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Utility of Styrylpyrazoloformimidate in the Synthesis of Fused Heterocyclic Compounds

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Abstract

Refluxing of (*E*)-5-amino-1-phenyl-3-styryl-1H-pyrazole-4-carbonitrile 2 with triethylorthoformate in acetic anhydride afforded the corresponding formimidate 3. Treatment of 3 with hydrazine hydrate in ethanol afforded amino imino compound 4. Reaction of 4 with diethyl dicarbonate at reflux gave (*E*)-7-phenyl-9-styryl-7H-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine 7. Refluxing of 4 with hydrazine hydrate afforded (*E*)-4-hydrazinyl-1-phenyl-3-styryl-1H-pyrazolo[3,4-*d*] pyrimidine 8. Treatment of the latter compound 8 with aldehydes in boiling ethanol in the presence of acetic acid afforded the corresponding hydrazone 10. Oxidative cyclization of the hydrazone 10 led to the formation of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine 11. The latter products rearranged to pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines 13. The structures of the new products were established on the basis of elemental analysis and spectral data.

Keywords

**(*Z*)-N'-Phenylcinnamohydrazonoyl Chloride,
(*E*)-5-Amino-1-Phenyl-3-Styryl-1H-Pyrazole-4-Carbonitrile, Formimidate,
Dimroth Rearrangement**

1. Introduction

The chemistry of hydrazonoyl halides has attracted the interest of many research groups as they have proved to be useful organic synthesis [1]-[10]. In continuation of our long standing interest for the utility of nitrilimines derived from hydrazonoyl halides in the synthesis of heterocycles [11]-[14], we are interested in (*Z*)-N'-phenylcinnamohydrazonoyl chloride **1** to study the effect of C=C double bond on the cycloaddition reactions [15]-[17]. We wish to report herein a simple and convenient route for the synthesis of pyrazolo[3,4-*d*]pyrimidine, pyrazo-

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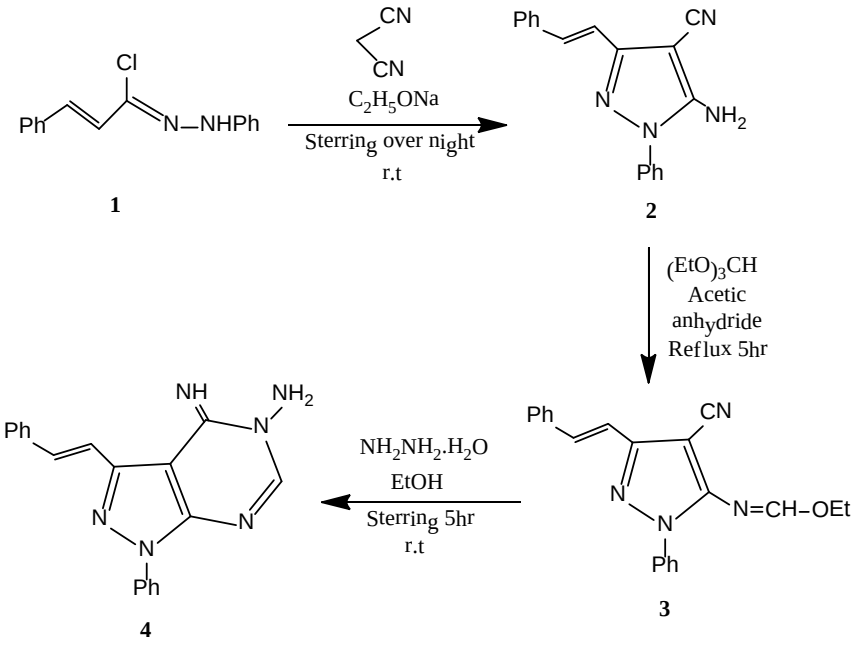
lo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines and its isomeric pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivative *via* Dimroth rearrangement. Such compounds have been used as a new pharmacological test for characterization of human A_3 adenosine receptors [18]-[20].

