β-Oxoanilides in Heterocyclic Synthesis: An Expeditious Synthesis of New Polyfunctionally Substituted Pyridine and Pyrazole Derivatives

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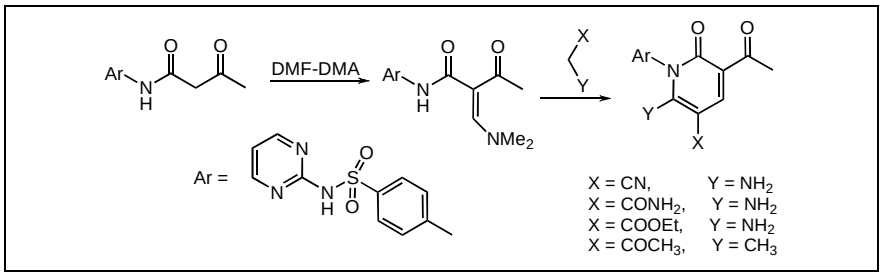

3-Oxo-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}butanamide **3** was condensed with (DMF-DMA) in refluxing dry dioxane to yield branched structure **4** not its linear isomeric **5**. Compound **4** readily reacted with active methylene to yield compounds **8a-c, 14, 17** and **20** respectively. Also enaminone **4** reacted with phenyl hydrazine giving **24** and **25**. In contrast, when compound **4** reacted with hydrazine hydrate in the same experimental conditions pyrazole derivative **27** was obtained. Furthermore, condensation of anilide **3** with triethylorthoformate in refluxing acetic anhydride afforded the ethoxy methylene derivative **28**. On the other hand, compound **28** was reacted with active methylene reagents, and hydrazines to afford the products identical in all respects (mp., mixed mp., and spectral data) with those corresponding to compounds **6-27** respectively. Similarly, compound **3** was reacted with hydrazine hydrate to afford the reaction product **29**. Also, compound **3** reacted with cyanoacetamide in refluxing ethanolic pipridine solution to yield the pyridine derivative **30**. Finally, **3** reacted with hydroxylamine hydrochloride in refluxing ethanol/sodium acetate solution to yield the acyclic oxime derivative **31**.

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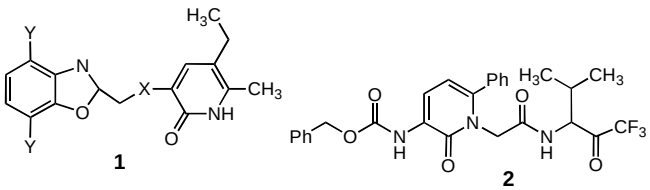
INTRODUCTION

Literature survey revealed that polyfunctionally substituted pyridones have played an important role in the development of bioactive compounds for the inhibition of enzymatic processes [1-3]. A number of representative pyridone derivative **1** are effective inhibitors of HIV reverse transcriptase. Pyridone **2** is a potent (4.5 nm), reversible nonpeptidic inhibitor of human leukocyte elastase (HLE) [4,5]. In view of our continued interest in developing efficient synthesis of polyfunctionally substituted heteroaromatics utilizing the readily obtainable starting materials [6-9], we report here the results of our investigations aiming to explore the synthetic potential of 3-Oxo-*N*-{4-[(pyrimidin-2-yl-amino)sulphonyl]phenyl}butanamide **3** to synthesis of substituted pyridones from enaminone using active methylene reagents.

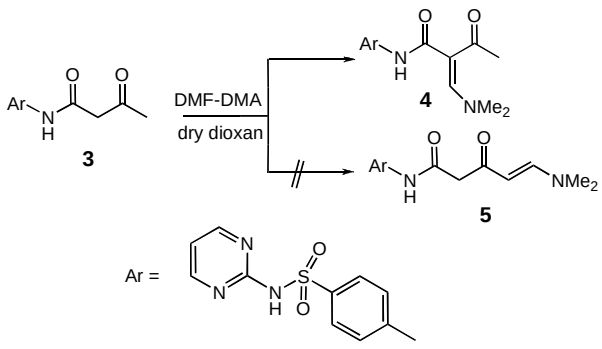
Scheme 1



RESULTS AND DISCUSSION

It has been found that 3-oxo-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}butanamide **3** was condensed with *N*,*N*-dimethylformamide-dimethylacetal (DMF-DMA) in refluxing dry dioxane to yield a product that may be either structure **4** or its isomeric **5**. Establishing the exact structure of the reaction product as structure **4** rather than **5** was based on elemental analysis and spectral data. ^{1}H nmr spectra revealed the presence of a singlet signal at δ = 1.2 ppm assigned to the acetyl functional group and absence of olefinic doublet-doublet which would be observed for structure **5**.

