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# STUDIES WITH FUNCTIONALLY SUBSTITUTED ENAMINES: SYNTHESIS OF 2-AROYL-3-DIMETHYLAMINO-2-PROPENENITRILE AND THEIR REACTIVITY TOWARD NITROGEN NUCLEOPHILES

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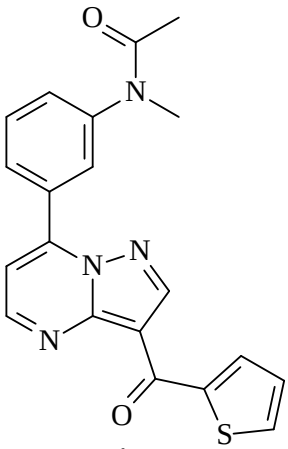
**Abstract** – A facile and efficient synthesis of 2-substituted 3-dimethylamino-2-propenenitrile **4a-c** is described. Reaction of **4a-c** with hydrazine hydrate afforded 3-substituted-1*H*-4-pyrazole carbonitrile **9a-c**. Compounds **4a-c** reacted with 5-methyl-1*H*-pyrazol-3-amine to give 7-substituted pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **12a-c** and 2-substituted 5-aminopyrazolo[1,5-*a*]pyrimidine **16a,b**, and with 1*H*-benzo[*d*]imidazol-2-amine to give 3-substituted 2-aminobenzo[4,5]imidazo[1,2-*a*]pyrimidine **19a,b** and 4-substituted benzo[4,5]imidazo[1,2-*a*]pyrimidine 3-carbonitrile **21c**. The structures of compounds obtained were deduced based on $^{1}$HNMR, HMBC-$^{15}$N and NOE difference experiments.

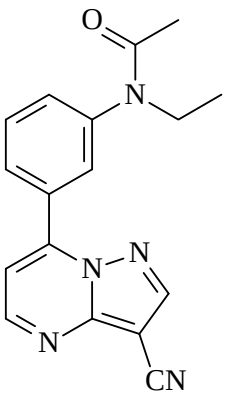
## INTRODUCTION

Interest in biological active pyrazolo[1,5-*a*]pyrimidines has recently been revived.[1,2] Indiplon **1** is a pyrazolo[1,5-*a*]pyrimidine derivative. It is a novel treatment for insomnia with sedative and hypnotic properties. It acts through allosteric potentiation of the $GABA_A$ receptor with a higher affinity than zaleplon **2**, which is also a sedative/hypnotic drug used for insomnia.[3] Indiplon is expected to be available on the market[4] in 2007. Pyrazolo[1,5-*a*]pyrimidine **3** has been reported recently as a novel class of p21 chemoselective anti-proliferative agents.[5] As a part of our program aimed at developing efficient syntheses for biologically interesting polyfunctional heteroaromatics, utilizing inexpensive and readily obtainable 2-aroyl-3-dimethylamino-2-propenenitrile **4a-c** as starting materials, we report here efficient synthetic routes to 2-substituted-5-aminopyrazolo[1,5-*a*]pyrimidine **16a,b**, 3-substituted 2-aminobenzo[4,5]imidazo[1,2-*a*]pyrimidine **19a,b** and 4-substituted-benzo[4,5]imidazo[1,2-*a*]pyrimidine 3-carbonitrile **21c**.



