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Synthesis of some condensed pyrrolo-, thieno-, furo-, pyrido- and pyranopteridines as well as isomeric pyrrolo- and thienopyrimido[4,5-*c*]pyridazines from alkynyl derivatives of 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione and 1,3-dimethyllumazine is represented.

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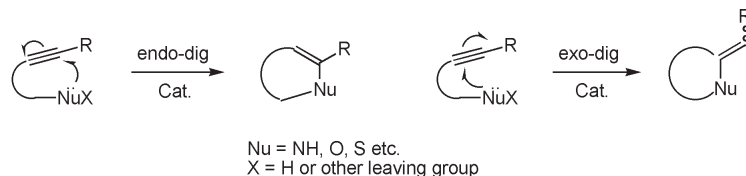
The cyclization of alkynes possessing a nucleophile in proximity to the triple bond has been shown to be extremely effective for synthesis of a wide variety of carbo- and heterocycles [1-4]. In general, such transformations proceed according to Scheme 1 and require a catalyst (a base, transition metal complex or electrophile).

its metabolite urothione and pigment russupteridine yellow (Scheme 2).

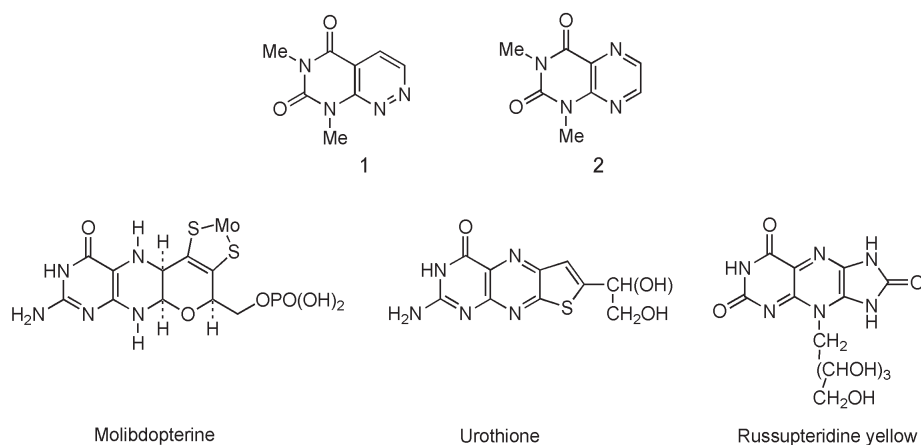
Thus, our initial goal consisted in introducing of alkynyl and nucleophilic groups into diazine nucleus of compounds **1** and **2** (Scheme 3).

One of the best synthetic methods for arylacetylenes is palladium-catalyzed Sonogashira cross-coupling of aryl-