Scheme 2



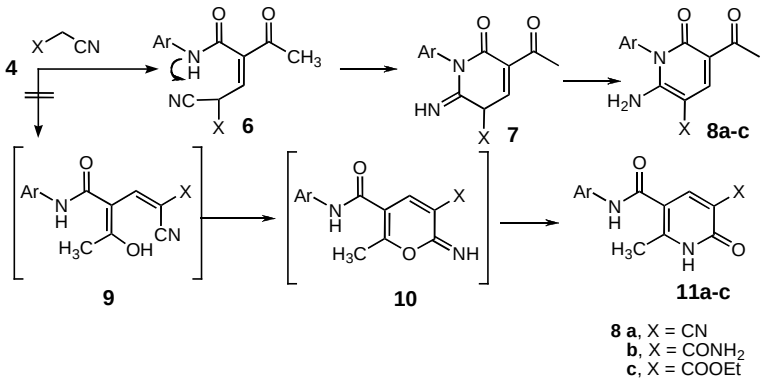
Compound **4** readily reacted with malononitrile in refluxing ethanolic piperidine solution to yield the product which may be formulated as structures **8a** or **11a**. Structure **11a** was ruled out and structure **8a** was considered to be only the reaction product based on spectroscopic data. Thus, the ^{1}H nmr spectrum of compound **8a** showed a singlet signal (3H) at δ = 3.56 ppm assigned for acetyl protons, a broad signal at δ = 5.75 ppm assigned for NH_2 protons, multiplet at δ = 6.51 - 7.58 ppm assigned for CH aromatic and 2 NH, and a singlet at δ = 8.35 ppm assigned for CH-pyridine. Also, its mass spectrum revealed a molecular ion peak at m/z = 411(M^{+1}) corresponding to the molecular formula $C_{18}H_{14}N_6O_4S$. Similarly, compound **4** reacted with cyanoacetamide and ethyl cyanoacetate to yield the pyridone derivatives **8b,c** rather than **11b,c** respectively.

reacted with enaminone **4** in ethanolic piperidine solution to yield compound **14**. Assignment of structure **14** for the reaction product was based on its correct elemental analysis and compatible spectroscopic data. Thus, the ^{1}H nmr spectrum showed, the presence of singlet signals at δ = 1.70, 2.05 ppm assigned for 2 $COCH_3$ protons besides the expected signals. Compound **14** is assumed to be formed by condensing acetyl acetone to enaminone **4** with elimination of dimethyl amine which would afford intermediate **13** which on cyclization *via* water elimination gives **14** (Scheme 4).

Similarly, ethyl acetoacetate was reacted with enaminone **4** at the same conditions to yield compound **17** (Scheme 5).

In contrast to the behavior of active methylene reagents to enaminone **4**, compound **4** readily reacted with

Scheme 3

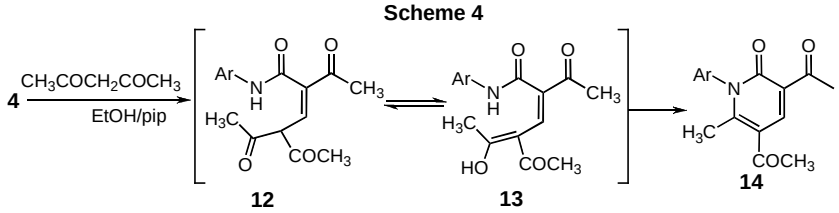


Formation of **8a-c** is believed to proceed *via* initial addition of active methylene moiety in malononitrile to afford the Michael adduct **6** *via* elimination of dimethyl amine, which cyclizes into **7** and aromatized to the pyridone derivatives **8a-c**.

