 (C≡N), 1621 (C=N), 1558, 1521 (C=C), 826 ($\delta_{2\text{-H}}$) cm$^{-1}$; $^1$HNMR ($CDCl_3$) δ: 1.79 (m, 4H, 2 $CH_2$), 2.49 (m, 4H, 2 $CH_2$), 4.62 (broad s, $NH_2$ exchangeable), 7.52 (dd, 2H, ArH, $J_{o-}$= 8.64 Hz, $J_{m-}$= 1.96 Hz), 7.74 (s, 1H, CH=), 7.86 (dd, 2H, ArH, $J_{o-}$= 8.6 Hz, $J_{m-}$= 1.9 Hz); MS m/z (%): 366 ($M^{+\cdot}$, missed), 190 ($M^{+\cdot}$+2 of 2c, 28), 188 ($M^{+\cdot}$ of 2c, 76), 180 ($M^{+\cdot}$+2 of 1a, 2), 178 ($M^{+\cdot}$ of 1a, 38) 177 (14), 163 (11), 161 (32) 154 (12), 152 (base), 151 (11), 150 (97), 137 (25), 126 (21), 100 (12), 99 (14), 76 (23), 75 (24), 74 (13), 63 (18), 62 (16), 51 (24), 50 (32). Anal. Calcd for $C_{19}H_{15}ClN_4S$: C, 62.20; H, 4.12; N, 15.27. Found: C, 61.88; H, 3.92; N, 15.48 %.

***E*-3-(4-Chlorophenyl)-2-(4-amino-5,6,7,8,-tetrahydrobenzo [b] thieno [2,3-*d*] pyrimidin-2-yl) propenonitrile**

**(*E*-3c)**, 0.18 g (16 % yield), m.p. 140-142 C° (dilute ethanol). IR: 3439, 3342, 3215 (NH), 3093 (aryl-H), 2939,2921, 2863 (alkyl-H), 2220 (C≡N), 1641 (C=N), 1595, 1560 (C=C), 819 ($\delta_{2\text{-H}}$) $cm^{-1}$; $^1$HNMR ($CDCL_3$) δ: 1.87 (m, 4H, 2 $CH_2$), 2.69 (m, 4H, 2 $CH_2$), 4.75 (broad s, $NH_2$ exchangeable), 7.44 (dd, 2H, ArH, $J_{o\text{-}}$= 8.6 Hz, $J_{m\text{-}}$=1.85 Hz), 7.88 (dd, 2H, ArH, $J_{o\text{-}}$= 8.6 Hz, $J_{m\text{-}}$=1.92 Hz), 8.38 (s, 1H, CH=); MS m/z (%): 366 ($M^{+\cdot}$, missed), 302 (31), 301 (24), 300 (base), 299 (21), 274 (25), 273 (16),272 (78), 271 (11), 89 (38), 77 (15), 76 (10), 75 (13), 63 (25), 58 (11), 51 (15). Anal. Calcd for $C_{19}H_{15}CLN_4S$: C, 62.20; H, 4.12; N, 15.27. Found: C, 62.48; H, 4.31; N, 15.42 %.

**Reactions of 4 with Arylidine malononitriles 2b,d**

A mixture of **4** (3 mmole) and each of arylidene malononitriles **2b**,**d** (3 mmole) in n-butanol (20 ml) is refluxed for 20 hrs. The reaction mixture is concentrated and chromatographed over silica gel. In case of reaction **4** with **2b**; successive elution with petroleum ether (b.p. 60-80 / ether) (4: 1 v/v) gave ***E*-5a**, then with petroleum ether (b.p. 60-80 / ether) (2:3 v/v) afforded ***Z*-5a**. However, in case of reaction **4** with **2d**; elution with petroleum ether (b.p. 60-80 / ether) (9:1 v/v) yielded ***E*-5b**, then with petroleum ether (b.p. 60-80 / ether) (1:1 v/v) gave ***Z*-5b**.

