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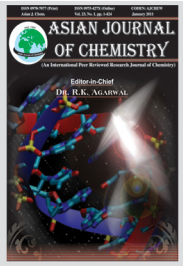

Synthesis of Some N-Alkylated and 1,2,4-Triazole, 1,3,4-Oxa-, Thiadiazoles Containing 1*H*-Pyrazolo[3,4-b]pyridine Derivatives

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N-Furan-2-yl-methylidene-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-3-amine was prepared and alkylated, with the appropriate halo-compounds, to afford N-alkylated products. The hydrazide formation was converted into the key intermediate thiosemicarbazide which undergo the cyclization reactions under acidic and basic conditions, to give 1,2,4-triazole, 1,3,4-oxa- and thiadiazole derivatives. Condensation of the hydrazide with monosaccharide aldoses gave the corresponding sugar hydrazones, which readily undergo the cyclization reaction, on treatment with acetic anhydride, to afford the oxadiazoline derivatves. The synthesized compounds have been characterized by spectral and elemental analysis.

Key Words: Pyrazolopyridine, Thiosemicarbazide, Cyclization, Condensation, 1,2,4-Triazole, 1,3,4-Thiadiazole, 1,3,4-Oxadiazoline.

INTRODUCTION

1*H*-Pyrazolo[3,4-b]pyridines comprise a very interesting class of compounds because of their significant and versatile biological and pharmacological activities, such as antimalarial[1], antiproliferative[2], antimicrobial[3-5], inhibition of cyclin-dependent kinases[6] and cardiovascular[7-9], antiviral[10-12] and antileishmanial[13] activities.

Pyrazole fused pyridines and pyrimidines are known to posses a wide range of biological activity. Specifically pyrazolopyridines exhibit antitubercular, anxiolytic[14]. It has been reported that, certain compounds bearing 1,3,4-oxa-, thiadiazole and 1,2,4-triazole nucleus possess significant anti-inflammatory activity[15,16]. In view of these reports and in continuation of our recent work on the pyrazolo[3,4-b]pyridine derivatives, to synthesize a new heterocyclic compounds[17,18], we reported here the synthesis of a number of new alkylated 4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridine-3-amine and formation of 1,2,4-triazoles, 1,3,4-oxadiazole, 1,3,4-thiadiazoles and oxadiazolines derivative linked with N-furan-2-yl-methylidene]-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-3-amine.

EXPERIMENTAL

Melting points were determined on a Buchi melting point. NMR spectra were recorded at 300 MHz for ^{1}H NMR, 75.5 MHz for ^{13}C NMR on a Varian Germini-2000 (300 MHz) and registered in DMSO-d_6 and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were measured on a Kratos 50 tc spectrometers. Microanalysis performed in microanalysis lab at Cairo University. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedure. All reactions were monitored by TLC, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (254 and 360 nm) for detection.

N-(Furan-2-yl-methylene)-4,6-dimethyl-1*H*-pyrazolo-[3,4-b]pyridin-3-amine (2): To a solution of 3-amino-pyrazolopyridine (**1**) (0.58 g, 3.6 mmol) in acetonitrile (10 mL), furan-2-carbaldehyde (5.25 g, 5.47 mmol) and a catalytic amount of acetic acid was added and the reaction mixture was stirred for 5 h at room temperature. Acetonitrile was removed under vacuum and the reaction mixture was diluted with cold water. The separated solid was collected by filtration, washed with water and dried. The crude product was recrystallized from ethanol to afford the pale yellow powder of compound **2** (0.75 g, 87 %), m.p. 127-129 ºC. IR (KBr, ν_{max}, cm^{-1}): 3106 (NH), 2923, 2853 (CH aliphatic), 1596 (C=N). ^{1}H NMR ($CDCl_3$), δ, ppm: 2.70 (3H, s, CH_3), 2.79 (3H, s, CH_3), 6.57 (1H, s, H-5), 6.77 (1H, dd, J = 3.5 and J =1.7 Hz, furyl-H), 7.20 (1H, d, J = 3.3 Hz, furyl-H), 8.036 (1H, d, J = 1.7, furyl-H), 8.93 (1H, s, N=CH), 12.13 (1H, bs, NH). Mass spectrum, m/z (I, %): 241 [M$^+$+1] (35), 240 [M$^+$] (100), 161 (70), 131 (16). Found, %: C 64.81; H 4.95; N 23.18. $C_{13}H_{12}N_4O$ Calculated, %: C 64.99; H 5.03; N 23.32.

Alkylation of N-(furan-2-yl-methylene)-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-3-amine (3-5): (General method): To a stirred suspension of **2** (1.20 g, 5 mmol) in dry DMF (10 mL), K_2CO_3 (1.04 g, 7.5 mmol) and the appropriate halo-compound (7.5 mmol) ethyl chloroacetate, chloroaceto-nitrile and/or 2-bromoethyl acetate was added dropwise. The reaction mixture was stirred at room temperature for an additional 13 h and then poured into the ice cold water with stirring. The obtained solid product was collected by the filtration, washed with water and recrystallized from ethanol to afford the pale yellow crystals of compound **3-5** (Tables 1 and 2).