Scheme 1

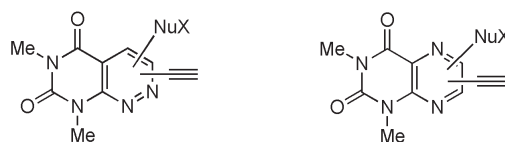


Scheme 2



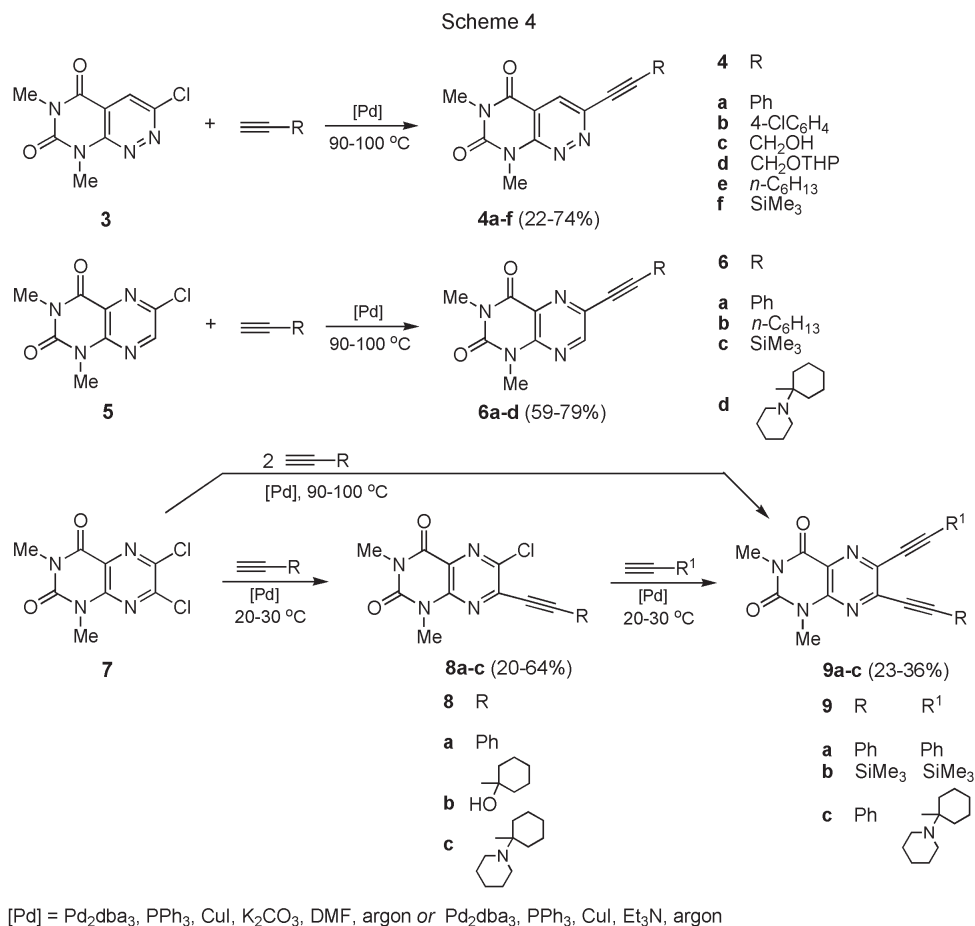
For some time we were interested in extending this methodology to pyrimidopyridazine **1** and lumazine **2** in hope to obtain analogues of some naturally occurring pteridines, such as molybdenum cofactor molibdopterine,

Scheme 3



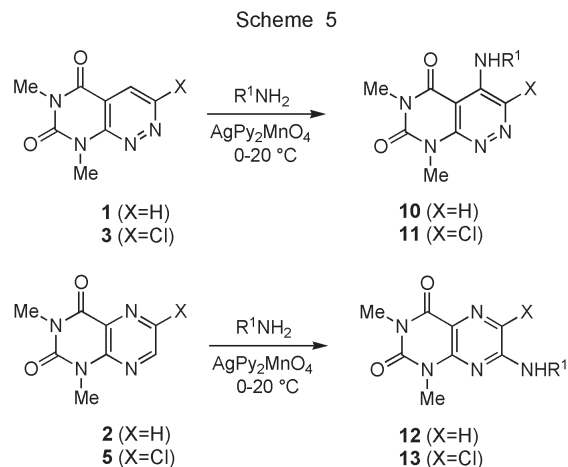
halides with terminal alkynes [5]. We have applied similar procedure for pyrimidopyridazine and lumazine chlorides **3** and **5** (Scheme 4). As a result alkynyl derivatives **4** and **6** were obtained in good yields. In 6,7-dichlorolumazine **7** the chlorine atoms exhibit strongly different lability making it possible to replace them successively: thus at room

Based on these data we have assumed that oxidative amination of alkynes **4** and **6** could also provide aminoacetylenes **14** and **16** capable to cyclization into pyrroles **15** and **17** (Scheme 6). Indeed, we were pleased to find that the interaction of compounds **4** and **6** with primary alkylamines in the presence of an oxidant at 0-20 °C



