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Alkynylation of Halopyridazines and Their *N*-Oxides¹⁾

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Various 3-alkynylpyridazines have been prepared by cross-coupling of 3-halopyridazines and monosubstituted acetylenes in Et₂NH with Pd(PPh₃)₂Cl₂-CuI as a catalyst. Though the alkynylation of 3-chloropyridazine 1-oxides afforded 3-alkynylpyridazine 1-oxides, attempts to obtain 3-chloropyridazine 2-oxides were unsuccessful. *N*-Oxidation of 3-alkynylpyridazines with *m*-chloroperbenzoic acid yielded their 1-oxides exclusively.

Keywords—alkynylation; alkynylpyridazine; alkynylpyridazine *N*-oxide; Pd-phosphine complex; monosubstituted acetylene; halopyridazine; chloropyridazine *N*-oxide

Although nucleophilic substitution reactions of halopyridazines have been widely investigated, only a few examples are known of direct replacement of their halogen atoms by carbon functional groups. In a previous paper,³⁾ we reported alkylation and arylation of chloropyridazines using Grignard reagents. Sonogashira *et al.*⁴⁾ found an alkynylation reaction of bromopyridine and iodobenzene using Pd(PPh₃)₂Cl₂-CuI as a catalytic system. Yamanaka *et al.*⁵⁻⁷⁾ applied this reaction to the alkynylation of pyrimidines, quinolines, isoquinolines, *etc.* However, the applications were mostly limited to the use of bromo- or iodo-substituted aromatics as starting materials because of the reactivities of the halogen atoms. In this paper, we report a modification of the substitution reaction of halogen atoms of 3-halopyridazines and their *N*-oxides by alkynyl groups, and in particular, a procedure which permits the direct alkynylation of 3-chloropyridazines (Chart 1). The use of a 3-chloropyridazine as the starting material is preferable to that of other 3-halo (*i.e.*, 3-iodo- or 3-bromo-) pyridazines in terms of their preparation (Chart 1).

Chart 1

The alkynylation of 3-iodo-6-methylpyridazine (Ia) and 3-chloro-6-methylpyridazine (Ib) was examined as shown in Table I. The nuclear magnetic resonance (NMR) spectrum(CDCl₃) of 6-methyl-3-phenylethynylpyridazine (IIa) showed a singlet at δ 2.76 (3H, Me) as well as a multiplet at δ 7.2—7.8 (7H, aromatic protons) and the triple bond of the compound gave an absorption at 2200 cm⁻¹ ($\nu_{\text{C}\equiv\text{C}}$) in the infrared (IR) spectrum. Upon catalytic reduction, IIa yielded 6-methyl-3-phenethylpyridazine (III), which was identified by comparison with an authentic sample.⁸⁾

- 1) A preliminary report of this work has appeared: Y. Abe, A. Ohsawa, H. Arai, and H. Igeta, *Heterocycles*, **9**, 1397 (1978).
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Run 1 was carried out under the conditions described by Sonogashira *et al.*⁴⁾ Although IIa was obtained in a yield of 30% from Ia, with a high recovery of the starting material (60%), the use of iodopyridazines as starting materials is unfavorable because methods for their preparation are not always established. Thus, we investigated this reaction under some modified conditions (runs 2—4) and a satisfactory result was obtained when Ib was heated with phenylacetylene at 70° for 4 hr in the presence of a reduced amount of Et₂NH and an increased amount of the metallic catalyst (run 4).

Other 6-substituted 3-phenylethynylpyridazines (IIc—e) were also synthesized by modified treatments of the corresponding chloropyridazines (Ic—e) with phenylacetylene, as shown in Table II.

TABLE I. Phenylethynylation of 3-Iodo- and 3-Chloro-6-methylpyridazines

Run	I (mmol)	PhC≡CH (mmol)	Et ₃ NH (ml)	Pd* (mmol)	CuI (mmol)	Temp. (°C)	Time (hr)	IIa (yield, %)	I (recovery, %)
1	Ia (5)	6	30	0.05	0.025	rt ^{a)}	15	30	60
2	Ib (10)	12	60	0.1	0.05	rt	15	9	74
3	Ib (10)	12	60	0.1	0.05	70	15	37	tr ^{b)}
4	Ib (10)	24	5	0.2	0.05	70	4	56	tr

a) Room temperature.

b) Trace.

