Polycyclic *N*-Heterocyclic Compounds. Part 54.† Ring-cleavages and Ring-closures of *N*-(Benzo[*h*]quinazolin-4-yl)amidine and its Amide Oxime Derivatives with Hydroxylamine

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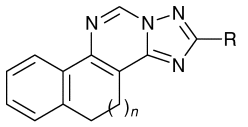
Kenji Sasaki,[a] Ying-Xue Zhang,[a] Hiroshi Yamamoto,[a] Setsuo Kashino[b] and Takashi Hirota*[a]

[a]*Faculty of Pharmaceutical Sciences, Okayama University, 1-1, Tsushima-Naka, Okayama, 700-8530, Japan*
[b]*Faculty of Science, Okayama University, 3-1, Tsushima-Naka, Okayama, 700-8530, Japan*

The synthesis of abnormal cyclization products, 2-(3-alkyl(or aryl)[1,2,4]oxadiazol-5-yl)-3,4-dihydro-1-naphthylaminoformaldehyde oximes and their homologues, by the reaction of *N*-(benzo[*h*]quinazolin-4-yl)amidine or its amide oxime derivatives with excess $NH_2OH \cdot HCl$ are described.

In the previous paper, we reported the synthesis of 2-alkyl-4,5-dihydrobenzo[*h*][1,2,4]triazolo[1,5-*c*]quinazoline derivatives (**1**) and their antidepressive activity in mice.[1] As a modification of compound **1**. The synthesis of 2-aryl-4,5-dihydrobenzo[*h*][1,2,4]triazolo[1,5-*c*]quinazoline derivatives (**9**) was planned. Thus, 4-chloro-*N*,*N*-dimethyl-*N*′-(5,6-dihydrobenzo-[*h*]quinazolin-4-yl)benzamidine (**5a**) was initially prepared by the Vilsmeier reaction[2] of 4-amino-5,6-dihydrobenzo[*h*]-quinazoline (**2a**)[3] with 4-chloro-*N*,*N*-dimethylbenzamide and $POCl_3$. However, treatment of the resulting **5a** with 6 equiv. of $NH_2OH \cdot HCl$ at room temperature gave an abnormal product, 2-{3-(4-chlorophenyl)[1,2,4]oxadiazol-5-yl}-3,4-dihydro-1-naphthylaminoformamide oxime (**12a**) the structure of which was revealed by an X-ray structure analysis,[4] and a normal oxime (**8**) could not be obtained. A similar reaction of *N*-(5,6-dihydrobenzo[*h*]quinazolin-4-yl)-acetamide oxime (**19a**)[1] with 6 equiv. of $NH_2OH \cdot HCl$ in refluxing MeOH also gave the corresponding abnormal product **23a**.[4] These results encouraged us to be engaged in investigation of this abnormal reaction.



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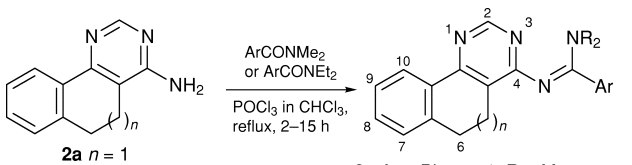
This paper deals with the ring-cleavage and ring-closure reaction of *N*-heterylarylamidines and *N*-heterylalkylamide oximes with excess $NH_2OH \cdot HCl$.

As shown in Scheme 1, *N*-heterylarylamidines were prepared by the reaction of **2a**[3] or 4-amino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**2b**)[5] with the Vilsmeier reagent[2] which was prepared from $POCl_3$[1] and commercially available *N*,*N*-dimethylbenzamide, *N*,*N*-diethylnicotinamide, *N*,*N*-dimethyl-4-chlorobenzamide, *N*,*N*-dimethyl-4-fluorobenzamide, or *N*,*N*-diethyl-3-methylbenzamide, respectively.