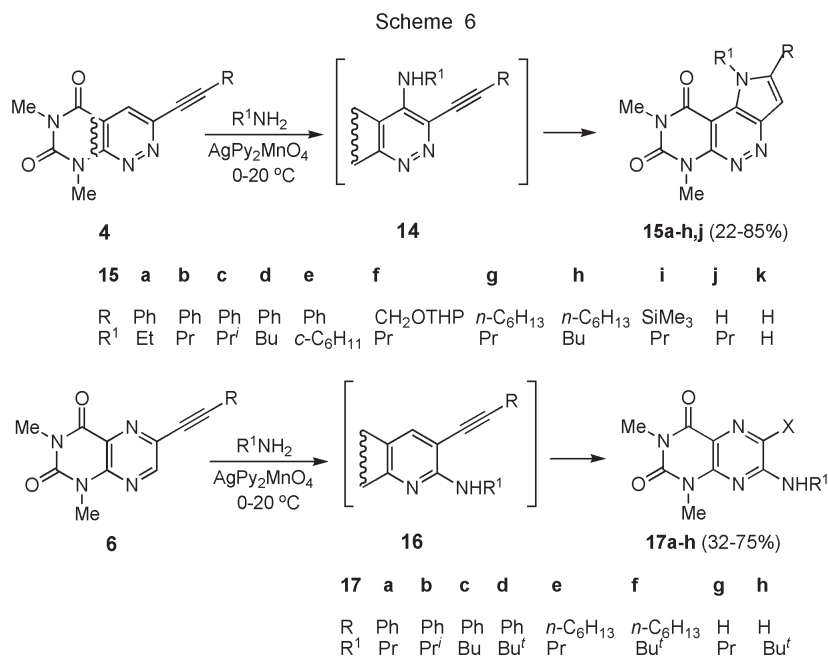
temperature monoacetylenes **8** are formed, whereas at a higher temperature diacetylenes **9** can be obtained. Compounds **8** are converted into **9** by the same way [6-8].

It is well known that common strategy for inserting of amino and other nucleophilic functions into an azine ring is replacement of good-leaving groups. However, in last years nucleophilic substitution of hydrogen finds ever-increasing use for this aim [9,10]. Recently [11,12], we have shown that pyrimidopyridazine **1** and its 3-chloride **3** undergo oxidative amination with ammonia and alkylamines at position 4 (Scheme 5). Under the same conditions the lumazines **2** and **5** affords 7-amino derivatives **12** and **13** [7,13,14].



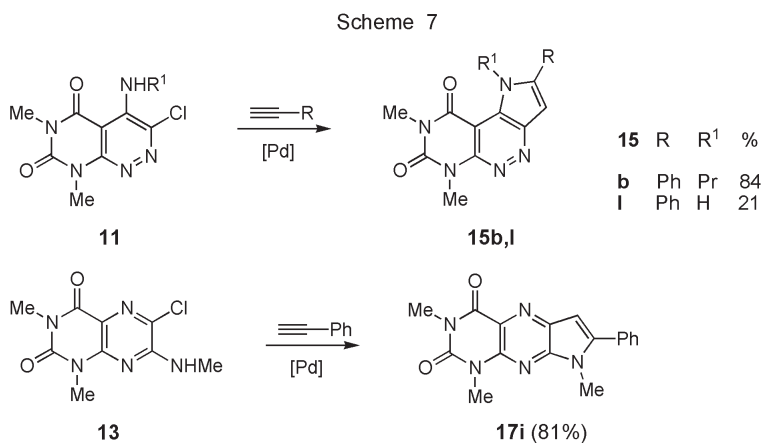
produced right away pyrroles **15** and **17** [6,7]. Apparently, these transformations proceed through intermediate *ortho*-aminoacetylenes **14**, **16** and their cyclizations are likely promoted by coordination of silver ion with the carbon-carbon triple bond.

to a procedure recently reported by English chemists [15]. It involves the addition of bromine to the arylalkyne's triple bond and subsequent cyclization of the resulted dibromide at treatment with sodium trithiocarbonate. Using acetylenes **4**, **6** as starting material and



Both pyrroles **15** and **17** were also obtained by Sonogashira cross-coupling of *ortho*-aminoaldehydes **11**, **13** with terminal alkynes (Scheme 7) [7,12].