TABLE II. Phenylethynylation of 6-Substituted 3-Chloropyridazines

Run	I (mmol)	Y	Et ₂ NH (ml)	Time (hr)	II (yield, %) ^{d)}
4	Ib (10)	Me	5	4	IIa (56)
5	Ic (5)	Ph	3	4	IIc (78)
6	Id (5)	OMe	3	24	IIId (49)
7	Ie (5)	N(CH ₂) ₅	3	24	IIe (42)

a) Reaction temperature; 70°.

b) $\text{PhC}\equiv\text{CH}/\text{I}$; 2.4 mmol/mmol.

c) Pd*/I; 0.02 mmol/mmol, CuI/I; 0.005 mmol/mmol.

d) Recoveries of the starting materials (I) were trace for all runs in this table.

When the 6-position of 3-chloropyridazines is substituted by a methoxyl or piperidino group, the yields of the expected products (IIId and IIe) were low in the reaction under the conditions described (70° for 4 hr), significant amounts of the starting materials (Id and Ie) being recovered. The yields of IIId and IIe (runs 6 and 7) were a little lower than those in

Chart 3

other cases (runs 4 and 5) even when the reaction mixture were heated for 24 hr at the indicated temperature. The results suggest that increased electron density at the reaction center caused by these electron-donating groups lowers the reactivity of the starting material.

The reaction of 3,6-dichloropyridazine (If) with phenylacetylene was also examined (Chart 3). The use of 1.1 eq. of phenylacetylene (run 8) gave 3-chloro-6-phenylethynylpyridazine (IIf, 37%), 3,6-bis(phenylethynyl)pyridazine (IV, 15%), and 3-diethylamino-6-phenylethynylpyridazine (V, 17%), together with the starting material (If, 8%), and the yield of the product (IIf) was improved to 55% when Et₃N was used (run 9) instead of Et₂NH. The use of excess (3.6 eq.) phenylacetylene (run 10) gave IV in a yield of 92%. It was assumed that V was formed by the reaction of IIf with Et₂NH, not from 3-chloro-6-diethylaminopyridazine (VI), because only a trace of VI was formed despite the recovery of If (70%) when

TABLE III. Alkynylation of 3-Iodo- and 3-Chloro-6-methylpyridazines

Ia, b		RC≡CH/amine		cat. ^{a)}		II			
Run	I (mmol)	R	RC≡CH (mmol)	Amine (ml)	Temp. (°C)	Time (hr)	II (yield, %)	Other product (yield, %)	
4	Ib (10)	Ph	24	Et ₂ NH (5)	70	4	IIa (56)	—	
11	Ib (5)	Bu	11	Et ₂ NH (3)	50	12	IIg (90)	—	
12	Ib (10)	CH ₂ OH	22	Et ₂ NH (5)	70	4	IIh (2)	VII (major)	
13	Ib (5)	CH ₂ OH	11	Et ₂ NH (10)	30	4	IIh (5)	VII (1.5)	
14	Ib (5)	CH ₂ OH	11	Et ₃ N (10)	70	4	IIh (12)	—	
15	Ia (5)	CH ₂ OH	11	Et ₂ NH (10)	30	4	IIh (48)	VII (tr)	
16	Ib (5)	H	^{b)}	Et ₂ NH (30)	tr ^{c)}	5	IIi (0)	VIII (0)	
17	Ia (5)	H	^{b)}	Et ₂ NH (30)	tr	5	IIi (0)	VIII (13)	
18	Ib (5)	C(OH)Me ₂	11	Et ₂ NH (3)	70	4	IIj (46)	—	

a) Pd*/I; 0.02 mmol/mmol, CuI/I; 0.005 mmol/mmol.

b) See the experimental section for these runs.

c) Trace.

If was heated with Et_2NH in the absence of phenylacetylene under similar conditions. It was also assumed that the formation of IV and V from II f is competitive in the system, that of the former being much faster than that of the latter.

Next, other acetylenes were employed for the alkylation of Ia and Ib as shown in Table III.