2-(3-(Furan-2-yl-methyleneamino)-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-1-yl)ethanol (6): A mixture of **5** (1.30 g, 4 mmol), methanol (30 mL) and concentrated aqueous ammonia (25 %, 30 mL) was stirred at room temperature for 24 h. The solvent was evaporated *in vacuo* and the residue was triturated with a small volume of ethanol. A yellow precipitate was collected by filteration, dried and recrystallized from methanol to give compound **6** (0.82 g, 73 %). mp 170-172 ºC. IR (KBr, ν_{max}, cm^{-1}): 3261 (OH), 2922, 2849 (CH aliphatic), 1593 (C=N). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.43 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.33 (2H, t, *J* = 7.5 Hz, $HOCH_2CH_2$) 4.21 (2H, t, *J* = 7.5 Hz, $HOCH_2CH_2$), 4.65 (1H, bs, OH), 6.32 (1H, s, H-5), 6.67 (1H, dd, *J* = 7.1 and 2.2, furyl-H), 6.91 (1H, d, *J* = 2.2, furyl-H),7.18 (1H, d, *J* = 2.2, furyl-H), 8.44 (1H, s, N=CH). ^{13}C NMR (DMSO-d_6), δ, ppm: 18.81, 20.01 (2 CH_3), 45.45, 57.42 ($2CH_2$), 102.12, 112.05, 118.54, 122.15, 144.06, 145.14, 149.09, 150.32, 154.17, 158.11. Mass spectrum, m/z (I, %): 285 [M^++1] (2), 284 [M^+] (6), 164 (3), 206 (13), 175 (100). Found %: C 63.22; H 5.42; N 19.61. $C_{15}H_{16}N_4O_2$ calculated, %: C 63.37; H 5.67; N 19.71.

N-(Furan-2-yl-methylidene)-1-(2-hydrazinylethyl)-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-3-amine (7): To a suspension of ester **5** (0.65 g, 2 mmol) in ethanol (15 mL), an excess of hydrazine hydrate (4 mL) was added. The reaction mixture was refluxed for 4 h, cooled, the solid product was collected by filteration, deried and recrystallized from methanol to give the pale yellow crystals of compound **7** (0.32 g, 54 %). m.p. 150-152 °C IR (KBr, ν_{max}, cm^{-1}): 3343-3202 ($NHNH_2$), 2938, 2892 (CH aliphatic), 1589 (C=N). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.45 (3H, s, CH_3), 2.51 (3H, s, CH_3), 3.21 (2H, t, *J* = 7.5, NH-CH_2CH_2), 3.86 (2H, m, $NHCH_2CH_2$), 4.87 (2H, bs, NH_2), 6.19 (1H, s, H-5), 6.57 (1H, dd, *J* = 3.4 and 1.4, furyl-H) 7.08 (1H, d, *J* = 1.4, furyl-H), 7.32 (1H, d, *J* = 1.4, furyl-H), 8.51 (1H, s, N=CH), 9.16 (1H, bs, NH). Mass spectrum, m/z (I, %): 298 [M^+] (8), 252 (25), 219 (23), 175 (100). Found, %: C 60.23; H 5.92; N 28.09. $C_{15}H_{18}N_6O$ calculated, %: C 60.39; H 6.08; N 28.17.

2-[3-(Furan-2-yl-methylidene)amino]-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-1-yl)acetohydrazide (8): A mixture of pyrazolopyridine ester (**3**) (2.11 g, 6.5 mmol) and $N_2H_4{\cdot}H_2O$ (1.25 g, 25 mmol) in ethanol (20 mL) was heated under reflux for 6 h. The excess of ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol and recrystallized from methanol to give a white powder of compound **8** (1.86 g, 92 %), m.p. 236-238 °C. IR (KBr, ν_{max}, cm^{-1}): 3298-3428 ($NHNH_2$), 3184-3046 (CH aromatic), 2978, 2918 (CH aliphatic), 1655 (CONH), 1632 (C=N). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.43 (3H, s, CH_3), 2.49 (3H, s, CH_3), 4.88 (2H, s, NCH_2), 5.14 (2H, bs, $NHNH_2$), 6.71 (1H, s, H-5), 7.33 (1H, d, *J* = 6.0 Hz, furyl-H), 7.55 (1H, d, *J* = 6.0 Hz, furyl-H), 7.98 (1H, bs, furyl-H), 8.41 (1H, s, N=CH), 10.14 (1H, bs, CONH). Mass spectrum, m/z (I, %): 313 [M^+ + 1] (5), 312 [M^+] (16), 232 (51), 201 (7), 159 (100). Found, %: C 57.83; H 5.29; N 26.98. $C_{15}H_{16}N_6O_2$ calculated, %: C 57.68; H 5.16; N 26.91.

2-(2-(3-Furan-2yl-methyleneamino)-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridine-1-yl)acetyl)-N-phenylhydrazine-carbothioamide (9): To a suspension of **8** (3.12 g, 10 mmol) in absolute ethanol (20 mL), PhNCS (1.35 g, 10 mmol) was added. The reaction mixture was heated under reflux for 2 h. The product that separated on cooling was filtered off, washed with ethanol and dried and recrystallized from methanol to give a colourless crystals of compound **9** (4.20 g, 94 %), m.p. 119-121 °C. IR (KBr, ν_{max}, cm^{-1}): 3336-3244 (NH), 4035 (CH aromatic), 2978, 2886 (CH aliphatic), 1697 (CONH), 1593 (C=N), 1195-1130 (C=S). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.55 (3H, s, CH_3), 2.68 (3H, s, CH_3), 4.95 (2H, s, CH_2CO), 6.98 (1H, s, H-5), 7.34 (1H, dd, *J* = 3.5 and 1.5 Hz, furyl-H), 7.77 (1H, d, *J* = 1.5 Hz, furyl-H), 7.93-8.54 (7H, m, furyl-1H, NH, ph), 8.77 (1H, s, N=CH), 9.07 (1H, bs, CSNH), 10.43 (1H, bs, CONH). Mass spectrum, m/z (I, %): 448 [M^+ + 1] (2), 447 [M^+] (6), 351 (26), 312 (100), 276 (24), 175 (100). Found, %: C 60.11; H 4.88; N 22.07. $C_{22}H_{21}N_7O_2S$ calculated, %: C 59.05; H 4.73; N 21.91.

