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Believes versus evidence-based regio-orientation in the structure assignment of pyrazolo[1,5-a]pyrimidines

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ABSTRACT

This review aims to focus and highlight the regio-orientation and regioselectivity of the reactions of 3(5)-aminopyrazoles with 1,3-bielectrophilic reagents that lead to the formation of pyrazolo[1,5-a]pyrimidines. To clarify the significance of regio-orientation, reactions of 3(5)-aminopyrazoles with symmetric 1,3-bielectrophilic reagents such as acetylacetone and malononitrile are also included. The comparable nucleophilicity of the exocyclic NH_2 group and endocyclic NH in 3(5)-aminopyrazoles is considered as it causes literature controversy associated with regio-orientation of the substituents on the pyrimidine ring of pyrazolo[1,5-a]pyrimidine when unsymmetrical 1,3-bielectrophilic reagent reacts with 3(5)-aminopyrazole. To the best of our knowledge, this review would be the first collective and confined report to the regio-orientation of pyrazolo[1,5-a]pyrimidines.

INTRODUCTION

The medicinal value of pyrazolo[1,5-a]pyrimidines

Being purine analogs, the chemistry of pyrazolo[1,5-a] pyrimidines has been extensively investigated. Such compounds have diverse pharmacological, medicinal, and pharmaceutical value. Zaleplon®, Ocinaplon®, Indiplon®, and Lorediplon® are pyrazolo[1,5-a]pyrimidine analogs that act as GABA A receptor agonists and used as sedative, hypnotic, anxiolytic, and in the treatment of insomnia (Ancoli-Israel *et al*., 1999; Chilman-Blair *et al*., 2003; Neubauer, 2005; d'Aniello *et al*., 2015). Dinaciclib® inhibits cyclin-dependent kinases and evaluated in clinical trials for various cancer indications (Parry *et al*., 2010). Anagliptin® is used for the treatment of type 2 diabetes mellitus in Japan (Ervinna *et al*., 2013).

Pyrazophos is used as a fungicide and an insecticide (de Waard, 1974). PHTPP® (Chan *et al*., 2014; Iorga *et al*., 2018) is used in scientific research as a nonsteroidal highly selective antagonist of β-estrogen receptors. DPA714® is a radiopharmaceutical for imaging translocator protein in living systems using positron emission tomography (PET), and its radiolabeled analog with C-11, DPA713®, is used as a radiotracer for imaging the TSPO using PET (Fig. 1) (Banister *et al*., 2012; Reynolds *et al*., 2010; Selleri *et al*., 2001).

Our approach to handling the subject

Regio-orientation assignment of substituents on the pyrazolo[1,5-a]pyrimidines, compounds formed via condensation of 3-aminopyrazoles with 1,3-bielectrophilic reagents requires: first, to investigate the chemical reactivity of 3(5)-aminopyrazoles with special emphasis on the sites of the nucleophilicity of such compounds [NH_2 (exocyclic) and NH (ring)]. Second, classification

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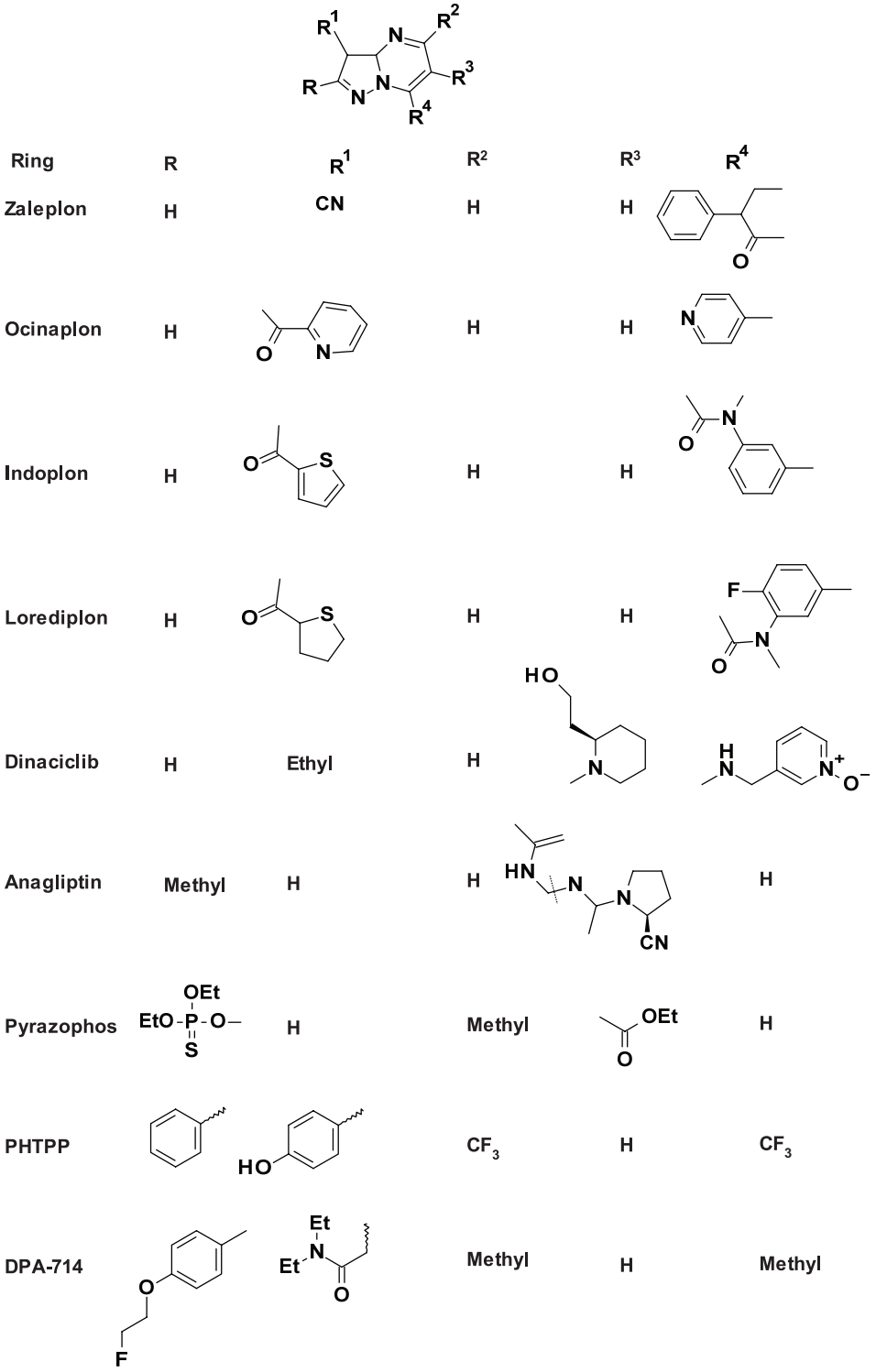


Figure 1. The general structural formula for pyrazolo[1,5-a]pyrimidines of pharmacological, medicinal, and pharmaceutical value.

of the bielectrophilic reagents and locating the more electrophilic and less steric hindered site according to the rules of chemistry. Third, to assign the regio-orientation based on just believes, assumption, or weighing previous literature reports. In addition to insufficient or unreliable spectral data or irrelevant unambiguous synthesis are considered. Most importantly, evidence-based regio-orientation assignment of substituents around the pyrimidine ring using X-ray crystallography, ^{1}H-^{15}N Heteronuclear Multiple Bond Correlation, Nuclear Overhauser Effect (NOE) effect, and relevant unambiguous synthesis are highlighted.

COMPARABLE REACTIVITY OF THE EXOCYCLIC AND ENDOCYCLIC NH_2/NH IN 3(5)-AMINOPYRAZOLES

3(5)-aminopyrazole tautomers

The literature survey indicates that 3(5)-aminopyrazoles of type 1 have three nucleophilic centers, namely, exocyclic NH_2, endocyclic NH, and the 3° N of the pyrazole ring. In addition to the fourth one if, and only if, the fourth position is unsubstituted. Such nucleophilicity could be referred to the behavior of the molecule as an enamine (Fig. 2).

Relative nucleophilicity of the amino and imino groups

Noteworthy, some authors believed (no evidence has been provided) that the endocyclic NH group is the most nucleophilic center in these compounds, although the experimental results (Al-Shiekh *et al*., 2004; Al-Omran and El-Khair, 2006; Dawood *et al*., 2005; Ege and Gilbert, 1979a; Ege *et al*., 1984; Elagamey *et al*., 1986; Elnagdi *et al*., 1976; 1981; El-Ghandour Ahmed Hafez *et al*., 1992; Joshi *et al*., 1983; Kočevar *et al*., 1976) showed that such compounds could be successfully diazotized at the cost of the exocyclic NH_2 group which is consistent with the fundamentals of chemistry (Scheme 1).

Reactivity of aminopyrazoles in diazotization and coupling was discussed in 2009 (Moyano *et al*., 2008) and the pattern demonstrated previously was confirmed (Moyano *et al*., 2008).

Diazotization (Ege and Gilbert, 1979b; Wu *et al*., 2005) of 5-aminopyrazole derivative (3) gave diazo-3-(methylsulphonyl)-1H-pyrazole (4) that reacted with arylisocyanates in CH_2Cl_2 to give the corresponding pyrazolo[1,5-a]tetrazine analogs **5** (Scheme 2).

Relative nucleophilicity of NH_2 group

Acylation of 5-aminopyrazole derivative (6) afforded a mixture of 3(5)-aminoacylpyrazole (7) and the two acyl analogs (8) and (9) (Scheme 3). Michon *et al*. reported that the major amide derivative isolated was due to the acylation reaction of exocyclic amino group (7) of percent yield (24%), while the percent yields of the other amides (8) and (9), afforded from the acylation of the endocyclic nitrogen, were (13%) and (6.5%), respectively (Graubaum, 1993; Michon *et al*., 1995; Quiroga *et al*., 2008).

Acylation (El-Emary *et al*., 2002) is restricted to the 5-NH_2 group, especially when the endocyclic NH is blocked. Thus, 5-amino-1-substituted pyrazole analogs 10 gave the corresponding 5-acylamino derivatives when different acylating reagents were used (Scheme 4).

Isocyanates and isothiocyanates, respectively, reacted with aminopyrazoles 14 giving the corresponding urea derivatives $15_{a,b}$ (Bagley *et al*., 2006; Schenone *et al*., 2004; Winters *et al*., 1984) (Scheme 5).

