Utility of 3-Amino-4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine in Heterocyclic Synthesis

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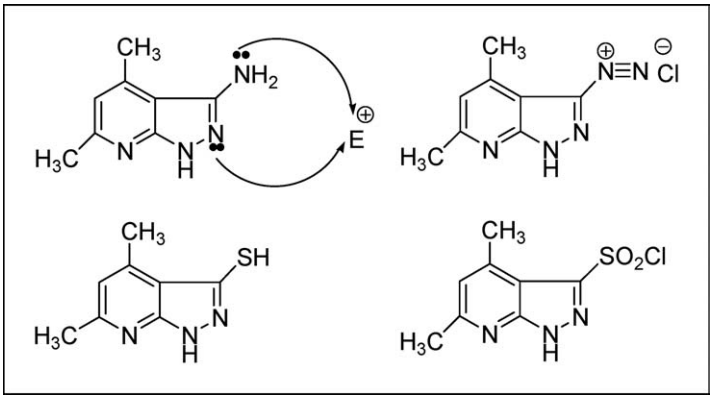
The author dedicates this article to his mother.



This review describe the synthesis and reactions of 3-amino-4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine as building block for the synthesis of polyfunctionalized heterocyclic compounds with pharmacological interest.

J. Heterocyclic Chem., **48**, 1 (2011).

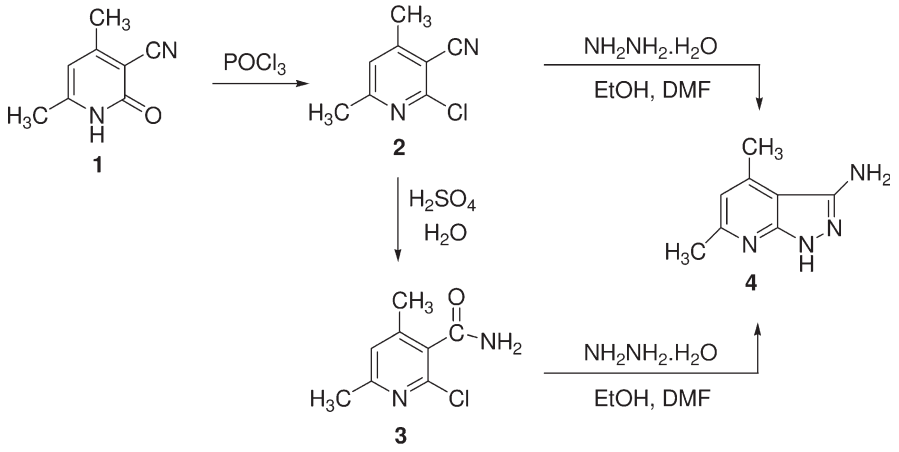
Contents

1. INTRODUCTION

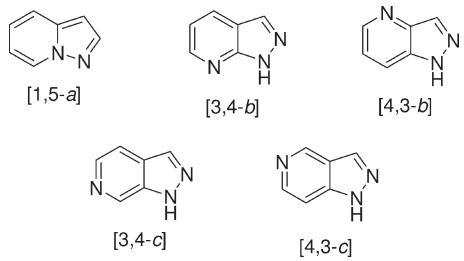
When pyrazole and pyridine ring systems are fused together various condensed ring systems may arise from such fusion. The pyrazolopyridines comprise of five isomers.

4,6-Dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**4**) has been used as versatile precursor to prepare several heterocyclic compounds. The amidine moiety (—N=C—NH_2) moiety of the molecule is a favorable unit to react with dinucleophiles usually result in the formation of bridge head nitrogen heterocyclic systems [1,2]. Furthermore, diazotized 3-amino-4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**7**) has been used to synthesize several azodyes [3] and pyridopyrazolotriazine [4–8]. Pyrazolo[3,4-*b*]pryridines have received considerable attention as a result of their biological activity. It has been shown that many of pyrazolopyridines especially pyrazolo[3,4-*b*]pryridines have antibacterial [9] and antiviral effects [10]. Some of the derivatives act as anti-metabolites and those are effective in the control of cancer [11]. Pyrazolopyridines were found to be among many systems which affects on the

Scheme 1



central nervous systems. Various pyrazolo[3,4-*b*]pryridines have been found to exhibit pharmacological properties. Some of the derivatives of pyrazolo[3,4-*b*]pryridines have been tested for anti-inflammatory [12], action, whereas others have been demonstrated to be good anxiolytic [13]. Our research deals with effective use of 3-amino-4,6-dimethylpyrazolo[3,4-*b*]pyridine in the synthesis of variety of polyfunctionalized heterocyclic compounds exhibited biological interest.

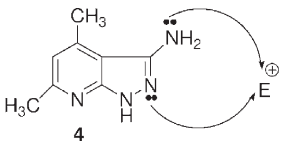


2. SYNTHESIS

Chlorinating 3-cyano-4,6-dimethylpyridin-2(1*H*)-one (**1**) with $POCl_3$ in dry DMF afforded 2-chloro derivative **2**, which was partially hydrated with conc. H_2SO_4 to give **3**. Cyclocondensation of **1** and **3** with hydrazine hydrate in EtOH-DMF gave 4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**4**) [14]. Also, refluxing of 2-chloro-3-cyano-4,6-dimethylpyridine (**2**) and hydrazine hydrate in ethylene glycol or ethanol yielded the amine derivative **4** [3,15] (Scheme 1).

