HETEROCYCLES, Vol.9, No.10, 1978

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

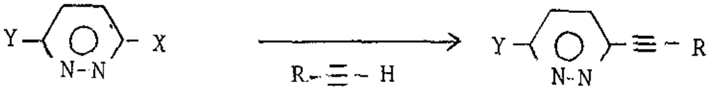
Yoshihito Abe, Akio Ohsawa, Heihachiro Arai
and Hiroshi Igeta*
School of Pharmaceutical Sciences, Showa University,
Shinagawa-ku, Tokyo 142, Japan

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 alkynylation of aryl iodides using [Pd(PPh$_3$)$_2$Cl$_2$-CuI] and Et$_2$NH (Sonogashira's method). The N-oxidation of 3-alkynylpyridazines occured 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$_3$)$_2$Cl$_2$-CuI] and large excess of diethylamine at room temperature. And Edo *et al*. applied this reaction to the alkynylation of iodopyrimidines.

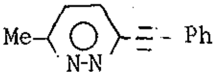
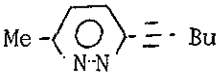
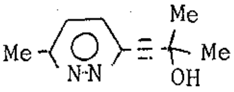
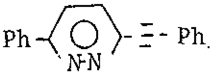
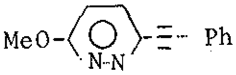
Although wide applications of alkynylpyridazines and their N-oxides are expected, the direct introduction of the alkynyl group into the pyridazine ring has not been reported. We wish to describe that the improved conditions of this reaction enabled 3-chloropyridazines(Ia-c) and their 1-oxides (III), which are much more readily prepared than the corresponding iodo derivatives, to be substituted by alkynyl groups.

First, we tried the alkynylatin 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), $Pd(PPh_3)_2Cl_2$(37mg,0.05mmol), CuI (5mg,0.025mmol) and Et_2NH(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 Et_2NH 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), $Pd(PPh_3)_2Cl_2$ (146mg,0.2mmol), CuI(10mg,0.05mmol) and 5ml of Et_2NH 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.

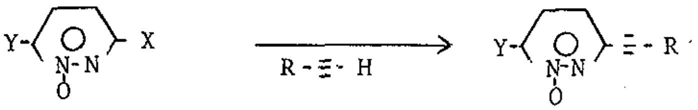


Ia: X=Cl, Y=Me
Ib: X=Cl, Y=Ph
Ic: X=Cl, Y=MeO
Id: X=I, Y=Me

Table I

I	R	Conditions	II	Yield(%)	mp(°C)
a	Ph	70°, 4hr		56	109-110
a	Bu	50°, 12hr		90	$bp_5$100
a	$C(OH)Me_2$	70°, 4hr		46	113-114
b	Ph	70°, 4hr		78	170-171
c	Ph	70°, 15hr		59	98

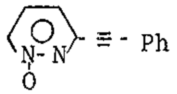
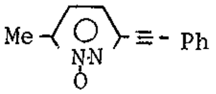
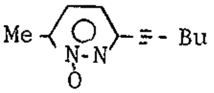
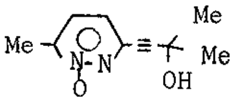
Further, the modified procedure was applied to the alkynylation of 3-chloropyridazine 1-oxides(III), and the results were satisfactory(Table II).



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 <u>m</u>-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).

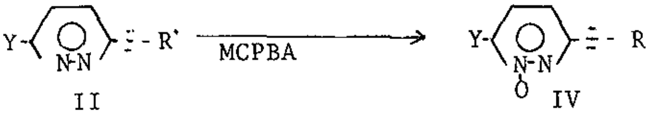


Table III

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).

Received, 3rd July, 1978