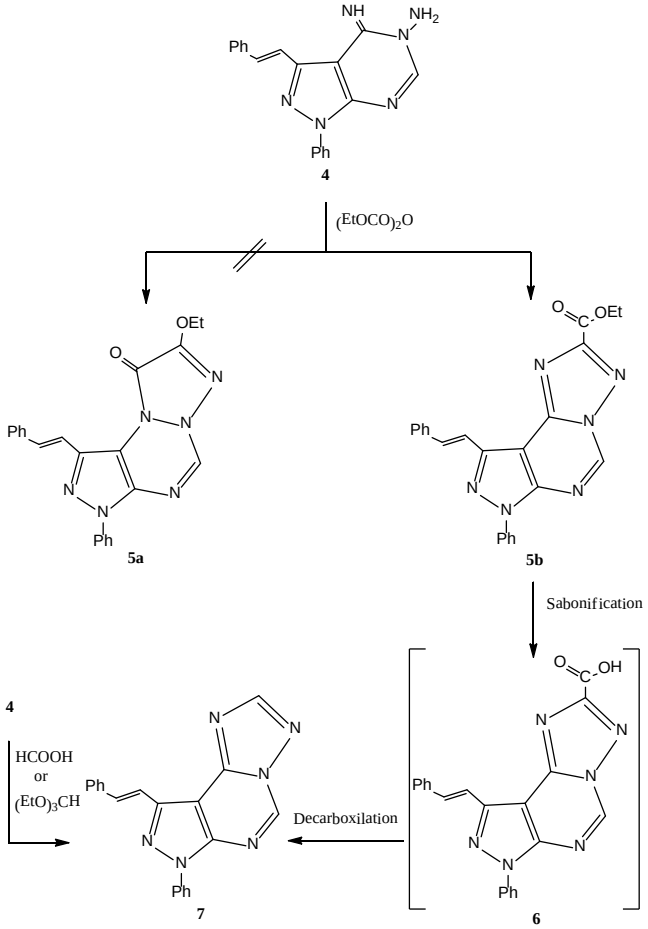
2. Results and Discussion

Compound (*E*)-5-amino-1-phenyl-3-styryl-1H-pyrazole-4-carbonitrile **2** was prepared from our laboratory *via* reaction of (*Z*)-N'-phenylcinnamohydrazonoyl chloride **1** with malononitrile in ethanolic sodium ethoxide solution (**Scheme 1**) [21]. Refluxing of compound **2** with triethylorthoformate in acetic anhydride afforded ethyl N-(4-cyano-1-phenyl-3-((*E*)-styryl)-1H-pyrazol-5-yl)formimidate **3** (**Scheme 1**). The structure of compound **3** was established on the basis of elemental analysis and spectral data. The IR spectrum of **3** revealed the absence of amino group, while it showed a characteristic band at υ 2215 cm^{-1} assignable to cyano group. Its ^1H NMR data showed signals at *δ*, 1.29 (t, 3H, CH_3), 4.32 (q, 2H, CH_2), 7.15 - 7.69 (m, 12H, Ar H), and 8.60 (s, 1H, NCH). Also, its ^{13}C-NMR spectrum showed 17 carbon atoms. Moreover, the mass spectrum showed molecular ion peak as a base peak at *m/z* 342 (100%). Reaction of **3** with hydrazine hydrate in ethanol at room temperature yielded a product **4** which analyzed correctly for $C_{19}H_{16}N_6$ (**Scheme 1**). The IR spectrum of **4** showed the absence of cyano group and it showed bands at υ 3351, 3309, 3177 cm^{-1} assignable to amino and imino groups. Also, the mass spectrum revealed a base peak at *m/z* 328 (100%) corresponding to its molecular ion peak. On the basis of elemental analysis and spectral data, the product is (*E*)-4-imino-1-phenyl-3-styryl-1H-pyrazolo [3,4-*d*]pyrimidin-5(4H)-amine **4**.

When compound **4** was refluxed with diethyl dicarbonate a single product was obtained, its mass spectrum and elemental analysis are consistent with the molecular formula $C_{23}H_{18}N_6O_2$ (**Scheme 2**). Two possible structures were proposed for the isolated product **5a** and **5b**. The identity of the isolated product was confirmed to be (*E*)-ethyl-7-phenyl-9-styryl-7H-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-2-carboxylate **5b**. Thus, saponification of the reaction product obtained **5b** gave the intermediate acid **6** which decarboxylated to a product identical to all respects (m.p., mixed m.p., IR) with (*E*)-7-phenyl-9-styryl-7H-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **7**. The latter product **7** was also confirmed *via* its alternative synthesis by treatment of compound **4** with triethylorthoformate or formic acid. Structure of **5a** was accordingly discarded. In addition, structure **5b** was further substantiated by IR and ^1H NMR spectra. Its IR spectrum exhibits a carbonyl band at υ 1743 cm^{-1} and ^1H NMR spectrum showed signals at: *δ* 1.42 (t, J = 7 Hz, 3H), 4.49 (q, J = 7 Hz, 2H), 7.37-8.78 (m, J = 7 Hz, 12H), and 9.84 (s, 1H, pyrimidine-CH).



Scheme 1. Synthesis of formimidate 3 and amino imino compound 4.



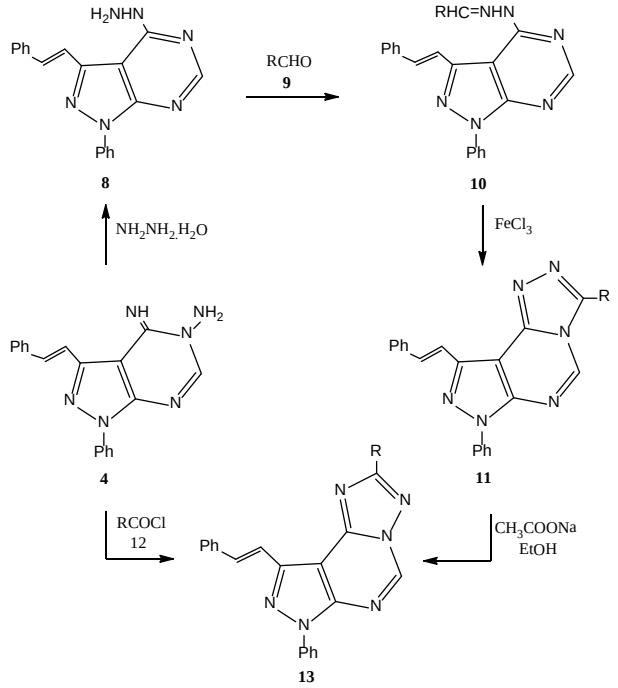
Scheme 2. Synthesis of pyrazolotriazolopyrimidine 7.