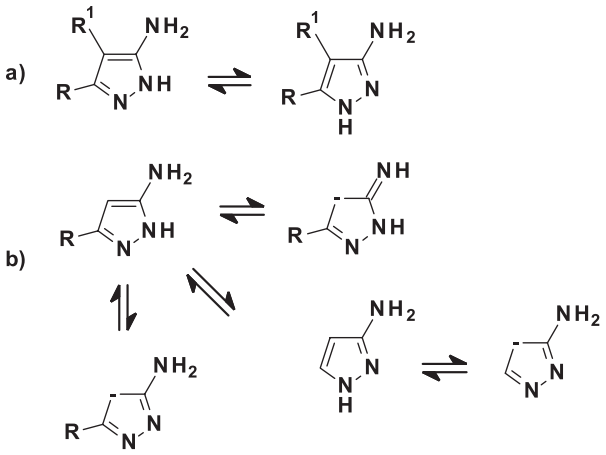
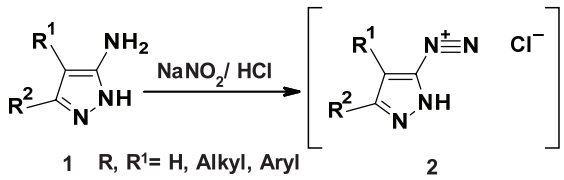
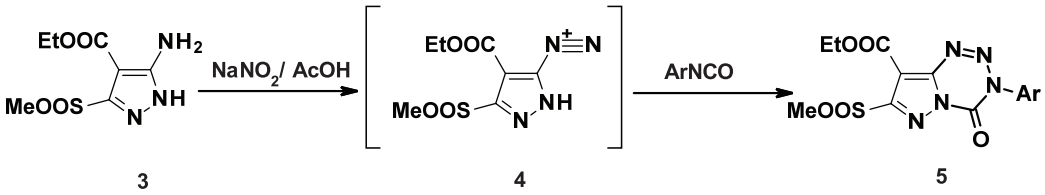


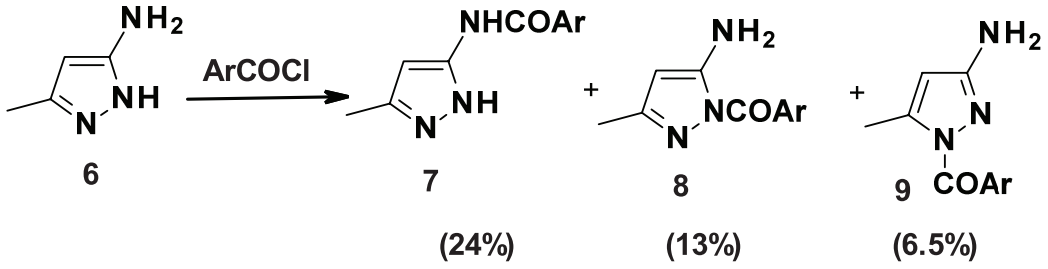
Figure 2. a) 4-substituted pyrazole b) unsubstituted pyrazole



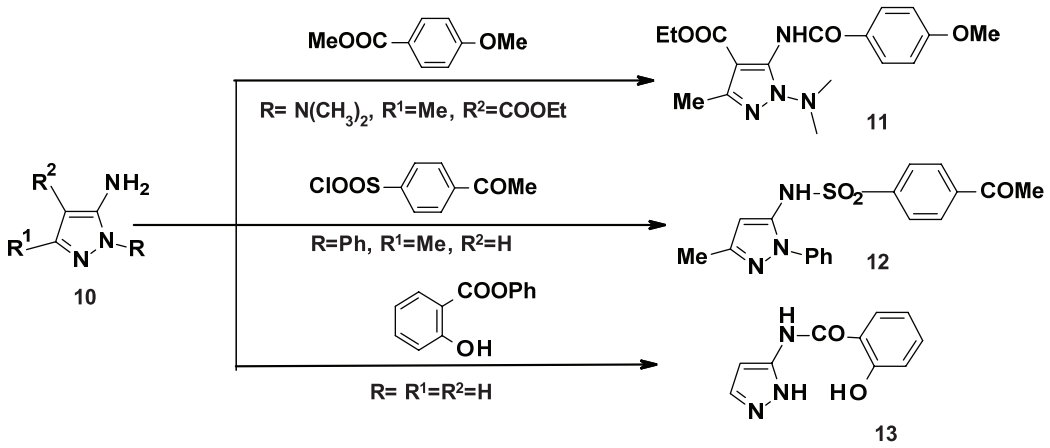
Scheme 1.



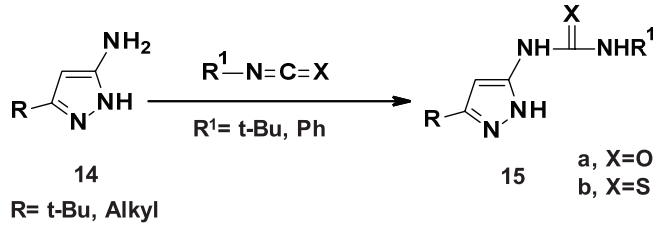
Scheme 2.



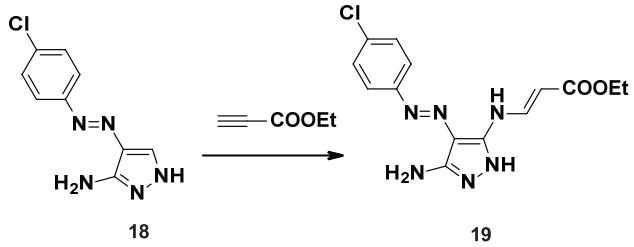
Scheme 3.



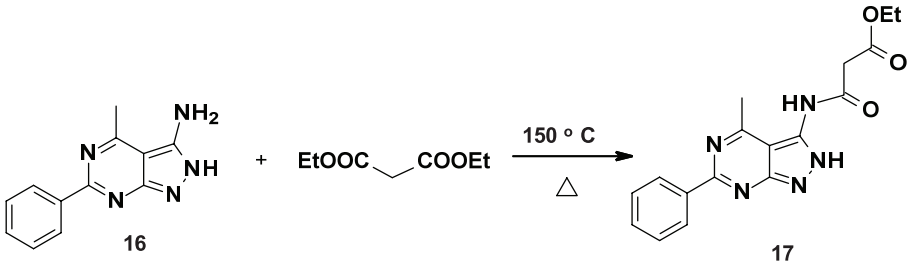
Scheme 4.



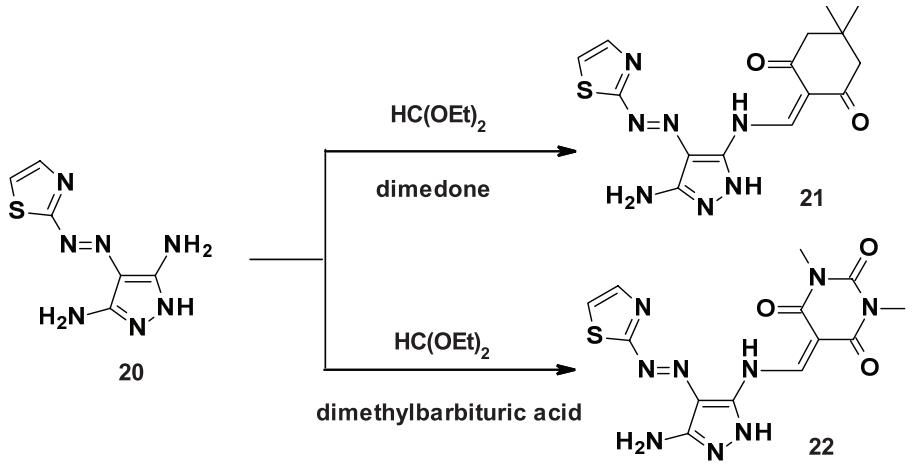
Scheme 5.



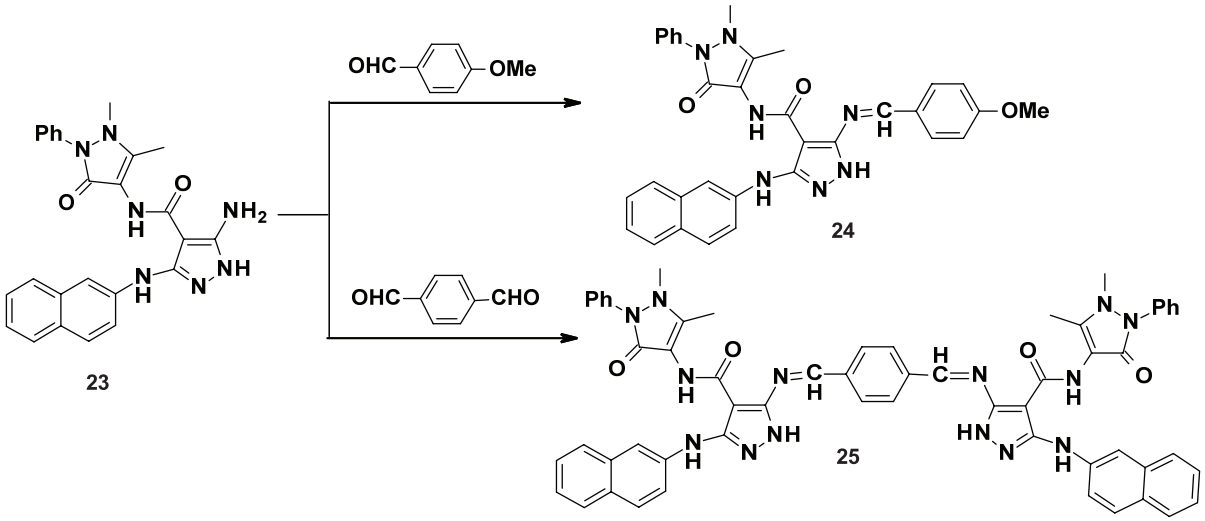
Scheme 7.



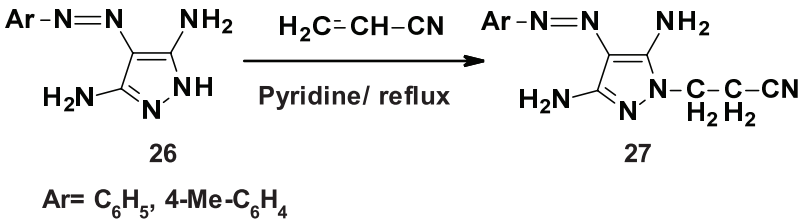
Scheme 6.



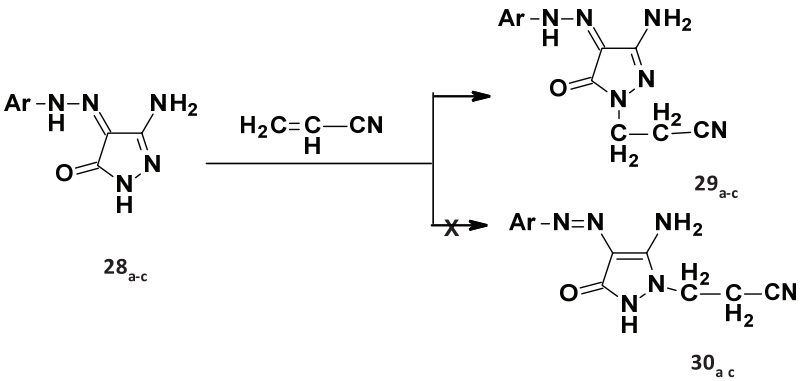
Scheme 8.



Scheme 9.



Scheme 10.



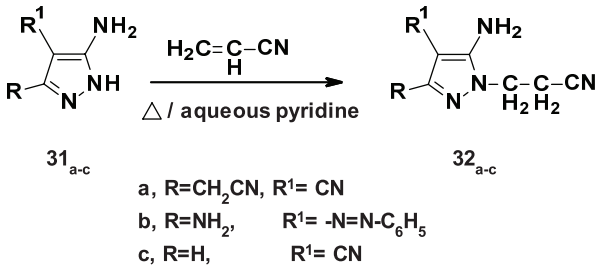
Scheme 11.

Ho and Yao (2003) reported that heating 3-aminopyrazolo[3,4-d]pyrimidine derivative (16) with diethyl malonate at 150°C gave ethyl 2-[(4-methyl-6-phenylpyrazolo[3,4-d] pyrimidinyl)amido]ethanoate (17) (Scheme 6).