3. REACTIVITY

4,6-Dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**4**) was polyfunctional compound possessing nucleophilic properties. Typical nucleophilic positions are NH_2 and C=N with reactivity order NH_2 > C=N. These chemical properties have been used to design different heterocyclic moieties; such as diazine and triazine derivatives.



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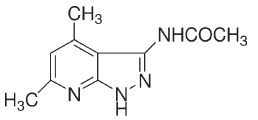
4. REACTIONS

4.1. Acetylation.

4.1.1. Using acetic anhydride Treatment of **4** with acetic anhydride afforded the corresponding acetyl derivative **5** [15].



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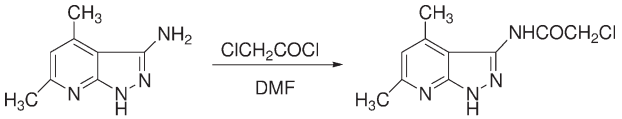
4.1.2. Using chloroacetyl chloride Reaction of **4** with chloroacetyl chloride in dry DMF achieved 3-(*N*-chloroacetyl-amino)pyrazolo[3,4-*b*]pyridine (**6**) [2].



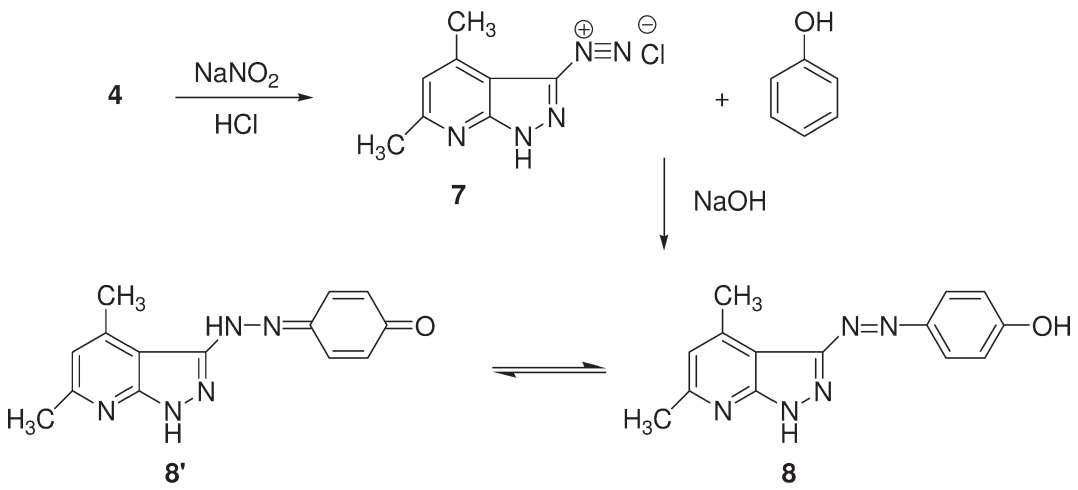
4 6

4.2. Diazotization. Treatment of **4** with sodium nitrite in the presence of conc. HCl afforded 4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-diazonium chloride (**7**), which upon coupling with phenol or 8-hydroxyquinoline in the presence of sodium hydroxide afforded the corresponding azo derivatives **8**,**8′**, and **9**,**9′**, respectively [2] (Scheme 2).

According to the previous DFT calculations at the B3LYP/6-31G* level [5], the azo tautomer **9** was found to be more stable by 3.6 kcal/mol than the hydrazono tautomer **9′** [2] (Scheme 3).

Also, coupling of diazonium salt **7** with 3-(methyl (phenyl)amino)propanenitrile gave compound **10**.

Scheme 2



Successive treatment of **10** with dimethyl sulfate and magnesium oxide with zinc chloride solution gave the basic azo dye **11**, fast red on acrylic and acid-modified polyester fibers [3] (Scheme 4).

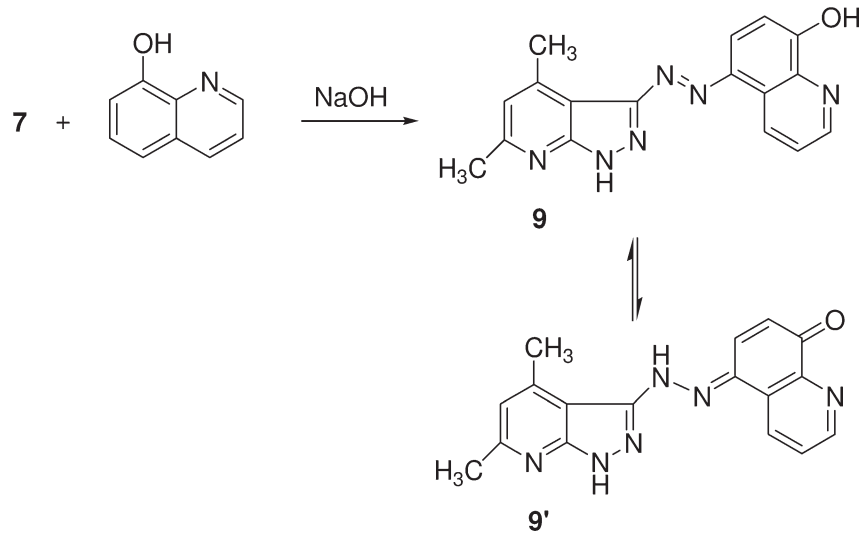
Diazotized 3-amino-4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**7**) has been used as a versatile precursor for the preparation of several heterocyclic compounds. Diazonium salt **7** coupled with active methylene compounds such as ethyl cyanoacetate, malononitrile, diethyl malonate, ethyl acetoacetate, acetylacetone, 3-(1,4-dioxo-3,4,4e,5,10,10a-hexahydro-1*H*-5,10-benzeno-benzo[*g*]phthalazine-2-yl)-3-oxopropiononitrile [16], and 2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide [17], to give the corresponding hydrazono derivatives **12a–g**, respectively. Refluxing of **12a–c** and **12f, g** in acetic acid furnished the pyridopyrazolotriazines **13a–d** and **14** [4,6–8] (Scheme 5 and 6).

