

ALKYNYLATION OF HALOPYRIDAZINES AND THEIR
N-OXIDES USING Pd-PHOSPHINE COMPLEX

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3-Alkynylpyridazines and their 1-oxides were synthesized from 3-chloropyridazines and their 1-oxides, respectively, by the modification of the original method for the alkyynylation of aryl iodides using $[Pd(PPh_3)_2Cl_2-CuI]$ and Et_2NH (Sonogashira's method). The N-oxidation of 3-alkynylpyridazines occurred exclusively at the nitrogen atom in the 1-position.

Recently, Sonogashira et al.¹ found that iodobenzene was transformed into alkynylbenzenes by the reaction with monosubstituted acetylenes in the presence of $[Pd(PPh_3)_2Cl_2-CuI]$ and large excess of diethylamine at room temperature. And Edo et al. applied this reaction to the alkyynylation of iodopyrimidines.

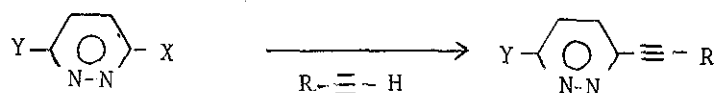
Although wide applications of alkynylpyridazines and their N-oxides are expected, the direct introduction of the

alkynyl group into the pyridazine ring has not been reported.

We wish to describe that the improved conditions of this reaction enabled 3-chloropyridazines(Ia-c) and their 1-oxides(III), which are much more readily prepared than the corresponding iodo derivatives, to be substituted by alkynyl groups.

First, we tried the alkynylation of 3-iodopyridazines according to the reported procedures.^{1,2} For example, the mixture of 3-iodo-6-methylpyridazine(Id, 1.1g, 5mmol), phenylacetylene(0.6g, 5.5mmol), Pd(PPh₃)₂Cl₂ (37mg, 0.05mmol), CuI (5mg, 0.025mmol) and Et₂NH(30ml, as solvent) was stirred for 15hr at room temperature. The yield of 3-phenylethynyl-6-methylpyridazine(IIa, R=Ph, Y=Me) was only 0.29g(30%), and 0.66g(60%) of Id was recovered. Also, the alkynylation of 3-chloro-6-methylpyridazine(Ia) with phenylacetylene under the same conditions was attempted, while the yield of IIa was 9%. Next, in order to remove the difficulties in the alkynylation of 3-chloropyridazines, some attempts were made.

The alkynylation of Ia-c proceeded fairly successfully when the amount of Et₂NH was far reduced compared with former procedure and the mixture was heated. For example, a mixture of Ia(1.3g, 10mmol), phenylacetylene(2.4g, 22mmol), Pd(PPh₃)₂Cl₂ (146mg, 0.2mmol), CuI(10mg, 0.05mmol) and 5ml of Et₂NH was heated at 70° for 4hr. The yield of IIa was 1.1g(56%) without recovery of Ia. Other data of the alkynylation by this improved procedure are collected in Table I.



Ia: X=Cl, Y=Me

Ib: X=Cl, Y=Ph

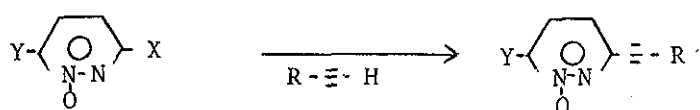
Ic: X=Cl, Y=MeO

Id: X=I, Y=Me

Table I

I	R	Conditions	II	Yield(%)	mp(°C)
a	Ph	70°, 4hr	Me-C ₅ H ₃ N ₂ -C≡C-Ph	56	109-110
a	Bu	50°, 12hr	Me-C ₅ H ₃ N ₂ -C≡C-Bu	90	bp ₅ 100
a	C(OH)Me ₂	70°, 4hr	Me-C ₅ H ₃ N ₂ -C≡C-C(Me) ₂ OH	46	113-114
b	Ph	70°, 4hr	Ph-C ₅ H ₃ N ₂ -C≡C-Ph	78	170-171
c	Ph	70°, 15hr	MeO-C ₅ H ₃ N ₂ -C≡C-Ph	59	98

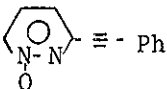
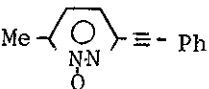
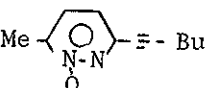
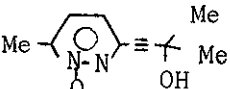
Further, the modified procedure was applied to the alkynylation of 3-chloropyridazine 1-oxides(III), and the results were satisfactory(Table II).



IIIa: X=Cl, Y=H

IIIb: X=Cl, Y=Me

Table II

III	R	Conditions	IV	Yield(%)	mp(°C)
a	Ph	70°, 4hr		56	153-155
b	Ph	70°, 16hr		77	207-208
b	Bu	70°, 15hr		24	58-60
b	C(OH)Me ₂	60°, 4hr		72	158-159

Additionally, the N-oxidation of 3-alkynylpyridazines was carried out. The products obtained from the oxidation of IIa (R=Ph, Y=Me) and IIb (R=Bu, Y=Me) with m-chloroperbenzoic acid were identical with IVa (R=Ph, Y=Me) and IVb (R=Bu, Y=Me), respectively. These facts show the oxidation of IIa and IIb proceeds exclusively at the nitrogen atom in the 1-position of the 3-alkynylpyridazines (Table III).

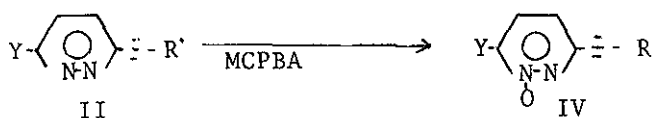


Table III

II	Y	R	IV	Yield(%)
a	Me	Ph	a	92
b	Me	Bu	b	64

References

- 1) K. Sonogashira, Y. Tohda and N. Hagihara, Tetrahedron Letters, 1975, 4467.
- 2) K. Edo, H. Yamanaka and T. Sakamoto, Heterocycles, 9, 271 (1978).

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