Although the reaction of Ib and propargyl alcohol under the conditions described afforded 2-methyl-7-diethylaminopyrrolo[1,2-*b*] pyridazine (VII), as reported previously,⁹⁾ the reaction of Ia with propargyl alcohol at 30° afforded the expected product (IIh). When acetylene was bubbled into a mixture of Ib, the catalyst, and Et_2NH at room temperature, the starting material was recovered. On the other hand, the reaction with Ia as the starting material afforded bis(6-methyl-3-pyridazinyl)acetylene (VIII) instead of 3-ethynyl-6-methylpyridazine (IIi).

Moreover, the alkylation of 3-chloropyridazine *N*-oxides was examined as shown in Table IV.

When 3-chloropyridazine 1-oxide (IXa) was allowed to react with phenylacetylene, 3-phenylethynylpyridazine 1-oxide (Xa) was obtained in 56% yield, and the treatment of 3-chloro-6-methylpyridazine 1-oxide (IXb) with some acetylenes gave similar results (runs 20–22). In contrast, 3-chloropyridazine 2-oxides did not give the expected products (runs

TABLE IV. Alkylation of 3-Chloropyridazine *N*-Oxides

Run	IX or XI ^{a)}	Y	R	RC≡CH (mmol)	Et ₂ NH (ml)	Time (hr)	X or XII (yield, %)
19	IXa	H	Ph	12	3	4	Xa (56)
20	IXb	Me	Ph	12	3	16	Xb (77)
21	IXb	Me	Bu	11	3	15	Xc (24)
22	IXb	Me	C(OH)Me ₂	11	3	4	Xd (72)
23	XIa	H	Ph	12	3	16	^{b)}
24	XIb	OMe	Ph	12	3	16	^{c)}
25	XIc	Cl	Ph	12	5	2	^{d)}

a) IX or XI; 5 mmol, Pd*; 0.1 mmol, CuI; 0.025 mmol.

b) Formation of a tarry product and 32% recovery of XIa were observed.

c) Compound XIb was recovered quantitatively.

d) All the starting material (XIc) was decomposed to give a tar.

Chart 4

9) A. Ohsawa, Y. Abe, and H. Igeta, *Chem. Lett.*, 1979, 241.

23—25) and the starting materials were recovered, except in the case of the highly reactive 3,6-dichloropyridazine *N*-oxide (run 25, decomposition). The electron-donating character of the *N*-oxide groups may be responsible for the low reactivities of the compounds.

3-Alkynylpyridazines (IIa and IIg) were also treated with *m*-chloroperbenzoic acid (MCPBA) to examine the effect of the alkynyl groups of the orientation in the *N*-oxidation. The oxidations of IIa and IIg exclusively afforded the corresponding 1-oxides. These results suggest that an alkynyl group at the 3-position of a pyridazine acts as an electron-withdrawing group and reduces the nucleophilic activity of the nitrogen atom in the 2-position.

Experimental

All melting points and boiling points are uncorrected. IR spectra were measured with a JASCO A-2 instrument. NMR spectra were recorded on Hitachi R-20 and R-22 instruments. The properties of the products are listed in Table V. The alkynylation was carried out under a nitrogen atmosphere except for runs 16 and 17.