The quantitative diazotizations of solid aromatic amines with NO_2 gas are most versatile [18–20]. Further applications are the diazotizations of 3-aminopyrazolo[3,4-*b*]pyridine derivative **4** which quantitatively give the monohydrate of the diazonium nitrates **15**,**15′** without nitrosation of NH group [5] (Scheme 7).

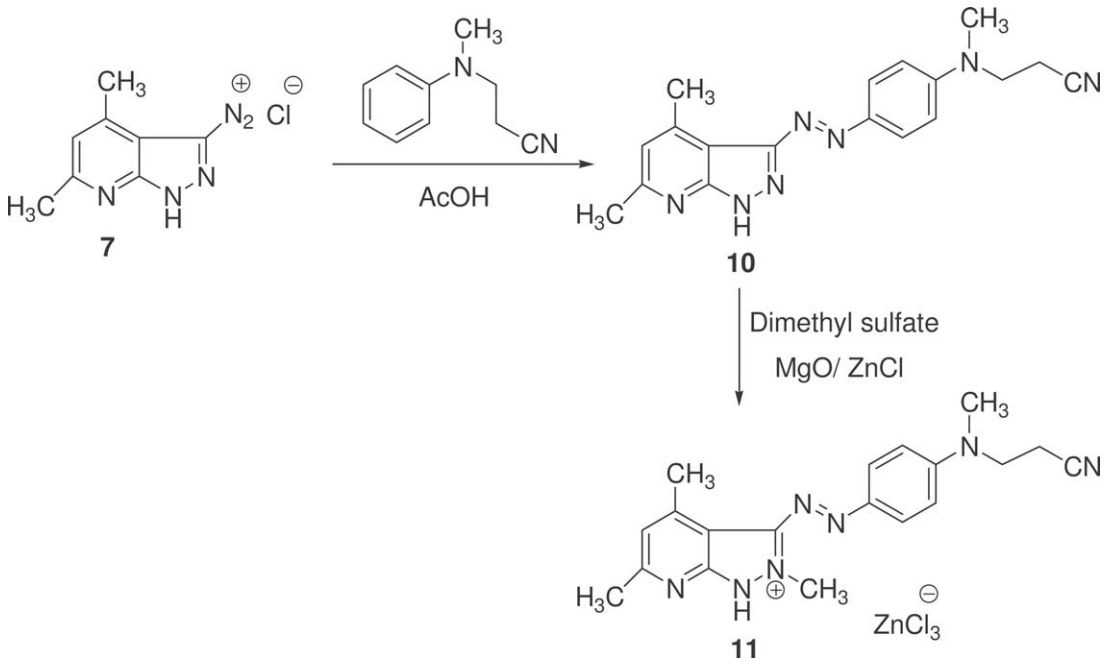
Careful co-grinding of crystalline **15** with (thio)barbituric acid **16a–e** gives quantitative yields of the tautomeric 5-arylazobarbituric acid **18** [5] (Scheme 8).

The azo coupling between **15** and the open-chain C—H acidic acetoacetanilide derivatives **19a–e** did not stop at the salts **20** formation, but cyclized directly to afford compound **21** in an interesting solid-state cascade [21–23], to give the heterocyclic salts **21**. The pyrido[2′,3′:3,4]pyrazolo[5,1-*c*]triazine derivative **22** can be obtained from **21** in quantitative yield by the action of base [5,24] (Scheme 9).

Scheme 3



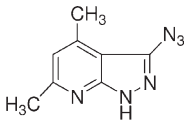
Scheme 4



The C-couplings of solid diazonium salts **15** are not restricted to C—H acidic β-dicarbonyl compounds. The solid state azo coupling between **15** and β-naphthol or 2,6-dimethylphenol is the preparative useful and the ''azo'' dyes **23** or **24** are obtained in quantitative yield after neutralization [5] (Schemes 10 and 11).

1-Heteroaryl-3-aryltriazines **27** were obtained in qualitative yields *via* co-grinding of the anilines **25a–c** with **15** [5] (Scheme 12).