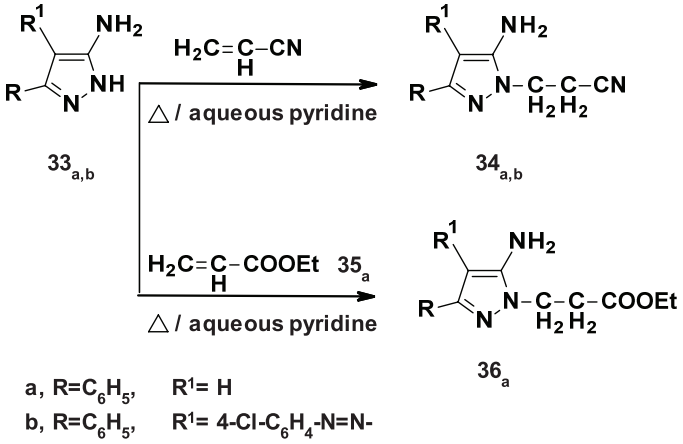
A further evidence for the relative higher nucleophilicity of the exocyclic NH_2 group in 3(5)-aminopyrazole derivatives has been reported by Al-Zaydi (2009a) since the author isolated the ethyl (pyrazol-5-ylamino)acrylate derivative (19) via reaction of 5-aminopyrazole derivative (18) with ethyl propiolate under microwave irradiation (Scheme 7).

Furthermore, El-Mekabaty and Hasel (2015) reported that the condensation of 3,5-diaminopyrazle derivative (20) with triethylformate and certain active methylene containing compounds, dimedone, and diethyl barbituric acid led to the isolation and identification of the two intermediates (21), (22) (Scheme 8).

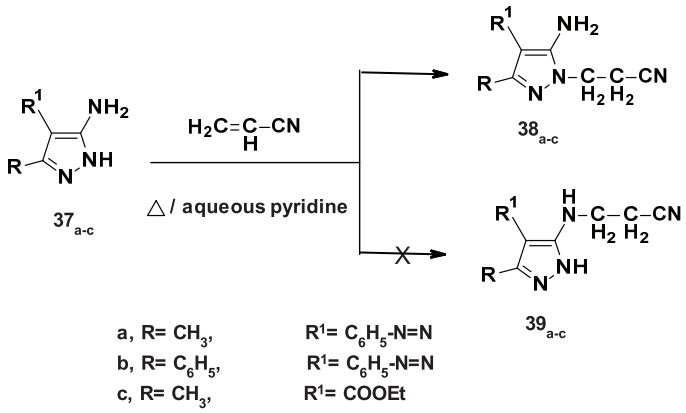
Recently, Helal *et al*. (2017) reported that reaction of 5-aminopyrazole derivative (23) with 4-methoxybenzaldehyde and terenaphthaldehyde afforded the corresponding mono and bis-(azomethine) derivatives (24) and (25). Noteworthy, the



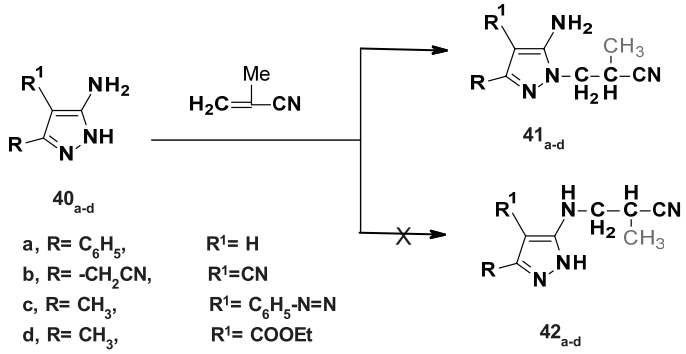
Scheme 12.



Scheme 13.



Scheme 14.



Scheme 15.

reaction, in both cases, occurs on the exocyclic NH_2 group (Scheme 9).

Elnagdi and Abd Allah (1973) reported that 3,5-diaminopyrazole derivatives 26 reacted with acrylonitrile in refluxing pyridine to yield the corresponding 1-β-cyanoethyl derivatives 27 (or possible tautomers) (Scheme 10).

Elnagdi *et al*. (1974) reported that treatment of 4-arylhydrazono-3-amino-2-pyazolin-5-ones 28_{a-c} with acrylonitrile afforded 3-amino-1-β-cyanoethyl-4-arylhydrazone-2-pyazolin-5-ones, the mono-β-cyano derivatives, 29_{a-c} (or possible tautomers) rather than the isomeric compounds 30_{a-c} (Scheme 11).

In the same year, in 1974, Elnagdi (1974) reported that refluxing the 5-aminopyrazole derivative 31_{a-c} with acrylonitrile, in aqueous pyridine, the corresponding 5-amino-1-(β-cyanoethyl) pyrazole derivatives 32_{a-c} were obtained (Scheme 12).

In another publication, Elnagdi *et al*. (1975) reported that reaction of 5-aminopyrazole analogs $33_{a,b}$ with acrylonitrile in aqueous pyridine at reflux, afforded the corresponding 5-amino-1-(β-cyanoethyl)pyrazoles $34_{a,b}$. Also, the condensation of 5-amino-3-phenylpyrazole (35_a) with ethyl acrylate, in refluxing aqueous pyridine gave the corresponding 5-amino-1-β-(ethoxycarbonyl) ethylpyrazole derivative (36_a) (Scheme 13).

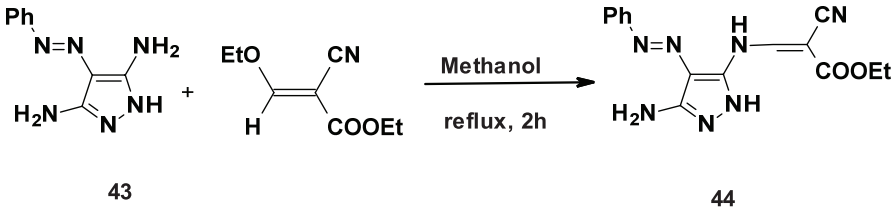
Elnagdi *et al*. (1975) continued their previous work (Elnagdi, 1974; Elnagdi and Ohta, 1973; Elnagdi and Allah, 1973; Elnagdi *et al*., 1974; 1975a) which involved cyanoethylation of 5-aminopyrazoles that gave 5-amino-1-β-cyanoethyl pyrazole derivatives. Thus, the reaction of 5-aminopyrazole 37_{a-c} with acrylonitrile in aqueous pyridine afforded the corresponding 5-amino-1-β-cyanoethyl pyrazole analogs 38_{a-c} rather than 5-cyanoethylamino analogs 39_{a-c} (Scheme 14).

Analogously, 5-aminopyrazole analogs reacted with methyl acrylonitrile to afford the corresponding 5-amino-1-β-cyanoisopropylpyazole 41_{a-d} rather than the 5-β-cyanoisopropylamine analogs (Scheme 15) (Elnagdi Mohamed *et al*., 1975).

Elnagdi *et al*. (1977) isolated and identified the product obtained from the reaction of 3,5-diaminopyrazole derivative (43) with ethylethoxymethylenecyanoacetate, in refluxing methanol, as the corresponding aminomethylene derivative (44) (Scheme 16).

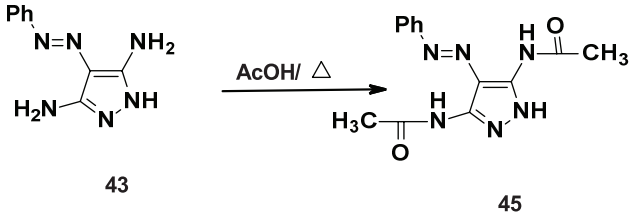
Noteworthy, quoted as reported by Elnagdi *et al*., at that time, *"since the previous result indicate that ring N-1 is the most electrophilic center in the molecule the formation of aminomethylene derivative* (*2*) *might be assumed to proceed via intermediate formation of the ring N-1 alkylated product. The later then isomerizes into 2. The ready isomerization of 1-β-cyanomethylene-5-aminopyrazoles into the corresponding 5-aminomethylene derivatives has been recently reported* (Reimlinger *et al*., 1970)."

In the same article, the authors reported that when (43) was heated under reflux in AcOH, the corresponding 3,5-diacetamido-4-phenylazopyrazole (45) was obtained (Scheme 17), notice, how these results are contradicting.



43 44

Scheme 16.



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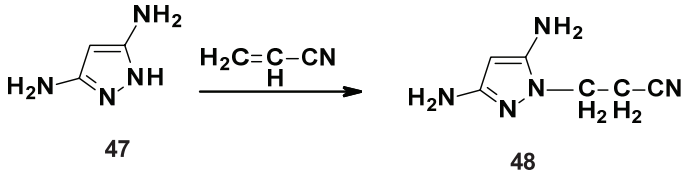
Scheme 17.



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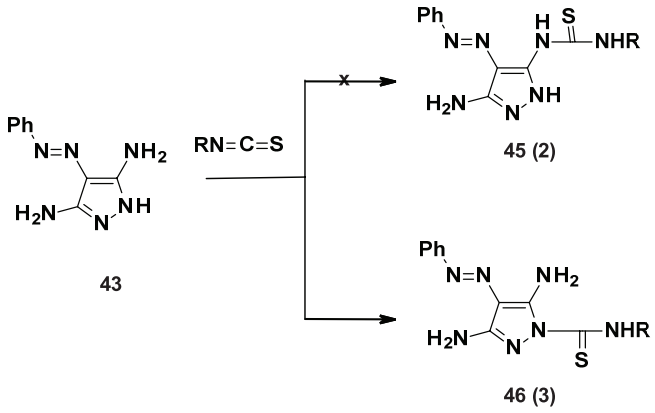
Scheme 19.



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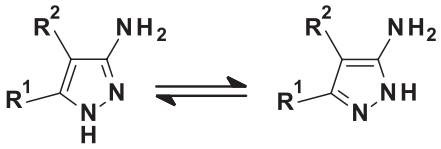
Scheme 18.



R^1= H, Me, 4-Me-C_6H_5, Ph, 4-$MeOC_6H_4$, 4-Br-C_6H_4, 4-Cl-C_6H_4
R^2= CN, SCN, 4-$MeOC_6H_4$, Ph, 4-Cl-C_6H_4, 3-Br-C_6H_4

Figure 3. Tautomerism of some 3(5)-aminopyrazoles.

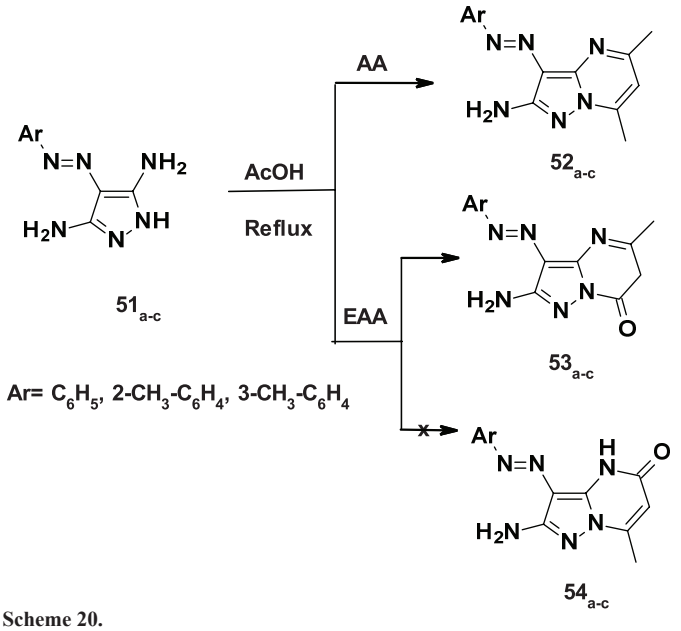
In contrast, Elnagdi *et al*., in the same article, quoted as reported (Reimlinger *et al*., 1970) *"Although 5-aminopyrazoles were reported to react with isocyanate to yield compounds similar to structure 2 where the addition would involve the amino nitrogen* (Reimlinger *et al*., 1970; Vogel and Troxler, 1975; Dymek *et al*., 1965). *We* (*Elnagdi et al*.) *obtained products that proved to be 3."* That is involved in the endocyclic N-1 nitrogen (Scheme 18).