5-((3-(Furan-2-yl-methyleneamino)-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-1-yl)methyl)-N-phenyl-1,3,4-thiadiazol-2-amine (10): The phenylhydrazinecarbothio-

TABLE-1
CHARACTERIZATION AND PHYSICAL DATA OF COMPOUNDS **3-5**, **14a-d** AND **15a-c**

Compound	m.f.	Elemental analysis (%): Found (calcd.)			m.p. (ºC)	Yield (%)
		C	H	N		
3	$C_{17}H_{18}N_4O_3$	62.41 (62.57)	5.33 (5.56)	17.10 (17.17)	96-98 (Ethanol)	92
4	$C_{15}H_{13}N_5O_3$	64.39 (64.51)	4.42 (4.69)	24.89 (25.07)	110-112 (Ethanol)	86
5	$C_{17}H_{18}N_4O_3$	62.44 (62.57)	5.40 (5.56)	17.11 (17.17)	120-121 (Ethanol)	82
13a	$C_{21}H_{26}N_6O_7$	53.23 (53.16)	5.33 (5.52)	17.63 (17.71)	259-261 (DMF)	65
13b	$C_{21}H_{26}N_6O_7$	53.12 (53.16)	5.67 (5.52)	17.87 (17.71)	282-284 (DMF)	52
13c	$C_{20}H_{24}N_6O_6$	54.13 (54.05)	5.66 (5.44)	18.82 (18.91)	266-268 (DMF)	59
13d	$C_{20}H_{24}N_6O_6$	53.98 (54.05)	5.34 (5.44)	19.03 (18.91)	273-274 (DMF)	52
14a	$C_{33}H_{38}N_6O_{13}$	54.75 (54.54)	5.27 (5.42)	11.32 (11.56)	144-146 (Methanol)	71
14b	$C_{33}H_{38}N_6O_{13}$	54.41 (54.54)	5.18 (5.27)	11.73 (11.56)	161-163 (Methanol)	64
14c	$C_{30}H_{34}N_6O_{11}$	54.97 (55.04)	5.11 (5.24)	12.44 (12.84)	155-157 (Methanol)	74