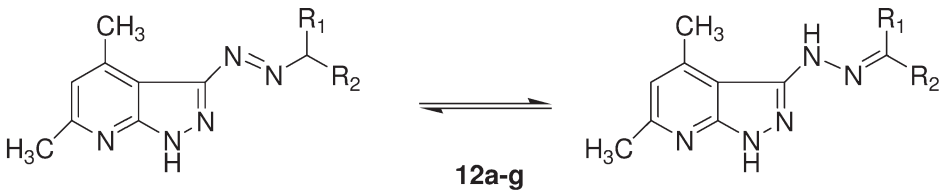
The diazonium salt **7** was reduced with $Na_2S_2O_4$ to give the azide derivative **28** [25].



28

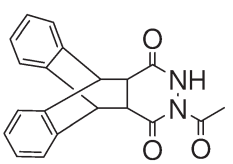
The diazonium salt **7** when treated with SO_2 and $CuCl_2$ produces the sulfonyl chloride **29**. Compound **29** easily

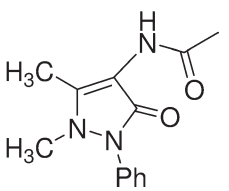
Scheme 5



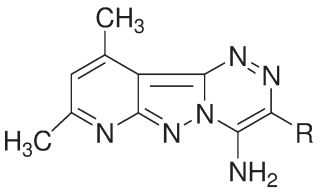
12a, R_1= CN, R_2= COOEt, **12b**, R_1= R_2= CN, **12c**, R_1= R_2= COOEt,

12d, R_1= COOEt, R_2= $COCH_3$, **12e**, R_1= R_2= $COCH_3$,

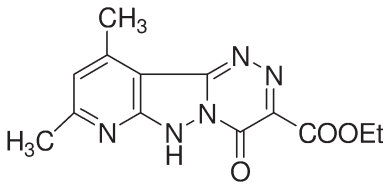
12f, R_1= CN, R_2= 

12g, R_1= CN, R_2= 

Scheme 6

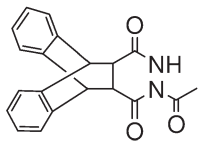


13a-d

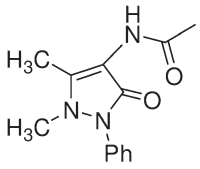


14

13a, R= CN; **13b**, R= COOEt; **13c**, R=



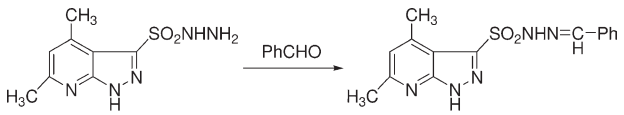
13d, R=



reacts with hydrazine, ammonia, aromatic, or heterocyclic amines to produce the corresponding sulfohydrazide (**30**), sulfonamide (**31**) or *N*-sulfonamide derivatives **32** [26] (Scheme 13).

Sulfohydrazide **31** reacts with acetylacetone to produce pyrazolyl pyrazolopyridinyl sulfone **33** which is also obtained by the reaction of **29** with dimethyl pyrazole [26] (Scheme 14).

Furthermore, sulfonyl hydrazide **31** condensed with benzaldehyde to give the corresponding hydrazone **34** [26].



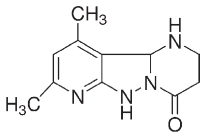
31 **34**

The diazonium salt **7** can be converted into pyrazolopyridinthiol **35** by the reaction with ethyl dithioxanthate [26] (Scheme 15).

The pyrazolopyridinthiol derivative **35** reacted with phenacyl chloride, ethyl bromoacetate, 2-methylbromoacetate, methyl iodide, chloroacetonitrile, or acrylonitrile to produce *S*-alkylated derivatives **36–41** [26] (Scheme 16).

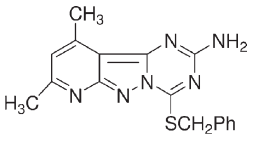
Treatment of ethyl 2-(4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-ylthio)acetate (**37**) with hydrazine hydrate in ethanol yielded the corresponding hydrazine derivative **42** which condensed with *p*-anisaldehyde to afford the hydrazone derivative **43** [26] (Scheme 17).

4.3. Reaction with 3-bromopropionic acid. Cyclocondensation of **4** with 3-bromopropionic acid furnished the diazine derivative **44** [25].



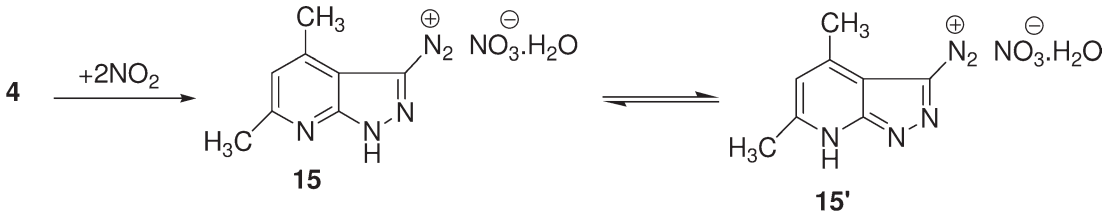
44

4.4. Reaction with dibenzyl cyanocarbonimidodithioate. Mayer and coworkers have been reported that triazine derivative **45** could be obtained by boiling of **4** with dibenzyl cyanocarbonimidodithioate in pyridine [27].