Refluxing of compound **4** with hydrazine hydrate in ethanol, gave (*E*)-4-hydrazinyl-1-phenyl-3-styryl-1H-pyrazolo[3,4-*d*]pyrimidine **8**, *via* Dimroth type rearrangement, which has not been reported hitherto (**Scheme 3** and **Scheme 4**). This is consistent with a similar rearrangement that was reported recently [22]. The structure of **8** was confirmed by elemental and spectral data (see experimental) and its reaction described below.

Thus, treatment of hydrazine derivative **8** with the appropriate aldehydes **9a-i** in refluxing ethanol in the presence of acetic acid led to the formation of the new condensation products, 4-(2-arylhydrazinyl)-1-phenyl -3-styryl-1H-pyrazolo[3,4-*d*]pyrimidine **10a-i**. The structures of **10a-i** were confirmed by their elemental analysis and spectral data. For example their IR spectra showed the characteristic band for NH at υ 3199 - 3352 cm^{-1}. Also, their ^{1}H NMR spectra revealed in each case, a signal in the region 11.97 - 12.13 assignable to NH proton which disappeared upon shaking its DMSO solution with D_2O.

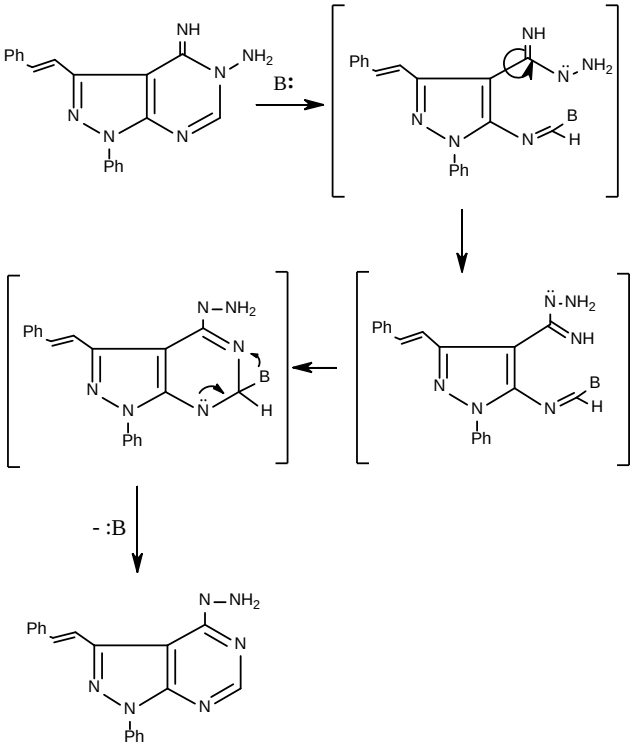
Oxidative cyclization of hydrazone **10a-h** led to the formation of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine derivatives **11a-h** (**Scheme 3** and **Scheme 5**). Thus, stirring of **10a-h** with 4 equivalent of Fe(III) chloride in ethanol overnight gave, in each case, a single product as evidenced by TLC analysis. Mass spectra revealed that, each product has 2 hydrogen atoms less than that of the respective hydrazone. Also, IR and ^{1}H NMR revealed the absence of NH band and CH=N proton, respectively.

Compounds **11a,e** were isomerized to the thermodynamically more stable pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives **13a,e** through tandem ring opening and ring closure reactions *via* heating of **11a,e** in ethanol in the presence of sodium acetate (**Scheme 3**). This rearrangement is consistent with those reported in earlier reports [23]. The structures of **13a,e** were established by elemental and spectral analysis (see experimental). Also, the structures of **13a,e** were confirmed *via* their alternative synthesis. Thus, treatment of **4** with acid chlorides **12a,e** in refluxing pyridine gave a products identical in all respects (m.p., mixed m.p., IR and ^{1}H NMR spectra) with those obtained above from base-catalyzed rearrangement of **11a,e** (**Scheme 3**). Also,

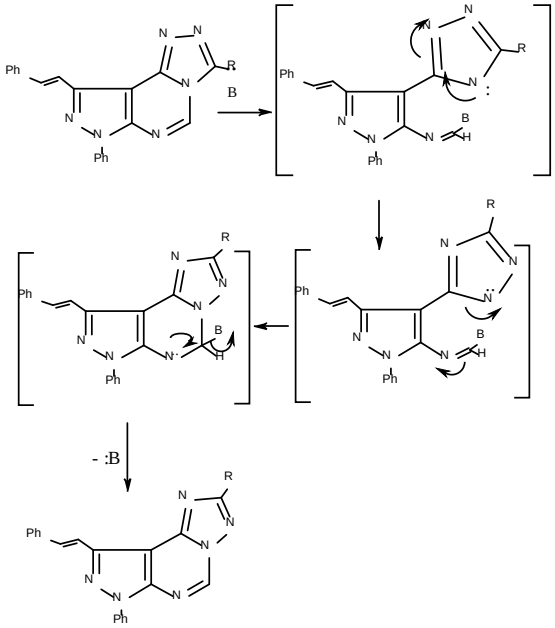


R: a) = Ph; b) = 3-$CH_3C_6H_4$; c) = 4-$(CH_3)_2NC_6H_4$; d) = 4-OHC_6H_4; e) = 4-ClC_6H_4; f) = 4-FC_6H_4; g) = 2-thienyl; h) = 4-pyridyl; i) = 3,4-methylenedioxyphenyl; j) = CH_3; K) = 4-BrC_6H_4; l) 2-furyl.