TABLE-2
SPECTRAL DATA OF COMPOUNDS **3-5**, **14a-d** AND **15a-c**

Compd.	IR (KBr, ν_{max}, cm^{-1})	^1H NMR δ, ppm (*J*, Hz)	MS, m/z (I, %)
3	2965, 2929 (CH aliphatic), 1742 (COOEt), 1589 (C=N)	1.25 (3H, t, J = 7.0 Hz, CH_3CH_2), 2.55 (3H, s, CH_3), 2.65 (3H, s, CH_3), 4.41 (2H, q, *J* = 7.0, CH_3CH_2), 4.95 (2H, s, N-CH_2), 6.60 (1H, s, H-5,), 6.79 (1H, dd, *J* = 3.3 and *J* = 1.5 furyl-H), 7.33 (1H, d, *J* = 1.5, furyl-H), 8.22 (1H, d, *J* = 1.5, furyl-H), 8.77 (1H, s, N=CH)	326 [M^+] (35), 281 (100), 240 (31), 131 (10)
4	2957, 2921 (CH aliphatic), 2219 (CN), 1590 (C=N)	2.66 (3H, s, CH_3), 2.69 (3H, s, CH_3), 4.65 (2H, s, N-CH_2), 6.33 (1H, s, H-5), 6.71 (1H, t, *J* = 1.4, furyl-H), 7.53 (1H, d, *J* = 1.4, furyl-H), 7.77 (1H, d, *J* = 1.5, furyl-H), 8.81 (1H, s, N=CH)	280 [M^+ + 1] (100), 279 [M^+] (60), 201 (15), 174 (13), 118 (16).
5	2956, 2925 (CH aliphatic), 1725 ($OCOCH_3$), 1590 (C=N)	2.61 (3H, s, CH_3), 2.64 (3H, s, CH_3), 2.91 (3H, s, $OCOCH_3$), 3.65 (2H, t, *J* = 7.5, OCH_2CH_2) 4.33 (2H, t, *J* = 7.5, OCH_2CH_2), 6.41 (1H, s, H-5), 6.77 (1H, dd, *J* = 3.5 and *J* = 1.5, furyl-H), 7.23 (1H, d, *J* = 1.5, furyl-H), 7.33 (1H, d, *J* = 1.5, furyl-H), 8.75 (1H, s, N=CH)	327 [M^+ + 1] (51), 326 [M^+] (100), 294 (20), 265 (12), 221 (10), 141 (33)
13a	3460-3350 (OH), 3210 (NH), 2944-2921 (CH aliphatic), 1632, 1567 (C=N)	2.63 (3H, s, CH_3), 2.65 (3H, s, CH_3), 3.41-4.21 (4H, m, alditoyl-H), 3.99-4.11 (5H, bs, 5 OH), 5.06 (2H, s, N-CH_2), 5.21 (2H, bs, CH_2OH), 6.74 (1H, s, H-5), 7.87 (2H, dd, *J* = 7.6 and 1.8, furyl-H), 8.12 (1H, d, *J* = 1.4, furyl-H), 8.45 (1H, s, N=CH), 8.72 (1H, s, N=CH-furan), 8.93 (1H, bs, NH)	475 [M^+ + 1] (4), 474 [M^+] (10), 225 (2), 155 (3), 175 (41), 110 (100)
13b	3360-3280 (OH), 3247 (NH), 2940-2933 (CH aliphatic), 1647, 1589 (C=N)	2.59 (3H, s, CH_3), 2.66 (3H, s, CH_3), 3.54-4.32 (4H, m, alditoyl-H), 4.43-4.56 (5H, bs, 4 OH), 4.86 (2H, s, N-CH_2), 5.42 (2H, bs, CH_2OH), 6.55 (1H, s, H-5), 6.72 (1H, dd, *J* = 3.3 and 1.4, fury-H), 7.55 (1H, d, *J* = 1.4, furyl-H), 7.66 (1H, d, *J* = 1.5, furyl-H), 7.81 (1H, s, N=CH), 8.16 (1H, s, N=CH-furan), 8.75 (1H, bs, NH)	475 [M^+ + 1] (3), 444 [M^+] (100), 225 (2), 155 (3), 175 (41)
13c	3360-3280 (OH), 3247 (NH), 2940-2933 (CH aliphatic), 1647, 1589 (C=N)	2.59 (3H, s, CH_3), 2.66 (3H, s, CH_3), 3.54-4.32 (3H, m, alditoyl protons), 4.43-4.56 (4H, bs, 4 OH), 4.86 (2H, s, N-CH_2), 5.42 (2H, bs, CH_2OH), 6.55 (1H, s, H-5), 6.72 (1H, dd, *J* = 3.5 and 1.5, fury-H), 7.55 (1H, s, furyl-H), 7.66 (1H, d, *J* = 1.4, furyl-H), 7.81 (1H, s, N=CH), 8.16 (1H, s, N=CH-furan), 8.75 (1H, bs, NH)	445 [M^+ + 1] (3), 444 [M^+] (100), 225 (2), 155 (3), 175 (41)
13d	3459-3360 (OH), 3242 (NH), 2933-2922 (CH aliphatic), 1643, 1577 (C=N)	2.55 (3H, s, CH_3), 2.61 (3H, s, CH_3), 3.61-4.22 (3H, m, alditoyl-H), 4.42-4.57 (4H, bs, 4 OH), 4.84 (2H, s, N-CH_2), 5.39 (2H, bs, CH_2OH), 6.56 (1H, s, H-5), 6.77 (1H, dd, J= 3.3 and *J* = 1.4 furyl-H). 6.94 (1H, d, *J* = 1.4, furyl-H), 7.59(1H, d, *J* = 1.4, furyl-H), 7.88 (1H, s, N=CH), 8.20 (1H, s, N=CH-furan), 8.77 (1H, bs, NH).	445 [M^+ + 1] (12), 444 [M^+] (60), 225 (10), 155 (26), 175 (100).
14a	2925-2919 (CH aliphatic), 1755 (OAc), 1675-1630 (NCO, C=N)	1.91, 1.94, 1.95, 1.98, 2.12 (15H, s, 5 $OCOCH_3$), 2.39 (3H, s, CH_3), 2.41 (3H, s, CH_3), 3.65 (3H, s, N-$COCH_3$), 4.41-5.08 (4H, m, alditoyl-H), 5.19 (2H, s, N-CH_2), 5.22 (2H, d, *J* = 7.2 Hz, CH_2OAc), 6.23 (1H, s, O-CHR^1-N), 6.65 (1H, s, H-5), 6.85 (1H, dd, *J* = 7.6 and *J* = 1.8, furyl-H), 7.46 (1H, d, *J* = 1.8, furyl-H), 7.55 (1H, d, *J* = 1.8, furyl-H), 7.68 (1H, s, N=CH)	727 [M^+ + 1] (3), 726 [M^+] (30), 225 (100)
14b	2930-2922 (CH aliphatic), 1745 (OAc), 1671-1625 (NCO, C=N)	1.89, 1.90, 1.93, 1.96, 2.11 (15H, s, 5 $OCOCH_3$), 2.41 (3H, s, CH_3), 2.51 (3H, s, CH_3), 3.62 (3H, s, N-$COCH_3$), 4.39-5.12 (4H, m, alditoyl-H), 5.17 (2H, s, N-CH_2), 5.09 (2H, d, *J* = 7.2 Hz, CH_2OAc), 6.24 (1H, s, O-CHR^1-N), 6.66 (1H, s, H-5), 7.03 (1H, dd, J= 7.7 and *J* = 1.8, furyl H), 7.43 (1H, d, *J* = 1.8, furyl-H), 7.68 (1H, d, *J* = 1.8, furyl-H), 7.75 (1H, s, N=CH)	727 [M^+ + 1] (10), 726 [M^+] (32), 451 (16), 340 (21), 225 (100)
14c	2940-2898 (CH aliphatic), 1756 (OAc), 1665-1621 (NCO, C=N)	1.85, 1.88, 1.96, 2.06 (12H, s, 4 $OCOCH_3$), 2.51 (3H, s, CH_3), 2.56 (3H, s, CH_3), 3.59 (3H, s, N-$COCH_3$), 4.45-5.20 (3H, m, alditoyl-H), 5.06 (2H, s, N-CH_2), 5.17 (2H, d, *J* = 7.2 Hz, CH_2OAc), 6.26 (1H, s, O-CHR^1-N), 6.72 (1H, s, H-5), 7.12 (1H, d, *J* = 1.5, furyl-H), 7.43 (1H, d, *J* = 1.4,	655 [M^+ + 1] (11), 654 [M^+] (6), 451 (15), 340 (10), 225 (100)