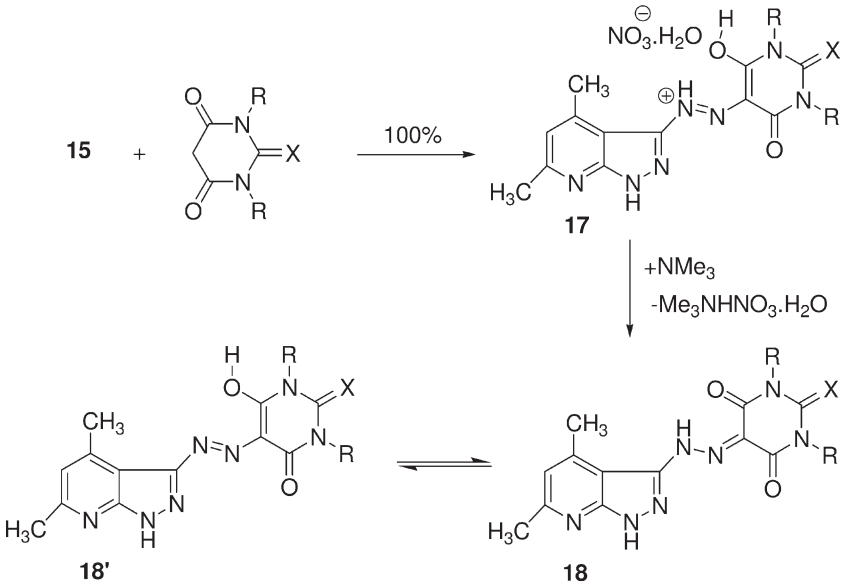
45

Scheme 7. Quantitative gas–solid synthesis of the stable diazonium nitrate hydrate **15** by treatment of **4** with gaseous NO2.



15 **15'**

Scheme 8. Quantitative solid-state couplings of **15** with (thio)barbituric acid derivatives.



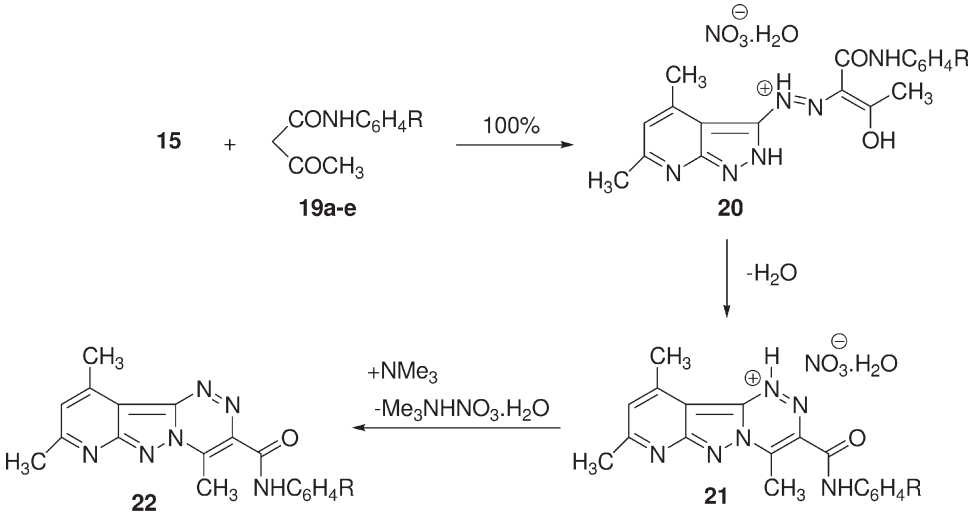
a, R= H, X= O; **b**, R= CH_3, X= O; **c**, R= Ph, X= O;

d, R= H, X= S; **e**, R= Et, X= S.

4.5. Reaction with ethyl 2-cyano-3,3-bis(methylthio) acrylate. Treatment of 3-amino-4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**4**) with ethyl 2-cyano-3,3-bis(methylthio)acrylate (**46**) [28], in DMF afforded the corresponding pyridopyrazolopyrimidine derivative **47**. Condensation of **47** with hydrazine hydrate afforded the corresponding fused tetracyclic derivative **48** [2] (Scheme 18).

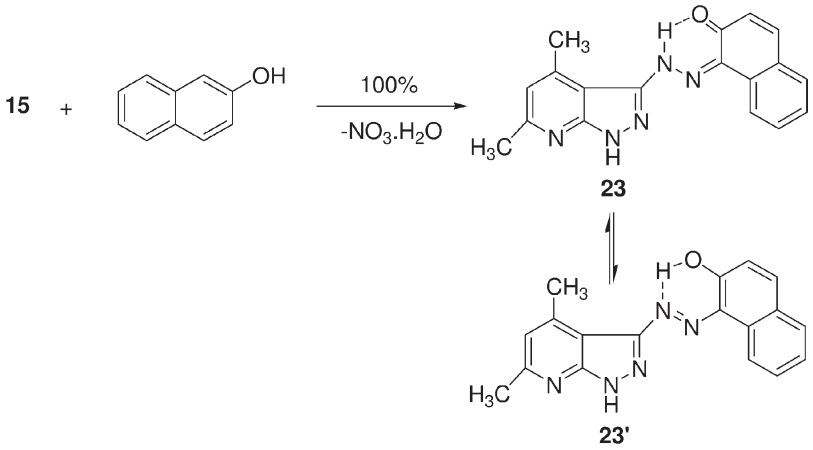
4.6. Reaction with isocyanate, isothiocyanate, and thiocyanate derivatives. Compound **4** was reacted with phenyl isothiocyanate in boiling pyridine to afford the

Scheme 9. Quantitative solid-state couplings and solid-state *in situ* cyclizations with acetoacetanilides.