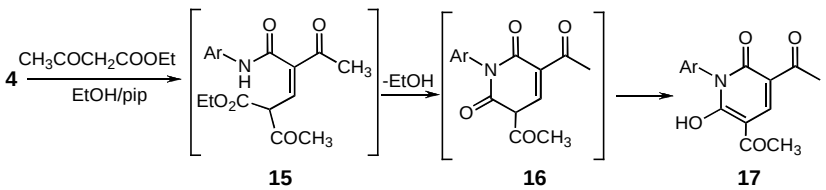
Also, the behavior of enaminone **4** towards active diketone reagents was investigated. Thus, acetyl acetone

cyanothioacetamide in refluxing ethanolic pipridine solution to yield the product which may be formulated as pyridinethione **20** neither **22** nor **23**. Structure **20** was considered to be the reaction product based on its spectroscopic data and further confirmed on the bases of its chemical behavior towards different chemical reagents (Scheme 6).

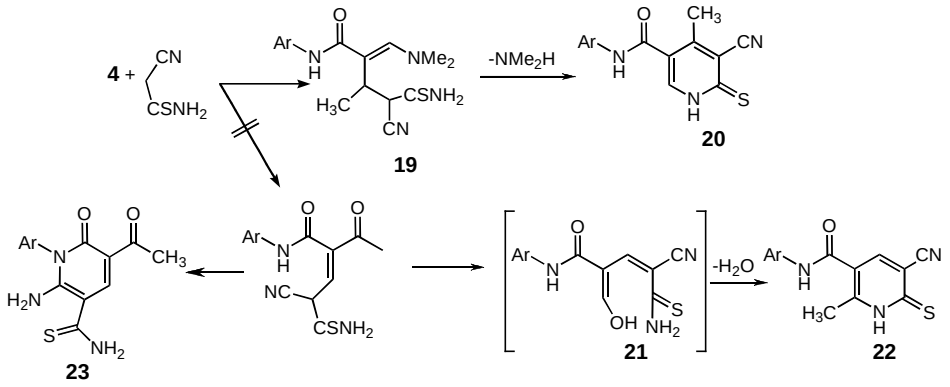
Scheme 4



Scheme 5

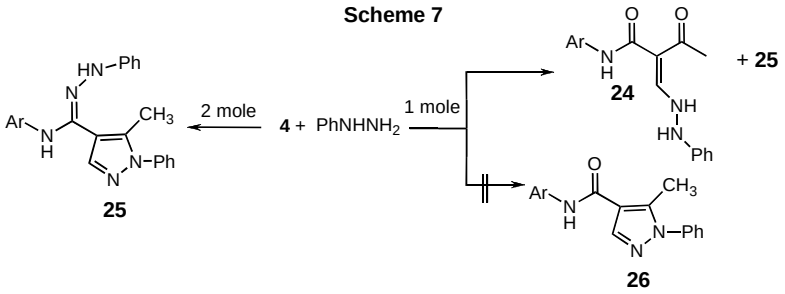


Scheme 6



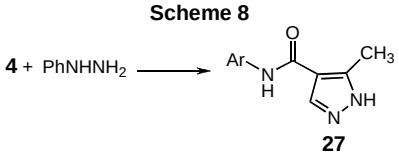
Furthermore, the behavior of enaminone **4** towards phenyl hydrazine and hydrazine hydrate was also investigated. Thus, enaminone **4** reacted with phenyl hydrazine giving products depending on the ratio between the reactants. Thus, the reaction between **4** and phenyl hydrazine in equimolar ratio yielded two products **24** and **25**. However, when the reaction is carried out using one mole of **4** with two moles of phenyl hydrazine, product **25** was isolated as the only reaction product. The exact structure of such reaction product is based on its elemental analysis and spectroscopic data. Thus, the mass spectrum of compound **24** revealed a molecular ion peak at m/z = 452 (M^+) corresponding to the molecular formula $C_{21}H_{20}N_6O_4S$. Compound **25** was confirmed based on its spectroscopic data (Scheme 7).

Scheme 7



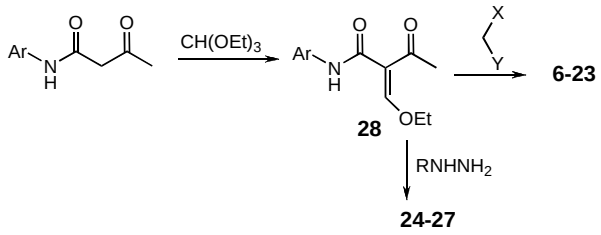
In contrast, when compound **4** reacted with hydrazine hydrate under the same experimental conditions the pyrazole derivative **27** was afforded (Scheme 8).