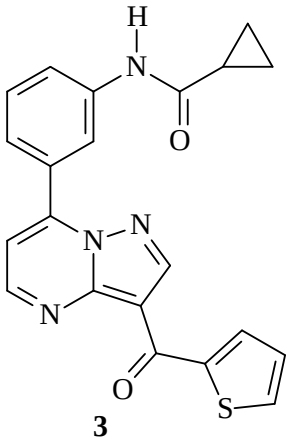
**1**

Indiplon



**2**

Zaleplon

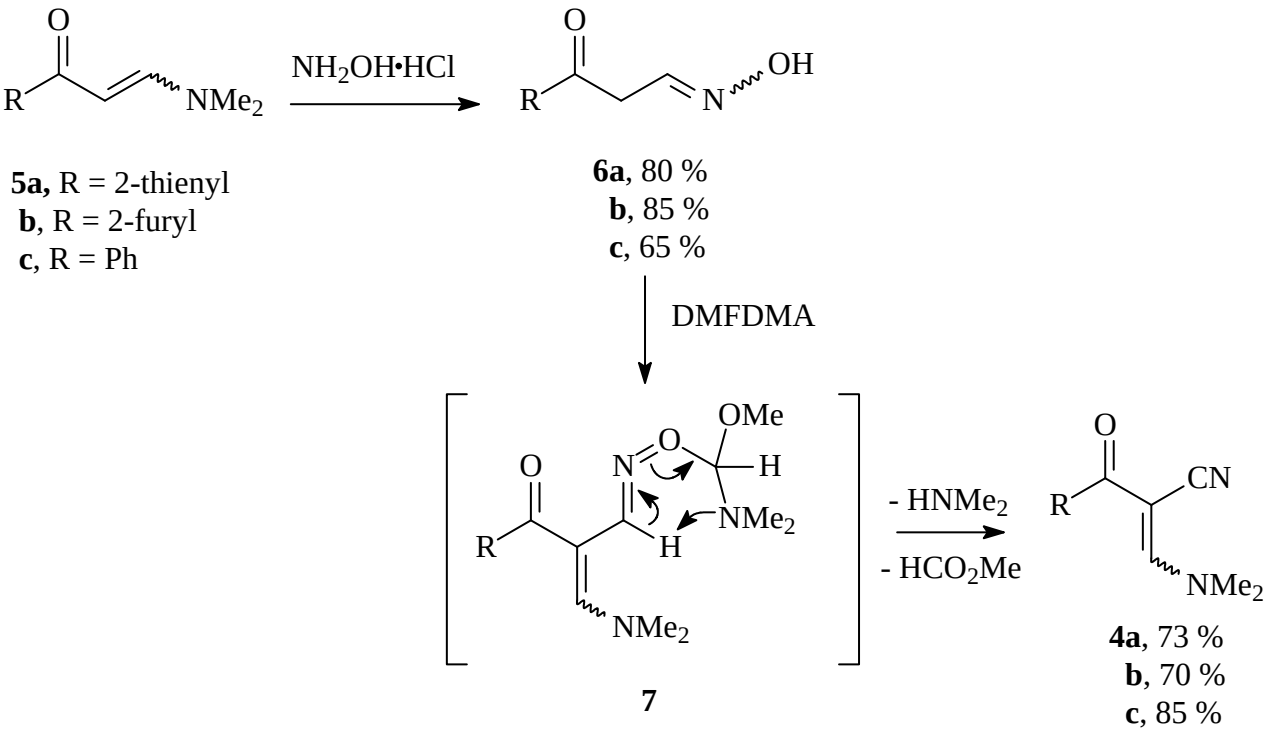


**3**

## RESULTS AND DISCUSSION

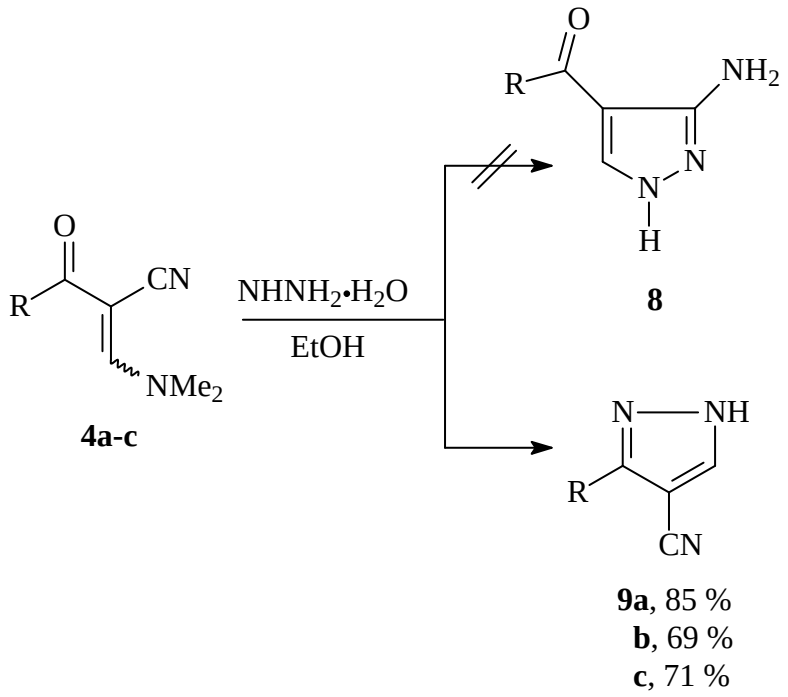
Previously, we have utilized 2-benzoyl-3-dimethylamino-2-propenenitrile **4c** as building blocks for synthesis of aminoazoles[6] and azolopyrimidines.[7,8] In conjunction to this work, the reactivity of **4** toward hydrazines as well as aminoazoles was investigated. Compound **4** could be prepared *via* condensing 3-oxoalkanonitrile with dimethylformamide dimethylacetal. Earlier, we utilized this methodology for synthesis of **4c**[7]. However trials to synthesize derivatives of **4** (R = substituted aryl or heteroaryl) were hindered by the fact that synthesis of such derivatives are multistage. We looked to alternate approach for synthesis of these derivatives *via* converting the aldoximes **6a-c** into nitriles as we described earlier for the synthesis of arylhydrazonopropionitrile from arylhydrazonopropionaldehyde oxime.[9] We found that compounds **4a-c** are produced *via* the corresponding aldoximes **6a-c**, generated from enaminones **5a-c** and hydroxylamine hydrochloride in ethanol / sodium acetate at ambient temperature *via* dimethylamine elimination. The aldoximes **6a-c** were found to exist as an equilibrium mixture of *syn* and *anti* forms based on $^1$H NMR which revealed two doublets at $\delta_H$ = ca. 3.92 and 4.02 ppm for $CH_2$ protons and two triplets at $\delta_H$ = ca. 7.00 and 7.50 ppm for aldoxime CH in addition of two signals at $\delta_H$ = ca. 11.23 and 10.84 ppm for OH protons. Conversion to the corresponding **4a-c** was achieved by treatment with dimethylformamide dimethyl acetal (DMFDMA). The reactions are exothermic and the heat generated is sufficient to drive the reactions to completion within few minutes. It is believed that **7** is initially formed followed by elimination of dimethylamine and methyl formate *via* a six membered transition state (cf. Scheme 1). Although **4a-c** could be in either *E* or *Z* form, however only one form has been detected as indicated in the $^1$H NMR spectral data. Moreover, it is not easy to assign the *E* or *Z* structure for the formed product based on given data. The reported synthesis[5] of [(3-amino-1*H*-pyrazol-4-yl)thiophen-2-yl]methanone **8a** has attracted our attention, as this 3-aminopyrazole derivative might be an excellent potential precursor for synthesis of pyrazolo[1,5-*a*]pyrimidines. Some references[10-12] described the use of β-oxoarylpropanenitriles, in the preparation of substituted enaminonitriles of general structure **4** that

condensed with hydrazine hydrate, giving rise to a series of [(3-amino-1*H*-pyrazol-4-yl)aryl]methanone of general structure **8** and / or 3-aryl-1*H*-4-pyrazole carbonitriles of general structure **9**. The obtained products depended on the applied reaction conditions, or the electronic and steric effect of the substituted aromatic ring. Herewith, we report the reaction of 2-aroyl-3-(dimethylamino)-2-propenenitrile **4a-c** with hydrazine hydrate in ethanol to afford 3-aryl-1*H*-4-pyrazole carbonitrile **9a-c** as the sole product (cf. Scheme 2). In addition, we examined the reaction products of **4a-c** with 5-methyl-1*H*-pyrazol-3-amine **10** and 1*H*-benzo[*d*]imidazol-2-amine **18** based on the results of two-dimensional HMBC-$^{15}$N experiment and NOE difference experiment.