Elnagdi *et al*. (1978) reported that 3,5-diaminopyrazole (47) reacted with acrylonitrile in refluxing aqueous pyridine to afford the corresponding 3,5-diamino-1-β-cyanoethyl pyrazole (Scheme 19).

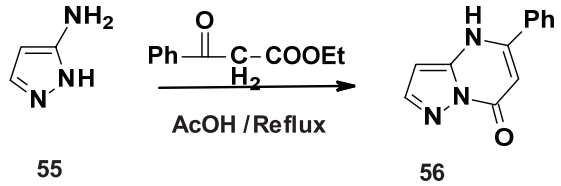
FACTORS DETERMINE THE REGIO-ORIENTATION OF PYRAZOLO[1,5-A]PYRIMIDINES

Literature survey indicated that regio-orientation in pyrazolo[1,5-a]pyrimidines are controlled by the comparable nucleophilicity of the exocyclic NH_2 group and the endocyclic NH group of the pyrazole ring. As we aforementioned, most authors reported that the isolation of reaction products indicated the relative higher nucleophilicity of the exocyclic NH_2. On the other hand, some other authors believed that the endocyclic NH group is the most nucleophilic center in such molecules and consequently assigned their reaction products as N1-substituted 5-aminopyrazoles. In 2014, tautomerism of certain 3(5)-aminopyrazoles has been studied (Emelina *et al*., 2014) by ^{1}H and ^{13}C NMR in solution, cross-polarization and magic-angle spinning ^{13} C NMR in the solid-state, and ab *initio* quantum chemical calculations (B3LYP/6-31G**). The results proved that the maximum electron density in tautomers 49 and 50 is localized on the exocyclic amino nitrogen atom. The negative charge in the pyrazole ring is localized mainly on the nitrogen atoms, in going from the gas phase to DMSO solution, the charge on NH remains almost unchanged, whereas the charge on N2 increases in both tautomers (Fig. 3).

The second factor that controls regio-orientation in pyrazolo[1,5-a]pyrimidine structures is the comparable electrophilicity of the 1,3-bielectrophilic reagents. The following cases could be summed: 1) When the 1,3-dielectrophilic reagent is a symmetrical molecule, such as acetylacetone or malononitrile, regio-orientation is nonsense, and should not be considered. 2) when the 1,3-dielectrophilc reagent is unsymmetrical such as EAA, ECA, unsymmetrical 1,3-diketones or β-ketocycloalkanes, α,β-unsaturated carbonyl compounds, α,β-unsaturated nitriles,



Scheme 20.

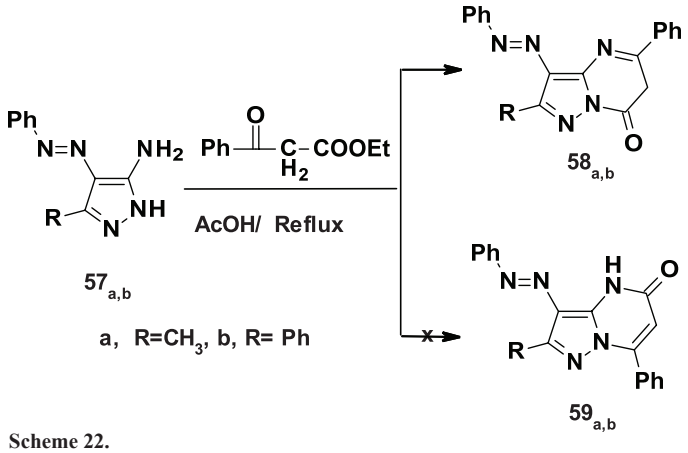


Scheme 21.

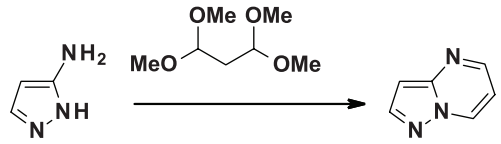
enaminonitriles or ketone dithioacetals, regio-orientation should be carefully considered. That is the comparable electrophilicity of the 1,3-dielectrophile is decided on the basic rules of chemistry and the regio-orientation of the reaction product should be proved by reliable advanced spectroscopic techniques such as NOE, ^{1}H-^{15}N NMR spectroscopy, and X-ray crystallography data.

SYNTHETIC ROUTES TO PYRAZOLO[1,5-A] PYRIMIDINE

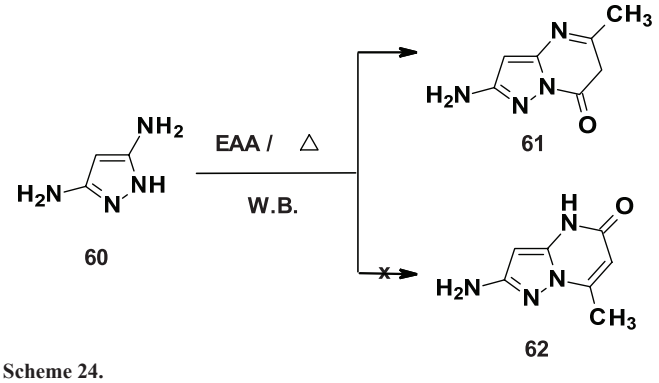
General reactions of 3(5)-aminopyrazole derivatives with dielectrophilic reagents are the most common routes to synthesize the pyrazolo[1,5-a]pyrmidines. Such reactions when involving symmetrical 1,3-dielectrophilic reagent lead to a single product of pyrazolo[1,5-a]pyrimidine. On the other hand, when the reaction involves unsymmetrical 1,3-bielectrophilic reagent, unambiguous assignment of the regio-orientation of the product requires extensive investigations and evidence-based structural elucidation rather than believes and assumptions. Also, insufficient or unreliable spectral data and even irrelevant independent routes of synthesis could not be conclusive. However, advanced spectral techniques such as ^{1}H-^{15}N NMR and X-ray crystallography, in addition to isolation and identification of associated reaction intermediate could be conclusive. In the following paragraphs, the synthesis of pyrazolo[1,5-a]pyrimidines via reactions of 3(5)-aminopyrazoles with 1,3-bielectrophilic reagents based on literature survey is reported.



Scheme 22.



Scheme 23.

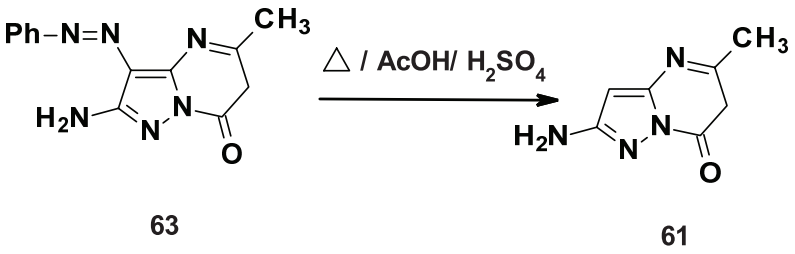


Scheme 24.

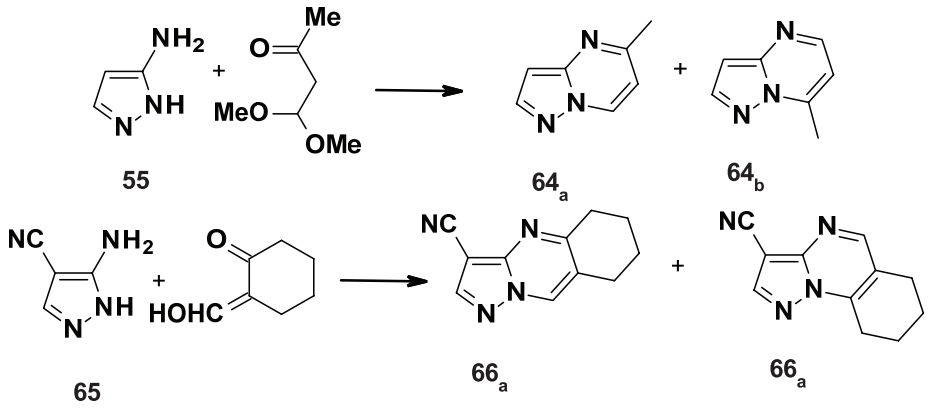
Reactions of 3(5)-aminopyrazoles with 1,3-dicarbonyl compounds

Elnagdi *et al*. (1975) reported that 3,5-diamino-4-phenylazopyrazoles (51_{a-c}) reacted with acetylacetone at reflux in AcOH to afford the corresponding pyrazolo[1,5-a]pyrimidine derivatives 52_{a-c}. On the other hand, (51_{a-c}) reacted with EAA under the same conditions to afford the pyrazolo[1,5-a]pyrimidine analogs 53_{a-c} rather than the regio-isomer 54_{a-c}. The structure of the regio-isomer 53_{a-c} was supported by traditional elemental analysis and interpretation of the IR spectral data in addition to previously reported (Reimlinger *et al*., 1970) reactions, in 1970 (Scheme 20) which involved the reaction of 5-aminopyrazole (55) with ethyl benzoylacetate to afford the corresponding pyrazolo[1,5-a]pyrimidine derivative (56) (Scheme 21).

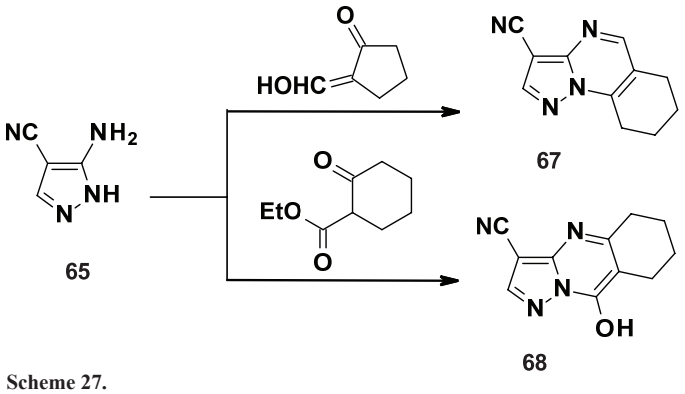
Also, Elnagdi *et al*. (1975) reported that reaction of the 5-aminopyrazole derivatives ($57_{a,b}$) with ethyl benzoylacetate, in refluxing AcOH afforded the corresponding pyrazolo[1,5-a]



Scheme 25.



Scheme 26.

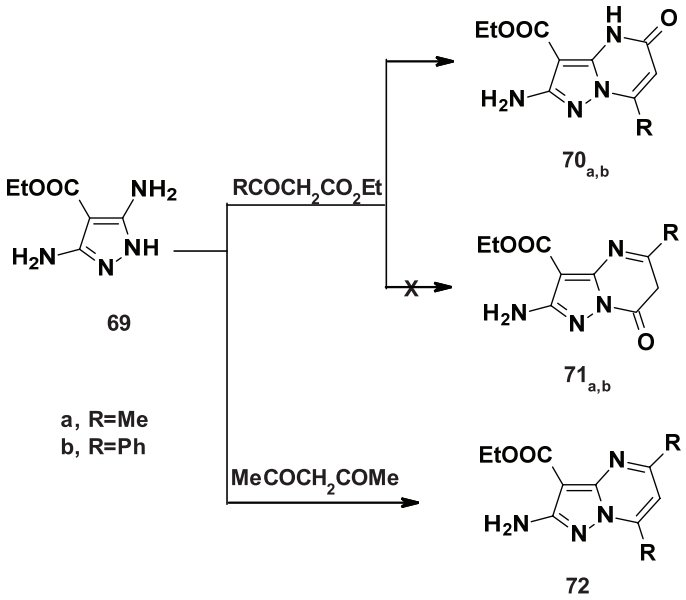


Scheme 27.

pyrimidine derivatives ($58_{a,b}$) rather than the regio-isomer ($59_{a,b}$) (Scheme 22).