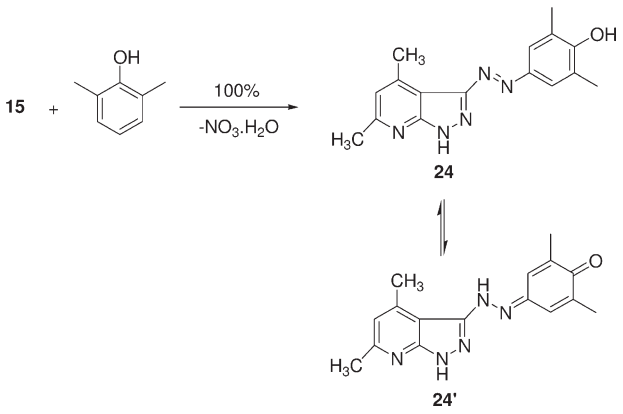


a, R= H; **b**, R= 4-CH_3; **c**, R= 4-OCH_3; **d**, R= 4-NO_2; **e**, R= 4-Br; **f**, R= 4-Cl.

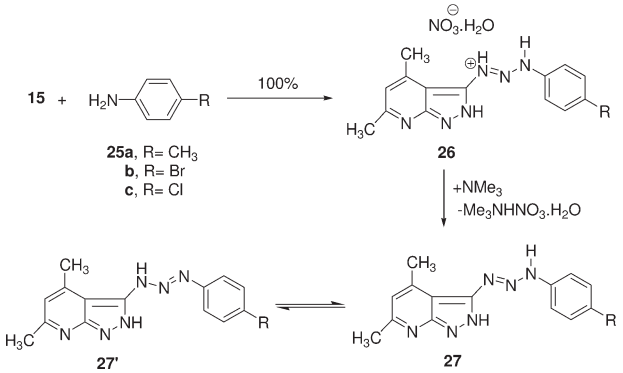
Scheme 10. Quantitative solid-state coupling between **15** and β-naphthol.



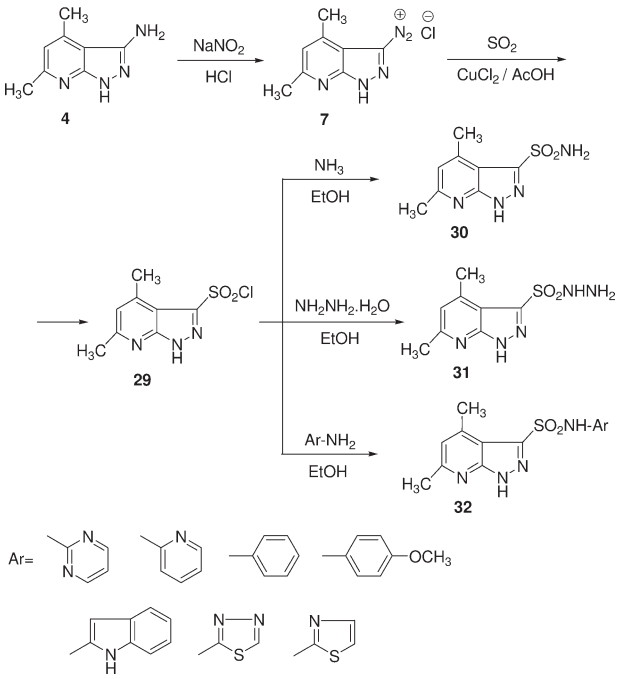
Scheme 11. Quantitative solid-state coupling between **15** and 2,6-dimethylphenol.



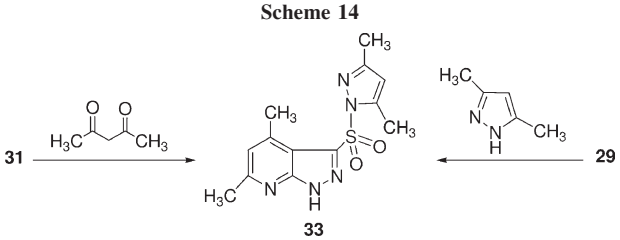
Scheme 12. Quantitative solid-state synthesis of the tautomeric triazines **27**/**27′**.



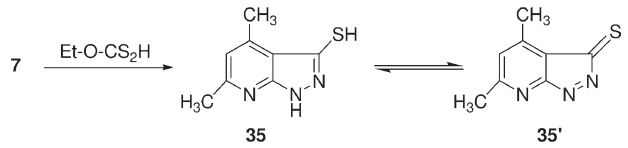
Scheme 13



Scheme 14

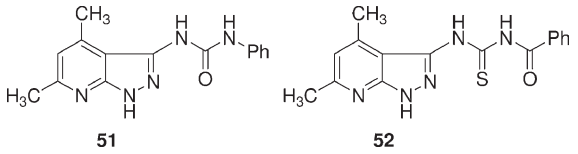


Scheme 15



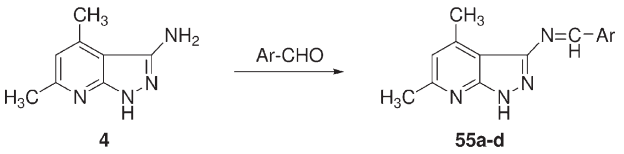
corresponding thiourea derivative **49**, which underwent cyclization to thiazolidinone derivative **50** by reacting with ethyl chloroacetate in ethanol-pyridine mixture [2] (Scheme 19).