**Scheme 1**

Compounds **4a-c** reacted with 5-methyl-1*H*-pyrazol-3-amine **10** to yield products whose structures depend on the applied reaction conditions and the reactivity of the ketone. Thus in ethanolic / piperidine, products of addition and subsequent water and dimethylamine elimination were obtained. Two isomeric pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile structures **12** and **15** seemed thus possible. Initial addition at exocyclic amino group, would yield **11** that readily cyclize into **12**. While initial addition involving endocyclic nitrogen atom N-2, Michael adducts **14** would be formed **t**hat cyclized further to yield **15** (cf. Scheme 3). The one dimensional $^{1}$H NMR spectra is not supportive for discrimination between **12** and **15**. However, the correlation observed in the HMBC-N$^{15}$ measurements enabled establishing structures **12a-c** as products of the reaction**.** Thus, HMBC-N$^{15}$ for compound **12a** for example showed chemical shift for



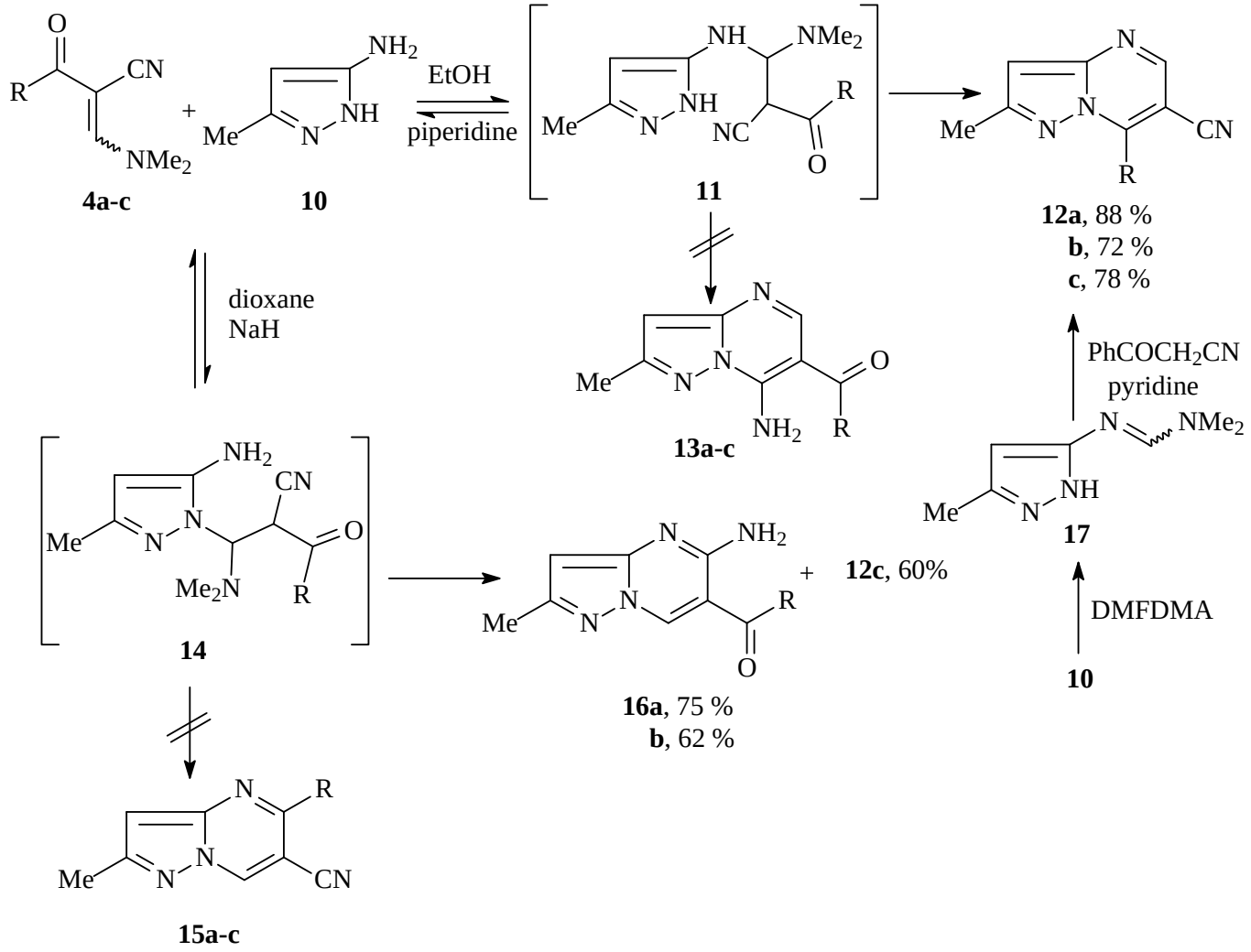

**Scheme 2**

N-7a at δ ($^{15}$N) = 270 ppm, N-4 at δ ($^{15}$N) = 310 ppm and N-1 at δ ($^{15}$N) = 335 ppm. Crosspeak for the coupling of pyrimidine proton was observed at δ ($^{1}$H) = 8.70 ppm with the bridgehead nitrogen atom N-7a at δ ($^{15}$N) = 270 ppm ($^{4}J$, N-7a). Alternative structure **15** (bearing the pyrimidine-H on C-7) would show this coupling to be with N-4 in the spectrum at δ ($^{15}$N) = 310 ppm. Coupling of methyl protons at δ ($^{1}$H) = 2.41 ppm with N-7a at δ ($^{15}$N) = 270 ppm $^{4}J$ (Me-H, N-7a), and H-3 proton at δ ($^{1}$H) = 6.84 ppm with N-1 at δ ($^{15}$N) = 335 ppm $^{3}J$ (H-3, N-1) were also observed. The correlations in the HMBC-N$^{15}$ measurements for compound **12c** showed similar coupling correlations as for **12a**. Compound **12c** (R = Ph) has been described earlier in our laboratory[7] from either reaction of (5-methyl-1*H*-pyrazol-3-yl)-dimethylaminoformamidine **17** with benzoylacetonitrile, or reaction of 5-methyl-1*H*-pyrazol-3-amine **10** with **4c** and proved to be identical with the product obtained (cf. Scheme 3). On the other hand, refluxing **4a-b** with 5-methyl-1*H*-pyrazol-3-amine **10** in dioxane in the presence of sodium hydride produce a product of addition *via* dimethylamine elimination and subsequent cyclization at the cyano group. These could be formulated as aminopyrazolo[1,5-a]pyrimidines derivatives **13a,b** or **16a,b** *via* intermediaries **11** or **14** (cf. Scheme 3). Measurements of HMBC-N,[15] established structures **16** in which, the amino group is on C-5 position. HMBC-N$^{15}$ for compound **16a** for example showed chemical shift for N-7a at δ ($^{15}$N) = 285 ppm, N-4 at δ ($^{15}$N) = 310 ppm and N-1 at δ ($^{15}$N) = 340 ppm. Crosspeak coupling was observed for the pyrimidine proton at δ ($^{1}$H) = 8.69 ppm with N-4 at δ ($^{15}$N) = 310 ppm, $^{4}J$ (H-7, N-4). Alternate structure **13**, would show a coupling correlation $^{4}J$ between H-5 at δ ($^{1}$H) = 8.69 ppm and N-7a at δ ($^{15}$N) = 285 ppm. Moreover, structure **13**, would show crosspeak coupling for the $NH_2$ at δ ($^{1}$H) = 9.01 ppm and