TABLE V. Properties of Alkynylpyridazines and Their *N*-Oxides

Compound	mp (°C) or bp (°C/mm)	Analysis (%)			IR C≡C cm ⁻¹ (KBr)	NMR (δ, <i>J</i> in Hz)
		Found (Calcd)	C	H	N	
IIa	109—110	80.48 (80.38)	5.00 5.10	14.41 14.42	2200	2.76 (3H, s), 7.2—7.8 (7H, m)
IIc	170—170.5	84.35 (84.35)	4.59 4.72	11.00 10.93	2220	7.3—8.3 (m)
II d	98	74.01 (74.27)	4.86 4.79	13.49 13.33	2210	4.16 (3H, s), 6.94 (1H, d, 9.2), 7.2—7.8 (6H, m)
IIe	163—165	77.14 (77.53)	6.43 6.51	16.20 15.96	Absent	1.70 (6H, brm), 3.70 (4H, brm), 6.84 (1H, d, 9.6), 7.2—7.8 (6H, m)
II f	107—108	67.46 (67.15)	3.09 3.29	13.03 13.05	2200	7.3—7.8 (m)
IV	183	85.78 (85.69)	4.18 4.32	10.01 9.90	2220	7.2—7.8 (m)
V	106—107	76.38 (76.46)	6.78 6.82	16.62 16.74	2200	1.16 (6H, t, 7.5), 3.54 (4H, q, 7.5), 6.58 (1H, d, 11.2), 7.3—7.8 (6H, m)
II g	100/5				2240	0.8—1.2 (3H, m), 1.3—1.9 (4H, m), 2.4—2.6 (2H, m), 2.74 (3H, s), 7.24 (1H, d, 8.8), 7.40 (1H, d, 8.8)
II h	122—123	65.17 (64.85)	5.58 5.44	18.99 18.91	2240 2210	2.74 (3H, s), 3.44 (1H, brs), 4.62 (2H, s), 7.30 (1H, d, 9.2), 7.50 (1H, d, 6.0)
VIII	247—248	68.32 (68.55)	4.73 4.79	26.88 26.65	Absent	2.76 (6H, s), 7.34 (2H, d, 9.0), 7.68 (2H, d, 9.0)
II i	113—114	67.91 (68.16)	6.96 6.86	16.10 15.90	2230	1.68 (6H, s), 2.74 (3H, s), 3.56 (1H, brs), 7.26 (1H, d, 9.2), 7.46 (1H, d, 9.2)
Xa	153—155	73.60 (73.46)	4.14 4.11	14.36 14.28	2210	7.1—7.8 (7H, m), 8.12 (1H, d, 6.0)
Xb	207—208	74.44 (74.27)	4.75 4.79	13.65 13.33	2200	2.52 (3H, s), 7.2—7.7 (7H, m)
Xc	60—61	69.54 (69.44)	7.41 7.42	14.93 14.73	2240	0.8—1.1 (3H, m), 1.2—1.9 (4H, m), 2.46 (2H, m), 2.50 (3H, s), 7.02 (1H, d, 8.0), 7.52 (1H, d, 8.0)
Xd	158—159	62.01 (62.48)	6.36 6.29	14.73 14.58	2230	1.62 (6H, s), 2.52 (3H, s), 2.64 (1H, brs), 7.08 (1H, d, 8.0), 7.56 (1H, d, 8.0)

Reaction of 3-Iodo-6-methylpyridazine (Ia) or 3-Chloro-6-methylpyridazine (Ib) with Phenylacetylene under the Described⁴⁾ Conditions (Runs 1 and 2)—A mixture of Ia (1.1 g), phenylacetylene (0.6 g), Pd(PPh₃)₂Cl₂ (0.037 g), CuI (0.005 g), and Et₂NH (30 ml) was allowed to stand at room temperature for 15 hr with stirring. Diethylamine was evaporated off, and the residue was chromatographed on silica gel (hexane-ether) to give 0.66 g (60%) of Ia and 0.29 g (30%) of 6-methyl-3-phenylethynylpyridazine (IIa) as

colorless needles of mp 109—110° (from iso-Pr₂O–hexane). Similar treatment of Ib (1.3 g) gave 0.96 g (74%) of Ib and 0.17 g (9%) of IIa.

Reaction of Ib with Phenylacetylene under the Modified Conditions (Run 4)—A mixture of Ib (1.3 g), phenylacetylene (2.4 g), Pd(PPh₃)₂Cl₂ (0.146 g), CuI (0.01 g) and diethylamine (5 ml) was heated at 70° for 4 hr with stirring. The amine was evaporated off, and the residue was chromatographed on silica gel (hexane–ether) to give a trace of Ib and 1.1 g (56%) of IIa.

Reaction of 3-Chloro-6-piperidinopyridazine (Ie) with Phenylacetylene (Run 7)—A mixture of Ie (1.0 g), phenylacetylene (1.2 g), Pd(PPh₃)₂Cl₂ (0.073 g), CuI (0.005 g) and diethylamine (3 ml) was heated at 70° for 24 hr. Diethylamine was evaporated off, and the residue was chromatographed on a column of aluminum oxide. The benzene eluate gave 0.56 g (42%) of 3-phenylethynyl-6-piperidinopyridazine (IIe) as colorless needles of mp 163—165° (from AcOEt). When the reaction time was reduced to 9 hr, the yield of IIe was 37%.