amide (**9**) (0.45 g, 1 mmol) was added gradually with stirring to cold conc. H_2SO_4 (10 mL) during 10 min. The mixture was further stirred for another 1 h in an ice bath. Then the mixture was poured over crushed ice with stirring. The solid separated out was filtered, washed with water, dried and recrystallized with methanol to give a pale yellow crystals of compound **10** (0.32 g, 74 %). m.p. 190-192 ºC. IR (KBr, ν_{max}, cm^{-1}): 3316-3285 (NH), 2955-2933 (CH aliphatic), 1598 (C=N). ^1H NMR (DMSO-d_6), δ, ppm: 2.51 (3H, s, CH_3), 2.64 (3H, s, CH_3), 5.33 (2H, N-CH_2), 6.33 (1H, s, H-5), 6.68 (1H, d, *J* = 1.5 Hz, furyl-H), 7.13 (1H, d, *J* = 1.5 Hz, furyl-H), 7.55-7.76 (6H, m, furyl-1H, Ph,), 8.19 (1H, s, N=CH), 11.55 (1H, bs, NHPh). Mass spectra, m/z (I, %): 430 [M^++1] (10), 429 [M^+] (20), 393 (9), 335 (5), 268 (5), 204 (26), 135 (60), 77 (100). Found, %: C 61.71; H 4.33; N 22.62. $C_{22}H_{19}N_7OS$ calculated, %: C 61.52; H 4.46; N 22.83.

5-[(3-(Furan-2-yl-methyleneamino)-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-1-yl)methyl]-4-phenyl-4*H*-1,2,4-triazole-3-thiol (11): A solution of **9** (0.45 g, 1 mmol) in ethanolic sodium hydroxid (4 N, 50 mL). The reaction mixture was refluxed for 4 h on water bath, concentrated, cooled and filtered. The pH of the filtrate was adjusted between 5-6 with HCl and kept aside for 1-2 h. The solid separated out was filtered, washed with water, dried and recrystallized from methanol to give yellow powder of compound **11** (0.29 g, 67 %), m.p. 217-219 ºC. IR (KBr, ν_{max}, cm^{-1}): 3022 (CH aromatic), 2955-2933 (CH aliphatic), 2786-2715 (SH) 1638 (C=N). ^1H NMR (DMSO-d_6), δ, ppm: 2.50 (3H, s, CH_3), 2.61 (3H, s, CH_3), 5.39 (2H, N-CH_2), 6.23 (1H, s, H-5), 6.94 (1H, dd, *J* = 3.5 and 1.5 Hz, furyl-H), 7.09 (1H, d, *J* = 1.5 Hz, furyl-H), 7.22-7.75 (6H, m, furyl-1H, Ph), 8.22 (1H, s, N=CH), 12.05 (1H, bs, SH). Mass spectrum, m/z (I, %): 429 [M^+] (10), 351

(10), 201 (15), 175 (41), 77 (100). Found, %: C 61.22; H 4.53; N 22.71. $C_{22}H_{19}N_7OS$ calculated, %: C 61.52; H 4.46; N 22.83.

5-((3-(Furan-2-yl-methyleneamino)-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-1-yl)methyl)-N-phenyl-1,3,4-oxadiazol-2-amine (12): Mercuric oxide (2.37 g, 11 mmol) was added to solution of **9** (4.47 g, 10 mmol) in methanol (20 mL) and the resulting mixture was refluxed for 3 h. The precipitated mercuric sulfide was filtered off and washed with hot methanol. The filtrate on cooling gave a solid product which was filtered, dried and recrystallized with methanol to give yellow crystals of compound **12** (3.58 g, 85 %). m.p. 210-212 ºC. IR (KBr, ν_{max}, cm^{-1}): 3230 (NH), 3055 (CH aromatic), 2944-2910 (CH aliphatic), 1635 (C=N). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.54 (3H, s, CH_3), 2.59 (3H, s, CH_3), 5.71 (2H, N-CH_2), 6.13 (1H, s, H-5), 6.88 (1H, dd, *J* = 3.5 and 1.4 Hz, furyl-H), 7.06 (1H, d, *J* = 1.4 Hz, furyl-H), 7.45-7.86 (6H, m, furyl-1H, Ph), 8.33 (1H, s, N=CH), 11.12 (1H, bs, NHPh). Mass spectrum, m/z (I, %): 413 [M^+] (10), 351 (10), 201 (15), 175 (41), 77 (100). Found, %: C 61.22; H 4.53; N 22.71. $C_{22}H_{19}N_2O_2$ calculated, %: C 63.91; H 4.63; N 23.27.

Condensation reaction of Acetohydrazide derivatives with aldoses (13a-d): (General method): A solution of the appropriate aldoses (10 mmol) in water (3 mL) was treated with a solution of **8** (3.12 g, 10 mmol) in ethanol (75 mL) and a few drops of glacial acetic acid. The mixture was refluxed for 5-7 h (TLC). The excess of ethanol was removed under *in vacuo* and the residue was triturated with small amount of ethanol, the solid product formed was filtered off, washed with little amount of waster, deride and recrystallized from DMF to give the coloured hydrazones compound **13a-d** (Tables 1 and 2).