***E*-3-(2,5-Dimethoxyphenyl)-2-(4-amino-5,8-dihydro-5,8-diphenyl-6-methyl pyrazolo [3',4' : 2,3 ] pyrano [2,3-*d*] pyrimidin-2-yl) but-2-enonitrile (*E*-5a)**, 0.6 g (36 % yield), m.p. 125-126 C° (light petroleum b.p. 40-60). IR: 3422, 3326, 3234 (NH), 3062 (aryl-H), 2925, 2847 (alkyl-H), 2212 (C≡N), 1661 (C=N), 1601, 1593 (C=C),756, 693 ($\delta_{5\text{-H}}$) $cm^{-1}$; $^1$HNMR ($CDCL_3$) δ: 1.82 (s, 3H, $CH_3$ pyrazolo), 2.29 (s, 3H, $CH_3$), 3.78, 3.82 (two singlets, 6H, 2 $OCH_3$), 4.85 (s, 1H, CH), 5.82 (broad s, $NH_2$ exchangeable), 6.97-7.69 (m, 13H, ArH); MS m/z (%): 556 ($M^{+\cdot}$, missed), 382 (11), 351 (12), 266 (14), 263 (18), 262 ($_{MeC=N\text{-}N(Ph)COC=CHPh}$, 70), 261 (36), 186 (16), 185 ($_{MeC=N\text{-}N(Ph)COC=CHPh}$-Ph, 87), 174 (32), 129 (17), 128 (36), 127 (12), 105 (18), 91 (61), 78 (10), 77 (base), 65 (12), 64 (18), 63 (15), 51 (58), 50 (14). Anal. Calcd for $C_{33}H_{28}N_6O_3$: C, 71.21; H, 5.07; N, 15.09. Found: C, 70.98; H, 5.26; N, 14.88 %.

***Z*-3-(2,5-Dimethoxyphenyl)-2-(4-amino-5,8-dihydro-5,8-diphenyl-6-methyl pyrazolo[ 3',4' : 2,3 ] pyrano [2,3-*d*] pyrimidin-2-yl) but-2-enonitrile (*Z*-5a)**, 0.5 g (30 % yield), m.p. 137-139 (ethanol). IR: 3404, 3330,3208 (NH), 3045 (aryl-H), 2931, 2839 (alkyl-H), 2216 (C≡N), 1642 (C=N), 1540 (C=C), 744, 673 ($\delta_{5\text{-H}}$) $cm^{-1}$; $^1$HNMR ($CDCL_3$) δ: 1.61 (s, 3H, $CH_3$ pyrazolo), 2.17 (s, 3H, $CH_3$), 3.77, 3.82 (two singlets, 6H, 2 $OCH_3$), 4.77 (s, 1H, CH), 5.85 (broad s, $NH_2$ exchangeable), 6.44-7.37 (m, 13H, ArH); MS m/z (%): 556 ($M^{+\cdot}$, missed), 448 ($M^{+\cdot}$-{ph+$OCH_3$}, 78), 418 (29), 417 (40), 351 (44), 333 (57), 332 (93), 167 (14), 166 (21), 165 (41), 154 (23), 139 (45), 124 (33), 104 (24), 92 (31), 91 (base), 77 (52), 76 (14), 67 (20), 66 (26), 65 (31), 64 (17), 63 (13), 55 (49), 51 (71), 50 (18). Anal. Calcd for $C_{33}H_{28}N_6O_3$: C, 71.21; H, 5.07; N, 15.09. Found: C, 71.35; H, 4.98; N, 15.29 %.

***E*-3-(4-Bromophenyl)-2-(4-amino-5,8-dihydro-5,8-diphenyl-6-methyl pyrazolo [3',4': 2,3 ] pyrano [2,3-*d*] pyrimidin-2-yl) but-2-enonitrile (*E*-5b),** 0.65 g (38 % yield), m.p. 218-220 C° (petroleum ether b.p. 80-100). IR: 3494, 3389 (NH), 3050 (aryl-H), 2920, 2852 (alkyl-H), 2207 (C≡N), 1608 (C=N), 1578, 1547 (C=C), 827 ($\delta_{2\text{-H}}$) 762, 693 ($\delta_{5\text{-H}}$) $cm^{-1}$; $^1$HNMR (CDCL3) δ: 1.79 (s, 3H, $CH_3$ pyrazolo), 2.30 (s, 3H, $CH_3$), 4.79 (s, 1H, CH), 5.75 (broad s, $NH_2$ exchangeable), 6.59-7.69 (m, 14H, ArH); MS m/z (%): 574 ($M^{+\cdot}$, missed), 354 ($M^{+\cdot}$- NC-C=C($CH_3$)$C_6H_4$Br-p, 1), 352 (21), 351 (91), 350 (41), 349 (base), 348 (25), 168 (18), 140 (21), 77 (14), 76 (13), 75 (15), 51 (20). Anal. Calcd for $C_{31}H_{23}BrN_6O$: C, 64.70; H, 4.03; N, 14.60. Found: C, 64.85; H, 4.19; N, 14.49 %.