Scheme 8



Also, condensation of anilide **3** with triethylorthoformate in refluxing acetic anhydride afforded the ethoxy methylene derivative **28**. Establishing of the structure **28** was based on elemental analysis and spectral data. On the other hand, compound **28** was reacted with the active methylene reagents, and hydrazines to afford products identical in all respects (mp., mixed mp., and spectral data) with those corresponding to compounds **6-27** respectively (Scheme 9).

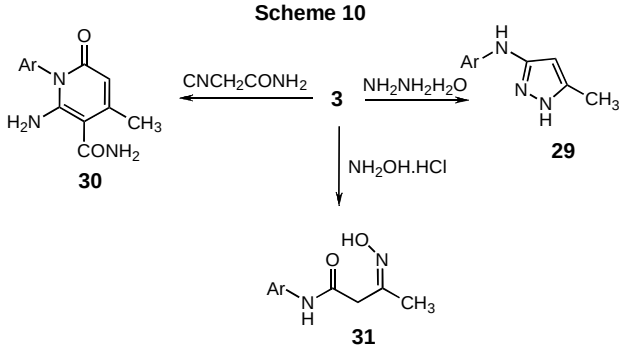
Scheme 9



On the other hand, the reactivity of anilide **3** towards hydrazine hydrate, cyanoacetamide, and hydroxyl amine hydrochloride was investigated. Thus, acetoacetanilide **3** was reacted with hydrazine hydrate to afford the reaction product **29**. Assignment of structure **29** for the reaction product was based on its correct elemental analysis and spectroscopic data. Also, anilide **3** reacted with cyanoacetamide in refluxing ethanolic pipridine solution to yield the product which may be formulated as pyridine derivative **30**. Furthermore, anilide **3** reacted with hydroxylamine hydrochloride in refluxing ethanol/sodium acetate solution to yield the acyclic oxime derivative **31**. Structure **31** was established based on its elemental analysis and spectroscopic data. Thus, its ^{1}H NMR

spectrum showed absorption peaks at δ = 2.5 ppm (CH_3) protons, at δ = 3.32 ppm assigned for (OH) proton, at δ = 5.97 ppm (CH_2) protons, and at δ = 11.22 ppm a broad signal assumed for (NH) proton beside the expected signals (Scheme 10).

Scheme 10



EXPERIMENTAL

All melting points are uncorrected and were determined on a Gallenkamp apparatus; IR spectra were recorded on Schimadzu 470 spectrophotometer in potassium bromide discs; ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrophotometer using TMS as internal standard, Mass spectrometer MS 30(AEL) at 70eV. Analytical data were obtained from the micro analytical data center at Cairo University.

3-Oxo-*N*-{4-[(pyrimidin-2-ylamino)sulphonyl]phenyl}-butanamide (3). Compound **3** was prepared as literature procedure [10].

2-Acetyl-3-(dimethylamino)-*N*-{4-[(pyrimidin-2-ylamino)-sulfonyl] phenyl}acrylamide (**4**). A mixture of anilide (**3**) (3.34 gm, 10.0 mmoles) and DMF/DMA (Dimethylformamide/ Dimethylacetal) (1.32 mL, 10.0 mmoles) in dry dioxane was heated under reflux for 3 hrs, then the solvent was evaporated under vacium. The solid product formed was collected by filtration and crystallized from ethanol as yellow crystals; yield 42%; mp 230°; ir: 3300 (NH), 3200 (NH), 1710 (CO), 1660 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 1.2 (s, 3H, CH_3), 2.47 (s, 6H, $2CH_3$), 7-7.7 (m, 8H, aromatic protons and 1H CH), 12.2 (br, 1H, NH); MS: m/z 389 (386 M^{-3}), 389 (387 M^{-2}). *Anal*. Calcd. for $C_{17}H_{19}N_5O_4S$: C, 52.42; H, 4.93; N, 17.97; S, 8.22. Found: C, 52.47; H, 5.12; N, 18.38; S, 8.33.

General procedure for preparation of 4-(3-Acetyl-6-amino-5-substituted-2-oxo-2*H*-pyridin-1-yl)-*N*-pyrimidin-2-ylbenzene-sulfonamide (8a-c, 14, 17, 20).