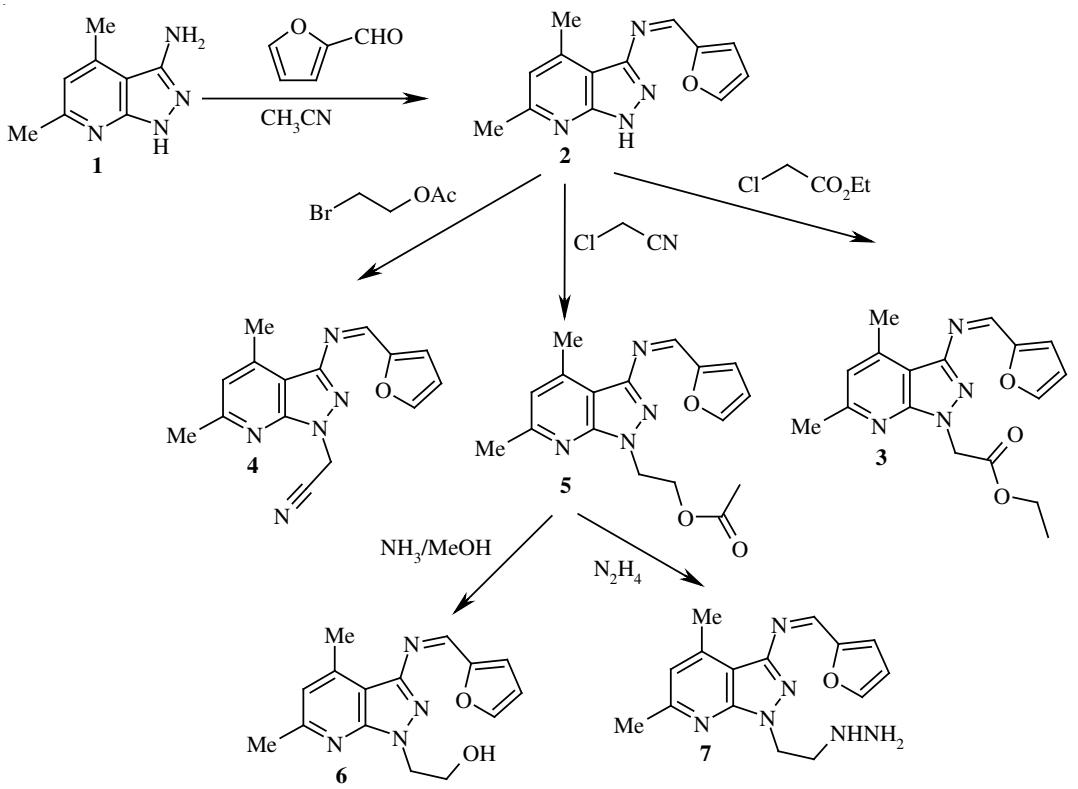
Formation of oxadiazoline derivatives *via* the acetylation reaction of alditoylpyrazolopyridine derivatives (14a-c): (General method): A solution of alditoylpyrazolopyridine **13a-c** (1 mmol) in an excess acetic anhydride (10 mL) was refluxed for 2-5 h. The reaction mixture was cooled and then poured onto cold water with stirring until the solid product separated which was collected by filtration. The product was washed by a solution of sodium carbonate followed by water, then dried and recrystallized from methanol to give compound **14a-c** (Tables 1 and 2).

