A New Synthesis of Pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones by Oxidative N-N Bond Formation of 6-Amino-5-(*N*-aryliminomethyl)uracils Using Iodobenzene Diacetate

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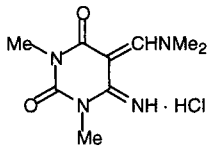
Abstract: The intramolecular cyclizations of 6-amino-5-(N-aryliminomethyl)-1,3-dimethyluracils (**2**) involving the N-N bond formation were effected *via* a hypervalent iodine oxidation using iodobenzene diacetate. This method enabled a facile synthesis of 2-aryl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (**3**) in moderate to excellent yields. The primary advantage of this N-N bond formation method is that various 2-aryl-substituted pyrazolo[3,4*d*]pyrimidines can be provided under mild oxidative conditions.

Pyrazolo[3,4-*d*]pyrimidine derivatives have attracted considerable attention as 7-deaza-8-aza analogs of purines and xanthines owing to the occurrence of biologically active products.[1] For examples, allopurinol, pyrazolo[3,4-*d*]pyrimidine-4(5*H*)-one, is clinically employed for the treatment of gouty arthritis[1a] and certain pyrazolo[3,4-*d*]pyrimidines exhibit potent activities as purine antagonists.[2] Although extensive synthetic methods for the pyrazolo[3,4-*d*]pyrimidine derivatives have been reported,[1,3,4] the creation of the N-N bond of the pyrazole ring in the last step of the ring construction has not yet been established to our best knowledge.[5] In this communication, we describe a convenient method for the preparation of pyrazolo[3,4-*d*]pyrimidine derivatives (**3**) including oxidative N-N bond formation using iodobenzene diacetate.

6-Imino-1,3-dimethyl-5-(dimethylamino)methylidene-5,6-dihydrouracil hydrochloride (**1**),[6] which is readily prepared by the Vilsmeier reaction of commercially available 6-amino-1,3-dimethyluracil, reacts with 2.1 equiv. of amine to give 6-amino-5-(substituted imino)methyl-1,3-dimethyluracil (Schiff base, **2**)[7] as the starting compounds.



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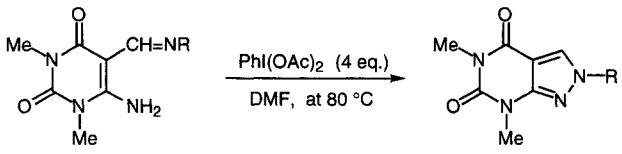
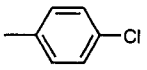
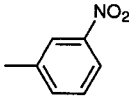
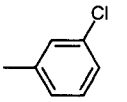
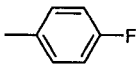
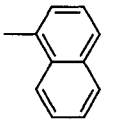
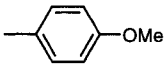
An initial attempt was made to carry out oxidation of 6-amino-1,3-dimethyl-5-(phenylimino)methyluracil (**2a**) for the N-N bond formation using several oxidants.

When 4 equiv. of *N*-bromosuccinimide (NBS) was used as an oxidant, the reaction gave only a complex mixture. On the other hand, the oxidation with 4 equiv. of lead tetraacetate in DMF at r. t. for 6 h gave 5,7-dimethyl-2-phenylpyrazolo[3,4-*d*]yrimidine-4,6(5*H*,7*H*)-dione (**3a**)[4b] in 47% yield. Furthermore, employment of iodobenzene diacetate (4 equiv.) instead of lead tetraacetate led to significant improvement of the yield up to 87% (entry 1 in Table 1). From these results, we chose iodobenzene diacetate as the oxidant for the oxidative N-N bond formation reactions. The results of the iodobenzene diacetate-mediated pyrazolo[3,4-*d*]yrimidine synthesis are summarized in Table 1. In the cases examined with 5-(aryl substituted imino)methyl congeners (**2a-g**), the isolation of the 2-arylpyrazolo[3,4-*d*]pyrimidines (**3a-g**) is very easy, requiring only evaporation of DMF, extraction with $CHCl_3$, trituration of the residue with ether and recrystallization.