9.13 ppm with N-1 at δ ($^{15}$N) = 340 ppm $^{4}J$ ($NH_2$, N-1). Thus, structure **13** can be ruled out. Coupling of methyl protons at δ ($^{1}$H) = 2.41 ppm with N-7a at δ ($^{15}$N) = 285 ppm $^{4}J$ (Me-H, N-7a) and of H-3 proton at δ ($^{1}$H) = 6.75 ppm with N-1 at δ ($^{15}$N) = 340 ppm. $^{3}J$ (3-H, N-1) were also observed. It should be noted that compound **4c** (R = Ph) under same reaction condition with **10** led exclusively to the pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **12c** as the sole product *via* intermediary **11**. This was somewhat surprising, as we had expected that at the same reaction condition, intermediary **14** would be involved. Consequently, it can be considered that intermediaries **11** and **14** exist in equilibrium with 5-methyl-1*H*-pyrazol-3-amine **10** and **4a-c**, as outlined in (Scheme 3), which are in principle, competing with one another. The cyclization of **11** and **14** would disturb that equilibrium, resulting in one of them dominating the other. To extend the synthetic use of the enaminonitriles derivatives **4a-c**, we investigated their reactivity with 1*H*-benzo[*d*]imidazol-2-amine **18**. Thus, reaction of **4a,b** with **18** in dioxane in the presence of NaH led to a product of addition **19a,b** or **20a,b** *via* dimethylamine elimination and subsequent cyclization at the cyano group (cf. Scheme 4). The structures of **19a,b** were elucidated based on NOE difference experiments that indicated a proximity between 4-H at δ = 8.93 ppm and 5-H at δ = 7.81 ppm for compound **19a.** Under same reaction condition, compound **4c** (R = Ph), reacted with **18**, to give exclusively a nitrile that may be assigned as structure **21c** or **22c**. NOE difference experiments indicated proximity of 4-H at δ = 9.17 ppm and 5-H at δ = 7.82 ppm, hence confirming structure **21c** to be the isolated product. Compound **21c** was previously obtained[7] in our laboratory as product of reaction of **4c** with **18** in pyridine and proved to be identical with the product obtained. The formation of **19a,b** and **21c** in the process corresponded well with our assumption of presence of equilibrium intermediaries analogue to that postulated in Scheme 3, in which intermediary involving attack at ring nitrogen atom N-2 dominate. This then either cyclizes at the cyano group, furnishing **19a,b** or closes preferentially to the ketone to yield **21c**. In conclusion, we have developed a general, simple, and efficient method for the synthesis of dimethylaminopropenenitrile. It demonstrated good generality in obtaining derivatives. In addition, we were able to establish the mode of reactions of these 2-aroyl-3-(dimethylamino)-2-propenenitrile **4a-c** with aminoheterocyclic compounds in different applied reaction conditions.

## EXPERIMENTAL

Melting points were determined on a Shimadzu-Gallenkamp apparatus and are uncorrected. Elemental analysis was obtained by means of a LECO CHNS-932 Elemental Analyzer. NMR spectra were measured using a Bruker DPX 400 MHz superconducting spectrometer, $^{1}$HMBC-$^{15}$N and NOE spectra were measured using Bruker Avance II 600 MHz superconducting spectrometer, and FT-IR measurements were from a Perkin Elmer 2000 FT-IR system. Mass spectrometric analysis was carried out on a VG-Autospec-Q high performance tri-sector GC/MS/MS.