As shown in Scheme 2, *N*-heterylarylamidines were allowed to react with $NH_2OH \cdot HCl$ in MeOH. In the previous case of **5a**,[4] 6 equiv. of $NH_2OH \cdot HCl$ had been required to complete the reaction at room temperature. For **3a**, treatment of 1.2 equiv. of $NH_2OH \cdot HCl$ at room temperature could not eliminate **3a** (TLC) and an additional 4.8 equiv. of $NH_2OH \cdot HCl$ was required to complete the reaction to give **10a**, just as for **5a**. The ^1H NMR specrum of **10a** in $CDCl_3$ showed a characteristic one proton doublet



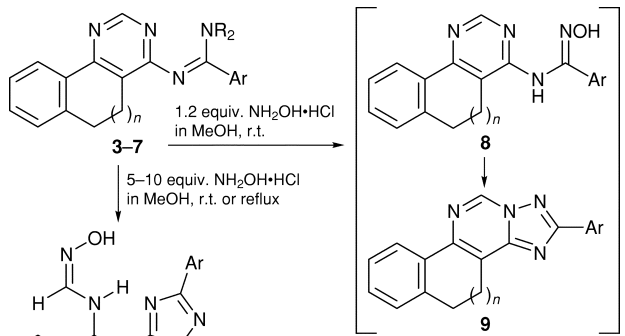
2a $n = 1$
2b $n = 2$

3a Ar = Ph, $n = 1$, R = Me
3b Ar = Ph, $n = 2$, R = Me
4a Ar = 3-pyridyl, $n = 1$, R = Et
4b Ar = 3-pyridyl, $n = 2$, R = Et
5a Ar = 4-ClC_6H_4, $n = 1$, R = Me
5b Ar = 4-ClC_6H_4, $n = 2$, R = Me
6a Ar = 4-FC_6H_4, $n = 1$, R = Me
7a Ar = 3-MeC_6H_4, $n = 1$, R = Et

Scheme 1

($J = 11$ Hz) at δ 7.38 which changed to a singlet after addition of D_2O. The IR spectrum of **10a** showed a broad absorption with a shoulder around 3100–3300 cm^{-1}. The EI-mass spectrum showed a parent peak at m/z 332 and all these data supported the structure of **10a**. Similar treatments of **3b**–**7** with 6 equiv. of $NH_2OH \cdot HCl$ afforded the corresponding products, all of which showed similar characteristic spectra. All elemental analyses (**10**–**14**) also supported their structures.

As shown in Scheme 3, treatment of **15a**,**b**[1] with 6 equiv. of $NH_2OH \cdot HCl$ at room temperature gave only normal amide oximes **18a**,**b**, respectively, and these structures were confirmed by comparison with authentic samples.[1] Although



3–7

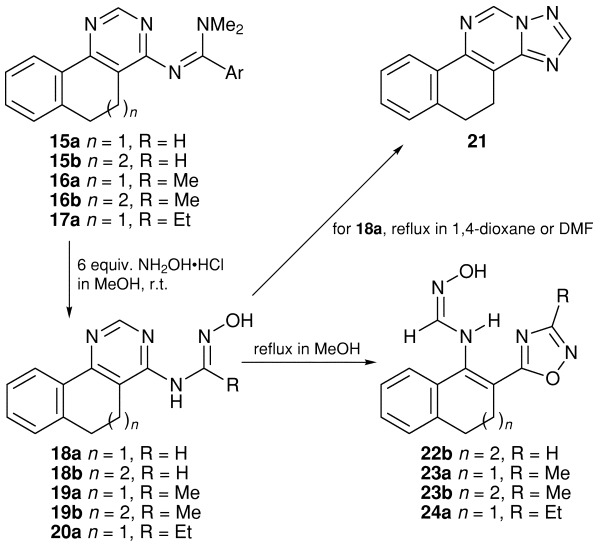
8

9

10a Ar = Ph, $n = 1$
10b Ar = Ph, $n = 2$
11a Ar = 3-pyridyl, $n = 1$
11b Ar = 3-pyridyl, $n = 2$
12a Ar = 4-ClC_6H_4, $n = 1$
12b Ar = 4-ClC_6H_4, $n = 2$
13a Ar = 4-FC_6H_4, $n = 1$
14a Ar = 3-MeC_6H_4, $n = 1$

Scheme 2

*To receive any correspondence.
†Part 53: K. Sasaki, A. Tsurumori, S. Kashino and T. Hirota, *Heterocycles*, in press.