Method (A). A mixture of enaminone (**4**) (0.01 mole) and active methylene reagents (0.01 mole) in ethanol (30 mL) containing a catalytic amount of pipridine (0.1 mL) was heated under reflux for 6 hrs. The solid product formed was collected by filtration and crystallized from the proper solvent.

Method (B). A mixture of ethoxy methylene derivative (**28**) (0.01 mole) and active methylene reagents (0.01 mole) in ethanol (30 mL) containing a catalytic amount of pipridine (0.1 mL) was heated under reflux for 6 hrs. The solid product formed was collected by filtration and crystallized from the proper solvent.

4-(3-Acetyl-6-amino-5-cyano-2-oxo-2*H*-pyridin-1-yl)-*N*-pyrimidin-2-ylbenzene-sulfonamide (**8a**). Compound **8a** was obtained as colorless crystals from ethanol; yield 40%; mp 210°; ir: 3400 (NH_2), 3200 (NH), 2240 (CN), 1700 (CO), 1650 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 1.55 (s, 3H, CH_3), 3.56 (s, 1H, NH), 5.75 (s, 2H, NH_2), 6.6 (d, 2H, CH-pyrimidine-γ-protons), 6.8-7.6 (m, 5H, Ar-H), 8.4 (s, 1H, CH-C-4-pyridine ring); MS: m/z 410 (411 M^{+1}). *Anal*. Calcd. for $C_{18}H_{14}N_6O_4S$: C, 52.66; H, 3.43; N, 20.47; S, 7.80. Found: C, 52.71; H, 3.49; N, 20.52; S, 7.91.

5-Acetyl-2-amino-6-oxo-1-{4-[(pyrimidin-2ylamino)sulfonyl]-phenyl}-1,6-dihydropyridine-3-carboxamide (**8b**). Compound **8b** was obtained as colorless crystals from ethanol; yield 35%; mp 180°; ir: 3450 (NH_2), 3200 (NH_2), 1700 (CO), 1650 (CO) cm^{-1} ; ^{1}H nmr (DMSO-d_6) δ: 1.78 (s, 3H, CH_3), 7.0-8.0 (m, 8H, Ar-H), 8.4 (s, 2H, NH_2), 10.33 (s, 1H, NH), 11.87 (s, 2H, NH_2); MS: m/z 428 (423 M^{-5}). *Anal*. Calcd. for $C_{18}H_{16}N_6O_5S$: C, 50.46; H, 3.76; N, 19.62; S, 7.48. Found: C, 50.49; H, 3.80; N, 19.68; S, 7.52.

5-Acetyl-2-amino-6-oxo-1-{4-[(pyrimidin-2ylamino)sulfonyl]-phenyl}-1,6-dihydropyridine-3-caroxylic acid ethyl ester (**8c**). Compound **8c** was obtained as brown crystals from toluene/ ethanol; yield 30%; mp 170°; ir: 3400 (NH_2), 3200 (NH), 1730 (CO), 1670 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 1.03 (t, 3H, CH_3), 1.24 (s, 3H, acetyl-CH_3), 2.52 (s, 2H, NH_2), 4.025 (q, 2H, CH_2), 7.0-8.0 (m, 7H, Ar-H), 8.4 (s, 1H, CH-C-4-pyridine ring), 10.34 (s, 1H, NH); MS: m/z 457. *Anal*. Calcd. for $C_{20}H_{19}N_5O_6S$: C, 52.51; H, 4.19; N, 15.31; S, 7.01. Found: C, 52.58; H, 4.22; N, 15.36; S, 7.10.

4-(3,5-Diacetyl-6-methyl-2-oxo-2*H*-pyridin-1-yl)-*N*-pyrimidin-2-ylbenzene-sulfonamide (**14**). Compound **14** was obtained as colorless crystals from methanol; yield 30%; mp 205°; ir: 3200 (NH), 1700 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 1.59 (s, 6H, $2CH_3$), 2.05 (s, 3H, CH_3), 6.4 (d, 2H, CH-pyrimidine-γ-protons); 7.4-7.9 (m, 5H, Ar-H), 8.2 (s, 1H, CH-C-4-pyridine ring), 10.11 (s, 1H, NH); MS: m/z 426. *Anal*. Calcd. for $C_{20}H_{18}N_4O_5S$: C, 56.33; H, 4.25; N, 13.14; S, 7.52. Found: C, 56.39; H, 4.28; N, 13.18; S, 7.58.

