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Reactivity of substituted Pyrimidines with Some Nucleophiles

A. E. Farrag, N. F. Abdel Ghaffar*, N. T. A. Dawood and F. H. Abd El-Salam

Chemistry Department, Faculty of Science (Girls), Al-Azhar University, Nasr City, Cairo Egypt

ABSTRACT

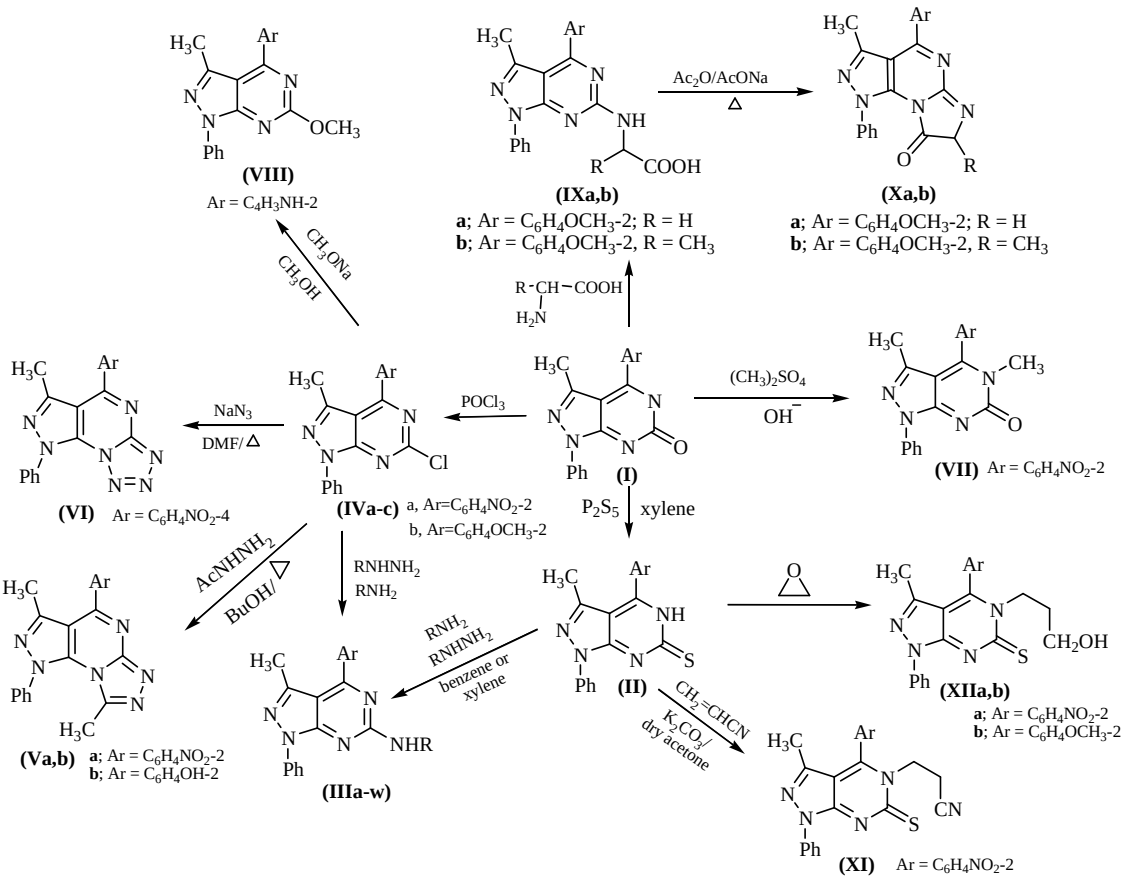
A series of five 3-methyl-1-phenyl-4-substituted pyrazolo[3,4-d]pyrimidin-6-ones ***(I_{a-e})*** *and five 3-methyl-1-phenyl-4-substituted pyrazolo [3,4-d]pyrimidin-6-thiones* ***(II_{a-e})*** *were prepared and some of them were subjected to aminolysis as well as hydrazinolysis. The reaction of the 6-chloro derivatives* ***(IV)*** *with amino acids to give pyrazolo pyrimidine derivatives* ***(IX)*** *was investigated. A few of the pyrimidin-6-thiones were cyanoethylated under drastic conditions to give* ***(XI)****, and some of them were also hydroxyethylated* ***(IX)****.*

Keywords: Pyrimidines, pyrazolopyrimidines, synthesis, nucleophiles, electrophiles.

INTRODUCTION

A large number of pyrimidine derivatives are reported to exhibit antimycobacterial[1], antitumor[2], antiviral[3] anticancer[4], anti-inflammatory[4], analgesic[4], antifolate[5], antimicrobial[6], anti-fungal[7], antiproliferative[8] and antihistaminic[9] activities. They are also effective as antiplatelet agents with analgesic activity [10] and as a new drug for treatment of insomnia [11].

In view of these reports and as continuation of our recent studies [12-13]; the syntheses of a new series of compounds containing the pyrimidine moiety are now reported. The one-pot reaction of 4-arylidene-3-methy-l-phenyl pyrazolin-6-ones with urea afforded the corresponding 3-methyl-1-phenyl-4-substituted pyrazolo[3,4-d] pyrimidin-6-ones ***(1_{a-e})*** Those derivatives have elicited a good deal of attention as they exhibited antimicrobial activity[14-16]. Their mode of reaction with some nucleophiles has also been studied in detail since the products are themselves very useful as synthetic intermediates.



a; Ar = $C_6H_4NO_2$-2, R = CH_3
b; Ar = $C_6H_4NO_2$-2, R = $C_6H_5CH_2$
c; Ar = $C_6H_4NO_2$-2, R = benzothiazolyl-2-yl
d; Ar = $C_6H_4NO_2$-2, R = pyridine-2-yl
e; Ar = $C_6H_4OCH_3$-2, R = $(CH_2)_3$-CH_3-n
f; Ar = $C_6H_4OCH_3$-2, R = $C_6H_4NO_2$-3
g; Ar = $C_6H_4OCH_3$-2, R = C_6H_5
h; Ar = $C_6H_4OCH_3$-2, R = benzothiazolyl-2-yl
i; Ar = $C_6H_4OCH_3$-2, R = C_6H_4Cl-4
j; Ar = C_6H_4OH-2, R = $C_6H_4NO_2$-2
k; Ar = C_6H_4OH-2, R = C_6H_5
l; Ar = 2-C_4H_3NH, R = $C_6H_5CH_2$
m; Ar = 2-C_4H_3NH, R = benzothiazolyl-2-yl
n; Ar = $C_6H_4OCH_3$-2, R = -NH_2
o; Ar = $C_6H_4OCH_3$-2, R = -NHC_6H_5
p; Ar = $C_6H_4OCH_3$-2, R = -$NHC_6H_4NO_2$-4
q; Ar = $C_6H_4OCH_3$-2, R = -$NHC_6H_3(NO_2)_2$-2,4
r; Ar = C_6H_4OH-2, R = -NHC_6H_5
s; Ar = C_6H_4OH-2, R = -$NHC_6H_4NO_2$-4
t; Ar = 2-C_4H_3NH, R = -NHC_6H_5
u; Ar = 2-C_4H_3NH, R = -$NHC_6H_3(NO_2)_2$-2,4
v; Ar = $C_6H_4NO_2$-2, R = -$NHCSNH_2$
w; Ar = $C_6H_4OCH_3$-2, R = -$NHCONH_2$

Scheme 1

EXPERIMENTAL SECTION

All melting points are uncorrected and measured in capillary tubes. The IR spectra were recorded on a Shimadzu FTIR 8201 PC in KBr discs (wafer technique). The ^{1}H NMR spectra were measured on a 300-(300 MHz) BRUKER proton NMR-Avance in DMSO-d_6 as a solvent and TMS as internal reference. The mass spectra (MS) were measured on a Varian (70 eV) MAT 112 Spectrophotometer.