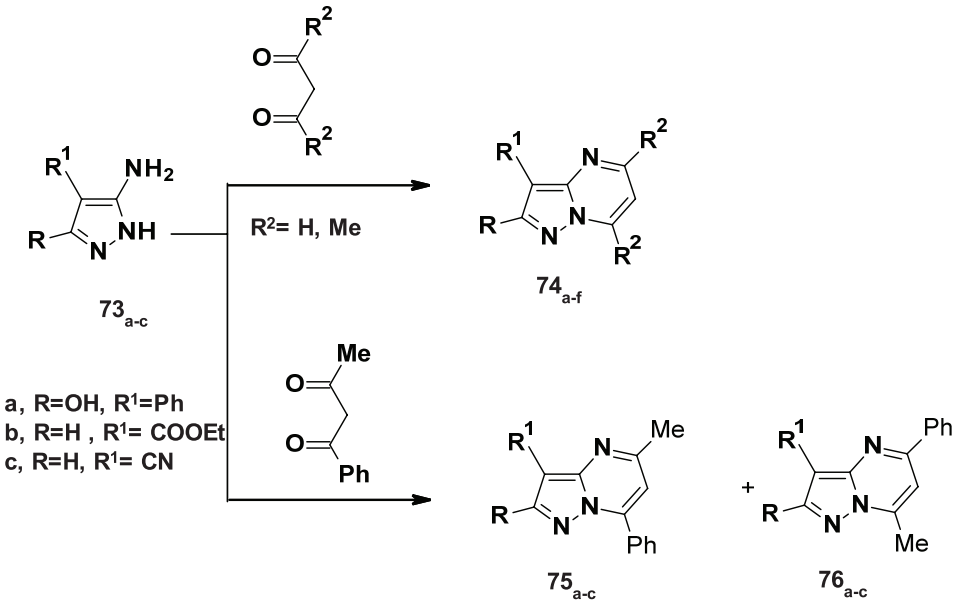
Lynch *et al*. (1975) prepared the parent pyrazolo[1,5-a] pyrimidine by condensation of 5-aminopyrazole with malondialdehyde-tertamethylacetal in excellent yield (Scheme 23).

Elnagdi *et al*. (1978) consistent with the above-mentioned results reported that when 3,5-diaminopyrazole (60) was heated with EAA in WB (in the absence of solvent), the corresponding pyrazolo[1,5-a]pyrimidine derivative (61) was obtained rather than the regio-isomer (62) (Scheme 24). Structure of the regio-isomer (61) was proved (Elnagdi *et al*., 1975b) by ^{1}H NMR and independent synthesis of (61) by decoupling of the phenylazo group from the previously prepared 2-amino-6,7-dihydro-5-methyl-7-oxo-3-phenylazopyrazolo[1,5-a]pyrimidine (63) (Scheme 25).

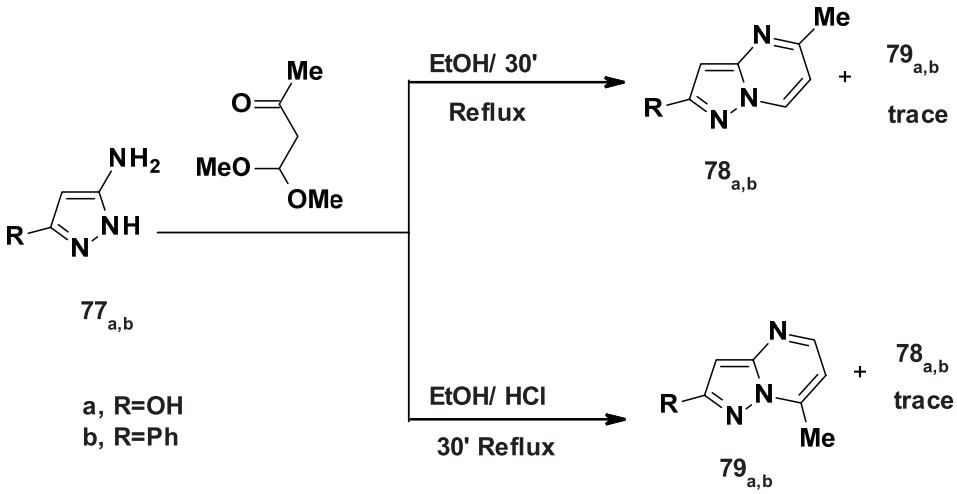


Scheme 28.

Bajwa and Skyes (1979) investigated the condensation of 5-aminopyrazole (55) with β-ketoacetal (4,4-dimethoxybutan-2-one), in dry toluene containing a catalytic amount of p-toluene sulfonic acid. The condensation of the 4-cyano analog of (65) with 2-hydroxymethylene cyclohexanone, 2-hydroxymethylenecyclopentanone, and with ethoxycarbonylcyclohexanone has been investigated. The reaction of (55) with 4,4-dimethoxybuta-2-one gave the corresponding



Scheme 29.



Scheme 30.

two regio-isomer pyrazolo[1,5-a]pyrimidine derivative ($64_{a,b}$). Similarly, the condensation of (65) with 2-hydroxymethylene cyclohexanone afforded the respective two regio-isomers ($66_{a,b}$) (Scheme 26).

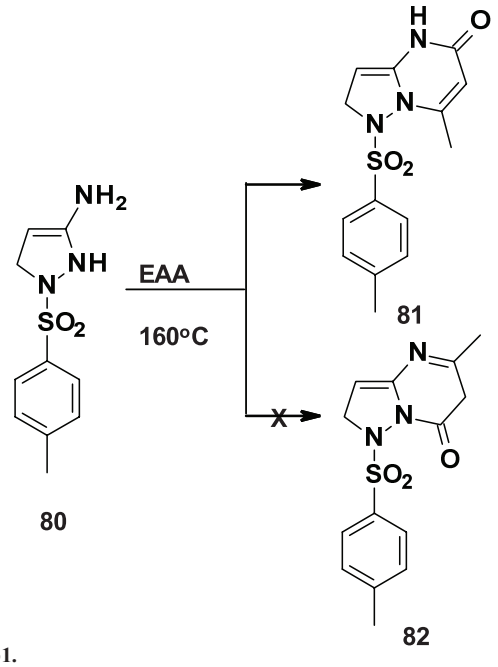
On the other hand, condensation of the 4-cyanoanalogue of (65) with 2-hydroxymethylenecyclopentanone and with 2-ethoxycarbonylcyclohexanone gave only the angular pyrazolo[5,1-b]pyrimidine regio-isomer (67) and only the linear pyrazolo[5,1-b]pyrimidine (68), respectively (Scheme 27).

The structure of the condensation products $64_{a,b}$, $66_{a,b}$, (67), and (68) has been distinguished by ^{1}H and ^{13}C NMR spectroscopy.

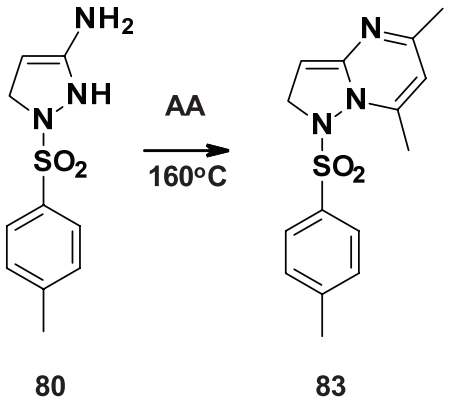
Kandeel *et al*. (1983) including Elnagdi reported that 3,5-diaminopyrazole derivative (69) reacted with EAA or with benzoyl acetoacetate to afford the corresponding pyrazolo[1,5-a] pyrimidine regio-isomer $70_{a,b}$ rather than the analogs $71_{a,b}$. The reaction of (69) with acetylacetone proceeded as expected to give the corresponding 5,7-diamethylpyrazolo[1,5-a]pyrimidine (72) (Scheme 28).

Maquestiau *et al*. (1992) reported the preparation of pyrazolo[1,5-a]pyrimidine 74_{a-f} via reaction of 3(5)-aminopyrazoles 73_{a-c} with malondialdehyde bis(dimethylacetal) and with acetylacetone, in refluxing AcOH. On the other hand, reaction of 73_{a-c} with the unsymmetrical 1-phenyl-1,3-butandione, under the same conditions, afforded a mixture of the two corresponding pyrazolo[1,5-a]pyrimidine regio-isomers 75_{a-c} and 76_{a-c} (Scheme 29), structural characterization of the products was based on ^{1}H NMR data and that regio-isomer assignment was confirmed by the magnitude of the corresponding 3J and 4J (H-H) coupling constants which is affected by C5-C6/ C7-C6 bond order (Barfield and Chakrabarti, 1969).

Chimichi *et al*. (1992) described the regioselective synthesis of certain pyrazolo[1,5-a]pyrimidines $78_{a,b}$ and $79_{a,b}$ via reacting the 5-aminopyrazoles $77_{a,b}$, independently, with



Scheme 31.



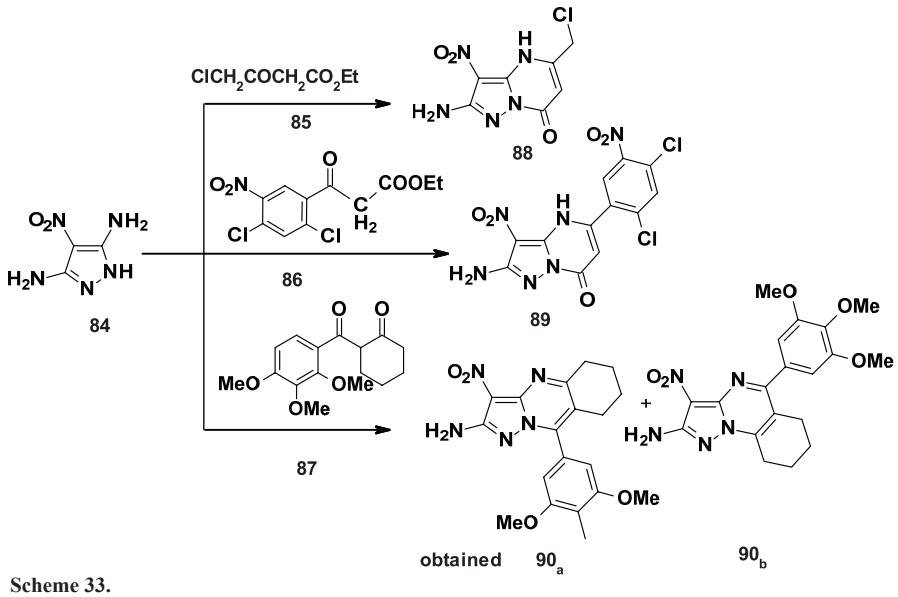
Scheme 32.

4,4-dimethoxybutan-2-one, under different reaction conditions. Heating the reactants in ethanol under reflux for 30' afforded mainly the 5-methylpyrazolo[1,5-a]pyrimidine derivatives $78_{a,b}$ and traces of the regio-isomer 7-methyl analog $79_{a,b}$. In contrast, when the reaction was carried out in refluxing ethanol containing a few drops of conc. HCl, the 7-methyl regio-isomers $79_{a,b}$ were obtained as the major products together with traces of the 5-methyl regio-isomer were critically assigned by means of ^{1}H-^{13}C 2 D experiments and gated decoupled spectra from which one-bond and long-range ^{13}C-^{1}H coupling constants were determined (Scheme 30).