4-(3,5-Diacetyl-6-hydroxy-2-oxo-2*H*-pyridin-1-yl)-*N*-pyrimidin-2-ylbenzene-sulfonamide (**17**). Compound **17** was obtained as yellow crystals from ethanol/acetic acid; yield 45%; mp 235°; ir: 3500 (OH), 3200 (NH), 1700 (CO), 1650 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 1.65 (s, 6H, $2CH_3$), 5.6 (s, 1H, OH), 6.6 (d, 2H, CH-pyrimidine-γ-protons), 7.4-7.8 (m, 5H, Ar-H), 8.2 (s, 1H, CH-C-4-pyridine ring), 9.63 (s, 1H, NH); MS: m/z 428. *Anal*. Calcd. for $C_{19}H_{16}N_4O_6S$: C, 53.27; H, 3.76; N, 13.08; S, 7.48. Found: C, 53.31; H, 3.80; N, 13.10; S, 7.51.

5-Cyano-2-methyl-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]-phenyl}-6-thioxo-1,6-dihydropyridine-3-carboxamide (**20**). Compound **20** was obtained as colorless crystals from ethanol; yield 48%; mp 248-250°; ir: 3300 (NH), 3200 (NH), 2220 (CN), 1650 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 2.06 (s, 3H, CH_3), 7.0-8.0 (m, 8H, Ar-H), 8.47 (s, 1H, NH), 10.27 (s, 1H, NH), 11.61 (s, 1H, NH); MS: m/z 426 (424 M^{-2}). *Anal*. Calcd. for $C_{18}H_{14}N_6O_3S_2$: C, 50.69; H, 3.31; N, 19.71; S, 15.04. Found: C, 50.72; H, 3.36; N, 19.76; S, 15.13.

3-Oxo-2-(*N*'-phenyl-hydrazinomethylene)-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}-butanamide (24).

Method (A). A mixture of enaminone (**4**) (0.01 mole) and phenyl hydrazine (0.01 mole) in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed during reflux (**25**) was collected by filtration and another product (**24**) was isolated after cooling the reaction mixture.

Method (B). A mixture of ethoxy methylene derivative (**28**) (0.01 mole) and phenyl hydrazine (0.01 mole) in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed during reflux (**25**) was collected by filtration and another product (**24**) was isolated after cooling the reaction mixture. Compound **24** was obtained as pale yellow crystals from ethanol; mp 220º; ir: 3400 (NH), 3200 (NH), 1710 (CO) cm^{-1}; MS: m/z 452. *Anal*. Calcd. for $C_{21}H_{20}N_6O_4S$: C, 55.74; H, 4.46; N, 18.57; S, 7.09. Found: C, 55.78; H, 4.50; N, 18.60; S, 7.12.

***N*-{4-[(Pyrimidin-2-ylamino)sulfonyl]phenyl}-5-methyl-*N*,1-diphenyl-1*H*-pyrazole-4-carbohydrazonamide (25).**

Method (A). A mixture of enaminone (**4**) (0.01 mole) and phenyl hydrazine (0.02 mole) in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed was collected by filtration and crystallized from ethanol as pale yellow crystals; yield 30%.

Method (B). A mixture of ethoxy methylene derivative (**28**) (0.01 mole) and phenyl hydrazine (0.02 mole) in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed was collected by filtration and crystallized from ethanol as pale yellow crystals; yield 62%; mp 260-262º; ir: 3400 (NH), 3200 (NH) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 2.5 (s, 3H, CH_3), 6.01 (s, 1H, NH), 6.55 (s, 1H, NH), 7.0-8.4 (m, 17H, Ar-H), 11.4 (s, 1H, NH); MS: m/z 524 (526 M^{+2}). *Anal*. Calcd. for $C_{27}H_{24}N_8O_2S$: C, 61.82; H, 4.61; N, 21.36; S, 6.11. Found: C, 61.86; H, 4.68; N, 21.40; S, 6.15.

3-Methyl-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}-1*H*-pyrazole-4-carbohydrazonamide (27).

Method (A). A mixture of enaminone (**4**) (0.01 mole) and excess of hydrazine hydrate in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed was collected by filtration and crystallized from 1,4-dioxane as colorless crystals.