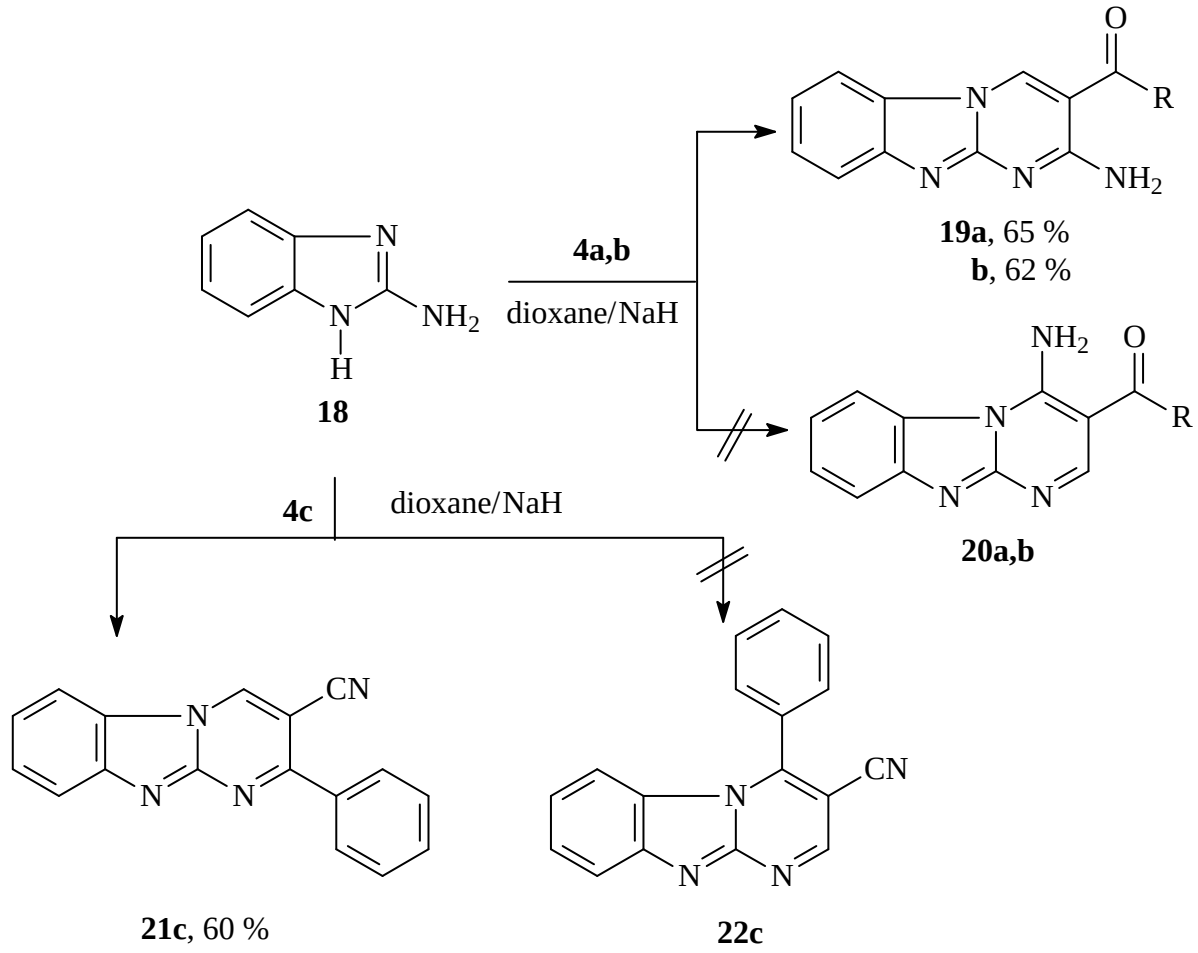

**Scheme 3**

**Reaction of enaminones 5a-c with hydroxylamine Hydrochloride for the preparation of 6a-c.**

To a cold solution of (10 mmol) of each of compound **5a-c** in EtOH (10 mL), a prepared solution of hydroxylamine hydrochloride (0.695g, 10 mmol) and sodium acetate (15 mmol) in water (10 mL) was added dropwise. The mixture was stirred for 3h and allowed to warm up to rt. During that time a precipitate was formed. The reaction mixture was filtered off and recrystallized from the appropriate solvent.

**3-Oxo-3-(2-thienyl)propanal oxime 6a.**

This compound was obtained as white crystals from EtOH, yield (80 %, 1.35 g); mp 113-114 $^{o}$C; IR (KBr): 3197 (OH) and 1653 cm$^{-1}$ (CO); MS m/z $(M)^{+}$ = 169; $^{1}$H NMR (DMSO-$d_6$): δ = 3.92 (d, 2H, $J$ = 5.0 Hz, $CH_2$), 4.02 (d, 2H, $J$ = 5.0 Hz, $CH_2$), 7.00 (t, 1H, $J$ = 5 Hz, oxime-CH), 7.26 (m, 2H, thienyl-H), 7.50 (t, 1H, $J$ = 5 Hz, oxime-CH), 8.02-8.05 (m, 4H, thienyl-H), 10.84 (s, 1H, OH), 11.23 (s, 1H, OH). Anal. Calcd for $C_7H_7NO_2S$: (169.20): C, 49.69; H, 4.17; N, 8.28; S, 18.95. Found: C, 49.82; H, 4.17; N, 8.46; S, 18.84.




**Scheme 4**

**3-(2-Furyl)-3-oxopropanal oxime 6b.**

This compound was obtained as white crystals from EtOH, yield (85 %, 1.30 g); mp 128-130 $^{o}$C; IR (KBr): 3199 (OH) and 1665 cm$^{-1}$ (CO); MS m/z $(M)^{+}$ = 153; $^{1}$H NMR (DMSO-$d_6$): δ = 3.77 (d, 2H, $J$ = 5.0 Hz, $CH_2$), 3.88 (d, 2H, $J$ = 5.0 Hz, $CH_2$), 6.73 (d, 2H, $J$ = 5 Hz, furyl H-3), 6.98 (t, 1H, $J$ = 5 Hz, oxime-CH), 7.44 (t, 1H, $J$ = 5 Hz, oxime-CH), 7.52-7.54 (m, 2H, furyl-H), 8.02 (t, 2H, $J$ = 5 Hz, furyl H-5), 10.83 (s, 1H, OH), 11.21 (s, 1H, OH). Anal. Calcd for $C_7H_7NO_3$ (153.14): C, 54.90; H, 4.61; N, 9.15. Found: C, 54.89; H, 4.60; N, 9.33.