Scheme 3. Synthesis of hydrazinylpyrazolo pyrimidine 8, arylhydrazinyl-pyrazolopyrimidine 10 and pyrazolotriazolopyrimidine derivatives 11, 13.



Scheme 4. Synthesis of (*E*)-4-hydrazinyl-1-phenyl-3-styryl-1H-pyrazolo [3,4-*d*]pyrimidine.



Scheme 5. Synthesis of (*E*)-2-alkyl-7-phenyl-9-styryl-7H-pyrazolo[4,3-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine.

compound **4** reacted with **12j,k,l** to give the corresponding **13j,k,l**. The latter compounds **13j,k,l** were confirmed by elemental and spectral analysis.

3. Experimental

3.1. General

All melting points were determined on an electrothermal GallenKamp melting point apparatus and are uncorrected. The IR spectra were recorded as KBr Pellets on a Jasco FTIR-460 plus Fourier transform infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at (300 MHz) and (75 MHz) respectively on Varian EM-300 MHz spectrometer. Chemical shifts (δ) are given from TMS (ppm) as internal standard for ^{1}H NMR and ^{13}C NMR. Mass spectra were recorded on AEI MS 30 mass spectrometer operating at 70 eV. The elemental analyses were performed at the Microanalytical Center of Cairo University. Compound **2** was prepared as previously described [18].

3.2. Preparation of Ethyl N-(4-Cyano-1-Phenyl-3-((*E*)-Styryl)-1H-Pyrazol-5-yl)Formimidate 3

To a solution of the compound (*E*)-5-amino-1-phenyl-3-styryl-1H-pyrazole-4-carbonitrile **2** (1.43 g, 5 mmol) in acetic anhydride (5 mL), triethylorthoformate (0.74 g, 5 mmol) was added. The reaction mixture was refluxed for 5 h and the solvent was evaporated under reduced pressure. The solid product was collected and crystallized from acetonitrile to afford the compound **3**. Yellow crystals; m.p: 170˚C - 171˚C; yield (82%); IR (KBr): υ = 2215 (CN) cm^{-1}; ^{1}H NMR (DMSO-*d*6): δ = 1.29 (t, 3H, CH_2CH_3), 4.32 (q, 2H, CH_3CH_2), 7.15 - 7.69 (m, 12H, Ar H), 8.60 (s, 1H, NCH); ^{13}C NMR (DMSO-*d*6): δ = 13.74, 64.07, 79.46, 114.46, 117.78, 123.78, 126.88, 128.00, 128.74, 128.85, 128.97, 132.88, 135.58, 137.46, 149.57, 151.51, 162.46. MS: *m/z* (%) = 342 (M^+, 100), 313 (31), 285 (45), 77 (41). Anal. for $C_{21}H_{18}N_4O$: Calcd. C, 73.67; H, 5.30; N, 16.36. found C, 73.31; H, 5.03; N, 16.11.

3.3. Preparation of (*E*)-4-Imino-1-Phenyl-3-Styryl-1H-Pyrazolo[3,4-*d*]Pyrimidin-5(4H)-Amine 4

To a solution of the compound **3** (17.1 g, 50 mmol) in ethanol (250 mL), hydrazine hydrate (2.5 mL, 50 mmol)

was added. The reaction mixture was stirred for 5 h at room temperature; the solid product was collected and crystallized from dioxane to afford the compound **4**. Yellow crystals; m.p. 200˚C - 202˚C; yield (91%); IR (KBr): υ = 3351 & 3309 (NH_2), 3177 (NH) cm^{-1}. MS: *m/z* (%) = 328 (M^+, 100), 313 (29), 77 (30). Anal. for $C_{19}H_{16}N_6$: Calcd. C, 69.50; H, 4.91; N, 25.59. found C, 69.07; H, 4.72; N, 25.39.

3.4. Preparation of (*E*)-9-Styryl-7H-Pyrazolo[4,3-*e*][1,2,4]Triazolo[1,5-*c*]Pyrimidine-2-Carboxylate Ethyl 7-Phenyl 5b

A solution of the compound **4** (1.64 g, 5 mmol) in diethyl dicarbonate (10 mL) was refluxed for **4** h. and then cooled. The solid product was filtered off, dried and finally crystallized from acetic acid to give **5b**. Yellow crystals; m.p. 212˚C - 214˚C; yield (88%); IR (KBr): υ = 1743 (CO) cm^{-1}; ^{1}H NMR (DMSO-d6): δ = 1.42 (t, 3H, CH_2CH_3), 4.49 (q, 2H, CH_3CH_2), 7.37 - 8.78 (m, 12H, Ar H), 9.84 (s, 1H, NCH). MS: *m/z* (%) = 410 (M+, 96), 409 (50), 77 (100). Anal. for $C_{23}H_{18}N_6O_2$: Calcd. C, 67.31; H, 4.42; N, 20.48. found C, 67.02; H, 4.37; N, 20.25.