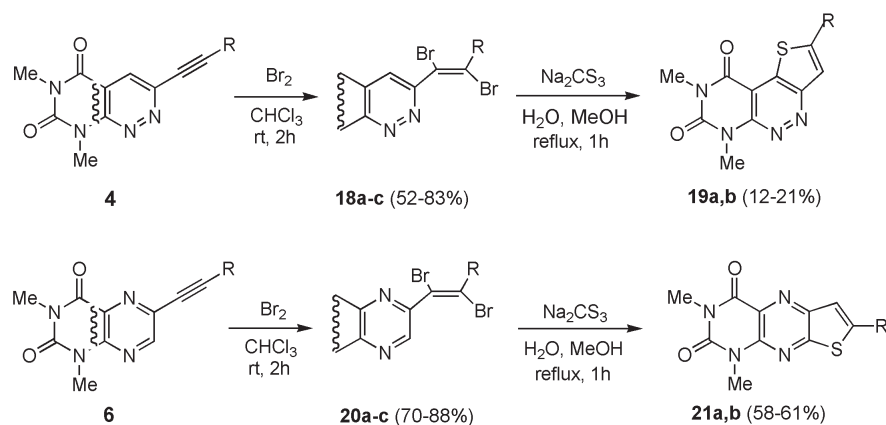
the pointed out conditions we have prepared desired thiophenes **19** and **21** in moderate to good yields (Scheme 8) [7,16].



Next, we attempted to annulate the thiophene ring to pyrimidopyridazine and lumazine systems according

To obtain pyrroles **23** and **24** isomeric to **17** (Scheme 9) we have studied the interaction of alkynyllumazines **8** and

Scheme 8

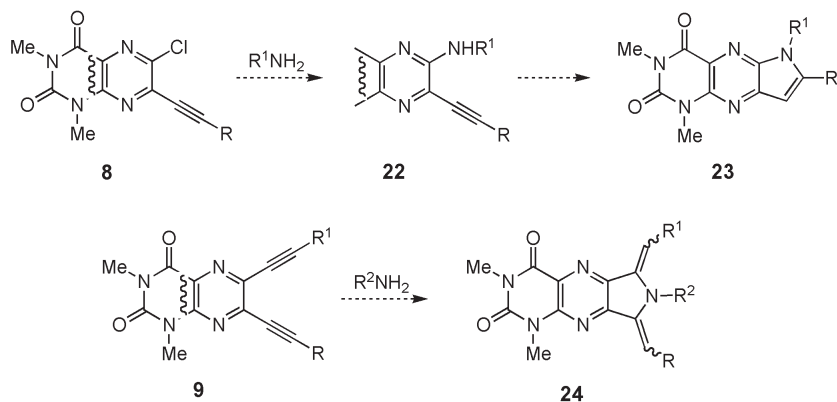


18-21: R=Ph (**a**), *n*-C₆H₁₃ (**b**), SiMe₃ (**c**)

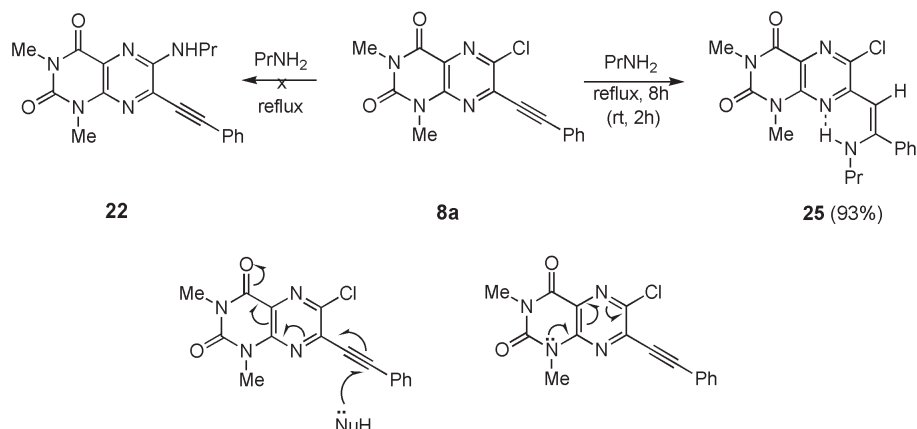
9 with alkylamines. However, we have found that treatment of alkynylchloride **8a** with propylamine at room temperature or under reflux afforded almost quantitative yield of enamine **25** instead of expected compound **22** or its cyclization product (Scheme 10) [8]. Perhaps the simplest

explanation for this behaviour of molecule **8a** is activation of the triple bond to nucleophilic attack due to its conjugation with carbonyl group. On the contrary, the 6-chlorine atom is deactivated by electron donating influence of the uracil nitrogen atom.