RESULTS AND DISCUSSION

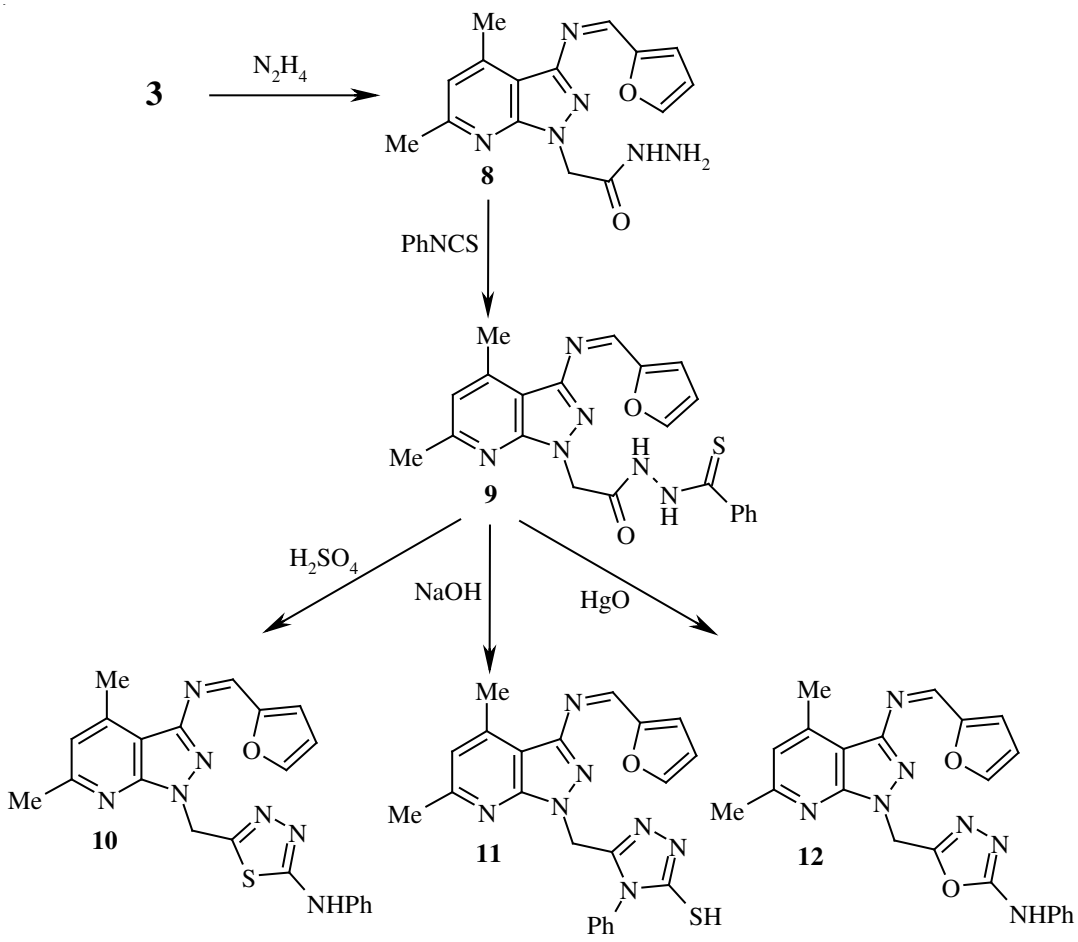
The starting material 4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-3-amine (**1**), was prepared according to the reported method[19,20], which was condensed with furan-2-carbaldehyde, in acetonitrile with a catalytic amount of glacial acetic acid, to afford N-furan-2-yl-methylidene-4,6-dimethyl-1*H*-pyrazolo-[3,4-b]pyridin-3-amine (**2**) which was confirmed by the ^{1}H NMR spectrum, showed a singlet at 8.54 ppm corresponding to the N=CH and, in aromatic region, multiplet at 6.84-7.65 ppm for the furan protons. The condensed derivative **2** was alkylated, after its treatment with anhydrous potassium carbonate in dry N,N-dimethyl formamide, with both ethyl-2-chloroacetate, 2-chloroacetonitrile and/or 2-bromo-ethylacetate to give ethyl (3-{[furan-2-yl-methylidene]amino}-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-1-yl)acetate (**3**), (3-{[furan-2-yl-methylidene]amino}-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-1-yl)acetonitrile (**4**) and 2-(3-{[furan-2-yl-methylidene]amino}-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-1-yl)ethyl acetate (**5**), in good yield, respectively. The ^{1}H NMR spectra of compounds **3**, **4** and **5** showed that N-CH_2 of the N-alkylated products **3**, **4** appeared as a singlet at δ 4.95 and 4.65 ppm, respectively, but, in the alkylated derivative **5** showed that two methylene protons appeared as a triplet at δ 3,65 and 4.44 ppm corresponding to the N-CH_2CH_2O. The latter derivative **5** was treated with ammonia in methanol (1/1), at room temperature, resulted in complete deprotection of the hydroxyl group and the corresponding 2-(3-{[furan-2-yl-methylidene]amino}-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-1-yl)ethanol (**6**) was obtained, the product identified, besides ^{1}H NMR, which showed the disappearance of methyl of acetate group at δ 2.91 ppm and the appearance of hydroxyl group at δ 4.65 ppm as a broad band, by a characteristic peak at 3261 cm^{-1} due to ν(OH) in the infrared spectrum. Also the derivative **5** was condensed with the hydrazine hydrate, in absolute ethanol, to afford N-[furan-2-yl-methylidene]-1-(2-hydrazinylethyl)-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-3-amine (**7**). IR, NMR, MS and elemental analysis established the structure of compound **7** (**Scheme-I**).

The ethyl ester derivative **3** was condensed with hydrazine hydrate to afford the corresponding hydrazide **8** which showed in its ^{1}H NMR spectra the disappearance of the ester group as a triplet at δ 1.25 and a quartet at δ 4.41 ppm and appearance a broads singlet at δ 5.14 and δ 10.14 ppm corresponding NH_2 and NH groups of hydrazide, respectively. The latter hydrazide **8** was reacted with PhNCS, in ethanol, to afford the thiosemicarbazide derivative **9**. The mass spectrum showed the molecular ion peak at m/z 448 corresponding to [M^+ + 1], m/z 447 corresponding to [M^+] and the most abundance peak at m/z 312 corresponding to M^+-PhNCS. When the thiosemicarbazide **9** was reacted with concentrated sulfuric acid, 1,3,4-thiadiazole derivative **10** was obtained. Its ^{1}H NMR spectrum showed the broad band of the NHPh at δ 11.55 ppm. The formation of the thiadiazole ring, under such acidic conditions, due to the loss of nucleophilicity of N-4 as a result of its protonation leading to an increase in the nucleophilicity of the sulfur atom toward the attack of the carbonyl carbon. On the other hand, when the cyclization of **9** was carried out under basic conditions, the nucleophilicity of N-4 was enhanced and affording cyclization with carbonyl carbon atom to afford 1,2,4-triazole derivative **11** in 67 % yield. On treatment of thiosemicarbazide **9** with mercuric oxide, the cyclization was performed, affording the 1,3,4-oxadiazole derivative **12**. The method of cyclization includes desulfurization by HgO. The ^{1}H NMR of triazole **11** showed a broad singlet at δ 12.05 ppm corresponding the SH group. The oxadiazole derivatve **12** was elucidated besides, NMR, elemental analysis, by the mass spectrum which showed a [M^+] peak, in agreement with its molecular formula (**Scheme-II**).