3.5. Preparation of (*E*)-7-Phenyl-9-Styryl-7H-Pyrazolo[4,3-*e*][1,2,4]Triazolo[1,5-*c*]Pyrimidine 7

A solution of the compound **4** (1.64 g, 5 mmol) in triethylorthoformate or formic acid (10 mL) was refluxed for 4 h. left to cool and the solid product was filtered, dried and finally crystallized from acetic acid to afford **7**. Pale yellow crystals; m.p. 198˚C - 200˚C (acetic acid); yield (86%); ^{1}H NMR (DMSO-*d*6): δ = 6.98 - 8.56 (m, 12H, Ar H), 9.77 (s, 1H, NCH), 9.79 (s, 1H, NCH). MS: *m/z* (%) = 338 (M^+, 98), 337 (100), 77 (30). Anal. for $C_{20}H_{14}N_6$: Calcd. C, 70.99; H, 4.17; N, 24.84. found C, 70.65; H, 4.12; N, 24.61.

3.6. Preparation of (*E*)-4-Hydrazinyl-1-Phenyl-3-Styryl-1H-Pyrazolo[3,4-*d*]Pyrimidine 8

A solution of the compound **4** (16.4 g, 50 mmol) in ethanol (250 mL) and hydrazine hydrate (10 mL) was refluxed for 5 h. The solvent was evaporated; the solid product was collected, dried and finally crystallized from acetonitrile to afford **8**. Yellow crystals; m.p. 202˚C - 204˚C; yield (90%); IR (KBr): υ = 3310 (NH), 3351 & 3309 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-*d*6): δ = 4.86 (s, 2H, NH_2), 7.31-8.41 (m, 13H, Ar H), 9.25 (s, 1H, NH). MS: *m/z* (%) = (M^+, 38), 313 (30), 297 (80), 77 (100). Anal. for $C_{19}H_{16}N_6$: Calcd. C, 69.50; H, 4.91; N, 25.59. found C, 69.22; H, 4.81; N, 25.33.

3.7. General Method for Preparation (*E*)-4-(2-Arylhydrazinyl)-1-Phenyl-3-Styryl-1H-Pyrazolo[3,4-*d*]Pyrimidine 10a-i

To a mixture of compound **8** (1.64 g, 5 mmol) in ethanol (30 mL), the appropriate aldehyde **9a-i** (5 mmol) was added. The reaction mixture was refluxed for 2 h and the solvent was evaporated. The solid product formed was collected, dried and finally crystallized from suitable solvent to afford **10a-i**.

4-((Z)-2-*Benzylidenehydrazinyl*)-1-*phenyl*-3-((E)-*styryl*)-1H-*pyrazolo*[3,4-d]*pyrimidine* 10a:

Yellow crystals; m.p. 188˚C - 189˚C (acetonitrile); yield (87%); IR (KBr): υ = 3205 (NH) cm^{-1}, ^{1}H NMR (DMSO-*d*6): δ = 7.15 - 8.58 (m, 19H, Ar H), 12.04 (s, 1H, NH). MS: *m/z* (%) = 416 (M^+, 14), 415 (42), 313 (43), 236 (41), 77 (100). Anal. for $C_{26}H_{20}N_6$: Calcd. C, 74.98; H, 4.84; N, 20.18. found C, 74.37; H, 4.71; N, 19.73.

4-((Z)-2-(3-*Methylbenzylidene*)*hydrazinyl*)-1-*phenyl*-3-((E)-*styryl*)-1H-*pyrazolo*[3,4-d]*pyrimidine* 10b:

Yellow crystals; m.p. 192˚C - 194˚C (acetonitrile); yield (81%); IR (KBr): υ = 3352 (NH) cm^{-1}, ^{1}H NMR (DMSO-*d*6): δ = 2.36 (s, 3H, CH_3), 7.24-8.52 (m, 18H, Ar H), 12.01 (s, 1H, NH); ^{13}C NMR (DMSO-*d*6): δ = 20.83, 99.47, 119.11, 121.83, 125.20, 126.783, 128.18, 128.41, 128.76, 129.01, 130.57, 132.80, 136.52, 137.80, 138.19, 147.89, 153.98. MS: *m/z* (%) = 430 (M^+, 79), 339 (52), 312 (100), 236 (79), 77 (80). Anal. for $C_{27}H_{22}N_6$: Calcd. C, 75.33; H, 5.15; N, 19.52. found C, 75.06; H, 4.92; N, 19.36.

N,N-*Dimethyl*-4-((Z)-(2-(1-*phenyl*-3-((E)-*styryl*)-1H-*pyrazolo*[3,4-d]*pyrimidin*-4-yl)*hydrazono*)*methyl*)*aniline* 10c:

Yellow crystals; m.p. 242˚C - 244˚C (dimethylformamide); yield (77%); IR (KBr): υ = 3199 (NH) cm^{-1}; ^{1}H NMR (DMSO-*d*6): δ = 2.99 (s, 6H, $N(CH_3)_2$), 6.75-8.43 (m, 18H, Ar H), 11.87 (s, 1H, NH). MS: *m/z* (%) = 459 (M^+, 34), 457 (62), 312 (100), 236 (65), 145 (60), 77 (91). Anal. for $C_{28}H_{25}N_7$: Calcd. C, 73.18; H, 5.48; N, 21.34. found C, 72.55; H, 5.23; N, 20.84.