**3-Oxophenylpropanal oxime 6c**

This compound was obtained as yellow crystals from benzene, yield (65 %, 1.05 g); mp 94-95 $^{o}$C; IR (KBr): 3210 (OH) and 1687 cm$^{-1}$ (CO); MS m/z $(M)^{+}$ = 163; $^{1}$H NMR (DMSO-$d_6$): δ = 3.98 (d, 2H, $J$ = 4.8 Hz, $CH_2$), 4.08 (d, 2H, $J$ = 4.8 Hz, $CH_2$), 7.05 (t, 1H, $J$ = 5 Hz, oxime-CH), 7.33-7.40 (m, 4H, arom-H), 7.51-7.56 (m, 6H, arom-H), 7.66 (t, 1H, $J$ = 5 Hz, oxime-CH), 10.81 (s, 1H, OH),11.19 (s, 1H, OH). Anal. Calcd for $C_9H_9NO_2$ (163.18): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.53; H, 5.60; N, 8.78.

**Reaction of aldoxime 6a-c with dimethylformamide dimethylacetal for the preparation of 4a-c.**

A mixture of each of compound **6a-c** (10 mmol) and excess dimethylformamide dimethylacetal (3 mL) was stirred in MeCN (3 mL) for 10 min. (exothermic reaction), then allowed to cool to ambient temperature. During that time a precipitate was formed. The reaction mixture was filtered off and recrystallized from EtOH. Compound **4c** was reported earlier and proved to be identical with the product obtained mp 128-129$^{o}$C, lit.[7] mp 129$^{o}$C.

**3-(Dimethylamino)-2-thienoyl-2-propenenitrile 4a**

This compound was obtained as yellow crystals, yield (73 %, 1.50 g); mp 153-154 $^{o}$C; IR (KBr): 2194 (CN) and 1633 cm$^{-1}$ (CO); MS m/z $(M)^{+}$ = 206; $^{1}$H NMR (DMSO-$d_6$): δ = 3.36 (s, 3H, NMe), 3.39 (s, 3H, NMe), 7.20 (t, 1H, *J* = 5 Hz, thienyl H-4), 7.89 (d, 1H, *J* = 5 Hz, thienyl H-3), 7.99 (d, 1H, *J* = 5 Hz, thienyl H-5), 8.05 (s, 1H, amidine-H). Anal. Calcd for $C_{10}H_{10}N_2OS$ (206.26): C, 58.23; H, 4.89; N, 13.58; S, 15.54. Found: C, 58.23; H, 4.63; N, 13.12; S, 15.32.

**3-(Dimethylamino)-2-furanoyl-2-propenenitrile 4b**

This compound was obtained as yellow crystals, yield (70 %, 1.35 g); mp 155 $^{o}$C; IR (KBr): 2196 (CN) and 1643 cm$^{-1}$ (CO); MS m/z $(M)^{+}$ = 190; $^{1}$H NMR (DMSO-$d_6$): δ = 3.31 (s, 3H, NMe), 3.38 (s, 3H, NMe), 6.68 (t, 1H, *J* = 5 Hz, furyl H-4), 7.37 (d, 1H, *J* = 5 Hz, furyl H-3), 7.93 (d, 1H, *J* = 5 Hz, furyl H-5), 8.05 (s, 1H, amidine-H). Anal. Calcd for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 62.92; H, 5.22; N, 14.96.

**2-Benzoyl-3-(dimethylamino)-2-propenenitrile 4c**

This compound was obtained as beige crystals, yield (85 %, 1.70 g); mp 128-129 $^{o}$C; IR (KBr): 2209 (CN) and 1680 cm$^{-1}$ (CO); MS m/z $(M)^{+}$ = 200; $^{1}$H NMR (DMSO-$d_6$): δ = 3.16 (s, 3H, NMe), 3.38 (s, 3H, NMe), 7.36-7.45 (m, 3H, arom. H), 7.65-7.92 (m, 2H, arom. H), 8.00 (s, 1H, amidine-H). Anal. Calcd for $C_{12}H_{12}N_2O$ (200.23): C, 71.98; H, 6.04; N, 13.99. Found: C, 71.87; H, 5.92; N, 14.06.

**Reaction of 4a-c with hydrazine hydrate for the preparation of 9a-c.**

A mixture of each of compound **4a-c** (10 mmol) and excess of hydrazine hydrate 85% (2 mL) was heated under reflux in EtOH (10 mL) for 30min. The solvent was removed under vacuum to deposit a solid that was recrystallized from absolute EtOH. Compound **9c** was reported earlier, and proved to be identical with the product obtained mp 134-136$^{o}$C, lit. [11] mp 136-138$^{o}$C.

**3-(2-Thienyl)-1*H*-4-pyrazole carbonitrile 9a**

This compound was obtained as buff crystals, yield (85 %, 1.50 g); mp 205-206 $^{o}$C; IR (KBr): 3323 (NH), 2212 cm$^{-1}$ (CN); MS m/z $(M)^{+}$ = 175; $^{1}$H NMR (DMSO-$d_6$): δ = 7.31 (t, 1H, *J* = 5 Hz, thienyl H-4), 8.06

(d, 1H, *J* = 5 Hz, thienyl H-3), 8.12 (d, 1H, *J* = 5 Hz, thienyl H-5), 8.48 (s, 1H, pyrazolyl H-5), 13.80 (br s, 1H, NH). Anal. Calcd for $C_8H_5N_3S$ (175.21): C, 54.84; H, 2.88; N, 23.98; S, 18.30. Found: C, 54.60; H, 3.00; N, 23.89; S, 18.26.