Inconsistent with what has been reported by Elnagdi (1983), the reaction behavior of 5-aminopyrazoles with β-ketoesters, Girges *et al*. (1993) reported that fusion of equimolar amounts of the p-tosylaminopyrazole derivative (80) and EAA at 160°C yielded 7-methyl-1,2,4,5-tetrahydro-1-(*p*-tosyl)pyrazolo[1,5-a] pyrimidin-5-one (81) rather than its 5-methyl (regio-isomer) 82 (Scheme 31) based on insufficient spectral information. The reaction of (80) with acetylacetone under the same conditions afforded the corresponding 5,7-dimethyl(pyrazolo[1,5-a] pyrimidine) derivative (83) (Scheme 32).

Makarov *et al*. (1998) reported that the reaction of 3,5-diaminopyrazole (84) with ethyl β-chloroacetoacetate (85), 2,4-dichloro-5-nitro-benzoyl acetate (86), and 2-(3,4,5-trimethoxybenzoyl)cyclohexanone (87), in methanolic HCl gave the corresponding pyrazolo[1,5-a]pyrimidine derivatives 88, 89, and $90_{a,b}$, respectively (Scheme 33).

According to the authors, the first step in the reaction of 84 with β-ketoesters involves a nucleophilic attack by the exocyclic NH_2 group followed by subsequent cyclization by the second nucleophilic attack caused by the endocyclic NH on the ester carbonyl. The reaction of 84 with the 1,3-diketone 87 may proceed through two pathways to afford, potentially, tricyclic products 90_a and 90_b. ^{1}H-NMR spectra indicate a single product rather than a mixture of two products. Structure 90_b was ruled out on the ground of evidence-based structural assignment of substituents on 90_a by X-ray diffraction analysis (Fig. 4).



Scheme 33.

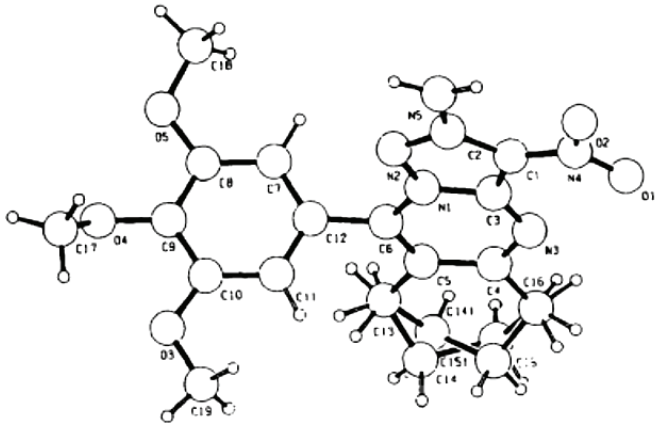
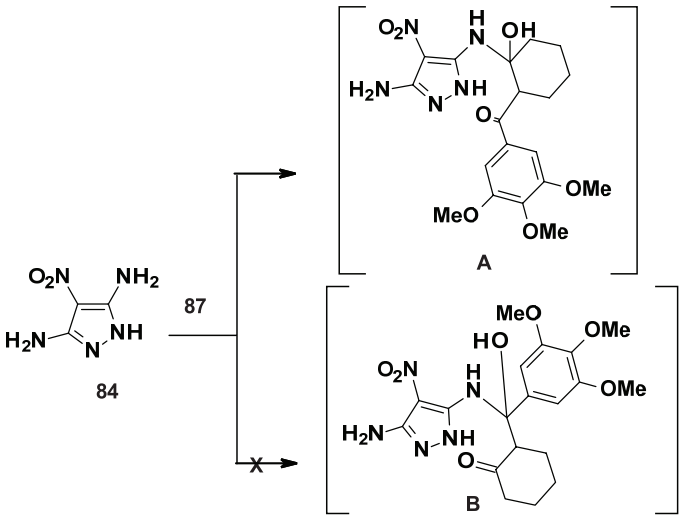
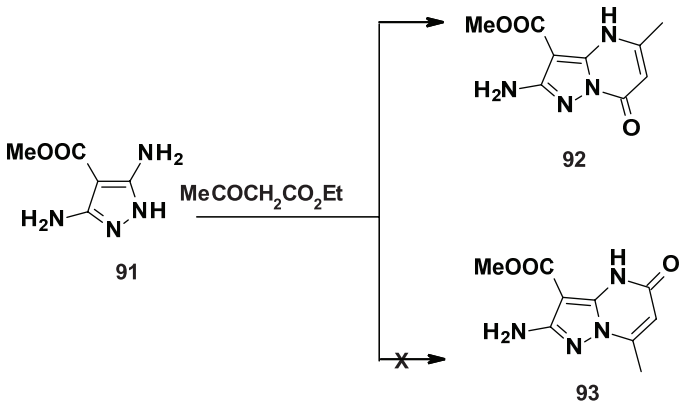


Figure 4. X-ray diffractional analysis of compound 90a. Makarov *et al.* (1998).

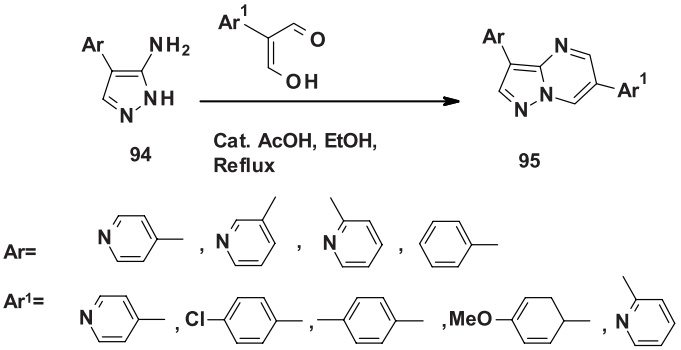


Scheme 34.



Scheme 35.

Noteworthy, the authors proposed the formation of intermediates A and B from the reaction of 84 with 87 assumed that intermediate A is energetically more favorable due to the conjugation of the carbonyl with the phenyl π-bond (Scheme 34).



Scheme 36.

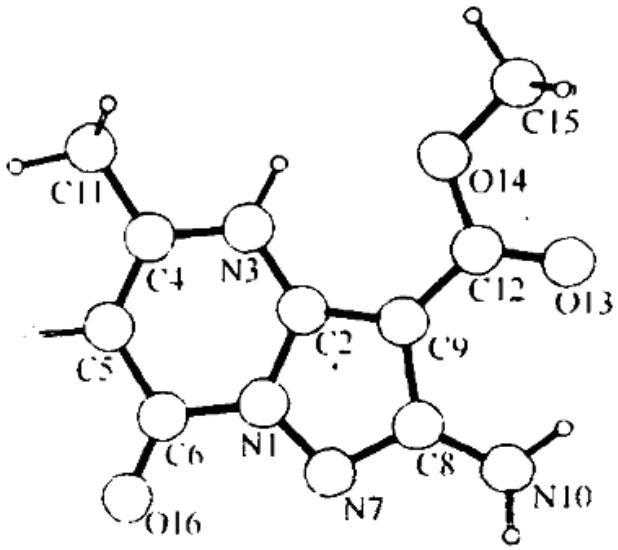
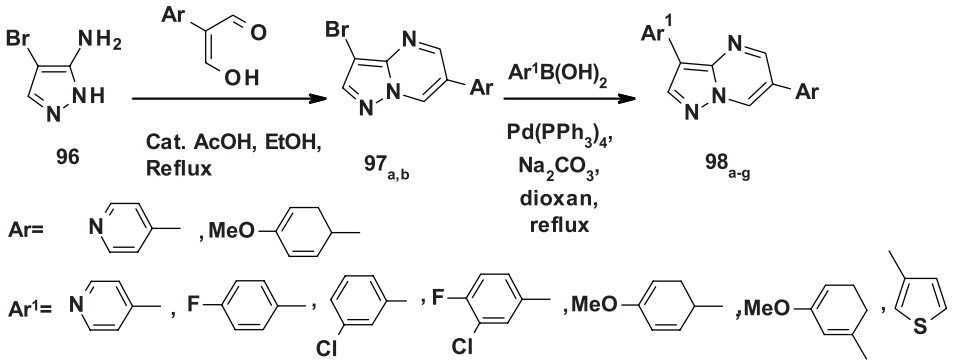


Figure 5. X-ray numbering of atoms and structure of compound 92 (Makarov *et al.*, 2000).

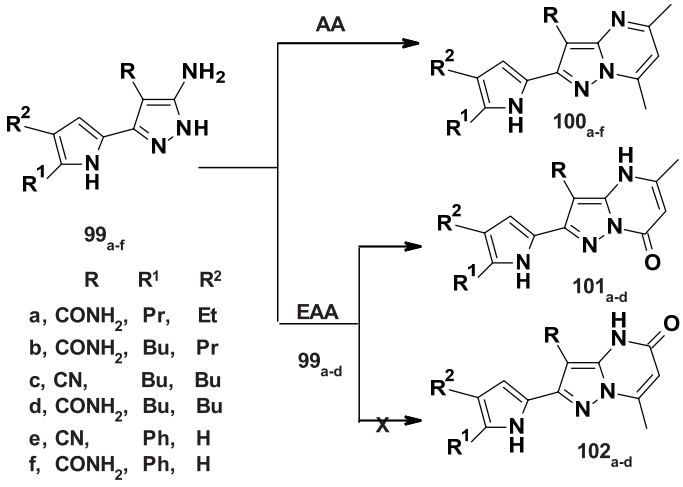
Makarov *et al.* (2000) reported that the reaction of 4-methoxycarbonyl-3,5-diaminopyrazole (91) with acetoacetic ester gave the corresponding 7-oxopyrazolo[1,5-a]pyrimidine analogue (92) rather than the regio-isomer 5-oxo pyrazolo[1,5-a] pyrimidine (93). This result is consistent with what has been reported by Makarov *et al.* (1998), concerning the reaction of 4-nitro-3,5-diaminopyrazole with acetoacetic ester while contradicts the results reported by Elnagdi *et al.* (1983). The structure of the regio-isomer 7-oxo pyrazolo[1,5-a]pyrimidine derivative 92 was confirmed by isotopic exchange experiment (NH for ND) in their ^{13}C NMR spectra and X-ray diffraction analysis -

Fraley *et al.* (2002) prepared in combinatorial fashion a set of 3,6-dichloro pyrazolo[1,5-a]pyrimidine 95 through a condensation reaction of a 3-amino-4-arylpyrazole 94 with 2-aryl malonaldehydes in ethanol containing a catalytic amount of acetic acid (Scheme 36).

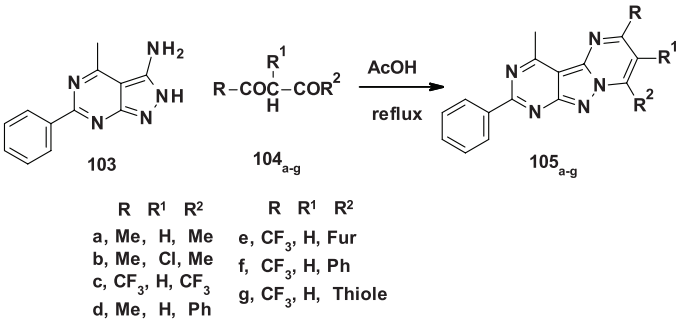
In this article (Fraley *et al.*, 2002), a convenient method for varying the substituents at the 3-position which avoids repetitious 3-aminopyrazole synthesis, involves reaction of 3-amino-4-bromopyrazole (96) with arylmalonoaldehydes to afford the corresponding 3-bromo-6-arylpyrazolo[1,5-a] pyrimidine $97_{a,b}$, which smoothly cross-coupled with arylboronic



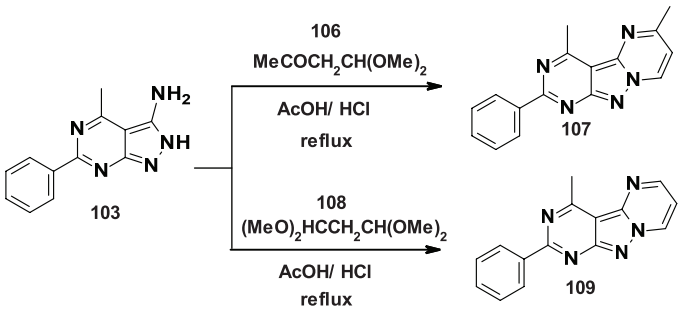
Scheme 37.