3-Methyl-1-phenyl-4-substituted phenyl pyrazolo[3,4-d]pyrimi-din-6-ones ***(I_{a-e})*** and 3-methyl-1-phenyl-4-substituted phenyl pyrazolo [3,4-d] pyrimidin-6-thiones ***(II_{a-e})*** were prepared according to Abd El-Ghaffar et al[13].

The mass spectrometry of ***II_b*** showed ion peaks at *m/e* 332 (1.9%), *m/e* 210 (2.4%), *m/e* 168 (2.2%), *m/e* 143(4) and 77 (100%) (c.f.Chart 1).

3-Methyl-(1-phenyl-4-substituted phenyl pyrazolo[3,4-d]pyrimidin-6-amino-(*III*$_{a-m}$), 6-hydrazino(*III*$_{n-u}$), 6-thiocarbamoyl (*IIIV*), and 6-carbamoyl (*III*w).

A mixture of ***I***$_{a-e}$, ***II***$_{a-e}$, ***IV***$_{a-c}$ (0.01 mol) and the appropriate amine such as methylamine, benzylamine, 2-amino-thiazole, 2-aminopyridine, butylamine, 3-nitroaniline, aniline, 4-chloroaniline and 2-nitroaniline (0.01 mol) in 30 ml of ethanol, benzene and/or xylene was heated under reflux for 6-18 hours. The mixture was filtered while hot, left to cool and the products that separated were recrystallized from the proper solvents to give***III***$_{a-m}$. A mixture of ***I***$_{a-e}$, ***II***$_{a-e}$, ***IV***$_{a-c}$ (0.01 mol) and the hydrazines namely, hydrazine hydrate, phenyl hydrazine, 4-nitrophenyl hydrazine, 2,4-dinitrophenyl hydrazine (0.01 mol) in 30 ml of ethanol, benzene or xylene and thiosemicarbazide or semicarbazide (0.01 mol, dissolved in 1 ml of water) in 30 ml of ethanol was refluxed for 6 hours. The products that separated after concentration and cooling were collected and recrystallized from the proper solvent to give ***III***$_{n-u}$ and ***III***$_{v,w}$.

The IR stretching absorption of compounds ***(III***$_{a-w}$**)** showed absorption bands around 3440 cm^{-1} *v*NH and 1620cm^{-1} for *v*C=V cyclic.

III$_a$**,** recrystallized from ethanol as pale yellow crystals, mp 177°C, 72% yield, $C_{19}H_{16}N_6O_2$ (360), C, 63.4;H, 4.4; N, 23.2%; IR (KBr): υNH, 3436, 3260; υC=N 1620; υ ring 1606. ^{1}H-NMR δppm: 1.01 (s, 3H, CH_3), 2.47 (d, 3H, NH–$\underline{CH_3}$), 4.4 (q, 1H, NH–CH_3), 6.46-8.14 (m, 9H, Ar–H); ^{13}C NMR δppm: 164(C=N), 158, 147.9, 146.3, 146.1, 134.8, 130, 129.6, 128.9 127.3, 121, 118.8, 116.3, 29.1 (CH_3–N), 18.2 (CH_3–C). MS: M+2$^{+\cdot}$ 3.62(2.1%), M$^{+\cdot}$ 360 (27.1%).

III$_b$**,** recrystallized from petroleum ether (bp 60-80°C) as pale yellow crystals, mp 162 °C, 69% yield, $C_{25}H_{20}N_6O_2$ (436), C, 68.8; H, 4.6; N, 19.3%; IR(KBr): υNH, 3442, 325.5; υC=N 1619, υ ring 1600. ^{1}H-NMR δppm: 1.03 (s, 3H, CH_3), 3.81 (d, 2H, CH_2–NH), 4.6 (t, 1H, NH), 6.49-8.15 (m, 14H, Ar–H). ^{13}C NMR δppm: 164(C=N), 158, 147.9, 146.3, 146.1, 136.5, 134.8, 130, 129.6, 128.9, 128.6, 128, 127.3, 127.1, 121, 118.8, 716.3, 91, 47.7 (CH_2NH), 18.2 (CH_3–C). MS: M+2$^{+\cdot}$ 438 (3.6%), M+1$^{+\cdot}$ 437 (9.2%), 436 (29.3%).

III$_c$, recrystallized from ethanol as yellow crystals, mp 198 °C, in 78% yield, $C_{25}H_{17}N_7O_2S$ (479), C, 62.6; H, 3.5; N, 20.5; S, 6.7%. IR(KBr): υNH, 3428, 3235; υC=N 1620; υ ring 1600. ^{1}H-NMR δppm: 1.08 (s. 3H, CH_3), 4.95 (s, 1H, NH), 6.48-8.16 (m, 13H, Ar–H). ^{13}C–NMR δppm: 174.5 (C–S), 164(C=N), 158, 149, 147, 146.3, 146.1, 134.8, 130, 129.6, 128.9, 127.3, 125.9, 125.2, 124.5, 121.9, 121.8, 121, 118.8, 116.3, 91, 86.9 (C–NH), 18.2 (CH_3–C). MS: M+2$^{+\cdot}$ 481(1.2%), M+1$^{+\cdot}$ 480 (4.7%), M$^{+\cdot}$ 479(22.9%).

III$_d$, recrystallized from benzene as yellow crystals, mp 138 °C, 69% yield, $C_{23}H_{17}N_7O_2$ (423), C, 65.2; H, 4.1; N, 23.2%. IR (KBr): υNH, 3438, 3230; υC=N 1620; υ ring 1606. ^{1}H–NMR δppm: 1.01 (s, 3H, CH_3), 4.89 (s, 1H, NH), 6.62-8.11 (m, 13H, Ar–H), ^{13}C–NMR δppm: 164(C=N), 158.6, 158, 148.2, 147.9, 146.3, 146.1, 138.3, 134.8, 130, 129.6, 128.9, 127.3, 121, 118.8, 116.3, 113.3, 109.9, 91, 87.2, 18.2 (CH_3–C). MS: M+2$^{+\cdot}$ 425 (3.2%); M+1$^{+\cdot}$ 424(3.1%); M$^{+\cdot}$ 423 (37.9%).

III$_e$**,** recrystallized from benzene as pale yellow crystals, mp 164 °C, 81% yield, $C_{23}H_{25}N_5O$ (387), C, 71.3; H, 6.5; N, 18.1%; IR(KBr): υNH 3440, 3230; υC=N 1620; υ ring 1590. MS: M+2$^{+\cdot}$ 389 (1.9%), M+1$^{+\cdot}$ 388 (2.1%), M$^{+\cdot}$ 387 (42.9%).

III$_f$, recrystallized from ethanol as yellow crystals, mp 202 °C, 87% yield, $C_{25}H_{20}N_6O_3$(452), C, 66.4; H, 4.4; N, 18.6%. IR (KBr): υNH 3448, 3235: υC=N 1619; υ ring 1599. ^{1}H-NMR δppm: 1.08 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3–Ar) 4.99 (s, 1H, NH), 6.47–7.85 (m, 13H, Ar–H). ^{13}C–NMR δppm: 164(C=N), 158, 157.7, 149.2, 148.5, 147.9, 146.3, 130.5, 129.6, 129, 127.4, 121, 119.6, 118.8, 116.3 114.2, 109.5, 109.5, 107.4, 107.2, 91, 87.2 (C–N), 56.3 (CH_3–O), 18.2 (CH_3) MS: M+2$^{+\cdot}$ 454 (2.2%), M+1$^{+\cdot}$ 453 (4.8%), M$^{+\cdot}$ 452 (47.4%).