Method (B). A mixture of ethoxy methylene derivative (**28**) (0.01 mole) and excess of hydrazine hydrate in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed was collected by filtration and crystallized from 1,4-dioxane as colorless crystals; yield 54%; mp 255º; ir: 3400 (NH), 3200 (NH), 1660 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 2.08 (s, 3H, CH_3), 2.52 (s, 1H, NH), 6.68-7.68 (m, 9H, Ar-H and NH proton), 10.23 (s, 1H, NH), 11.4 (s, 1H, NH); MS: m/z 358. *Anal*. Calcd. for $C_{15}H_{14}N_6O_3S$: C, 50.27; H, 3.94; N, 23.45; S, 8.95. Found: C, 50.34; H, 4.12; N, 23.49; S, 8.99.

2-Acetyl-3-ethoxy-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]-phenyl}acrylamide (**28**). A mixture of anilide (**3**) (0.01 mole) and triethylorthoformate (0.01 mole) in acetic anhydride (20 mL) was heated under reflux for 4 hrs, then the solvent was evaporated under vacuum. The solid product that formed was collected by filtration and crystallized from ethanol as colorless crystals; yield 55%; mp 240º; ir: 3300 (NH), 3100 (NH), 1700 (CO), 1650 (CO) cm^{-1} ; MS: m/z 390 (393 M^{+3}). *Anal*. Calcd. for $C_{17}H_{18}N_4O_5S$: C, 52.30; H, 4.65; N, 14.35; S, 8.21. Found: C, 52.34; H, 4.67; N, 14.38; S, 8.25.

4-(5-Methyl-1*H*-pyrazol-3-ylamino)-N-pyrimidin-2-yl-benzene-sulfonamide (29). A mixture of anilide (**3**) (0.01 mole) and excess of hydrazine hydrate was fused together in sand bath for 15 min., then pet. ether (60-80) was added. The solid product that formed was collected by filtration and crystallized from ethanol as colorless crystals; yield 40%; mp 168º; ir: 3400 (NH), 3343 (NH), 3221 (NH) cm^{-1} ; MS: m/z 330 (333 M^{+3}). *Anal*. Calcd. for $C_{14}H_{14}N_6O_2S$: C, 50.90; H, 4.27; N, 14.44; S, 7.71. Found: C, 50.94; H, 4.29; N, 14.48; S, 7.76.

2-Amino-4-methyl-6-oxo-*N*-{4-[(pyrimidin-2-ylamino)-sulfonyl]phenyl}-1,6-dihydro-pyridine-3-carboxamide (**30**). A mixture of anilide (**3**) (0.01 mole) and cyanoacetamide (0.01 mole) in ethanol (30 mL) containing a catalytic amount of pipridine (0.1 mL) was heated under reflux for 8 hrs. The solvent was evaporated under vacuum. The solid product that formed was collected by filtration and crystallized from ethanol as colorless crystals; yield 30%; mp 240º; ir: 3400 (NH_2), 3100 (NH), 1650 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 2.5 (s, 3H, CH_3), 3.18 (s, 1H, NH), 5.59 (s, 2H, NH_2), 6.47-7.54 (m, 8H, Ar-H), 8.25 (s, 2H, NH_2); MS: m/z = 400. *Anal*. Calcd. for $C_{17}H_{16}N_6O_4S$: C, 50.99; H, 4.03; N, 20.99; S, 8.01. Found: C, 51.14; H, 4.08; N, 21.14; S, 8.06.

3-Hydroxyimino-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]-phenyl}butanamide (**31**). To a mixture of anilide (**3**) (0.01 mole) and hydroxylamine hydrochloride (0.01 mole) in ethanol (20 mL), sodium acetate (0.01 mole) was added. The reaction mixture was heated under reflux for 2 hrs. The solid product formed was collected by filtration and crystallized from dioxane as colorless crystals; yield 50%; mp 250º; ir: 3500 (OH), 3400 (NH), 3200 (NH), 1650 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 2.5 (s, 3H, CH_3), 3.32 (s, 1H, OH), 5.97 (s, 2H, CH_2), 6.54-8.39 (m, 8H, Ar-H and NH proton), 11.22 (s, 1H, NH); MS: m/z 349 (345 M^{-4}). *Anal*. Calcd. for $C_{14}H_{15}N_5O_4S$: C, 48.13; H, 4.33; N, 20.05; S, 9.18. Found: C, 48.22; H, 4.42; N, 20.08; S, 9.25.

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