***Z*-3-(4-Bromophenyl)-2-(4-amino-5,8-dihydro-5,8-diphenyl-6-methyl pyrazolo [3',4' : 2,3 ] pyrano [2,3-*d*] pyrimidin-2-yl) but- 2-enonitrile (*Z*-5b)**, 0.4 g (23 % yield) m.p. 205-207 C° (ethanol). IR: 3395, 3307, 3207 (NH), 3076 (aryl-H), 2954, 2878, 2818 (alkyl-H), 2215 (C≡N), 1650, 1641 (C=N), 1606, 1542 (C=C), 832 ($\delta_{2\text{-H}}$) $cm^{-1}$; $^1$HNMR (CDCL3) δ: 1.74 (s, 3H, $CH_3$ pyrazole), 2.17 (s, 3H, $CH_3$), 4.72 (s, 1H, CH), 5.81 (broad s, $NH_2$ exchangeable), 6.24-7.70 (m, 14H, ArH); MS m/z (%): 574 ($M^{+\cdot}$, missed), 497 ($M^{+\cdot}$-Ph, 1.4), 479 ($M^{+\cdot}$-{Ph+18}, 2.7), 400 ($M^{+\cdot}$- {Ph+18+Br}, 7.2), 374 ($M^{+\cdot}$-{Ph+18+Br+CN}, 2), 291 (1.5), 289 (1.5), 287 (15), 286 (base), 285 (19), 284 (96), 116 (13), 102 (11), 91 (18), 77 (22), 76 (13), 75 (12), 51 (26), 50 (12). Anal. Calcd for $C_{31}H_{23}BrN_6O$: C, 64.70; H, 4.03; N, 14.60. Found: C, 64.52; H, 3.98; N, 14.75 %.

**Acetylation of 3a-c**

Each of benzothienopyrimidine derivatives **3a**-**c** (0.4 g) is refluxed in acetic anhydride (15 ml) for 4 hrs. The reaction mixture is cooled and poured into ice cold water to give 2-acetylamino-3-cyano-4,5,6,7-tetrahydrobenzo [ b ] thiophene (**1b**), 0.15- 0.21 g (65-87 % yield), m.p. 208-210 C° (petroleum ether b.p. 60-80 / benzene) (Lit[8]. m.p. 215-216 C°). IR: 3266, 3219 (NH), 2992, 2926, 2840 (alkyl-H), 2209 (C≡N), 1688 (C=O), 1637, 1551 (C=C) $cm^{-1}$; $^1$HNMR (DMSO-$d_6$) δ: 1.76 (m, 4H, 2$CH_2$), 2.18 (s, 3H, CH3), 2.58 (m, 4H, 2$CH_2$), 11.52 (broad s, NH exchangeable). This substance is identical in all respects (m.p., mixed m.p. and TLC) with an authentic sample prepared from reaction of **1a** with acetic anhydride.

**Reactions of 4 with Acetylenic Esters and Ketones 6a-d**

Acetylenic esters **6a**,**b** or ketones **6c**,**d** (2 mmole) each of them was added to a solution of **4** (2 mmole) in ethanol (20 ml) containing triethylamine (3 drops) and the mixture is refluxed for 20 hrs. The reaction mixture is concentrated and left to stand at room temperature overnight to give a solid. Recrystalization from the proper solvent gave the title compounds **7a**-**d**.

***Z*-5-Cyano-1,4-dihydro-1,4-diphenyl-3-methyl-6-(1,2-dicarboethoxy ethenyl amino) pyrano [ 2,3-*c*] pyrazole (*Z*-7a)**, 0.4 g (40 % yield), m.p. 100-102 C° (light petroleum b.p. 60-80 / benzene). IR: 3434 (broad NH), 2980, 2924, 2871 (alkyl-H), 2214 (C≡N), 1727 (C=O), 1631 (C=N), 1600, 1542 (C=C), 753, 692 ($\delta_{5H}$) $cm^{-1}$; $^1$HNMR (DMSO-$d_6$) δ: 1.20 (m, 6H, 2$CH_2\underline{CH_3}$), 2.08 (S, 3H, $CH_3$), 4.22 (m, 4H, 2$\underline{CH_2}CH_3$), 5.20 (s, 1H, CH), 6.57 (s, 1H, CH=), 7.26-7.43 (m, 10H, ArH), 8.60 (broad s, NH exchangeable); MS m/z (%): 498 ($M^{+\cdot}$, 1), 453 ($M^{+\cdot}$-OEt, 8), 425 ($M^{+\cdot}$-$CO_2$Et,12) 408 ($M^{+\cdot}$-2OEt, 15), 352 ($M^{+\cdot}$-2$CO_2$Et, 20), 328 (30), 262 (91), 185 (77), 174 (43), 128 (40), 119 (32), 93 (base), 91 (36), 77 (35). Anal. Calcd for $C_{28}H_{26}N_4O_5$: C, 67.46; H, 5.26; N, 11.24. Found: C, 67.29; H, 5.32; N, 11.35 %.