III$_g$: recrystallized from pet. ether (bp 60-80°C) as yellowish white crystals, mp 151 °C, 84% yield, $C_{25}H_{21}N_5O$ (407), C, 73.7; H, 5.2; N, 17.2%. IR (KBr): υNH 3440, 3230; υC=N 1620; υ ring 1589. ^{1}H–NMR δppm: 0.99 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 4.65 (s, 1H, NH), 6.46-7.19 (m, 14H, Ar–H) MS: M+2$^{+\cdot}$ 409 (3.6%), M+1$^{+\cdot}$408 (28.9%), M$^{+\cdot}$ 407 (37.9%).

***III$_h$*,** recrystallized from ethanol as yellow crystals, mp 204 °C, 77% yield, $C_{26}H_{20}N_6OS$ (464), C, 67.3; H, 4.3; N, 18.1; S, 6.9%; IR (KBr), υNH 3394, 3235, υC=N 1618; υ ring 1590. ^{1}H NMR δppm: 1.01 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.86 (s, 1H, NH), 6.62-8.13 (m, 13H, Ar–H), ^{13}C NMR δppm: 174.5 (N=C–S–), 164(C=N), 158, 157.5, 149, 147.9, 146.3, 129.6, 129, 127.4, 125.9, 125.2, 124.5, 121.9, 121.8, 121, 118.8, 116.3, 114.2 , 107.2, 91, 86.9 (N=C–N), 56.3(O–CH_3), 18.6(CH_3). MS: M+2$^{+\cdot}$ 466(1.4%), M+1$^{+\cdot}$ 465(4.9%), M$^{+\cdot}$ (29.2%).

***III$_i$*,** recrystallized from ethanol as dark yellow crystals, mp 213 °C, 88% yield, $C_{25}H_{20}N_5ON_5OCl$ (441.5), C, 68.0; H, 4.5, N, 15.9; Cl, 8.1%. IR (KBr): υNH3440, 3230, υC=N 1616, υ ring 1599. ^{1}H-NMR δppm: 1.11 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.59 (s, 1H, NH), 6.94-7.95 (m, 13H, Ar–H), MS: M+3$^{+\cdot}$ 444 (1.3%), M+2$^{+\cdot}$ 443 (5.8%), M+1$^{+\cdot}$ 442 (28%), M$^{+\cdot}$ 441(29)

***III$_j$*:** recrystallized from ethanol as gray crystals, mp 164 °C, 88% yield, $C_{24}H_{18}N_6O_3$ (438), C, 65.8; H, 4.1; N, 19.2%. IR (KBr): υNH 3404, 3260, υC=N 1615, υ ring 1590. ^{1}H-NMR δppm: 1.09 (s, 3H, CH_3), 4.95 (s, 1H, NH), 6.86-7.83 (m, 13H, Ar–H), 10.5 (s, 1H, OH), MS: M+2$^{+\cdot}$ 440 (1.2%), M+1$^{+\cdot}$ 439 (3.3%) M$^{+\cdot}$ 438 (28.3%).

III$_k$, recrystallized from ethanol as light green crystals, mp 189 °C, 89% yield, $C_{24}H_{19}N_5O$(393), C, 73.3; H, 4.8; N, 17.8%. IR (KBr): υNH 3436, 3255, υC=N 1620, υ ring 1599. ^{1}H-NMR δppm: 0.91 (s, 3H, CH_3), 4.39 (s, 1H, NH), 6.43-7.13 (m, 14H, Ar–H), 10.09 (s, 1H, OH). MS: M+2$^{+\cdot}$ 395 (1.8%), M+1$^{+\cdot}$ 394 (4.1%), M$^{+\cdot}$ 393 (26.2%).

***III$_l$*:** recrystallized from benzene as yellow crystals mp 201 °C, 77% yield, $C_{23}H_{20}N_6$ (380), C, 72.6; H, 5.3; N, 22.1%. IR (KBr): υNH 3432, 3255, υ C=N 1618, υ ring 1590. ^{1}H-NMR δppm: 0.90 (s, 3H, CH_3), 2.83 (s, 2H, CH_2–Ph), 4.15(s, 1H, NH), 5.31(s, 1H, NH), 6.69-7.17 (m, 13H, Ar-H). MS: M+2$^{+\cdot}$ 382 (3.0%), M+1$^{+\cdot}$ 381 (27.7%), M$^{+\cdot}$ 380 (42.1%).

***III$_m$*,** recrystallized from benzene as dark yellow crystals mp 212 °C, 76% yield, $C_{23}H_{17}N_7S$ (423), C, 65.3; H, 4.0; N, 23.2; S, 7.6. % IR (KBr): υNH 3428, 3255, υC=N 1618, υ ring 1600. ^{1}H-NMR δppm: 1.01 (s, 3H, CH_3), 4.73 (s, 1H, NH), 5.51 (s, 1H, NH), 6.94-8.12 (m, 12H, Ar–H). MS: M+2$^{+\cdot}$ 425 (3.2%), M+1$^{+\cdot}$ 424 (25.1%), M$^{+\cdot}$ 423 (39.4%).

***III$_n$*:** recrystallized from pet. ether (bp 60-80 °C) as pale yellow crystals, mp 128 °C, 71% yield, $C_{19}H_{18}N_6O$ (346) C, 65.9; H, 5.5; N, 24.3%. IR (KBr): υNH 3332, 3135; υC=N 1606, υ ring

1588. ^{1}H-NMR δppm: 0.91 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.95 (t, 1H, NH), 6.46-7.19 (m, 9H, Ar–H), 9.15 (d, 2H, NH_2). ^{13}C NMR δppm: 164(C=N), 158(C=N–N), 157.7; 147.9, 146.3, 129.6, 129, 127.4, 121, 118.8, 116.3, 114.2, 107.2, 91, 89.2, 56.3 (OCH_3), 18.2 (CH_3). MS: M+2⁾⁺· 348 (1.9%), M+1⁾⁺· 347 (12.7%), M⁾⁺· 346 (19.4%).

III$_o$: recrystallized from benzene as orange crystals, mp 169 °C, 73% yield, $C_{25}H_{22}N_6O$ (422), C, 71.1; H, 5.2; N, 20.0%. IR (KBr): υNH 3392, 3139; υC=N 1608, υ ring 1599. ^{1}H-NMR δppm: 1.06 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.95 (d, 1H, NH), 5.01 (d, 1H, NH), 6.96-7.92 (m, 14H, Ar–H).

***III$_p$*:** recrystallized from ethanol as dark orange crystals, mp 212 °C, 89% yield, $C_{25}H_{21}N_7O_3$(467), C, 64.2; H, 4.5, N, 21.0%. IR (KBr): υNH 3414, 3157; υC=N 1618, υ ring 1602. ^{1}H-NMR δppm: 1.19 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 4.86 (d, 1H, NH), 5.16 (d, 1H, NH), 6.99-8.15 (m, 13H, Ar–H). ^{13}C NMR δppm: 164 (C–N), 158 (C=N–N), 157.7, 157.1, 147.9, 146.3, 138.9, 129.6, 129.0, 127.4, 121.6, 121.0, 118.8, 116.3, 114.2, 114.1, 107.2, 91, 68.6, 56.3, 18.2. MS: M+2⁾⁺· 469(2.6%), M+1⁾⁺· 468 (4.9%), 467(31%).

III$_q$ recrystallized from ethanol as reddish crystals, mp 198 °C, 91% yield, $C_{25}H_{20}N_8O_5$ (512), C, 58.6; H, 3.9; N, 21.9%. IR (KBr): υNH 3419, 3310; υC=N 1618; υ ring 1604. ^{1}H-NMR δppm: 1.31(s, 3H, CH_3); 3.73 (s, 3H, OCH_3), 4.90 (d, 1H, NH), 5.18 (d, 1H, NH), 6.95-8.15 (m, 12, H, Ar–H). MS: M+2⁾⁺· 514 (4.7%), M+1⁾⁺· 513 (6.4%), M⁾⁺· 512 (30.1%).

