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COUPLING REACTION OF MONOSUBSTITUTED ACETYLENES WITH IODOPYRIMIDINES

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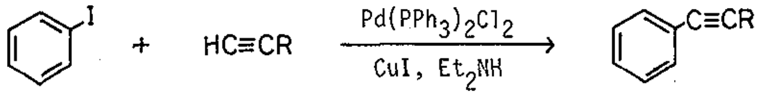
The pyrimidine derivatives containing an acetylenic side chain at the 2- or 4-position were synthesized by means of the reaction of alkyl(or phenyl)acetylenes with 2-iodo- or 4-iodopyrimidines in the presence of a palladium triphenylphosphine complex in yields ranging from 70 to 95 %. The reaction readily proceeded in both 2,4-diiodo- and 4,6-diiodopyrimidines to give the corresponding dialkynyl derivatives.

There has been reported no work on the synthesis of pyrimidine derivatives with an acetylenic side chain at the 2- or 4-position. Recently, remarkable progress of the carbon-carbon bond formation were made by means of reactions catalyzed by palladium complexes. For instance iodobenzene was reported to react with monosubstituted acetylenes in the presence of a palladium triphenylphosphine complex and cuprous iodide giving 1-alkyl-2-phenylacetylenes in good yield.1)



In this communication, we wish to report the application of this method to the synthesis of simple acetylenic pyrimidines from the corresponding 2- or 4-iodopyrimidines.

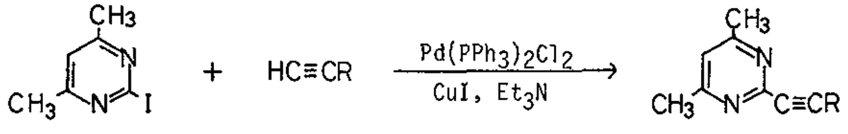
A typical experiment is as follows. 4,6-Dimethyl-2-iodopyrimidine (I) (10 mmole) and alkyl(or phenyl)acetylene (12 mmole) were dissolved in triethylamine (60 ml) with a catalytic amount of bis(triphenylphosphine)palladium dichloride1) (0.1 mmole) and cuprous iodide (0.05 mmole). After stirring of the above mixture for several hours in nitrogen atomosphere at room temperature, the reaction mixture was concentrated to dryness under reduced pressure. A proper quantity of water (40-50 ml) was added to the residue and the aqueous layer was extracted with benzene. From the benzene extract, 4,6-dimethyl-2-alkynyl(or phenylethynyl)-pyrimidines (III) were obtained by vaccum distillation or recrystallization. The same procedure was applicable to the cases of 2,6-dimethyl-4-iodopyrimidine (II) to afford the corresponding 4-acetylenic derivatives (IV).

On catalytic hydrogenation over Pd-charcoal catalyst, 2,6-dimethyl-4-phenylethynylpyrimidine (IIIe) absorbed 2 molar equivalent of hydrogen to give 2,6-dimethyl-4-(2-phenylethyl)pyrimidine.2) The spectral data of IIIe [NMRδ($CDCl_3$), 2.49 (6H, s), 6.98 (1H, s), 7.2-7.5 (3H, m), 7.5-7.8 (2H, m); IR cm^{-1} ($CHCl_3$), 2210 (C≡C)] are consistent with its assigned structure.

The results of this acetylene coupling reaction on the various iodopyrimidines were summarized in Table I and II.

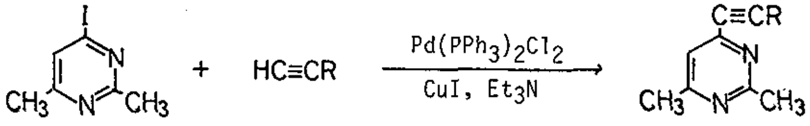
Although in the case of propargyl alcohol yields were not satisfactory, the coupling reaction with alkyl or phenylacetylenes generally afforded the products in high yield.

Table I


I IIIa-f

Compd. No.	R	Yield (%)	mp (°C)	bp (°C)(mmHg)	IR C≡C cm^{-1} ($CHCl_3$)
IIIa	CH_3	80	105-106	140 (18)	2255
IIIb	n-C_4H_9	70	——	135 (3)	2240
IIIc	n-C_5H_{11}	92	——	130 (3)	2250
IIId	n-$C_{14}H_{29}$	77	49-50.5	190 (1)	2240
IIIe	C_6H_5	95	87-88	160 (3)	2210
IIIf	CH_2OH	56	155-157	——	2250

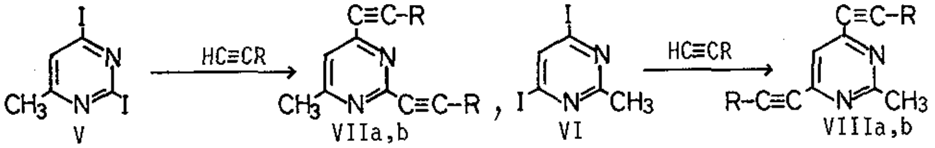
Table II


II IVa-f

Compd. No.	R	Yield (%)	mp (°C)	bp (°C)(mmHg)	IR C≡C cm^{-1} ($CHCl_3$)
IVa	CH_3	80	58-60	110 (3)	2240
IVb	n-C_4H_9	86	——	125 (3)	2240
IVc	n-C_5H_{11}	83	——	130 (3)	2240
IVd	n-$C_{14}H_{29}$	73	——	200 (1)	2235
IVe	C_6H_5	84	82-83.5	165 (3)	2220
IVf	CH_2OH	37	121.5-123	——	2240

Furthermore, in the case of 2,4-diiodo-6-methyl- (V) or 4,6-diiodo-2-methyl-pyrimidine (VI) the reaction with monoalkylacetylenes afforded the diacetylenic pyrimidines (VIIa,b and VIIIa,b).

These observations suggest that the coupling reaction proceeds without any selectivity to the iodine substituents.



a: R=Bu (31 %), bp 175 (3 mmHg)   a: R=Bu (41 %), bp 160 (3 mmHg)
b: R=C_6H_5(37 %), mp 156-157°   b: R=C_6H_5(55 %), mp 131-132°

In these acetylenic couplings, a quaternary ammonium salt was proved not to be the reaction intermediate. Namely, (2,6-dimethyl-4-pyrimidinyl)trimethylammonium chloride was not converted to the acetylenic compound under identical conditions. Since the starting materials are readily available$^{3)}$ from the corresponding chloropyrimidines,$^{4)}$ this method provides a facile route to simple alkynylpyrimidines which have not been prepared by the other method. The experiments on the synthetic utility of these products will be reported in later papers.

REFERENCES

1) K. Sonogashira, Y. Tohda, and N. Hagihara, Tetrahedron Letters, **1975**, 4467.

2) H. R. Sullivan and W. T. Caldwell, J. Am. Chem. Soc., 1955, **77**, 1559.

3) In general 2- or 4-iodopyrimidines were best prepared by treatment of the corresponding chloropyrimidines with conc. hydroiodic acid at room temperature. [M. P. L. Caton, D. T. Hurst, J. F. W. McOmie, and R. R. Hunt, J. Chem. Soc. (C), **1967**, 1204.]

4) Since the reaction of 4-chloro-2,6-dimethylpyrimidine with phenylacetylene afforded a trace amount of IVe, the conversion of the chloride to the iodide is in dispensable.

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