Scheme 9



Scheme 10

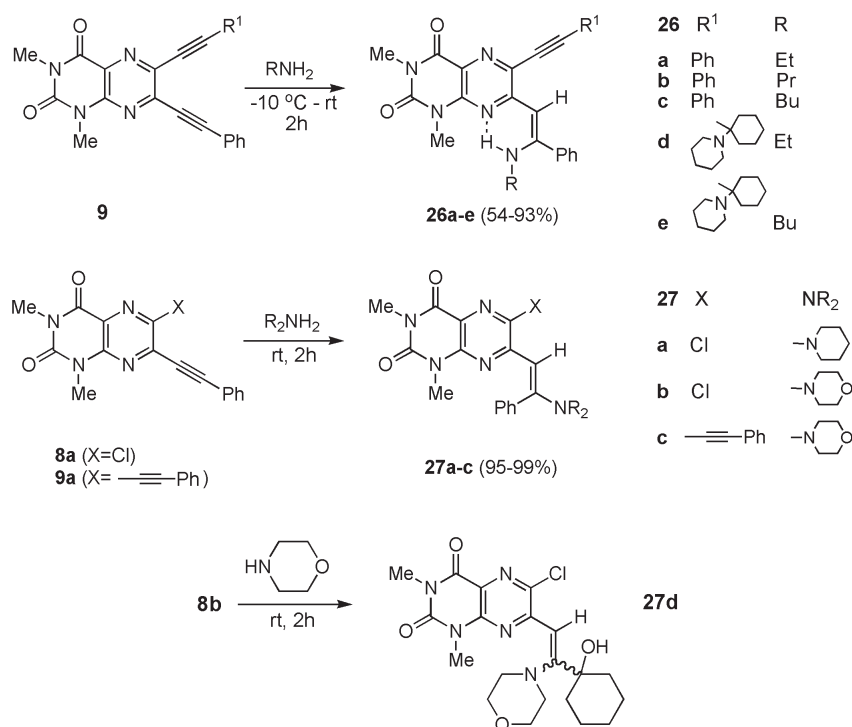


Dialkynyllumazines react with primary amines by the same way to yield adducts **26** (Scheme 11) [8]. As it follows from spectral data compounds both compounds **25** and **26** are stabilizing by intramolecular hydrogen bonding shown on Schemes 10,11. But it seems to be not sole reason for their stability, because of enamines **27** derived from secondary amines are also stable. Evidently, the conjugation of amino group with azine π -system should be also taken into account.

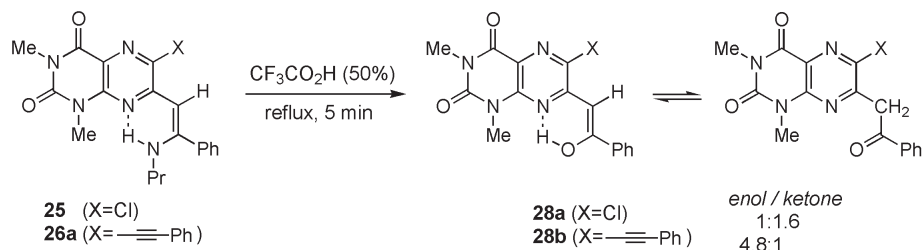
Enamines **25** and **26a** are hydrolyzed under reflux in aqueous trifluoroacetic acid to furnish compounds **28** existing as a mixture of enol and the corresponding ketone (Scheme 12) [8].