***IIIr*:** recrystallized from ethanol as green gray crystals, mp 161°C, 72% yield, $C_{24}H_{20}N_6O$ (408), C, 70.6; H, 4.9; N, 20.6%. IR (KBr): υNH 3340, 3220; υC=N 1616; υ ring 1599. ^{1}H–NMR δppm: 1.01 (s, 3H, CH_3), 4.15 (d, 1H, NH), 4.65 (d, 1H, NH), 6.66-7.18 (m, 14H, Ar–H). MS: M+2⁾⁺· 410(2.2%), M+1⁾⁺· 409(4.1%), M⁾⁺· 408 (26.9%).

***IIIs*,** recrystallized from ethanol as orange crystals, mp 188 °C, 83% yield, $C_{24}H_{19}N_7O_3$ (453), C, 63.6; H, 4.2; N, 21.6%. IR (KBr): υOH 3483; υNH 3269, 3135; υC=N 1620; υ ring 1601. ^{1}H-NMR δppm: 1.24 (s, 3H, CH_3); 4.34 (d, 1H, NH), 4.95 (d, 1H, NH), 6.95-8.11 (m, 13H, Ar–H); 10.19 (s, 1H, OH). MS: M+2⁾⁺· 455 (1.3%); M+1⁾⁺· 454 (3.3%); M⁾⁺· 453 (28.7%).

***III$_t$*,** recrystallized from benzene as dusty crystals, mp 113°C, 69% yield, $C_{22}H_{19}N_7$ (381), C, 69.3; H, 5.0; N, 25.7% IR (KBr): υNH 3448, 3130; υC=N 1599; υ ring 1589 ^{1}H-NMR δppm: 0.95 (s, 3H, CH_3), 4.13 (d, 1H, NH), 4.92 (d, 1H, NH), 5.0 (d, 1H, NH), 6.12-7.04 (m, 13H, Ar–H). MS: M+2⁾⁺· 383 (3.1%) M+1⁾⁺· 382 (2.2%); M⁾⁺· 381 (24.2%).

***III$_u$*:** recrystallized from ethanol as dark red crystals, mp 193 °C, 94% yield, $C_{22}H_{17}N_9O_4$ (471), C, 56.1; H, 3.6; N, 26.8. IR (KBr): υNH 3484, 3235; υC=N 1620; υ ring 1599. ^{1}H-NMR δppm: 1.35 (s, 3H, CH_3), 4.65 (s, 1H, NH), 5.35 '(d, 1H, NH), 5.67 (d, 1H, NH), 7.01-8.36 (m, 11H, Ar–H). MS: M-2⁾⁺·. 478 (1.3%); M+1⁾⁺· 472, (3.4%), 471(37.3%).

***III$_v$*:** recrystallized from pet. ether–benzene (bp 60-80°C) as dusty crystals, mp 142°C, 69% yield, $C_{19}H_{16}N_8O_2S$ (420), C, 54.3; H, 3.8; N, 26.7; S, 7.7%. IR (KBr): υNH 3440, 3394, 3255 υC=N 1618, υ ring 1601. ^{1}H–NMR δppm: 1.19 (s, 3H, CH_3) 4.61 (d, 1H, NH), 5.01 (d, 1H, NH), 7.01-8.14 (m, 9H, Ar–H), 9.89 (s, 2H, NH_2). ^{13}C–NMR δppm: 182.6 (), 164 (C=N), 158,

147.9, 146.3, 146.1, 134. 8, 130.0, 129.6, 128.9, 127.3, 121.0, 118.8, 116.3, 91 (C=N–N), 85.6, 18.2 (CH_3). MS: M+2 422 (4.2%), M+1 421 (4.5%), M 420 (70.1%).

III_w, recrystallized from ethanol as gray crystals, mp 151 °C, 71% yield, $C_{20}H_{19}N_7O_2$ (389), C, 61.7; H, 4.9; N, 25.2%. IR(KBr): υNH 3442, 3398, 3258, υC=N 1620 υ ring 1605. ^{1}H-NMR δppm: 1.29 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 4.69(d, 1H, NH), 5.13 (d, 1H, NH), 7.12-8.15 (m, 9H, Ar–H), 9.95 (s, 2H, NH_2), MS: M+2 391 (4.3%), M+1 390 (6.1%), M 389 (38.7%).

3-Methyl-1-phenyl-4-substituted phenyl-6-chloro-pyrazolo-[3,4-d]pyrimidine *(IV_{a-c})*
A suspension of **Ia-c** (0.01 mol) in 5 ml of $POCl_3$ and phosphorous pentachloride (0.01 mol) was heated on a steam-bath for 2 hours. After cooling, it was poured on to 50 ml of cooled ice water, stirred well, and the separated product was collected, washed well with cold water and recrystallised from ethanol as **IVa-c**

Triazolo[4',3'-b]pyrazolo[3,4-d]pyrimidine (Va):
A mixture of ***IV_a*** (0.01 mol) and acetyl hydrazine (0.01 mol) in 50 ml of *n*-butanol was heated under reflux, filtered while hot and left to cool. The product that separated was recrystallized from acetic acid as yellowish brown needless, mp 220 ºC, 70% yield. Cacld. for: $C_{20}H_{15}O_2N_7$ (385); req.: C, 62.33; H, 3.89; N, 25.45. Found: C, 62.3; H, 3.9; N, 25.5. IR: 1636 cm^{-1} (νC=N cyclic), 2880, 2940, 2950, 3044 cm^{-1} (νC-H). ^{1}H NMR: δ 2.79 ppm (s, 3H, CH_3), δ 2.35(s, 3H, CH_3-triazolo), δ 6.5-7.59 (m, 9H, Ar-H). ^{13}C–NMR δppm: 163.4, (pyrimidine –C), 152.5 (tirazole–C), 149.3, 146.9, 144.3, 139.7, 135.4, 131.6, 129.7,129.4, 128.7, 128.4, 126.3, 121.6, 120.2, 115.2, 15.6 (CH_3), 14.4(CH_3). MS: M+2 387 (1.2%), M+1 386 (2.1%), M (21.6%).

Triazolo[4',3'-b]pyrazolo[3,4-d]pyrimidine (*V_b*) :
A mixture of **Ic** (0.01 mol), phosphorus pentasulfide (0.05 mol) in 30 ml of xylene was heated under reflux for 6hrs, decanted and the product was washed well with petroleum ether (bp 60-80 ºC). The crude product ***(IIc)*** (0.01 mol) was heated with acetylhydrazine in *n*-butanol for 72 hours. The reaction mixture was cooled and the product was collected and recrystallised from isopropyl alcohol to give ***V_b*** *i*n 45% yield, mp 213 ºC Calcd. for $C_{20}H_{16}ON_6$ (356); Req.: C, 67.41; H, 4.49; N, 23.59. Found: C, 67.4; H, 4.5; N, 23.6%, IR: (KBr) 1626 cm^{-1} (νC=N), 2858, 2923 and 3020 cm^{-1} (νC-H) and 3420 cm^{-1} (νOH). ^{1}HNMR: δ 2.53 ppm (s, 3H, -CH_3), δ 2.75 ppm (s, 3H, CH_3-triazolo), δ 6.7-8.9 ppm (m, 9H, Ar-H) and at δ 11.1 ppm (s, 1H, OH-Ar). ^{13}C–NMR δppm : 163.4 (pyrimidine–C), 155.3(triazolo-C), 157.9, 149.6, 144.3, 139.7, 130.2, 129.4, 128.9, 128.7, 126.3, 121.9, 120.6, 120.2, 116.4, 115.2, 15.6(CH_3), 15.4(CH_3). MS: M+2 358(2.3%) M+1 357(2.1%), M 356 (27.9%).