4-((Z)-(2-(1-*Phenyl*-3-((E)-*styryl*)-1H-*pyrazolo*[3,4-d]*pyrimidin*-4-yl)*hydrazono*)*methyl*)*phenol* 10d:

Yellow crystals; m.p. 270˚C - 272˚C (acetonitrile); yield (83%); IR (KBr): υ = 3324 (NH) cm^{-1}; ^1H NMR (DMSO-*d*6): δ = 6.99 - 8.68 (m, 18H, Ar H), 11.98 (s, 1H, NH), 13.02 (s, 1H, OH). MS: *m/z* (%) = 432 (M^+, 82), 312 (100), 77 (93). Anal. for $C_{26}H_{20}N_6O$: Calcd. C, 72.21; H, 4.66; N, 19.43. found C, 71.76; H, 4.51; N, 19.11.

4-((Z)-2-(4-*Chlorobenzylidene*)*hydrazinyl*)-1-*phenyl*-3-((E)-*styryl*)-1H-*pyrazolo*[3,4-d]*pyrimidine* 10e:

Yellow crystals; m.p. 230˚C - 232˚C (dimethylformamide); yield (84%); IR (KBr): υ = 3205 (NH) cm^{-1}; ^1H NMR (DMSO-*d*6): δ = 7.02 - 8.70 (m, 18H, Ar H), 12.11 (s, 1H, NH). MS: *m/z* (%) = 450 (M^+, 100), 77 (72). Anal. for $C_{26}H_{19}ClN_6$: Calcd. C, 69.25; H, 4.25; Cl, 7.86; N, 18.64. found C, 68.76; H, 4.03; Cl, 7.65; N, 18.23.

4-((Z)-2-(4-*Fluorobenzylidene*)*hydrazinyl*)-1-*phenyl*-3-((E)-*styryl*)-1H-*pyrazolo*[3,4-d]*pyrimidine* 10f:

Yellow crystals; m.p. 192˚C - 194˚C (acetonitrile); yield (87%); IR (KBr): υ = 3199 (NH) cm^{-1}; ^1H NMR (DMSO-*d*6): δ = 7.04 - 8.71 (m, 18H, Ar H), 12.13 (s, 1H, NH). MS: *m/z* (%) = 434 (M^+, 87), 339 (32), 312 (100), 236 (79), 77 (56). Anal. for $C_{26}H_{19}FN_6$: Calcd. C, 71.88; H, 4.41; F, 4.37; N, 19.34. found C, 71.51; H, 4.30; F, 4.29; N, 19.03.

1-*Phenyl*-3-((E)-*styryl*)-4-((Z)-2-(*thiophen*-2-*ylmethylene*)*hydrazinyl*)-1H-*pyrazolo*[3,4-d]*pyrimidine* 10g:

Yellow crystals; m.p. 186˚C - 188˚C (acetonitrile); yield (83%); IR (KBr): υ = 3337 (NH) cm^{-1}; ¹H NMR (DMSO-d6): δ = 7.01 - 8.71 (m, 17H, Ar H), 12.01 (s, 1H, NH). MS: *m/z* (%) = 422 (M^+, 100), 312 (88), 236 (61), 77 (42). Anal. for $C_{24}H_{18}N_6S$: Calcd. C, 68.23; H, 4.29; N, 19.89; S, 7.59. found C, 67.81; H, 4.20; N, 19.64; S, 7.50.

1-*Phenyl*-4-((Z)-2-(*pyridin*-4-*ylmethylene*)*hydrazinyl*)-3-((E)-*styryl*)-1H-*pyrazolo*[3,4-d]*pyrimidine* 10h:

Yellow crystals; m.p. 284˚C - 286˚C (dimethylformamide); yield (84%); IR (KBr): υ = 3322 (NH) cm^{-1}; ^1H NMR (DMSO-*d*6): δ = 6.89 - 8.64 (m, 18H, Ar H), 11.97 (s, 1H, NH). MS: *m/z* (%) = 417 (M^+, 54), 312 (71), 77 (100). Anal. for $C_{25}H_{19}N_7$: Calcd. C, 71.93; H, 4.59; N, 23.49. found C, 71.58; H, 4.24; N, 23.11.

4-((Z)-2-(*Benzo*[d][1,3]*dioxol*-5-*ylmethylene*)*hydrazinyl*)-1-*phenyl*-3-((E)-*styryl*)-1H-*pyrazolo*[3,4-d]*pyrimidine* 10i:

Yellow crystals; m.p. 214˚C - 216˚C (acetonitrile); yield (82%); IR (KBr): υ = 3341 (NH) cm^{-1}; ^1H NMR (DMSO-*d*6): δ = 6.09 (s, 2H, CH_2), 6.97 - 8.47 (m, 17H, Ar H), 12.01 (s, 1H, NH). MS: *m/z* (%) = 460 (M^+, 54), 312 (100), 236 (63), 77 (92). Anal. for $C_{27}H_{20}N_6O_2$: Calcd. C, 70.42; H, 4.38; N, 18.25. found C, 70.01; H, 4.30; N, 18.11.