Furthermore, **4** reacted with phenyl isocyanate, benzoyl isothiocyanate to give the corresponding derivatives carbamide **51** and thiocarbamide **52**, respectively [25].



4.7. Reaction with carbon disulfide. The base-prompted nucleophilic addition of compound **4** to carbon disulfide in DMF containing potassium hydroxide afforded the corresponding nonisolable intermediate **53**. Subsequent treatment of the later compound with methyl iodide furnished the corresponding methyl-*N*-(pyrazolo[3,4-*b*]-3-pyridyl)dithiocarbamate (**54**) [2] (Scheme 20).

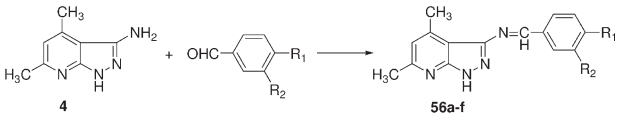
4.8. Reaction with aromatic aldehydes. Pyrazolopyridine derivative **4** undergoes condensation with 2-, 3-, 4-nitro and/or 4-methoxy benzaldehyde in refluxing ethanol containing few drops of piperidine to give the corresponding Schiff's bases **55a–d** [2,25].



55a, Ar= 2-$O_2NC_6H_4$; **b**, Ar= 3-$O_2NC_6H_4$;

c, Ar= 4-$O_2NC_6H_4$; **d**, Ar= 4-$OCH_3C_6H_4$.

Furthermore, azomethines **56** have been quantitative (100% yield at 100% conversion) obtained as hydrates by ball-milling together 3-amino-4,6-dimethylpyrazolopyridine with solid aldehydes without passing through liquid phases [29].

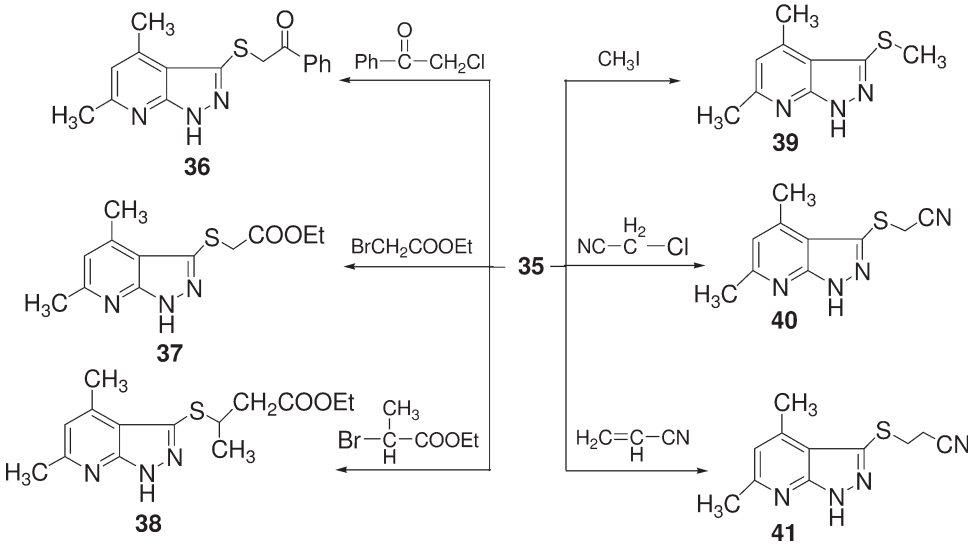


a, R_1= H, R_2= NO_2; **b**, R_1= OH, R_2= OCH_3; **c**, R_1= $N(CH_3)_2$, R_2= H;

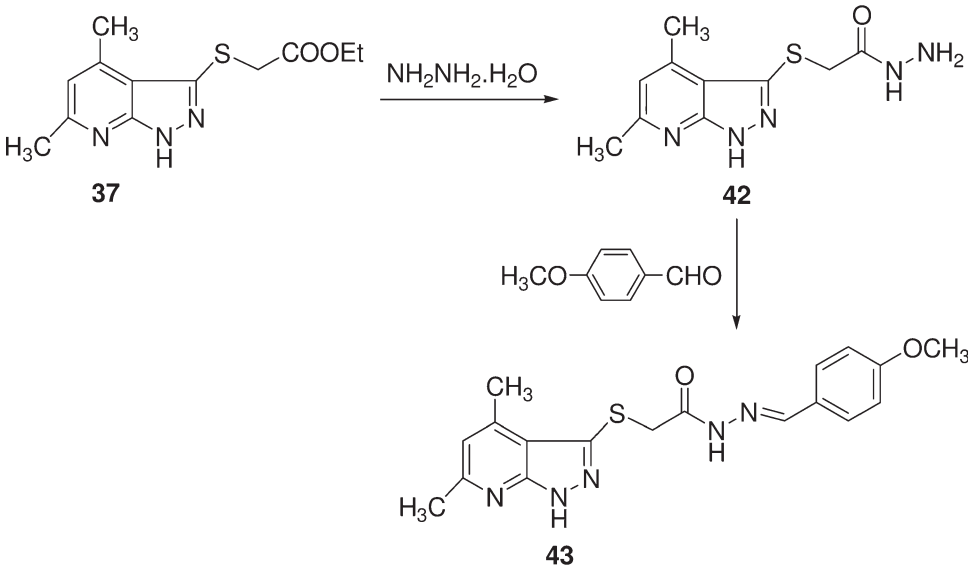
d, R_1= OH, R_2= H; **e**, R_1= Cl, R_2= H; **f**, R_1= NO_2, R_2= H.