Tetrazolo[5',4'-b]pyrazolo[3,4-d]pyrimidine (*VI)*
A mixture of ***IV_a*** (0.01 mol) and sodium azide (0.53 g) in 25 ml of DMF was heated under reflux for 6 hours the solvent was removed by distillation and the product that separated was collected, washed well with dilute alcohol and recrystallised from absolute ethanol as yellow crystals mp 133 ºC (35% yield). Calcd. for: $C_{18}H_{12}O_2N_8$ (372) :C, 58.06, H, 3.22; N, 30.107. Found: C, 58.1; H, 3.2; N, 30.1%. IR: 1615 cm^{-1} (ν C=N), 1430 cm^{-1} (ν C=N-N) and 3080 cm^{-1} (ν C-H aromatic). ^{1}H–NMR δppm: 2.79 (s, 3H, CH_3), 7.31-8.25 (m, 9H, Ar–H). ^{13}CNMR δppm: 163.4 (pyrimidine–C), 154.3, 148.4, 144.3 (tetrazole-C), 139.7, 139.2, 129.4, 128.7, 128.4, 126.3, 121.6, 120.2, 115.2 (pyrazole-C), 15.6(CH_3). MS: M+2 374(1.8%), M+1 373(3.0%), M 372 (29.2%).

a) Alkylation with dimethyl sulphate. Formation of *VII*

To a suspension of ***I_a*** (0.01 mol) in aqueous NaOH (10 ml of 10% solution) was added dropwise dimethyl sulphate with occasional shaking while keeping the solution alkaline (by adding excess NaOH) then the mixture was heated on a steam bath for 2hrs. after cooling it was diluted with water then extracted with ether and the ethereal layer was dried over anhydrous $MgSO_4$ then evaporated and the solid that separated was recrystallized from ethanol as ***VII***, mp. 231ºC (yield 61%). Calcd. for $C_{19}H_{15}O_3N_5$ (361). Req.: C, 63.15; H, 4.15; N, 19.35. Found: C, 63.2; H, 4.2; N, 19.4. IR: 1616 cm^{-1} (νC=N), 1668 cm^{-1} (νC=O amide), 3030 cm^{-1} (νC-H ring). ^{1}H–NMR δppm: 1.90 (s, 3H, CH_3), 2.74(s, 3H, N–CH_3), 6.62-8.14 (m, 9H, Ar–H). ^{13}C NMR δppm: 155.3 (N-C=O), 151.8, (N–C=N), 147.9, 146.3, 146.1, 145.0, 130.0, 129.6, 128.9, 127.3, 121.0, 118.9, 116.3, 93.0 (C=N–N), 32.9 (N–CH_3), 18.2(CH_3) MS: M+2$^{+\cdot}$ 363 (1.8%), M+1$^{+\cdot}$ 362(2.0%), M$^{+\cdot}$ 361 (20.2%).

b) With sodium methoxide. 3-Methyl-1-phenyl-4-substituted phenyl pyrazolo [3, 4-d] pyrimidin-6-methyl ether (*VIII)*

A mixture of ***IV_d*** (0.01 mol) and sodium methoxide (0.01 mol, prepared from 0.52 g of sodium metal in 32 ml of methanol) was stirred well and left overnight at room temperature. It was poured into 50 ml of water and the product was collected, washed well with water. Recrystallization from petroleum ether (bp 60-80 ºC) gave *VIII* as brown crystals, mp 101 ºC (60% yield). Calcd. for: $C_{17}H_{15}ON_5$ (305). Req.: C, 66.88; H, 4.91; N, 22.95. Found: C, 66.9; H, 4.9; N, 23.0. IR: 2860, 2930, 2960, 3000 and 3010 cm^{-1} (νC-H ring); methyl CH stretching at 2960, 2850 cm^{-1}, 1600-1498 cm^{-1} (νC= ring stretch), 1247 cm^{-1} (νC-O-C asymmetric), 1040 cm^{-1} (νC-O-C symmetric) and at 1610 cm^{-1} (νC=N, ring). ^{1}H NMR (δppm): 2.53 (s, 3H, CH_3-pyrazolo ring), δ 3.39 ppm (3, 3H, OCH_3), δ 4.91 (s, 1H, NH-cyclic) and δ 7.18-8.15 ppm (m, 8H, Ar-H). ^{13}C NMR δppm: 167.4, 164.6, 164 (N–C–N), 150.1 (–C=N), 147.0, 131.9, 130.0, 118.9, 116.4, 46.9 (OCH_3), 36.3, 23.0 (CH_3).

***N*-[3-Methyl-1-phenyl-4-(2-methoxyphneyl)pyrazolo[3,4-d]pyri-midin-6-yl) amino acids (*$IX_{a,b}$*)**

An aqueous solution of glycine (0.09 mol; 6.9g) or alanine (0.09 mol, 8.0g) dissolved in 5 ml of water and sodium carbonate (0.05 mol) and the pH was adjusted at 9-9.5 then ***I_b*** (0.04 mol) was added gradually while stirring. The reaction mixture was vigorously stirred at 100ºC for 6 hours, adjusted the pH at 9-9.5 then left 12 hours at room temperature. It was acidified with formic acid; the product that separated was collected, washed well with water and recrystallized from ethanol to give ***IX_a*** and ***IX_b*** respectively. ***IX_a***, mp 196 ºC (63% yield). Calcd. for $C_{21}H_{19}O_3N_5$ (389). Req.: C, 64.78; H, 4.88; N, 17.99. Found: C, 64.8; H, 4.9; N, 18.0. IR: 3488 cm^{-1} (νOH), 3432 cm^{-1} (νNH), 2870, 2924, 2950, 3010, 3060 cm^{-1} (νCH) and at 1700 cm^{-1} (νC=O). ^{1}HNMR: δ ppm: 2.79 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.01 (d, 2H, CH_2NH), δ 4.65-4.75 (t, 1H, $NHCH_2$), δ 6.85-8.05 (m, 9H, Ar-H) and at δ 9.3 ppm (s, 1H, COOH). ***IX_b***, m.p. 274ºC in 45% yield. Calcd. for: $C_{22}H_{21}O_3N_5$ (403). Req. C, 65.508; H, 5.21; N, 17.36. Found: C, 65.5; H, 5.2; N, 17.4. IR 3462 cm^{-1} (νOH), 3430 cm^{-1} (νNH), 2870, 2924, 2957, 3013, 3062 cm^{-1} (νC-H) and at 1701 cm^{-1} (νC=O). ^{1}HNMR (δppm):1.23 (d, 3H, CH_3CH), δ 2.79 ppm (s, 3H, CH_3-pyrazoline), δ 3.73 ppm (s, 3H, OCH_3-Ar), δ 3.9 (q, CH-CH_3), δ 4.7 ppm (d, 1H, NH-CH), δ6.71-7.8 ppm (m, 9H, Ar-H); and at δ 11.0 ppm (s, br, 1H, COOH). ^{13}CNMR δppm: 174.9(COOH), 165.7 (pyrimidine–c), 162.1, 157.4, 150.5 (pyrazole–C), 144.3, 139.7, 129.8, 129.4, 128.5, 126.3, 121.6, 120.2, 119.6, 115.2, 114.8, 56.2(OCH_3), 53.1 (C–CH_3–C=O), 17.0 (CH_3–CH), 15.6(CH_3–C–pyrazole). MS: M+2$^{+\cdot}$ 405 (1.8%), M+1$^{+\cdot}$ 404 (2.5%), M$^{+\cdot}$ 403 (389%).