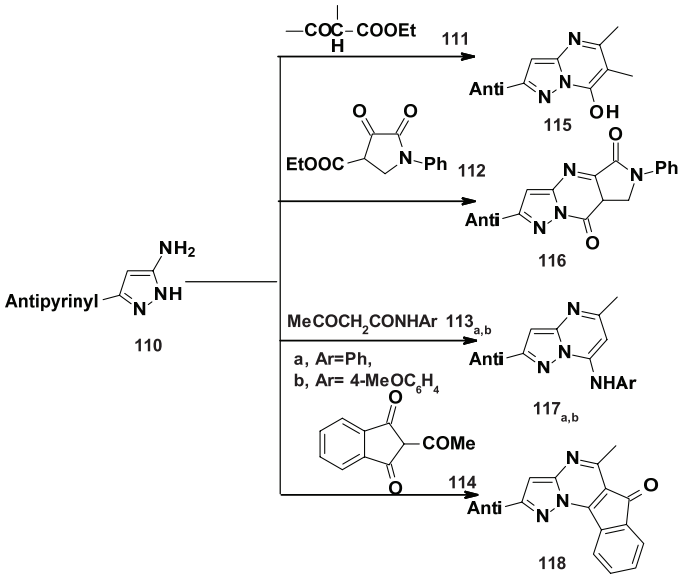
Scheme 38.



Scheme 39.



Scheme 40.



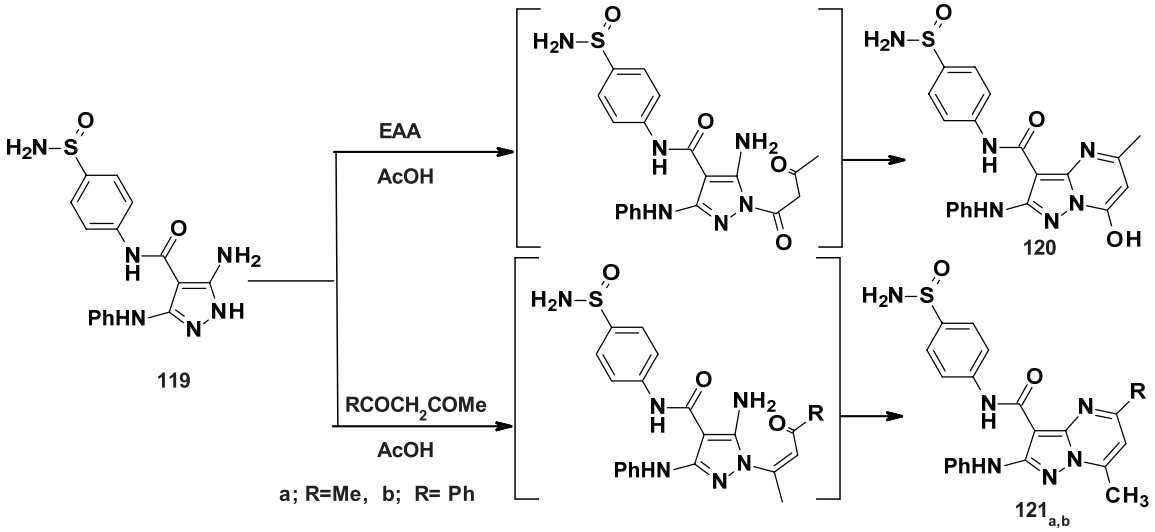
Scheme 41.

acids under Suzuki conditions to afford 3,6-diaryl pyrazolo[1,5-a] pyrimidines 98_{a-g} in fair yields (Scheme 37).

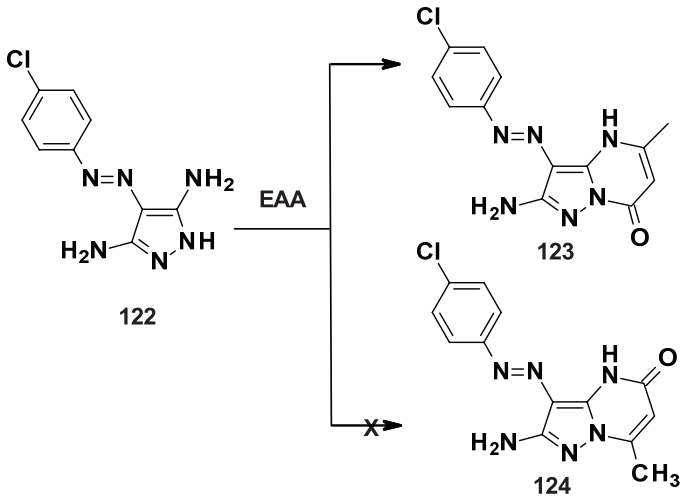
Petrova *et al*. (2003) reported that the condensation of 5-amino-3-(2-pyrrolyl)pyrazoles 99_{a-f} with acetylacetone and ethyl acetoacetate under different reaction conditions resulted in the formation of the corresponding pyrazolo[1,5-a]pyrimidine 100_{a-f} and 101_{a-d}, respectively (Scheme 38). In the case of EAA, the formation of the regio-isomer 101_{a-d} was selectively obtained rather than the regio-isomer 102_{a-d}.

Noteworthy, the authors criticized the method reported by Danagulyan *et al*. (2002) for the preparation of 100e, under the given conditions (ethanol containing a catalytic amount of AcOH 1 hour at room temperature).

Ho and Yao (2003) reported that the pyrazolopyrimidine 103 reacted with different 1,3-diketones 104_{a-g}, in refluxing acetic acid to afford the corresponding pyrimido pyrazolo[1,5-a] pyrimidines 105_{a-g} (Scheme 39). According to the authors, the



Scheme 42.



Scheme 43.

reaction probably involves the condensation of the 3-amino group of the pyrazolo[3,4-d]pyrimidine with the carbonyl group followed by dehydration and subsequent cyclization with loss of water.

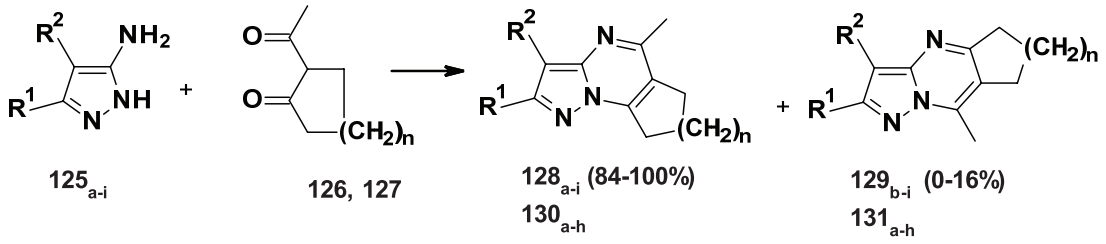
Condensation of 103 with 4,4-dimethoxy-2-butanone (106) in refluxing AcOH /HCl afforded 4,6-dimethyl-2-phenylprimido[2,3:4,3] pyrazolo[1,5-a]pyrimidine (107). Also, reaction of 103 with malonaldehyde-bis(dimethylacetal) (108) in EtOH/HCl gave 4-methyl-2-phenylpyrimido-pyrazolo[1,5-a] pyrimidine derivative (109) (Scheme 40).

Elmaaty and El-Taweel (2003) reported that 5-amino-2-antipyrinylpyrazole 110 reacted with ethyl α-methyl acetoacetate 111, β-ketoester 112, β-ketoamide $113_{a,b}$, and 2-acetyl indan-1,3-dione (114), under different reaction to afford the corresponding pyrazolo[1,5-a]pyrimidines 115, 116, $117_{a,b}$, and 118. Formation of such pyrazolo[1,5-a]pyrimidines was assumed to proceed via initial nucleophilic attack by the exocyclic NH_2 group of pyrazole on the ketonic function followed by cyclization with the elimination of ethanol or H_2O (Scheme 41). The same reaction pathway and mechanism were confirmed by other authors (Gregg *et al*., 2007).

Ammar *et al*. (2009) reported that the reaction of 3(5)-aminopyrazole 119 with EAA, acetylacetone, and benzoylacetone gave the respective pyrazolo[1,5-a]pyrimidines 120, $121_{a,b}$. The authors believed the relative higher nucleophilicity of the endocyclic NH group of the pyrazole ring based only on what they previously reported (Ammar *et al*., 1995; Zaharan *et al*., 2001) (Scheme 42).

Al-Zaydi (2009b) unambiguously assigned the structure of 3,5-diaminopyrazole 122 with EAA as 5-methyl-pyrazolo[1,5-a]pyrimidin-7-one derivative 123 rather than the regio-isomer 124 based on X-ray crystallographic data (Scheme 43).

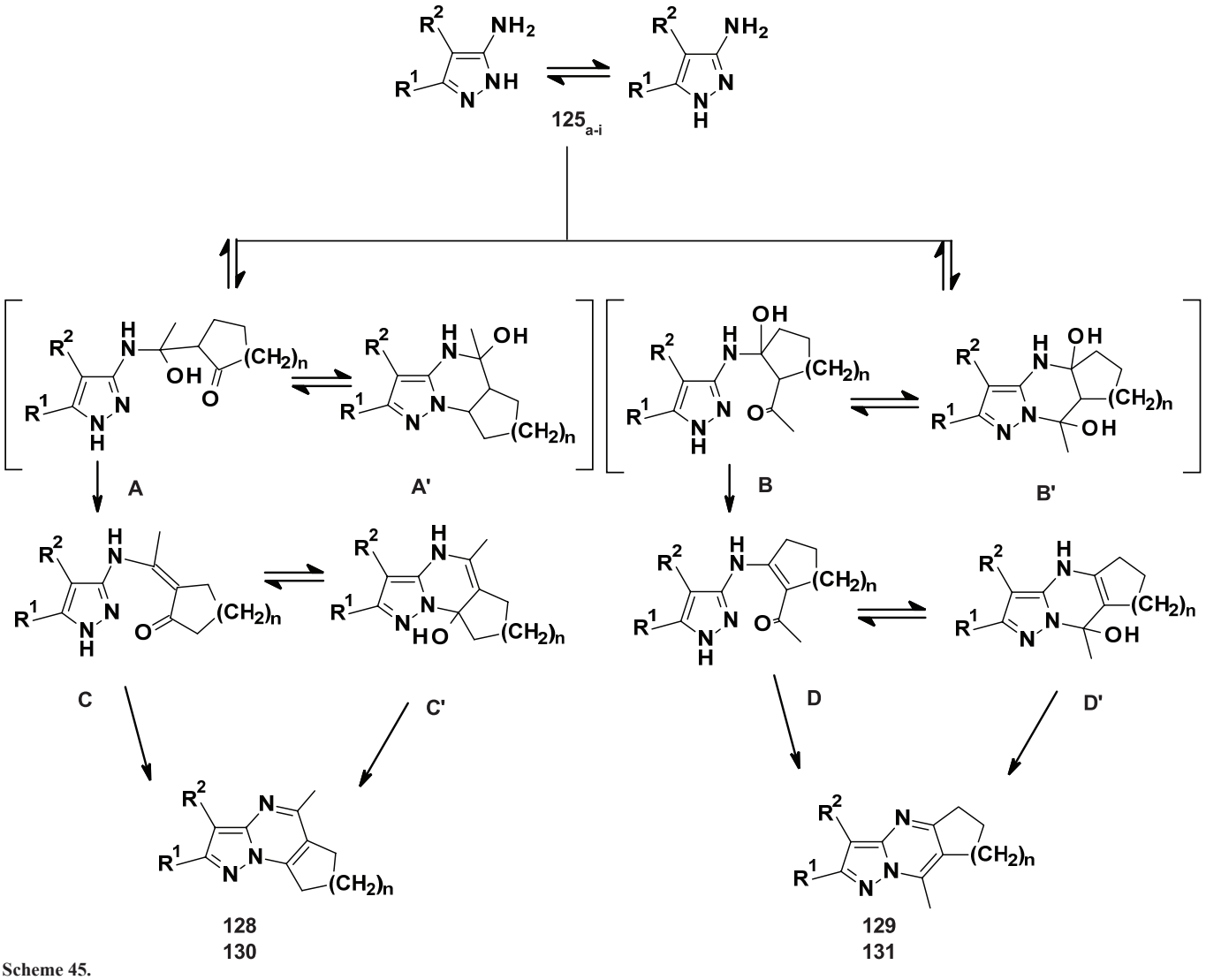
In 2012, regioselectivity of the reaction between nine different 3(5)-aminopyrazoles 125_{a-i} and 2-acetylcyclohexanone 126, 127 has been investigated (Petrov *et al*., 2012), under different conditions. The corresponding cycloalkane[e]pyrazolo[1,5-a] pyrimidines 128_{a-i}, 129_{b-i} and cycloalkane[d]pyrazolo[1,5-a] pyrimidines 130_{a-h}, 131_{a-h} were obtained. The regio-structure of the compounds was established by ^{1}H and ^{13}C NMR spectroscopy (Scheme 44).