3.8. General Method for Preparation of 7H-Pyrazolo[4,3-e][1,2,4]Triazolo[4,3-c]Pyrimidine 11a-h

To a solution of an appropriate arylhydrazinyl compound **10a-h** (5 mmol) in ethanol (20 mL), ferric chloride (4 mL, 2 M) was added, and the reaction mixture was stirred for 24 h. The solid that separated was collected, dried and finally crystallized from dimethylformamide to afford the corresponding 7H-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine **11a-h**.

(E)-3,7-*Diphenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[4,3-c]*pyrimidine* 11a:

White crystals; m.p. 276˚C - 278˚C; yield (87%); ^1H NMR (DMSO-*d*6): δ = 7.37 - 8.81 (m, 17H, Ar H), 9.32 (s, 1H, NCH). MS: *m/z* (%) = 414 (M^+, 100), 77 (80). Anal. for $C_{26}H_{18}N_6$: Calcd. C, 75.35; H, 4.38; N, 20.28. found C, 75.03; H, 4.32; N, 20.01.

(E)-7-*Phenyl*-9-*styryl*-3-(m-*tolyl*)-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[4,3-c]*pyrimidine* 11b:

White crystals; m.p. 182˚C - 184˚C; yield (86%); ^1H NMR (DMSO-*d*6): δ = 2.23 (s, 3H, CH_3), 7.31 - 8.47 (m, 16H, Ar H), 9.08 (s, 1H, NCH). MS: *m/z* (%) = 428 (M^+, 100), 77 (26). Anal. for $C_{27}H_{20}N_6$: Calcd. C, 75.68; H, 4.70; N, 19.61. found C, 75.22; H, 4.410; N, 19.15.

(E)-*N*,*N*-*Dimethyl*-4-(7-*phenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[4,3-c]*pyrimidin*-3-yl)*aniline* 11c:

Yellow crystals; m.p. 222˚C - 224˚C; yield (85%); ^1H NMR (DMSO-*d*6): δ = 3.02 (s, 6H, $N(CH_3)_2$), 6.89 - 8.41 (m, 16H, Ar H), 9.24 (s, 1H, NCH). MS: *m/z* (%) = 457 (M^+, 47), 77 (100). Anal. for $C_{28}H_{23}N_7$: Calcd. C, 73.50; H, 5.07; N, 21.43. found C, 73.21; H, 4.98; N, 21.24.

(E)-4-(7-*Phenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[4,3-c]*pyrimidin*-3-yl)*phenol* 11d:

Pale green crystals; m.p. 284˚C - 286˚C; yield (88%); ^1H NMR (DMSO-*d*6): δ = 6.93 - 8.45 (m, 16H, Ar H), 9.28 (s, 1H, NCH), 13.11 (s, 1H, OH). MS: *m/z* (%) = 430 ($M^{+\cdot}$, 18), 77 (100). Anal. for $C_{26}H_{18}N_6O$: Calcd. C, 72.55; H, 4.21; N, 19.52. found C, 72.31; H, 4.16; N, 19.39.

(E)-3-(4-*Chlorophenyl*)-7-*phenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[4,3-c]*pyrimidine* 11e:

Yellow crystals; m.p. 250˚C - 252˚C; yield (80%); ^{1}H NMR (DMSO-*d*6): δ = 7.33 - 8.12 (m, 16H, Ar H), 8.66 (s, 1H, NCH). MS: *m/z* (%) = 448 (M^+, 100), 77 (48). Anal. for $C_{26}H_{17}ClN_6$: Calcd. C, 69.56; H, 3.82; Cl, 7.90; N, 18.72. found C, 69.14; H, 3.75; Cl, 7.78; N, 18.59.

(E)-3-(4-*Fluorophenyl*)-7-*phenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[4,3-c]*pyrimidine* 11f:

White crystals; m.p. 228˚C - 230˚C; yield (81%); ^{1}H NMR (DMSO-*d*6): δ = 7.34 - 8.14 (m, 16H, Ar H), 8.81 (s, 1H, NCH). MS: *m/z* (%) = 432 (M^+, 100), 77 (21). Anal. for $C_{26}H_{17}FN_6$: Calcd. C, 72.21; H, 3.96; F, 4.39; N, 19.43. found C, 71.43; H, 3.90; F, 4.32; N, 19.31.

(E)-7-*Phenyl*-9-*styryl*-3-(*thiophen*-2-yl)-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[4,3-c]*pyrimidine* 11 g:

Green crystals; m.p. 262˚C - 264˚C; yield (84%); ^{1}H NMR (DMSO-*d*6): δ = 7.33 - 8.73 (m, 15H, Ar H), 9.48 (s, 1H, NCH); ^{13}C NMR (DMSO-*d*6): δ = 98.57, 118.90, 122.25, 126.39, 126.81, 127.59, 128.51, 128.88, 129.24, 129.72, 135.62, 136.38, 137.73, 138.69, 142.28, 144.87, 145.56. MS: *m/z* (%) = 420 (M^+, 100), 77 (18). Anal. for $C_{24}H_{16}N_6S$: Calcd. C, 68.55; H, 3.84; N, 19.99; S, 7.63. found C, 68.01; H, 3.80; N, 19.51; S, 7.52.