Enamines **25** and **27d** as well as enols **28a** were successfully employed in annulation reactions [8]. Thus, heating of enamine **25** with potash in DMF solution leads to formation of pyrrole **29a** (Scheme 13). Prolonged reflux of alkynylchloride **8a** with butylamine

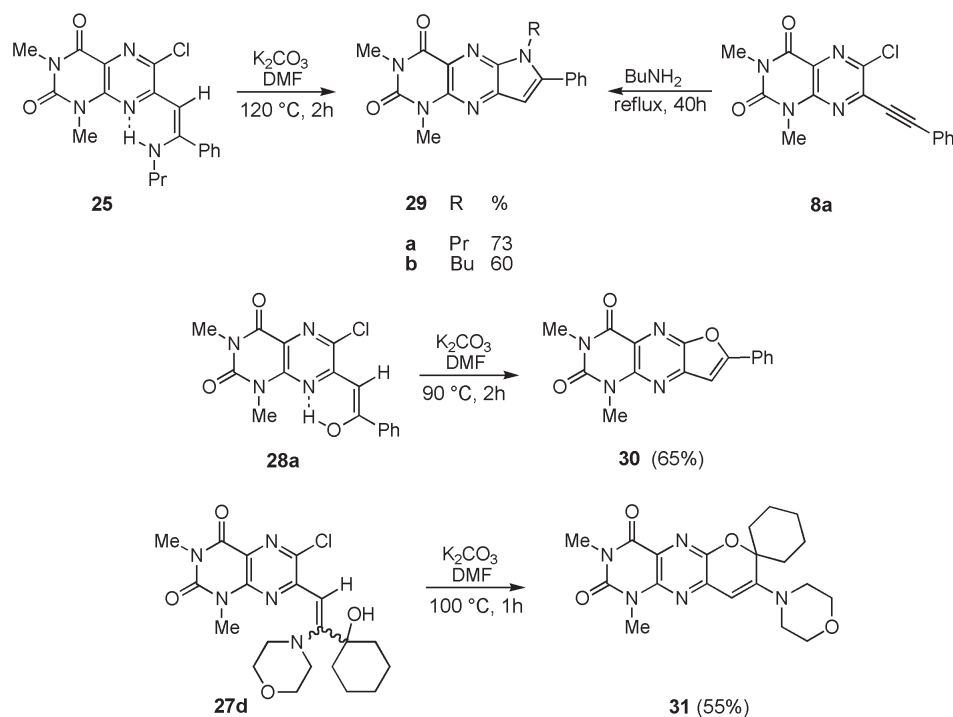
Scheme 11



Scheme 12



Scheme 13



is also resulted in pyrrole-ring annulation, undoubtedly proceeding via enamine intermediate of a type **29**. Using potash as a catalyst we performed cyclizations of compounds **28a** and **27d** into furopteridine **30** and pyra-nopteridine **31** respectively.

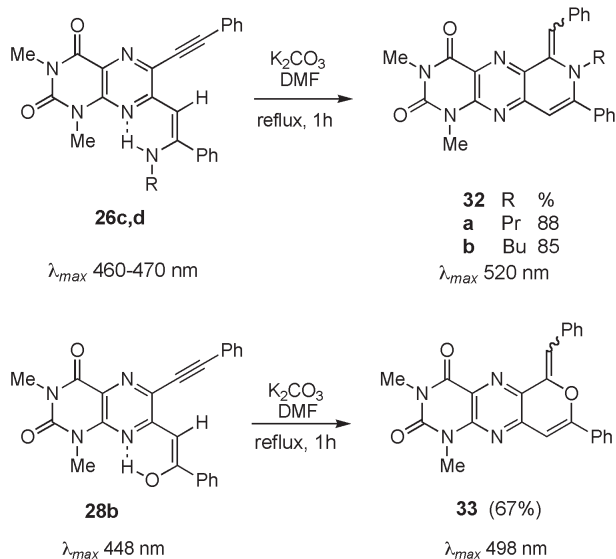
Interestingly, that enamines and enols derived from dialkynyllumazines are also able to cyclization. Thus, when compounds **26c,d** were heated with potassium carbonate cyclomerization products **32** were isolated (Scheme 14) [8]. Under similar conditions enol **28b** produced pyrane **33**. It should be noted, that the above transformations represent new routes for [c]-condensed pyridines and pyranes.