Cyclization of *IXa,b*:Formation of imidazole derivatives *($X_{a,b}$).*

A mixture of compounds ***(IX_a)*** or **(*IX_b*)** (0.01 mol), acetic anhydride (15 ml) and sodium acetate (0.01 mol) was refluxed at 120-130 ºC for 3 hours the product that separated was collected, washed well with water then recrystallized from ethanol as ***$X_{a,b}$***. ***X_a***, mp 220 ºC as red crystals (21% yield). Calcd. for $C_{21}H_{17}O_2N_5$ (371). Req. C, 67.92; H, 4.58; N, 18.86. Found: C, 67.9; H, 4.6; N, 18.9. IR: 2820, 2950, 2990, 3030 cm^{-1} (νC-H), 1640 cm^{-1} (νC=O cyclic amide) and devoid of νNH. ^{1}H NMR: δ 2.5 ppm (s, 3H, CH_3-pyrazoline), δ 3.4 ppm (s, 3H, OCH_3-Ar), δ 5.23 ppm (s, 1H, N-CHCO in imidazolo ring), δ 6.7-7.9 ppm (m, 9H, Ar-H). ^{13}C NMR δppm: 163.0 (C=N–C), 160.5 (C=N–C), 159.0 (N–C=O), 154.4, 147.8 (pyrazole–C), 141.0, 139.7 (N–N=C), 132.1, 130.2, 129.4, 126.3, 122.9, 121.2, 120.2, 114.4, 95.0, 92.3 (N–C(=N)–N), 55.9 (OCH_3), 18.1 (CH_3). MS: M+2 ⁻⁺· 373 (2.5%), M+1 ⁻⁺· 372 (1.8%), M ⁻⁺· 371 (29.8%).

X_b, mp 281 ºC as orange crystals (31% yield). Calcd. for $C_{22}H_{19}O_2N_5$ (385). Req. C, 68.57; H, 4.93; N, 18.18. Found C, 68.6; H, 4.9; N, 18.2. IR: 2827, 2960, 2970, 2993, 3030 cm^{-1} (νCH) and devoid of νNH. ^{1}H NMR: δ 1.25 ppm (d, 3H, CH_3-CH imidazolo), δ 2.5 ppm (s, 3H, CH_3-pyrazoline), δ 3.4 ppm (s, 3H, OCH_3-Ar), δ 3.99ppm (q, 1H, CH-CH_3 in imidazolo ring) and δ 7.1-8.75 ppm (m, 9H, Ar-H). MS: M+1 ⁻⁺· 386 (2.7%); M ⁻⁺· 385 (23.8%).

Cyanoethylation of 3-methyl-1-phenyl-4-(substituted phenyl)-pyrazolo[3,4-d] pyrimidine-6-thione. Formation of *(XI)*

a) Using sodium hydroxide

The thione derivative ***II_a*** (3.6 g, 0.01mol) was finely grounded with solid sodium hydroxide (1.5 g) and then suspended in 8 ml of acrylonitrile. The reaction mixture was maintained at 40-50ºC on a water bath for 10 hrs, then it was diluted with 40 ml of water and the excess of acrylonitrile was removed by distillation. The product that separated was recrystallised from ethanol to give ***XI***, mp 121 ºC (30% yield). Calcd. for: $C_{21}H_{16}O_2N_6S$ (416). Req.: C, 60.55; H, 3.84; N, 20.15; S, 7.65. Found: C, 60.6; H, 3.8; N, 20.2; S, 7.70%. IR: 2828, 2950, 2990, 3010 cm^{-1} (νC-H), 2210 cm^{-1} (νC=N), 1214 cm^{-1} (νC=S) and 670 cm^{-1} (νNO_2).^{13}C NMR δppm: 177.0 (N–C=S), 159.0 (C=N–N) 151.8 (N–C=N), 147.9 (C=N–N), 147.6, 146.3, 140.4, 129.6, 127.3, 121.0, 118.8, 117.7 (C≡N), 116.3, 91.0, 47.3 (CH_2–CN), 18.2 (CH_3). 17.3 (CH_2–CH_2).

b) Using anhydrous potassium carbonate.

A mixture of ***II_a*** (0.01 mol) in 50 ml of dry acetone containing (0.05 mol) of anhydrous K_2CO_3 and acrylonitrile (0.015 mol, 8 ml) was heated on a steam bath for 36 hrs then filtered while hot, and the excess solvent was removed (reduced pressure). The product was diluted with water, collected and recrystallised from benzene as ***XI*** (mp and mixed mp measurements showed no depression) MS: M+3 ⁻⁺· 419 (1.1%), M+2 ⁻⁺· 418(4.5%), M+1 ⁻⁺· 417 (22.7%), M ⁻⁺· 416 (31.8%).

Hydroxyethylation of 3-methyl-1-phenyl-4-(substitutedphenyl)-pyrazolo[3,4-d]pyrimidin-6-thiones (*$XII_{a,b}$*).

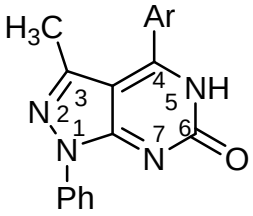
Compound (***II_a*** *or* ***II_b***) (0.01 mol) suspended in 30 ml of acetic acid was cooled to 0-5 ºC, then treated dropewise with 10 ml of ethylene oxide while cooling. The reaction mixture was kept at 5 ºC while stirring with a magnetic stirrer then left for 48 hrs. The solvent was removed (reduced pressure) and the residue was diluted with water then neutralized with ammonia. The product that separated was collected, washed well and recrystallized from ethyl acetate as ***XII_a*** and ***XII_b***.

XII$_a$, mp 170 ºC (23% yield). Calcd. for $C_{21}H_{19}O_3N_5S$ (421). Req. C, 59.85; H, 4.51, N; 16.62; S, 7.6. Found C, 59.9; H, 4.5; N, 16.6; S, 7.6. IR: 3460 cm^{-1} (ν OH), 2860, 2880, 2970, 2990, 3030 cm^{-1} (νC-H ring), 1248 cm^{-1} (νC=s). ^{1}H–NMR δppm: 0.99(s, 3H, CH_3), 2.45 (q, 2H, CH_2), 2.74 (q, 2H, CH_2), 3.53 (q, 2H, CH_2), 6.71-8.14 (m, 9H, Ar–H), 11.10(q, 1H, OH)

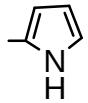
XII$_b$, mp 138 ºC (21% yield). Calcd. for $C_{22}H_{22}O_2N_4S$ (406). Req. C, 65.02; H, 5.41; N, 13.79; S, 7.88. Found: C, 65.0; H, 5.4; N, 13.8; S, 7.9. IR: 3466 cm^{-1} (νOH), 2877, 2920, 2989, 3030 cm^{-1} (νC-H ring), 1244cm^{-1} (νC=S). ^{1}H NMR δppm: 1.01 (s, 3H, CH_3), 2.45 (dd, 2H, CH_2), 2.65(dd, 2H, CH_2), 3.25 (dd, 2H, CH_2), 3.73(s, 3H, OCH_3), 6.46-7.19 (m, 9H, Ar–H), 10.09 (t, 1H, OH). ^{13}C NMR δ ppm: 177.0 (N–C=S), 158.0 (C=N–N), 157.7, 151.8, 147.9, 146.3, 129.6, 129.0, 127.4, 121.0, 118.8, 116.3, 114.2, 107.2, 91.0, 61.0 (CH_2–OH), 56.3 (OCH_3), 46.6 (CH_2), 30.5 (CH_2CH_2), 18.4(CH_3). MS: M+3$^{+\cdot}$ 409(1.1%), M+2$^{+\cdot}$ 408(2.7%), M+1$^{+\cdot}$ 407 (23.8%), M$^{+\cdot}$ 406(47.91%)

RESULTS AND DISCUSSION

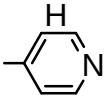
Compounds of type **(*I*)** were subjected to thionation and the resulting acid labile products ***(II)***, as well as the parent compounds ***(I)***, were found to be highly active against penicillium chrysogenum and mucor pasillius in animals and men[13].



(Ia-e)

a, Ar = $C_6H_4NO_2^{-2}$ **d**, Ar = 

b, Ar = $C_6H_4OCH_3^{-2}$

c, Ar = $C_6H_4OH^{-2}$ **e**, Ar = 

The pyrazolo[3,4-d]pyrimdin-6-ones ***(I$_{a-e}$)*** have shown a dynamic keto-enol equilibrium. This phenomenon allowed ***I$_{a-e}$*** to be attacked by a variety of nucleophiles, as well as an interesting series of interconversions.