(E)-7-*Phenyl*-3-(*pyridin*-4-yl)-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[4,3-c]*pyrimidine* 11 h:

Orange crystals; m.p. 268˚C - 270˚C; yield (83%); ¹H NMR (DMSO-*d*6): δ = 6.91 - 8.68 (m, 16H, Ar H), 9.36 (s, 1H, NCH). MS: *m/z* (%) = 415 (M^+, 100), 77 (41). Anal. for $C_{25}H_{17}N_7$: Calcd. C, 72.28; H, 4.12; N, 23.60. found C, 71.74; H, 4.06; N, 23.31.

3.9. General Methods for Preparation of Pyrazolo[4,3-*e*][1,2,4]Triazolo[1,5-*c*]Pyrimidine Derivatives 13

Method A: To a solution of the appropriate **11a,e** (1 mmol) in absolute ethanol (30 mL), sodium acetate (0.16 g, 2 mmol) was added and the mixture was refluxed for 8 h. The precipitated solid after cooling was filtered, washed with water, dried and finally crystallized from suitable solvent to give the respective products **13a,e**.

Method B: To a solution of the compound **4** (1.64 g, 5 mmol) in pyridine (20 mL), the appropriate acid chloride **12a,e,j,k,l** (5 mmol) was added. The reaction mixture was refluxed for 4 h, then cooled and poured over crushed ice containing hydrochloric acid (10%) with stirring. The solid product was filtered, washed with water, dried and finally crystallized from suitable solvent to afford **13a,e,j,k,l**.

(E)-2,7-*Diphenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[1,5-c]*pyrimidine* 13a:

Pale brown crystals; m.p. 210˚C - 212˚C (dimethylformamide); yield (80%); ^{1}H NMR (DMSO-*d*6): δ = 6.66 - 8.75 (m, 17H, Ar H), 9.78 (s, 1H, NCH). MS: *m/z* (%) = 414 (M^+, 100), 77 (28). Anal. for $C_{26}H_{18}N_6$: Calcd C, 75.35; H, 4.38; N, 20.28. found C, 74.98; H, 4.18; N, 19.89.

(E)-2-(4-*Chlorophenyl*)-7-*phenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[1,5-c]*pyrimidine* 13e:

Pale yellow crystals; m.p. 268˚C - 270˚C (dimethylformamide); yield (87%); ^{1}H NMR (DMSO-*d*6): δ = 6.68 - 8.84 (m, 16H, Ar H), 9.81 (s, 1H, NCH). MS: *m/z* (%) = 448 (M^+, 100), 447 (68), 77 (54). Anal. for $C_{26}H_{17}ClN_6$: Calcd C, 69.56; H, 3.82; Cl, 7.90; N, 18.72. found C, 69.31; H, 3.66; Cl, 7.69; N, 18.40.

(E)-2-*Methyl*-7-*phenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[1,5-c]*pyrimidine* 13j:

White crystals; m.p. 186˚C - 187˚C (acetic acid); yield (92%); ^{1}H NMR (DMSO-*d*6): δ = 2.57 (s, 3H, CH_3), 7.32 - 8.59 (m, 12H, Ar H), 9.50 (s, 1H, NCH); ^{13}C NMR (DMSO-*d*6): δ = 14.28, 118.81, 122.05, 126.82, 127.37, 128.54, 128.88, 129.22, 135.60, 136.37, 137.87, 140.16, 144.17, 164.41. MS: *m/z* (%) = 352 (M^+, 98), 351 (100), 77 (35). Anal. for $C_{21}H_{16}N_6$: Calcd. C, 71.58; H, 4.58; N, 23.85. found C, 71.01; H, 4.33; N, 23.52.

(E)-2-(4-*Bromophenyl*)-7-*phenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[1,5-c]*pyrimidine* 13k:

Pale yellow crystals; m.p. 290˚C - 292˚C (dimethylformamide); yield (85%); ^{1}H NMR (DMSO-*d*6): δ = 6.71 - 8.80 (m, 16H, Ar H), 9.84 (s, 1H, NCH). MS: *m/z* (%) = 492 (M^+, 100), 491 (75), 206 (30), 102 (29), 77 (81). Anal. for $C_{26}H_{17}BrN_6$: Calcd C, 63.30; H, 3.47; Br, 16.20; N, 17.03. found C, 63.01; H, 3.39; Br, 16.03; N, 16.86.

(E)-2-(*Furan*-2-*yl*)-7-*phenyl*-9-*styryl*-7H-*pyrazolo*[4,3-e][1,2,4]*triazolo*[1,5-c]*pyrimidine* 13l:

Pale yellow crystals; m.p. 264˚C - 266˚C (dimethylformamide); yield (86%); ¹H NMR (DMSO-*d*6): δ = 6.75 - 8.77 (m, 15H, Ar H), 9.62 (s, 1H, NCH). MS: *m/z* (%) = 404 (M^+, 100), 403 (65), 77 (53). Anal. for $C_{24}H_{16}N_6O$: Calcd C, 71.28; H, 3.99; N, 20.78. found C, 70.79; H, 3.63; N, 20.47.

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