The Schiff's base **55d** obtained from the reaction of **4** with anisaldehyde reacted with thioglycolic acid to yield the corresponding thiazolidinone derivative **57** [25].

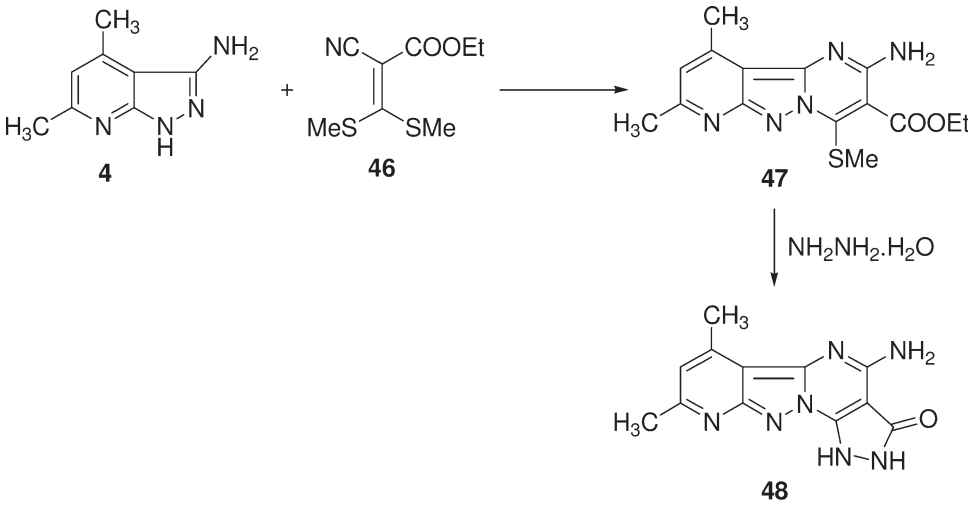
Scheme 16



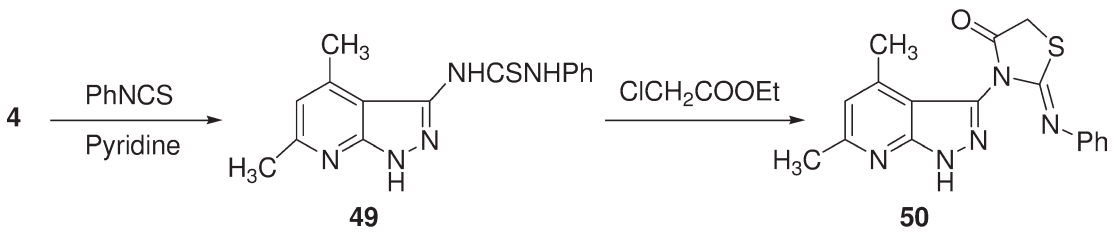
Scheme 17



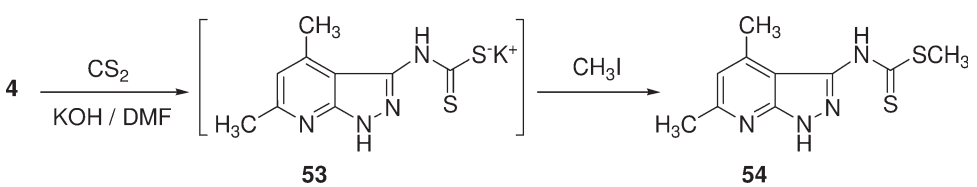
Scheme 18

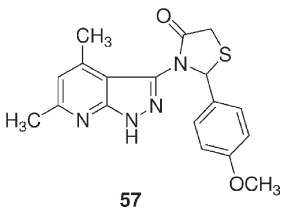


Scheme 19



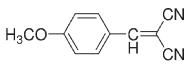
Scheme 20





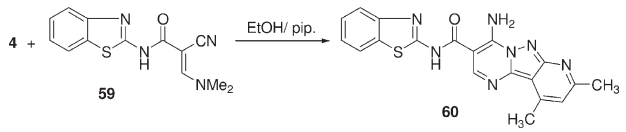
57

When equimolar amounts of azomethine **55d** and malononitrile were refluxed in ethanol in the presence of TEA, the amine **4** and the arylidine derivative **58** was obtained [25].



58

4.9. Reaction with enaminonitrile. Refluxing of **4** with the enaminonitrile **59** in ethanol containing a catalytic amount of piperidine afforded the corresponding 4-amino-*N*-(benzothiazol-2-yl)-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-3-carboxamide (**60**) [1].



59 60

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