***Z*-5-Cyano-1,4-dihydro-1,4-diphenyl-3-methyl-6-(1-phenyl-2-carbomethoxyethenyl amino) pyrano [ 2,3-*c*] pyrazole (*Z*-7b)**, 0.38 g (39 % yield), m.p. 145-148 C° (petroleum ether b.p. 80-100). IR: 3340, 3280, 3180 (NH), 3050 (aryl-H), 2960, 2900, 2840 (alkyl-H), 2160 (C≡N), 1720 (C=O), 1650 (C=N), 1590, 1550 (C=C), 760, 690 ($\delta_{5H}$) $cm^{-1}$; $^1$HNMR (DMSO-$d_6$) δ: 1.91 (s, 3H, $CH_3$), 3.93 (s, 3H, $OCH_3$), 4.59 (broad s, NH, exchangeable), 5.10 (s, 1H, CH), 6.48 (s, 1H, CH=), 7.05-7.81 (m, 15H, ArH); MS m/z (%): 488 ($M^{+\cdot}$, missed), 460 (25), 459 (22), 458 (52), 457 ($M^{+\cdot}$-$OCH_3$, 85), 265 (18), 264 (56), 263 (78), 261 (15), 197 (16), 195 (34), 185 (20), 138 (13), 137 (12), 136 (20), 131 (20), 129 (26), 128 (32), 127 (10), 116 (30), 115 (36), 105 (16), 103 (16), 102

(12), 101 (14), 89 (12), 77 (54), 75 (16), 64 (12), 59 (base), 51 (26). Anal. Calcd for $C_{30}H_{24}N_4O_3$: C, 73.76; H, 4.95; N, 11.47. Found: C, 73.51; H, 5.08; N, 11.69 %.

***Z*-5-Cyano-1,4-dihydro-1,4-diphenyl-3-methyl-6-(4-chlorobenzoyl- methylene benzamido) pyrano [ 2,3-*c*] pyrazole (*Z*-7*c*)**, 0.5 g (43 % yield), m.p. 142-145 C° (petroleum ether b.p. 80-100). IR: 3433 (broad NH), 3059 (aryl-H), 2971, 2921, 2857 (alkyl- H), 2205 (C≡N), 1658 (C= O), 1588 (C=N and/ or C=C), 830 ($\delta_{2H}$) $cm^{-1}$; $^1$HNMR ($CDCL_3$) δ: 2.10 (s, 3H, $CH_3$), 5.05 (broad s, NH exchangeable), 5.45 (s, 1H, CH), 6.45 (s, 1H, CH=), 7.19-7.85 (m, 19H, ArH); MS m/z (%): 570 ($M^{+\cdot}$+2, 0.2), 568 ($M^{+\cdot}$, 0.5), 459 ($M^{+\cdot}$+2-$C_6H_4$CL-p, 0.9), 457 ($M^{+\cdot}$- $C_6H_4$CL-p, 1.5), 263 (22), 246 (13), 219 (52), 139 ($COC_6H_4$CL-P, 32), 119 (19), 91 (base), 77 (30). Anal. Calcd for $C_{35}H_{25}CLN_4O_2$: C, 73.87; H, 4.43; N, 9.84. Found: C, 73.95; H, 4.64; N, 9.72 %.