**3-(2-Furyl)-1*H*-4-pyrazole carbonitrile 9b**

This compound was obtained as buff crystals, yield (69 %, 1.10 g); mp 152-154 $^oC$; IR (KBr): 3320 (NH), 2233 $cm^{-1}$ (CN); MS m/z $(M)^+$ = 159; $^1H$ NMR (DMSO-$d_6$): δ = 6.69 (t, 1H, *J* = 5 Hz, furyl H-4), 6.97 (d, 1H, *J* = 5 Hz, furyl H-3), 7.89 (d, 1H, *J* = 5 Hz, furyl H-5), 8.53 (s, 1H, pyrazolyl H-5), 13.97 (br s, 1H, NH).. Anal. Calcd for $C_8H_5N_3O$ (159.15): C, 60.38; H, 3.17; N, 26.40. Found: C, 59.98; H, 3.38; N, 26.75.

**3-Phenyl-1*H*-4-pyrazole carbonitrile 9c**

This compound was obtained as colorless needles, yield (71 %, 1.20 g); mp 134-136 $^oC$; IR (KBr): 3320 (NH), 2233 $cm^{-1}$ (CN); MS m/z $(M)^+$ = 169; $^1H$ NMR (DMSO-$d_6$): δ = 7.32-7.60 (m, 3H, arom. H), 7.82-7.97 (m,2H, arom. H), 8.71 (s, 1H, pyrazolyl H-5), 13.80 (br s, 1H, NH). Anal. Calcd for $C_{10}H_7N_3$ (169.19): C, 70.99; H, 4.17; N, 24.84. Found: C, 71.14; H, 4.20; N, 24.98.

**Reaction of 4a-c with 5-methyl-1*H*-pyrazol-3-amine for the preparation of 12a-c.**

A mixture of each of compound **4a-c** (10 mmol) and 5-methyl-1*H*-pyrazol-3-amine (0.79 g, 10 mmol) was heated under reflux in EtOH (10 mL) in the presence of piperidine (0.5 mL) for 1hr. The reaction mixture was reduced under vacuo. The reaction mixture poured onto water. Acidified with HCl to deposit a solid that was recrystallized from the appropriate solvent. Compound **12c** was also obtained following reaction condition for the preparation of compounds **16a,b**. Compound **12c** was reported earlier and proved to be identical with the product obtained mp 175-176 $^oC$, lit.[7] mp 171 $^oC$

**2-Methyl-7-(2-thienyl)pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile 12a**

This compound was obtained as yellow needles from EtOH, yield (88 %, 2.10 g); mp 186-187 $^oC$; IR (KBr): 2219 $cm^{-1}$ (CN); MS m/z $(M)^+$ = 240; $^1H$ NMR (DMSO-$d_6$): δ = 2.41 (s, 3H, $CH_3$), 6.75 (s, 1H, H-3), 7.38 (t, 1H, *J* = 5 Hz, thienyl H-4), 8.23 (d, 1H, *J* = 5 Hz, thienyl H-3), 8.51 (d, 1H, *J* = 5 Hz, thienyl H-5), 8.70 (s, 1H, H-5). Anal. Calcd for $C_{12}H_8N_4S$ (240.28): C, 59.98; H, 3.36; N, 23.32; S, 13.34. Found: C, 60.22; H, 3.27; N, 23.12; S, 13.24.

**7-(2-Furyl)-2-methylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile 12b**

This compound was obtained as yellow crystals from dioxane, yield (72 %, 1.6 g); mp 210-211 $^oC$; IR (KBr): 2225 $cm^{-1}$ (CN); MS m/z $(M)^+$ = 224; $^1H$ NMR (DMSO-$d_6$): δ = 2.55 (s, 3H, $CH_3$), 6.82 (s, 1H, H-3), 7.03 (t, 1H, *J* = 5 Hz, furyl H-4), 8.38 (d, 1H, *J* = 5 Hz, furyl H-3), 8.53 (d, 1H, *J* = 5 Hz, furyl H-

5), 8.75 (s, 1H, H-5). Anal. Calcd for $C_{12}H_8N_4O$ (224.22): C, 64.28; H, 3.60; N, 24.99. Found: C, 63.95; H, 3.70; N, 24.77.

**2-Methyl-7-phenylpyrazolo[1,5-a]pyrimidine-6-carbonitrile 12c**

This compound was obtained as yellow crystals from dioxane, yield (78 %, 1.8 g); mp 175-176 $^oC$; IR (KBr): 2221 $cm^{-1}$ (CN); MS m/z $(M)^+$ = 234; $^1H$ NMR (DMSO-$d_6$): $\delta$ = 2.41 (s, 3H, $CH_3$), 6.83 (s, 1H, H-3), 7.64-7.67 (m, 3H, arom. H), 7.87 (d, 2H, *J* = 7 Hz, arom. H), 8.82 (s, 1H, H-5). Anal. Calcd for $C_{142}H_{10}N_4$ (234.25): C, 71.78; H, 4.30; N, 23.92. Found: C, 71.81; H, 4.38; N, 23.94.

**Reaction of 4a-c with 5-methyl-1*H*-pyrazol-3-amine for the preparation of 16a,b.**

A mixture of each of compound **4a,b** (10 mmol) and 5-methyl-1*H*-pyrazol-3-amine (0.79 g, 10 mmol) was heated under reflux in dioxane (10 mL) in the presence of NaH (0.24 g, 10 mmol) for 1hr., during that time a precipitate was formed The reaction mixture was poured onto water, acidified with HCl to deposit a solid, that was recrystallized from absolute EtOH.