Scheme 3

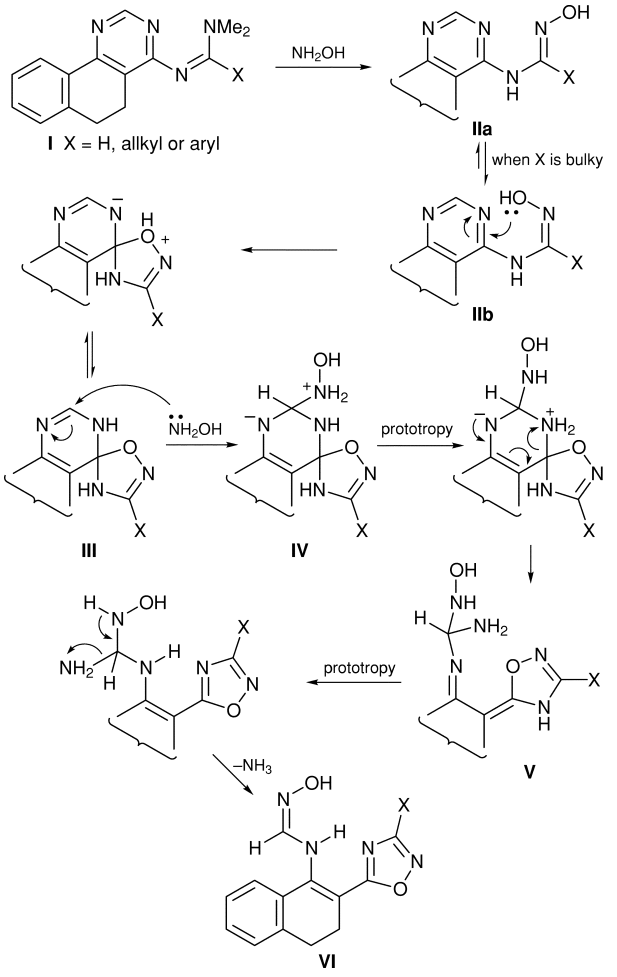
the further treatment of **18b** with 6 equiv. of $NH_2OH \cdot HCl$ in refluxing MeOH afforded the desired 6-([1,2,4]oxadiazol-5-yl)-*N*-(8,9-dihydro-7*H*-benzocyclohepten-5-yl)formamide oxime (**22b**) in low yield (19%) with many side products, similar treatment of **18a** with 6 equiv. of $NH_2OH \cdot HCl$ in refluxing MeOH (or even in refluxing DMF) did not give the corresponding oxadiazole and only the formation of tetraazasteroid **21**[1] was observed (TLC). Similar treatments of other alkylamidines, **16** and **17**, with 5–6 equiv. of $NH_2OH \cdot HCl$ at room temperature also gave only the corresponding normal alkylamide oximes, **19** and **20**. The desired alkyloxadiazoles **23** and **24** were afforded only from the treatment of the alkylamide oximes **19** and **20** with 6 equiv. of $NH_2OH \cdot HCl$ in refluxing MeOH.

A possible reaction mechanism is proposed in Scheme 4. After formation of the amide oxime **II** from amidine **I**, adduct **IV** was produced *via* spiro **III** followed by the covalent amination of NH_2OH at the 2 position of the pyrimidine ring. Then the ring was cleaved after prototropy. Finally oxadiazole **VI** was obtained from **V** after prototropy and elimination of an amino group. It seems that the difference of the reactivities between compounds **3**–**7** having a bulky substituent and compounds **15**–**17** having a smaller substituent is caused by the difference of the stereochemistry of their intermediate state **II**.

All the ^1H NMR chemical shifts are given in the Experimental section of the full paper.

Techniques used: ^1H NMR, IR, EI-MS and FAB-MS

References: 5



Scheme 4

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