Table 1. Synthesis of Pyrazolo[3,4-*d*]pyrimidines (3) by the Intramolecular N-N Bond Formation of 2

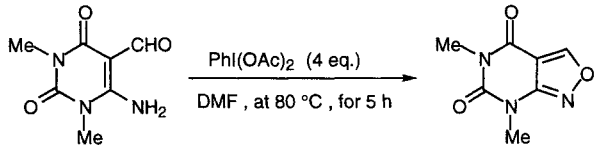


2 **3**

Entry	Substrate	R	Time (h)	Product	Yield (%)
1	**2a**	Ph	1	**3a**[3b]	87
2	**2b**		1	**3b**	76
3	**2c**		3	**3c**	55
4	**2d**		2	**3d**	80
5	**2e**		1	**3e**	92
6	**2f**		5	**3f**	97
7	**2g**		5	**3g**	40
8	**2h**	Me	12	**3h**	ND[a]

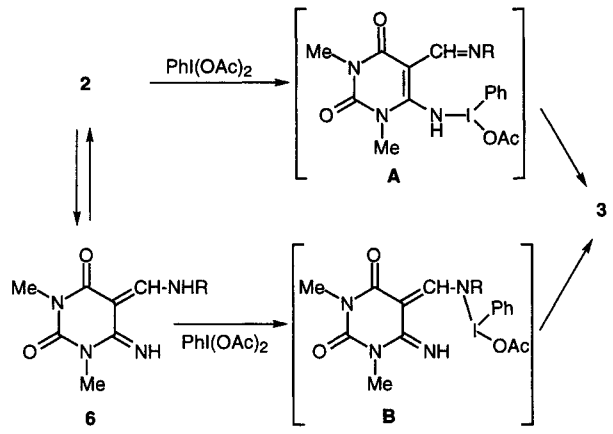
[a]ND: Not detectable

When the same reaction was carried out with 6-amino-5-(methyliminomethyl)uracil (**2h**), the formation of the corresponding 2-methylpyrazolo[3,4-*d*]pyrimidine (**3h**)[4a] could not be observed by TLC analysis and only a complex mixture was obtained (entry 8 in Table 1). Therefore, the present method was not applicable for the synthesis of 2-alkyl-substituted pyrazolo[3,4-*d*]pyrimidine derivatives.



4 **5**

Scheme 1



Scheme 2

Interestingly, this methodology could be applied to the oxidative N-O bond formation. Thus, treatment of 6-amino-5-formyl-1,3-dimethyluracil (**4**) with 4 equiv. of iodobenzene diacetate in DMF at 80 °C gave the corresponding isoxazolo[3,4-*d*]pyrimidine derivative **5**, though the yield was not so good (37%).[8,9]

From these facts, taking into consideration that stabilization of **2** presumably is due to be tautomerism into 5-aminomethylidene-6-iminouracil structure (**6**) in solution, two plausible intermediates **A** and **B** for the oxidative N-N bond formation reaction are indicated in Scheme 2.

In summary, a new method for the synthesis of pyrazolo[3,4-*d*]pyrimidines including the N-N bond formation of the pyrazole ring has been developed. In contrast to the multitude of effective methods for the synthesis of 1-substituted pyrazolo[3,4-*d*]pyrimidines, few efficient synthetic methods for 2-substituted derivatives are known. [1,4] The most striking feature of the present method is that various 2-aryl-substituted derivatives **3** can be provided conveniently.

A typical experimental procedure is described for the synthesis of **3a**. 6-Amino-1,3-dimethyl-5-(*N*-phenyliminomethyl)uracil (**2a**)[7] (0.50 g, 1.94 mmol) was suspended in DMF (20 ml) followed by the gradual addition of iodobenzene diacetate (2.49 g, 7.74 mmol). After being stirred at 80 °C for 1 h, the reaction mixture was evaporated under reduced pressure and the residue was extracted with chloroform (15 ml x 2). The combined organic layer was washed with water (20 ml) and then brine (20ml), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was triturated with ether (10 ml) and filtered to give 5,7-dimethyl-2-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**3a**), which was recrystallized from MeOH (0.43 g, 87%); mp 288-291 °C (lit.[4b] 285-287 °C). This product was identical with the authentic sample previously reported[4b].

The structures of all the new compounds were determined by their IR, MS, ^{1}H-NMR spectral and elemental analyses.

References and Notes

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(5) The creation of the N-N bond as the last step of the ring onstruction is common in indazoles and very rare in pyrazoles, see ref. (lb) p. 274. Recently, Kotali and Harris reported the synthesis of 2-arylaminoindazoles *via* oxidative N-N bond formation of *o*-aminoarylketone acylhydrazones with iodobenzene diacetate, Kotali, A.; Harris, P. A. *J. Heterocycl. Chem.* **1996**, *33*, 605.

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