***Z*-5-Cyano-1,4-dihydro-1,4-diphenyl-3-methyl-6-(4-methoxybenzoyl- methylene benzamido) pyrano [ 2,3-*c*] pyrazole (*Z*-7*d*)**, 0.3 g (26 % yield), m.p. 158-160 C° (petroleum ether b.p. 60-80 / benzene). IR: 3446, 3358, 3246 (NH), 3060 (aryl-H), 2934, 2839 (alkyl-H), 2214 (C≡N), 1645 (C=O), 1610 (C=N), 1574, 1515 (C=C), 832 ($\delta_{2H}$), 764, 696 ($\delta_{5H}$) $cm^{-1}$; $^1$HNMR (CDCL3) δ: 1.56 (s, 3H, $CH_3$), 3.87 (s, 3H, $OCH_3$), 4.76 (broad s, NH exchangeable), 5.37 (s, 1H, CH), 6.87 (s, 1H, CH=), 7.02 (dd, 2H, ArH, $J_{o-}$= 8.8 Hz, $J_{m-}$= 2.0 Hz), 7.36-7.61 (m, 15H, ArH), 7.55 (dd, 2H, ArH, $J_{o-}$= 8.8 Hz, $J_{m-}$= 2.4 Hz); MS m/z (%): 564 ($M^{+\cdot}$, missed), 327 ($M^{+\cdot}$- $C_6H_5C$=CHCOC$_6H_4$OMe-p, 3), 326 (21), 325 (base), 324 (14), 310 (12), 255 (19). Anal. Calcd for $C_{36}H_{28}N_4O_3$: C, 76.58; H, 4.99; N, 9.92. Found: C, 76.70; H, 4.66; N, 10.15 %.

**Reactions of 2-amino-3-cyanobenzo [b] thiophene (1a) with acetylenic ketones 6c-e**

A mixture of **1a** (3 mmole), each of **6c**-**e** (3 mmole) and few drops of piperidine was refluxed in n- butanol (15 ml) for 20 hrs. The reaction mixture is concentrated and allowed to stand at room temperature overnight to give a semisolid material. Trituration with methanol gave solid. Recrystallization from ethanol afforded 0.1-0.2 g recovered unchanged **1a**. On leaving the mother liquor at room temperature overnight afforded solid. Recrystallization from proper solvent gave **8a**-**c**.

**3-cyano-2-(4-chlorobenzoylmethylenebenzamido-4,5,6,7-tetrahydro- benzo [b] thiophene (8a) as amino-imino tautomer**, 0.4 g (32 % yield), m.p. 181-183 C° (petroleum ether b.p. 80-100). IR: 3445 (broad NH, 3059 (aryl-H), 2940, 2837 (alkyl-H), 2205 (C≡N), 1645 (C=O), 1584, 1519 (C=N and / or C=C), 845 ($\delta_{2H}$), 779, 695 ($\delta_{5H}$) $cm^{-1}$; $^1$HNMR ($CDCL_3$) δ: 1.75 (m, 4H, 2 $CH_2$), 2.48 (m, 4H, 2 $CH_2$), 4.76 (broad s, NH exchangeable for amino-tautomer), 6.11 (s, 1H, CH=), 7.36-7.94 (m, 9H, ArH), 13.67 (broad s, OH exchangeable for imino- tautomer); MS m/z (%): 420 ($M^{+\cdot}$+2, 10), 418 ($M^{+\cdot}$, 22), 279 ($M^{+\cdot}$-$COC_6H_4$CL-p, 17), 141 (27), 139 ($COC_6H_4$CL-p, base), 138 (15), 111 (28), 77 (11). Anal. Calcd for $C_{24}H_{19}CIN_2OS$: C, 68.81; H, 4.57; N, 6.69. Found: C, 68.65; H, 4.71; N, 6.52 %.

**3-Cyano-2-(4-methoxybenzoylmethylenebenzamido)-4,5,6,7-tetra- hydrobenzo[b] thiophene (8b) as amino-imino tautomer**, 0.3 g (24 % yield), m.p. 188-190 C° (methanol / benzene). IR: 3432, 3335, 3218 NH, 2937, 2903, 2837 (alkyl-H), 2196 (C≡N), 1620 (C=O), 1590, 1519 (C=N and / or C=C) $cm^{-1}$; $^1$HNMR ($CDCL_3$) δ: 1.57 (broad s, 4H, 2$CH_2$), 2.28 (broad s, 4H, 2$CH_2$), 3.66 (s, 3H, $OCH_3$), 4.49 (broad s, NH exchangeable for amino-tautomer), 5.93 (s, 1H, CH=), 6.70-7.78 (m, 9H, ArH), 13.45 (broad s, OH exchangeable for imino-tautomer); MS m/z (%): 416 ($M^{+\cdot}$+2, 8), 414 ($M^{+\cdot}$, 30), 415 (20), 135 ($COC_6H_4$OMe-p, base), 77 (15). Anal. Calcd for $C_{25}H_{22}N_2O_2S$: C, 72.44; H, 5.35; N, 6.76. Found: C, 72.61; H, 5.12; N, 6.92 %.