In summary, we have elaborated the synthesis of the following nine types of heterocyclic systems, closely related to naturally occurring pteridines (Scheme 15).

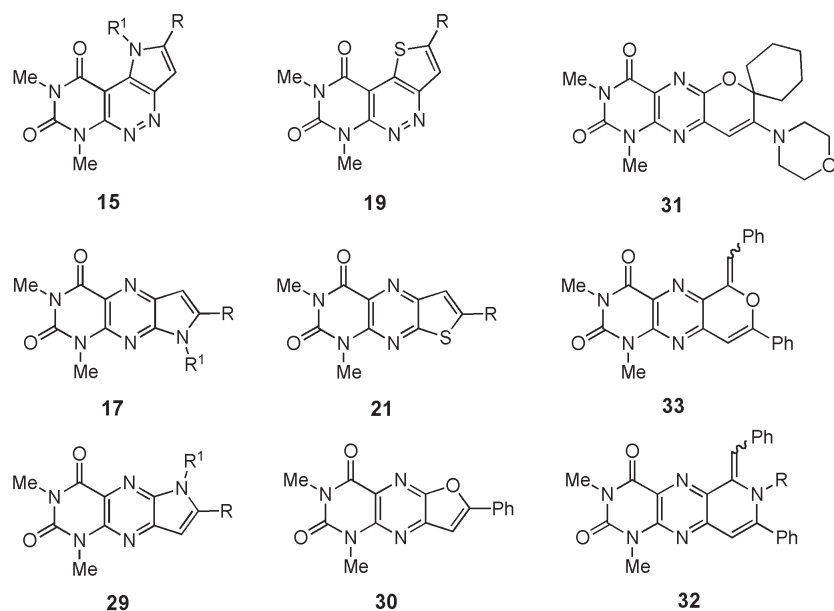
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Scheme 14



Scheme 15



REFERENCES AND NOTES

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- [1] S. Cacchi, F. Fabrizi and A. Goggiomani, *Heterocycles*, **58**, 667 (2002).
- [2] S. Cacchi, F. Fabrizi and A. Goggiomani, *Heterocycles*, **56**, 613 (2002).
- [3] G. Zeni and R.C. Larock, *Chem. Rev.*, **104**, 2285 (2004).
- [4] J.J. Li and G.W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, New York, 2000.
- [5] K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 4467 (1975).
- [6] V.V. Gorunenko, A. V. Gulevskaya and A. F. Pozharskii, *Russ. Chem. Bull., Int. Ed.*, **52**, 441 (2003).
- [7] A.V. Gulevskaya, Dang Van Shee and A. F. Pozharskii, *Russ. Chem. Bull., Int. Ed.*, **52**, 1328 (2003).

[8] Shee Van Dang, A.V. Gulevskaya, A. F. Pozharskii and R.V. Kotelevskaya, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **41**, 000 (2005), in print.

- [9] H. van der Plas, *Adv. Heterocycl. Chem.*, **86**, 1 (2004).
- [10] M. Makosza and K. Wojciechowski, *Chem. Rev.*, **104**, 2631 (2004).
- [11] A.V. Gulevskaya, D.V. Besedin and A.F. Pozharskii, *Russ. Chem. Bull., Int. Ed.*, **48**, 1150 (1999).
- [12] V.V. Goryunenko, A.V. Gulevskaya and A. F. Pozharskii, *Russ. Chem. Bull., Int. Ed.*, **53**, 846 (2004).
- [13] A.V. Gulevskaya, A.F. Pozharskii and L. V. Lomachenkova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **26**, 1316 (1990).
- [14] A.V. Gulevskaya, A. F. Pozharskii, A. I. Chernyshev and V. V. Kuz'menko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **28**, 1015 (1992).
- [15] M. Armengol and J.A. Joule, *J. Chem. Soc., Perkin 1*, 154 (2001).
- [16] A.V. Gulevskaya and A.F. Pozharskii, unpublished results.