Thus, starting with the premise that the exotic combination of groups obtainable from thionation of ***(I)*** may lead to the possibility of encountering an altered spectrum of reactivity, a series of five 3-methyl-1-phenyl-4-substituted pyrazolo[3,4-d]pyrimidin-6-thiones ***(II$_{a-e}$)*** were prepared according to procedure described by Abd El-Ghaffar and co-workers[13]. Compared to their oxo analogues ***(I$_{a-e}$)***, compounds **(IIa-e)** were found to be more stable and less reactive (c.f. Chart 1).

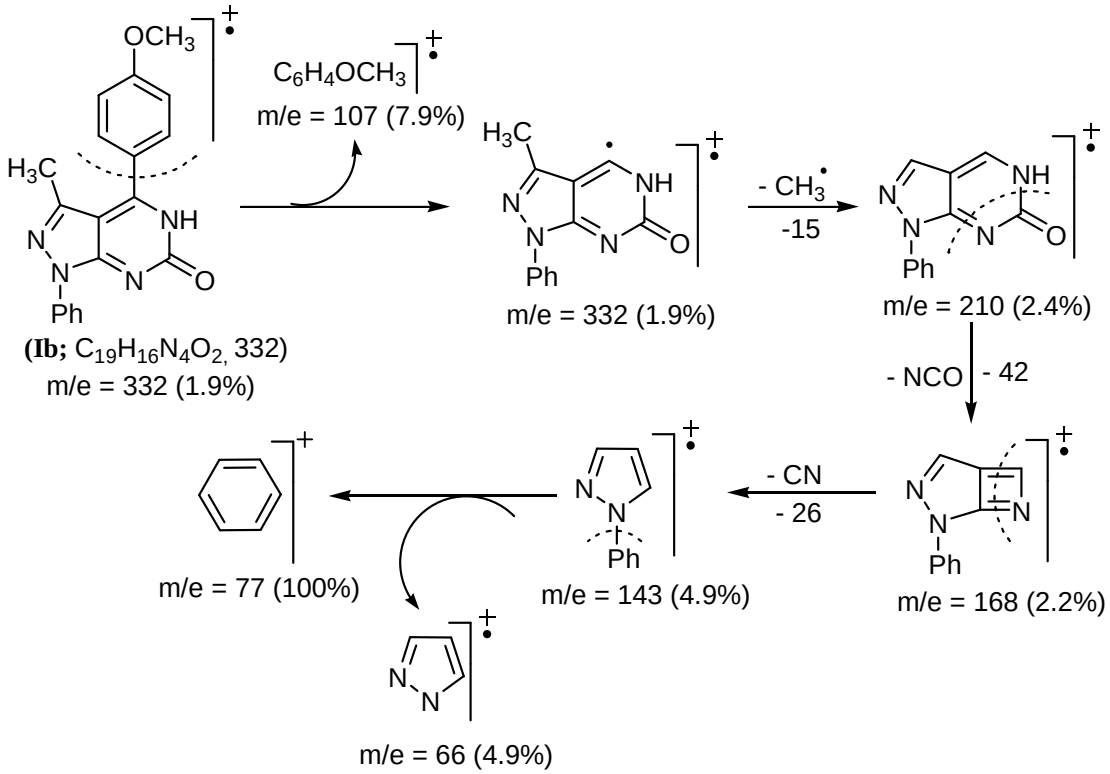


Chart 1

The molecular ion of compound IIb has shown its m/e 332(1.9%) on fragmentation it gave two molecular ions m/e 332(1.9%)of $C_{12}H_9N_4O$ and other fragment of m/e 107(7.9%) of C_7H_7O then it gave a molecular ion peak of $C_{12}H_9N_4O$-CH_3 of m/e 210(2.4%) followed by loss of isocyanate radical of m/e 42 to give the molecular ion of $C_{10}H_6N_3$ with m/e 168(2.2%) which loses a cyano fragment of m/e 26 to give a molecular ions one $C_9H_7N_2$ with m/e 143(4.9%) which gives two molecular ion one the phenyl radical of m/e 77(100%) (base peak) and the pyrazole radical of m/e 66 for $C_3H_2N_2$.

It is well known that addition of nucleophiles to pyrazolo-[3,4-d]pyrimidines at position 4 is easier than position 6 [17-19]. Thus, nucleophilic displacement by nitrogen nucleophiles at position 6 necessarily needs higher reaction temperature and prolonged reaction time. Thus, compounds **(I_{a-e}),** and the 6-chloro derivatives **(IV_{a-c})** were subjected to aminolysis and hydrazinolysis in boiling ethanol, benzene and/or xylene with various aliphatic, aromatic, amines, and heterocyclic amines namely, as well as hydrazines, such as hydrazine hydrate, phenyl hydrazine, 4-nitrophenyl hydrazine, 2,4-dinitrophenyl hydrazine, thiosemicarbazide and/or semicarbazide to give the corresponding 6-amino-3-methyl-1-phenyl-4-substituted **(III_{a-m})**, 6-hydr-azino-3-methyl-1-phenyl-4-substituted**(III_{n-u})**,3-methyl-1-phenyl-4-substituted-6-thiocarbamoyl **(III_v)**, and 6-carbam-oyl-(**III_w**), pyrazolo[3,4-d]pyrimidines respectively.

A comparison of the IR spectra of **I_{a-e}, II_{a-e}** and **III_{a-w}** has shown considerable differences. Compounds **(Ia-e)** revealed the presence of νC=O band as a sharp peak in the region 1700-1680 cm^{-1} and νNH/OH in the region 3444-3240cm^{-1}, while for compounds **(II_{a-e})**, revealed the presence of νC=S in the region 1249-1240 cm^{-1} and a weak νSH in the region 2600-2565 cm^{-1}. However, compounds **(III_{a-w})**, revealed the presence of νNH in the region 3448, 3260-3320, 3130 cm^{-1}, νC=N cyclic in the region 1620-1602 cm^{-1} and νC=C ring in the region 1606-1589 cm^{-1}.

The structure of compounds ***(III_{a-w})*** was further proved by their preparation in a stepwise fashion. Thus, ***Ia-e*** were treated with $PCl_5/POCl_3$ on a steam bath to give 6-chloro-3-methyl-1-phenyl-4-substituted pyrazolo[3,4-d]pyrimidines***(IV_{a-e})*** respecti-vely. When ***IV_{a-c}*** were treated with primary amines as well as hydrazines in boiling ethanol they yielded the corresponding 6-amino ***($III_{a,b}$*** and ***g)*** and the 6-hydrazino***(III_{n-p}*** and ***III_t)*** derivatives respectively. They were identified via melting point and mixed melting point measurements).

The mass spectrum of III $_p$ has taken its fragmentation pattern via two paths:

path (a) in which a loss of CH_3 radical to give the molecular ion $C_{24}H_{18}N_7O_3$ with m/e 452(10%) which looses another free radical of m/e15 to give a molecular ion of m/e 438(27%) then two fragments of C_6H_6O (m/e 94, 20.8%) and $C_{17}H_{13}N_7O_2$ m/e 347 (65 %) then two molecular ions of m/e 77(100%) (base peak) and m/e 270 (27%) of C11H8N7O2. The molecular ion of $C_{11}H_8N_6$ m/e 224 (23%) gave three fragments of C_5H_5 m/e 65(13.4%), m/e52 (55%) and $C_5H_2N_5$ m/e 132 (76%).