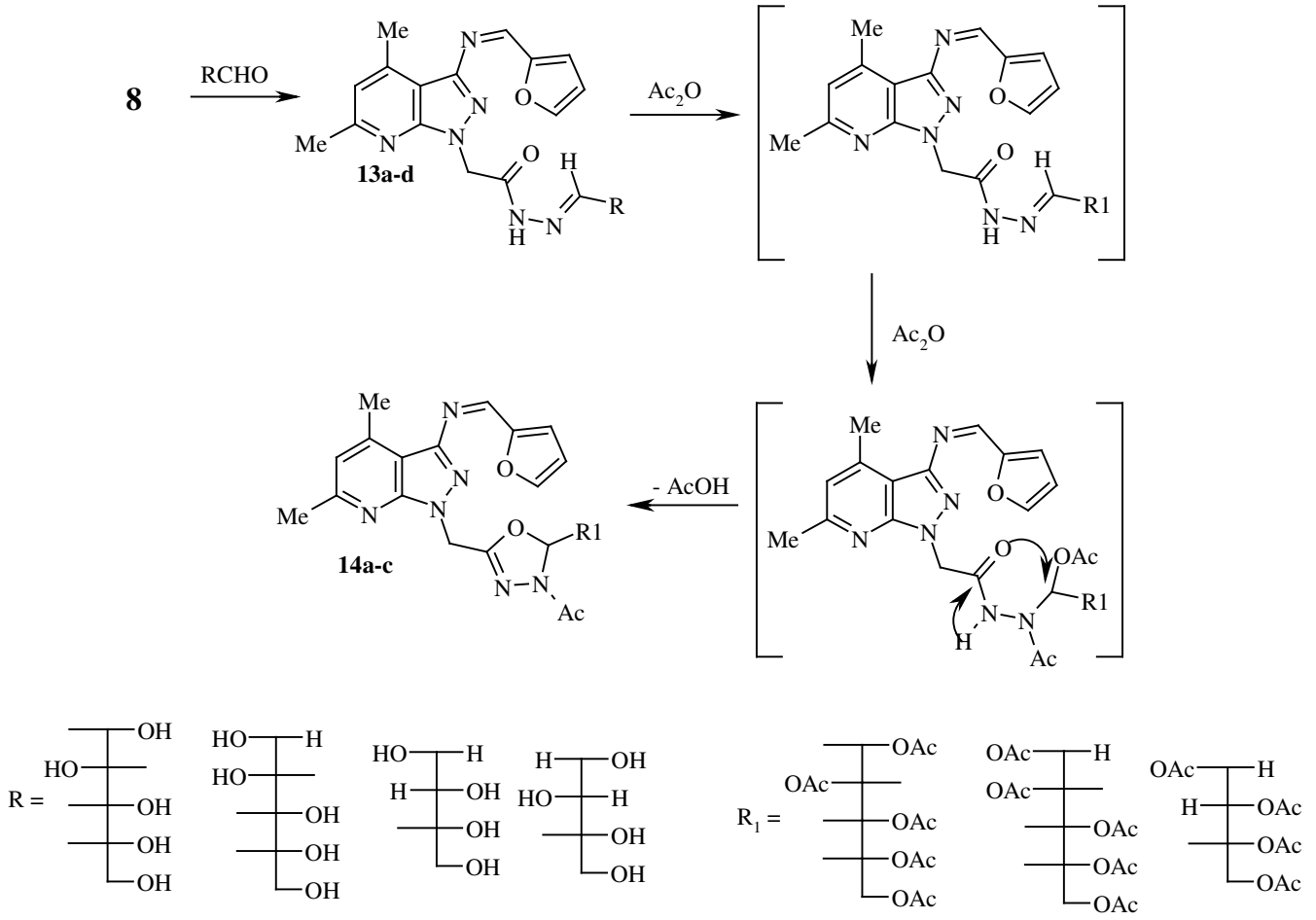
Condensation of hydrazide **8** with aldoses, D-galactose, D-mannose, D-arabinose and D-xylose, gave the corresponding sugar hydrazones **13a-d** (52-65 %). The ^{1}H NMR spectra of the hydrazones **13a-d** confirmed the presence of sugar protons in the range δ 3.33-4.32 ppm and the assignment of NH and OH groups, in these hydrazones, were achieved by D_2O. Formations of the oxadiazolines derivative **14a-c** were



Scheme-I



Scheme-II



Scheme-III

achieved on treatment of hydrazones **13a-c** with acetic anhydride under reflux. The mechanism of formation of the oxadiazolines[21-25], as shown in the **Scheme-III**, starts with introduction of the acetic anhydride molecule into the C=N of the hydrazones residue (where there are partially positive centers, presumably the carbon atom attacked by the acetate anion and the acetyl ion that becomes attached to the nitrogen atom) to give the intermediates. This route is similar to that obtaining for the benzaniline and simple ketone hydrazones on reaction with acetic anhydride. These intermediates then readily lose an acetic acid molecule to afford the substituted oxadiazoline **14a-c**. The purity of various synthesized oxadiazolines was checked by TLC and elemental analysis. Spectral data (IR, 1H NMR and mass) of the oxadiazolines were in full agreement with the proposed structures. As shown in ^{1}H NMR spectra the proton of the oxadiazoline derivatives (O-CHR1-N) appeared as a singlet at δ 6.23-6.25 ppm and $NCOCH_3$ appeared as a singlet at δ 3.59-3.65 ppm (**Scheme-III**).

Conclusion

We reported here an efficient synthetic route to prepare an N-alkylated of the condensed aminopyrazolopyridine derivatives and also formation of 1,2,4-triazole, 1,3,4-oxa-, thiadiazoles and oxadiazoline linked with pyrazolopyridine moiety *via* the condensation and cyclization reactions.

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