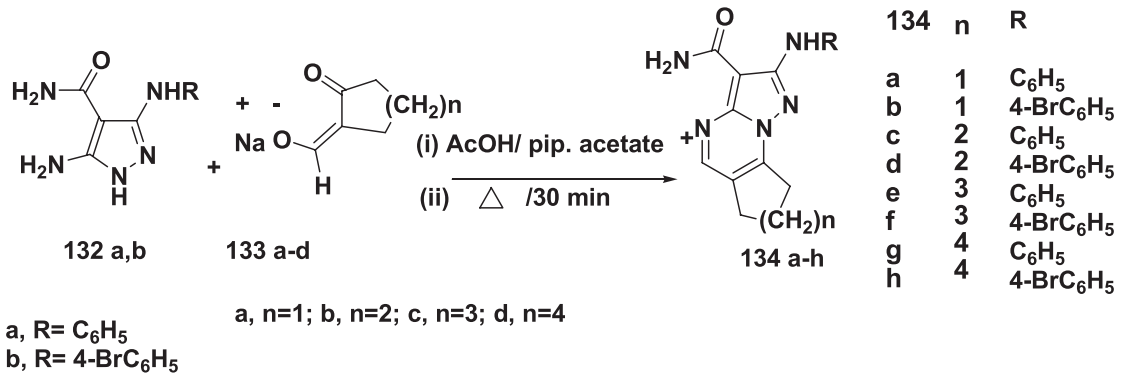
a, R^1=Me, R^2=H; b, R^1=4-MeC_6H_4, R_2=H
c, R^1=H, R^2=CN; d, R^1=H, R^2=C_6H_5
e, R^1=H, R^2=4-Cl-C_6H_4, f, R^1=H, R^2=4-MeO-C_6H_4
g, R^1=Me, R^2=Ph, h, R1=Me, R^2=4-MeOC_6H_4
i, R^1=Me, R^2=2-MeOC_6H_4

n=1 (126,128,130), 2 (127, 129, 131)

Scheme 44.

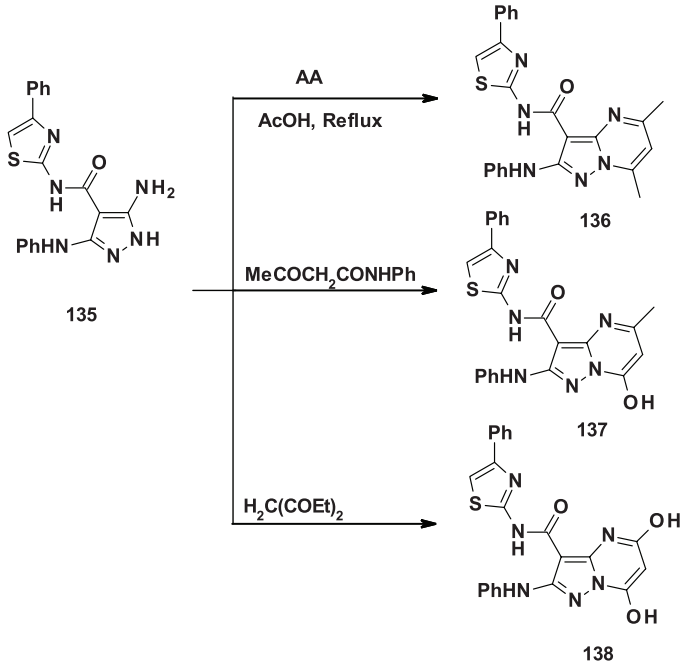


Scheme 45.

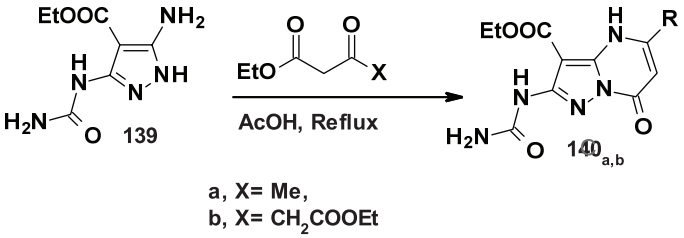


134	n	R
a	1	C_6H_5
b	1	4-BrC_6H_5
c	2	C_6H_5
d	2	4-BrC_6H_5
e	3	C_6H_5
f	3	4-BrC_6H_5
g	4	C_6H_5
h	4	4-BrC_6H_5

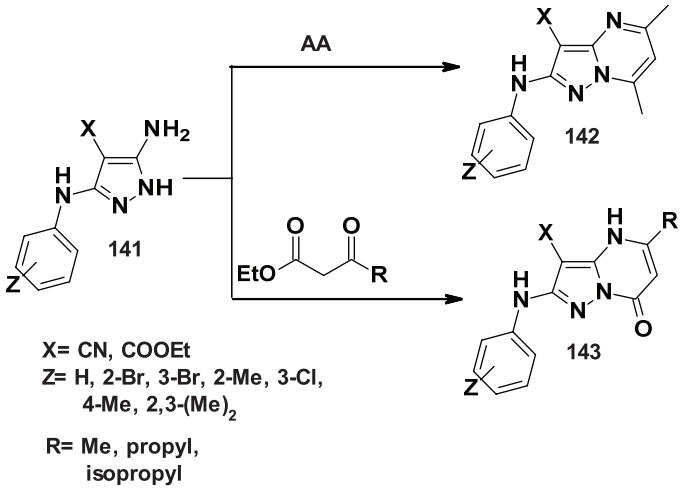
Scheme 46.



Scheme 47.



Scheme 48.

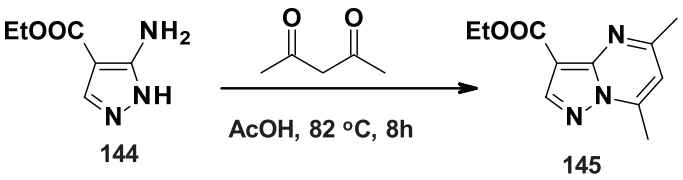


Scheme 49.

The reaction sequence involves the nucleophilic addition of the exocyclic NH_2 group of the pyrazole on the acetyl carbonyl or the ring carbonyl of the 1,3-dicarbonyl reagent forming intermediates A(A') or B(B'). Then in succession two molecules of water were eliminated with the formation of the final products 128-131. The presence of intermediates C (and or C') alongside with products 128_d, 129_d was detected by high-resolution mass spectroscopy: in a solution, in DMSO, of a mixture of aminopyrazole 125_d and 2-acetylcyclopentanone 126 after 3 days masses $[M+H]^+$ 250.1339 and 268.1446 (Scheme 45).

7,8-dihydro-6H-cycloalkan[e]pyrazolo[1,5-a] pyrimidine-3-carboxamide derivatives 134a–h were prepared (Abdallah and Elgemeie, 2018) by reacting aminopyrazoles 132a,b with the sodium salt of (hydroxymethylene)-cycloalkanones 133a-d and piperidine acetate. The reaction mixture was heated and was in the water for 25 min, and then acetic acid was added in the middle of the reaction time (Scheme 46).

Bondock *et al*. (2015) reported that condensation of 3(5)-aminopyrazole derivative 135 with acetylacetone, in boiling AcOH, gave the corresponding pyrazolo[1,5-a]pyrimidine 136. Similarly, the reaction of 135 with acetoacetamide afforded the regio-isomer pyrazolo[1,5-a]pyrimidine 137 based on what has been reported by Kleschick in 1989. They assumed that the initial nucleophilic attack induced by the exocyclic NH_2 group of pyrazole on the ketonic carbonyl of acetoacetanilide, followed by cyclization via nucleophilic substitution on the amide carbonyl by the endocyclic NH of the pyrazole and loss of the aniline molecule. The solvent-free reaction of 135 with diethyl malonate at 160°C, afforded the corresponding 5,7-dihydroxy pyrazolo[1,5-a] pyrimidine 138 (Scheme 47).



Scheme 50.

Abbas-Temirek and Abo-Bakr (2016) reported that the reaction of 3(5)-aminopyrazole 139 with EAA and diethyl-3-oxoglutarate produced the corresponding pyrazolo[1,5-a] pyrimidines $140_{a,b}$. Regio-orientation was not discussed and the structures of the products were supported by ^{1}H and ^{13}C NMR (not reliable without deep investigation) in addition to what has been previously reported by Elnagdi *et al*. (1993) (Scheme 48).

Marjani *et al*. (2015) reported the synthesis of pyrazolo[1,5-a]pyrimidine analogs 142, 143 via condensation of substituted 3(5)-aminopyrazoles 141, independently, with acetylacetone and certain ketoesters in the presence of H_2SO_4 using AcOH as solvent (Scheme 49).

According to the authors, the reaction mechanism involves an initial nucleophilic attack by the exocyclic NH_2 group on the ketonic function followed by subsequent cyclization. Although the regioselectivity of the reaction was not discussed, the structures of the products were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR, and elemental analysis.

5,7-dimethylpyrazolo[1,5-a]pyrimidine carboxylic acid 145 was synthesized (Kumar *et al*., 2016) by heating ethyl 3(5)-aminopyrazole-4-carboxylate (144) with acetylacetone in the acetic acid medium at 82°C, in good yield (Scheme 50).

ABBREVIATIONS

AcOH: acetic acid, DMSO: dimethylsulfoxide, EAA: ethyl acetoacetate, ECA: ethyl cyanoacetate, EtOH: ethanol, HCl: hydrochloric acid, WB: water bath.

CONFLICT OF INTEREST

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of this article.

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