The latter fragment was readily obtained from the former molecular ion of $C_{24}H_{18}N_7O_3$ by a loss of the radical $C_6H_5N_2O_2$ m/e 137(13.2%) C_6H_6O m/e 94 (20.8%) and the base peak C_6H_5 m/e 77 (100%). The path (b) on fragmentation gave the following fragments: C_2H_3N m/e55 (63%), C_6H_5 m/e 77(100%), C_6H_6O m/e 94 (20.8%) and a fragment of m/e 236 which was $C_{10}H_8N_5O_2$ (1.2%) which gave the molecular ion of m/e 132(7.6%) and loses $C_6H_5NH_2$ m/e 93(34%) and O_2(c.f.Chart 2).

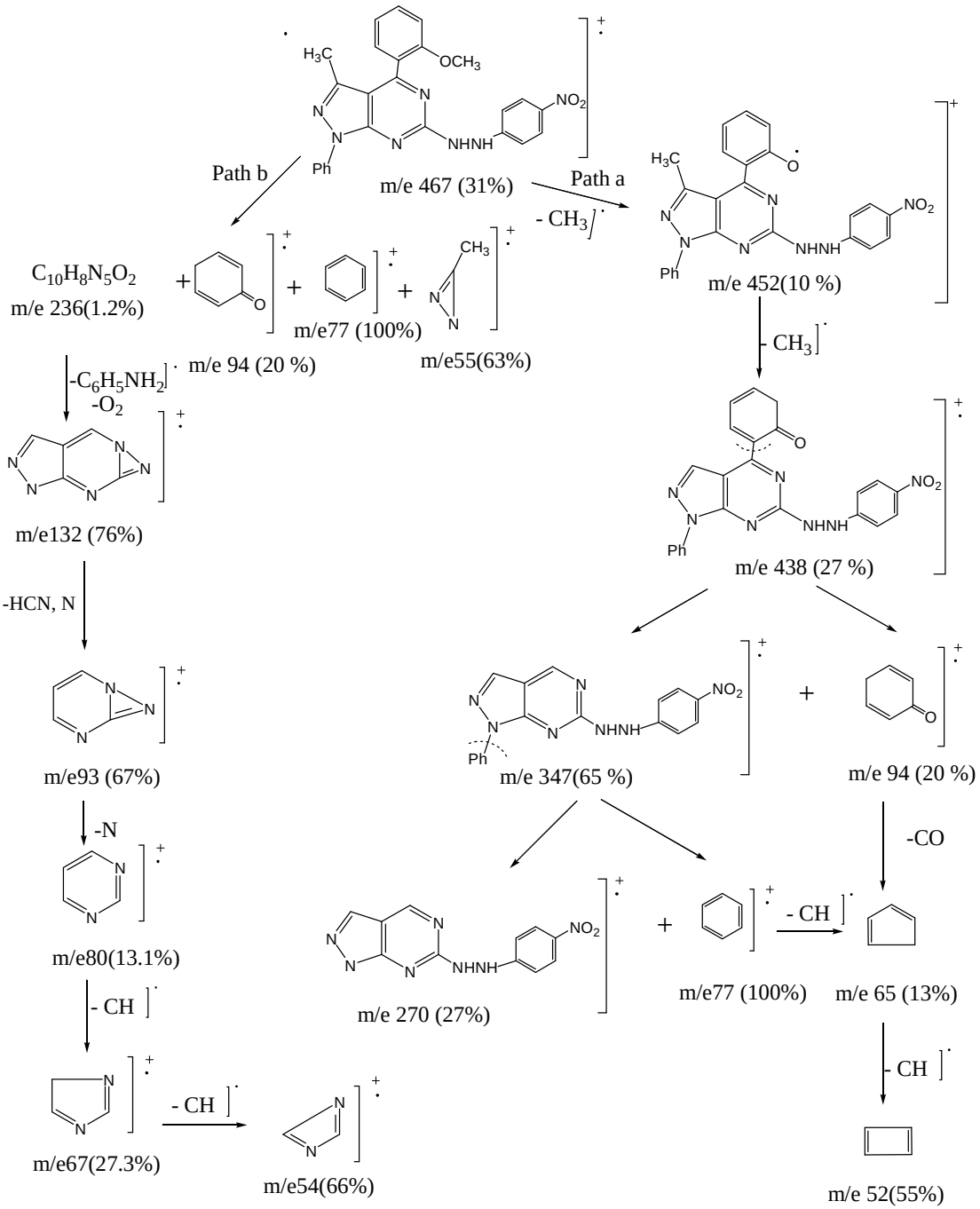


Chart 2

Treatment of compound ***(IVa)*** with acetylhydrazine in boiling *n*-butanol affected cyclization to the corresponding triazolo-[4', 3'-b] pyrazolo [3,4-d]pyrimidine ***(V_a)***; whereas compound ***(V_b)*** was achieved by thionation of ***I_c*** followed by treatment of the thio product with acetylhydrazine in boiling *n*-butanol (long period).

The reaction of ***IVa*** with sodium azide in refluxing DMF yielded a product identified as tetrazolo[5',4'-b]pyrazolo[3,4-d]-pyrimdine ***(VI)***.

Alkylation of ***Ia*** with dimethyl sulphate in aqueous NaOH afforded the corresponding *N*-methyl derivative ***(VII)***. The site of alkylation was determined by comparison of its IR spectrum with that of 6-methoxy-3-methyl-1-phenyl-4-substituted pyrazolo-[3,4-d]pyrimidine ***(VII)*** obtained

by treatment of ***IVc*** with sodium methoxide in methanol (Scheme 1). The IR spectrum of ***VII*** revealed the presence of νC=O at 1668 cm^{-1} an intense peak at 1620 cm^{-1} for νC=N, and absence of υC=O.

The behaviour of 6-chloropyrazolo [3,4-d]pyrimidine ***(IV$_b$)*** towards amino acids was also investigated. Thus, the reaction of ***IV$_b$*** with the sodium salt of glycine and/or alanine under reflux at pH adjusted (9-9.5) afforded the corresponding *N*-[3-methyl-1-phenyl-4-(-4-methoxyphenyl) pyrazolo[3,4-d]pyrimidin-6-yl) amino acids ***(IX$_{a,b}$)*** respectively.

Compounds **(*IX*$_{a,b}$)** were cyclized by acetic anhydride in the presence of anhydrous sodium acetate to give the corresponding pyrazolo[3,4-d]imidazolo[3',2'-b]pyrimidines **(*X*$_{a,b}$)** via dehydration of one molecule of water and internal cyclization.

Unlike other azaheterocyclic systems as pyrazoles [20], thia-zoles [21] or pyri-midinethiones [22] where a lot of work has been done on cyanoethylation, the pyrazolo [3, 4-d] pyrimdinethiones have not been studied in this regard. Attempted cyanoethylation of ***II$_a$*** with acrylonitrile in aqueous ammonium chloride [23] or in alkaline solution [24] was not successful, however, a finely ground mixture of ***II$_a$*** and anhydrous potassium carbonate, with acrylonitrile [25] in dry acetone yielded the required cyanoethylated products ***(XI)*.**

The pyrazolo [3,4-d] pyrimidin-6-thiones **(*II*$_{a,b}$)** were also condensed with ethylene oxide to affect hydroxyethylation at the 5-position. Reaction at 5ºC for 48 horsr of ***II$_{a,b}$*** dissolved in glacial acetic acid with ethylene oxide[(25)] gave the corresponding 5-hydroxy ethyl-pyrazolo[3,4-d]pyrimidin-6-thione **(*XII*$_{a,b}$)**.

The IR absorption bands at 3460 cm^{-1} and 3620 cm^{-1} in their IR spectra were assigned to the hydroxy stretching vibrations while the bands at 1448 cm^{-1} and 1219 cm^{-1} could only be compatible with a thione structure.

CONCLUSION

It can be concluded from this work that the introduction of nucleophiles at position-6 which well known to be difficult of the pyrazolo pyrimidine ring system was easier in case of the presence of a highly electronegative atoms (such as O,S,or halogen)via nucleophilic displacement.

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