Reaction of 3,6-Dichloropyridazine (If) with 1.1 eq. Phenylacetylene in Et₂NH (Run 8)—A mixture of If (0.75 g), phenylacetylene (0.55 g), Pd(PPh₃)₂Cl₂ (0.073 g), CuI (0.005 g), and Et₂NH (3 ml) was heated at 70° for 4 hr. The amine was evaporated off, and the residue was dissolved in CH₂Cl₂. The extract was washed with water, dried over MgSO₄ and evaporated to dryness, then the residue was chromatographed on silica gel (hexane–CH₂Cl₂). The eluates gave 0.06 g (8%) of If, 0.40 g (37%) of 3-chloro-6-phenylethynylpyridazine (IIIf) as colorless needles of mp 107—108° (from AcOEt), 0.21 g (15%) of 3,6-diphenylethynylpyridazine (IV) as colorless flakes of mp 183° (from AcOEt), and 0.21 g (17%) of 3-diethylamino-6-phenylethynylpyridazine (V) as colorless needles of mp 106—107° (from iso-Pr₂O).

Reaction of If and 3.6 eq. Phenylacetylene (Run 10)—A mixture of If (0.75 g), phenylacetylene (1.8 g), Pd(PPh₃)₂Cl₂ (0.073 g), CuI (0.005 g), and Et₂NH (3 ml) was heated at 70° for 4 hr. The residue obtained by the removal of Et₂NH was subjected to alumina column chromatography. The benzene eluate afforded 1.3 g (92%) of IV.

Reaction of Ia or Ib with Acetylene (Runs 16 and 17)—Acetylene gas was bubbled at room temperature for 5 hr into a mixture of Ia (1.1 g), Pd(PPh₃)₂Cl₂ (0.073 g), CuI (0.005 g), and Et₂NH (30 ml). The loss of Et₂NH by evaporation was compensated for by occasional additions of fresh amine. The amine was then evaporated off, and the residue was chromatographed on aluminum oxide. The hexane–ether eluate gave 0.70 g (64%) of Ia. The AcOEt eluate gave 0.07 g (13%) of bis(6-methyl-3-pyridazinyl)acetylene (VIII) as colorless needles of mp 247—248° (from AcOEt–MeOH). Similar treatment of Ib (0.65 g) gave only the starting material (Ib) quantitatively.

Reaction of 3-Chloropyridazine 1-Oxide (IXa) with Phenylacetylene (Run 19)—Compound IXa (0.65 g), phenylacetylene (1.2 g), Pd(PPh₃)₂Cl₂ (0.073 g), CuI (0.005 g) and Et₂NH (3 ml) were treated as shown in Table IV, and aluminum oxide chromatography (benzene) of the residue gave 0.55 g (56%) of 3-phenylethynylpyridazine 1-oxide (Xa) as colorless flakes of mp 153—155° from AcOEt.

Catalytic Reduction of IIa—A solution of IIa (0.2 g) in 90% EtOH (20 ml) with 5% Pd-C (0.05 g) was shaken under a hydrogen atmosphere. After absorption of 2 eq. hydrogen, the mixture was filtered, and the solvent was evaporated off to give 0.19 g (97%) of 6-methyl-3-phenethyl-6-pyridazine (III), whose picrate (mp 119—120°) was found to be identical with an authentic sample (mixed melting point test).

Reaction of If with Et₂NH—A mixture of If (0.75 g) and Et₂NH (3 ml) was heated at 70° for 4 hr. The amine was evaporated off, and the residue was chromatographed on silica gel (hexane–CH₂Cl₂) to give 0.57 g (76%) of If and a trace of 3-chloro-6-diethylaminopyridazine (VI).

Oxidation of 3-(1-Hexynyl)-6-methylpyridazine (IIg) by MCPBA—CH₂Cl₂ solution (3 ml) containing IIg (0.02 g) and m-chloroperbenzoic acid (0.04 g) was kept at room temperature for 6 hr. The solvent was evaporated off, and the residue was applied to an aluminum oxide column (benzene eluent) to give 0.014 g (64%) of 3-(1-hexynyl)-6-methylpyridazine 1-oxide (Xc) as colorless needles of mp 60—61° (from pentane–ether); this material was identical with the sample obtained in run 11.