**(5-Amino-2-methylpyrazolo[1,5-*a*]pyrimidin-6-yl)(2-thienyl)methanone 16a**

This compound was obtained as yellowish needles, yield (75 %, 1.90 g); mp 224-225 $^oC$; IR (KBr): 3340 ($NH_2$) and 1648 $cm^{-1}$ (CO); MS m/z $(M)^+$ = 258; $^1H$ NMR (DMSO-$d_6$): $\delta$ = 2.43 (s, 3H, $CH_3$), 6.41 (s, 1H, H-3), 7.26 (t, 1H, *J* = 5 Hz, thienyl H-4), 7.76 (d, 1H, *J* = 5 Hz, thienyl H-3), 8.01 (d, 1H, *J* = 5 Hz, thienyl H-5), 8.68 (s, 1H, H-7). 8.95 and 9.13 (br , 2H, $NH_2$), Anal. Calcd for $C_{12}H_{10}N_4OS$ (258.30): C, 55.80; H, 3.90; N, 21.69; S, 12.41. Found: C, 55.57; H, 3.94; N, 21.71; S, 12.28.

**(5-Amino-2-methylpyrazolo[1,5-*a*]pyrimidin-6-yl)(2-furyl)methanone 16b**

This compound was obtained as yellowish crystals from dioxane, yield (62 %, 1.5 g); mp 200-201 $^oC$; IR (KBr): 3338 $cm^{-1}$ ($NH_2$); MS m/z $(M)^+$ = 242; $^1H$ NMR (DMSO-$d_6$): $\delta$ = 2.55 (s, 3H, $CH_3$), 6.20 (br, 2H, $NH_2$), 6.83 (s, 1H, H-3), 7.04 (t, 1H, *J* = 5 Hz, furyl H-4), 8.39 (d, 1H, *J* = 5 Hz, furyl H-3), 8.54 (d, 1H, *J* = 5 Hz, furyl H-5), 8.76 (s, 1H, H-7). Anal. Calcd for $C_{12}H_{10}N_4O_2$ (242.24): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.62; H, 4.23; N, 23.12.

**Reaction of 4a-c with 1*H*-benzo[*d*]imidazol-2-amine for the preparation of 19a,b and 21c.**

A mixture of each of compound **4a-c** (10 mmol) and 1*H*-benzo[*d*]imidazol-2-amine (1.33 g, 10 mmol) was heated under reflux in dioxane (10 mL) in the presence of NaH 60% (0.4 g, 10 mmol) for 1h, during time a precipitate is formed The reaction mixture was poured onto water, acidified with HCl to deposit a solid, that was recrystallized from absolute EtOH. Compound **21c** was reported earlier and proved to be identical with the product obtained mp >300 $^oC$, lit.mp [7] >300 $^oC$.

**2-Aminobenzo[4,5]imidazo[1,2-*a*]pyrimidin-3-yl)(2-thienyl)methanone 19a**

This compound was obtained as beige crystals from dioxane, yield (65 %, 1.90 g); mp 287-289 $^{o}$C; IR (KBr): 3425 and 3392 ($NH_2$) and 1641 $cm^{-1}$ (CO); MS m/z $(M)^+$ = 294; $^1$H NMR (DMSO-$d_6$): δ = 7.29 (t, 1H, *J* = 5 Hz, thienyl H-4), 7.43 (t, 1H, *J* = 7.6 Hz, arom-H), 7.57 (t, 1H, *J* = 7.8 Hz, arom-H), 7.80-7.82 (m, 2H, thienyl H-3 and arom-H), .8.53 (d, 1H, *J* = 8.0 Hz, arom-H), 8.93 (s, 1H, arom-H), 9.49 (br, 2H, $NH_2$). Anal. Calcd for $C_{15}H_{10}N_4OS$ (294.33): C, 61.21; H, 3.42; N, 19.04; S, 10.89. Found: C, 61.19; H, 3.49; N, 19.17; S, 10.85.

**2-Aminobenzo[4,5]imidazo[1,2-*a*]pyrimidin-3-yl)(2-furyl)methanone 19b**

This compound was obtained as brown crystals from dioxane, yield (62 %, 1.72 g); mp 240-242 $^{o}$C; IR (KBr): 3425 and 3386 ($NH_2$) and 1648 $cm^{-1}$ (CO); MS m/z $(M)^+$ = 278; $^1$H NMR (DMSO-$d_6$): δ = 6.99 (t, 1H, *J* = 5 Hz, furyl H-4), 7.16 (d, 1H, *J* = 5 Hz, furyl H-3), 7.40 (t, 1H, *J* = 7.6 Hz, arom-H), 7.62 (t, 1H, *J* = 8.0 Hz, arom-H), 7.33-7.35 (m, 2H, furyl 3-H and arom-H), .8.53 (d, 1H, *J* = 8.0 Hz, arom-H), 9.19 (s, 1H, arom-H), 9.50 (br, 2H, $NH_2$). Anal. Calcd for $C_{15}H_{10}N_4O_2$ (278.27): C, 64.74; H, 3.62; N, 20.13. Found: C, 64.57; H, 3.33; N, 20.26.

**2-Phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile 21c**

This compound was obtained as beige crystals from EtOH, yield (60 %, 1.62 g); mp > 300 $^{o}$C; IR (KBr): 2229 $cm^{-1}$ (CN); MS m/z $(M)^+$ = 270; $^1$H NMR (DMSO-$d_6$): δ = 6.32 (d, 1H, *J* = 8.4 Hz, H-5), 7.16 (t, 1H, *J* = 8 Hz, arom-H), 7.53-7.59 (m, 2H, arom-H), 7.78-7.86 (m, 5H, arom-H), 7.94 (d, 1H, *J* = 8 Hz, arom-H), .9.16 (s, 1H, arom-H). Anal. Calcd for $C_{17}H_{10}N_4$ (270.29): C, 75.54; H, 3.73; N, 20.73. Found: C, 75.32; H, 3.79; N, 20.66.

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