**3-Cyano-2-(benzoylmethylenebenzamido)-4,5,6,7-tetrahydrobenzo [b] thiophene (8c) as amino-imino tautomer**, 0.5 g (43 % yield), m.p. 201-203 C° (methanol / benzene). IR: 3448 (broad NH), 3062 (aryl-H), 2922, 2840 (alkyl-H), 2203 (C≡N), 1654 (C=O), 1611, 1591, 1569 (C=N and / or C=C), 769, 694 ($\delta_{5H}$) $cm^{-1}$; $^1$HNMR ($CDCL_3$) δ: 1.61 (m, 4H, 2$CH_2$), 2.27 (m, 4H, 2$CH_2$), 4.58 (broad s, NH exchangeable for amino-tautomer), 5.97 (s, 1H, CH=), 7.05-7.79 (m, 10H, ArH), 13.46 (broad s , OH exchangeable for imino-tautomer); MS m/z (%): 386 ($M^{+\cdot}$+2, 4), 385 (52), 384 ($M^{+\cdot}$, 25), 383 (11), 356 (10), 282 (14), 281 (10), 280 (14), 279 (17), 105 ($COC_6H_5$, base), 77 (41). Anal. Calcd for $C_{24}H_{20}N_2OS$: C, 74.97; H, 5.24; N, 7.29. found:C, 74.62; H, 4.99; N, 7.46 %.

## BIBLIOGRAPHY


1. Tompson, M.; Forbes, I.; Johnson, C.N.: *Eur.Pat*. Appl.EP. 327, 223 (CL. C07D495 / 04; 09 Aug. 1989, CB Appl. 88 / 1, 491, 22 Jan 1988, 18 pp.; [C. A. 1990,112, 55831h].
2. Youssef, A. S. A.; Kandeel, K. A.; Fouli, F. A.; Abou El-Magd, W. S. I.:*Heteroatom Chem*., 2005, 6, 16.
3. Delaszlo, S. E.; Patchett, A. A.; Allen,E. E.; Greenle, W. J.: *Eur. Pat*. 1992, 502, 725; [C. A. 1993, 118, 22249].
4. Robinson, G. E.; Quire, C. J.: *Eur. Pat*. 1988, 253, 507; [C. A. 1988, 109, 6318].
5. Joshi, K. C.; Jain, R.; Damdi, A.; Sharma, K.: *J. Heterocyclic Chem*., 1988, 25, 1641.
6. Boehm, R; Hanbold, G.; Pech, R.; Laban, G.: *Ger. Pat*. 1985, 226, 893; [C. A. 1986, 104, 186437].
7. Youssef, A. S. A.: *Chem. Pap*., 2002, 56 (2), 132.
8. Ramanathan, J. D.; Namboothiri, D. G.; Shah, G. F.; Radhakrishnan, A. V.; Mehta, H. J.; Padhya, A. C.: *J. Indian Chem. Soc*., 1978, Vol. LV, 822.
9. Tacconi, G.; Gatti, G.; Desimoni, G.: *J. Prakt. Chem*., 1980, 322 (5), 831; [C. A. 1981, 94, 174962 w].
10. Mowry, D. T.: *J. Am. Chem. Soc*., 1943, 65, 991.
11. Benghiate, I.; Becker, E. I.: *J. Org. Chem*., 1985, 33, 885.
12. Parker, W.; Raphael, R. A.; Wilkinson, O. I.: *J. Chem. Soc*., 1958, 3871.
13. Suesse, M.; Johne, S., DD 155167 (CL. C07D 495 / 14), 19 May 1982, Appl. 225874, 09 Dec. 1980, 9 pp.; [C. A. 1982, 97, 216211 V].
14. Basyouni, M. N.; Omar, M. T.; El-Khamry, A. A.; Ghali, E. A.: *Egypt J. Chem*., 1980, 23 (4), 237.
15. Baddar, F. G.; Al-Hajjar, F. A.; El-Rayyes, N. R.: *J. Heterocyclic Chem*., 1978, 15, 105.
16. Fouli, F. A.; Shaban, M. E.; El-Nagdy, E. I.; Youssef, A. S. A.: *Indian J. Chem*., 1988, 27B, 86.