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SYNTHESIS OF 13-METHYL[10](4,6)PYRIMIDINOPHANE

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Abstract—— The palladium-catalyzed reaction of 4,6-diiodo-2-methylpyrimidine with 5-trimethylsilylpent-4-yn-1-ylzinc iodide gave 4,6-bis(5-trimethylsilylpent-4-yn-1-yl)-2-methylpyrimidine. Desilylation of the product followed by treatment with cupric acetate gave 13-methyl[10](4,6)pyrimidinophane.

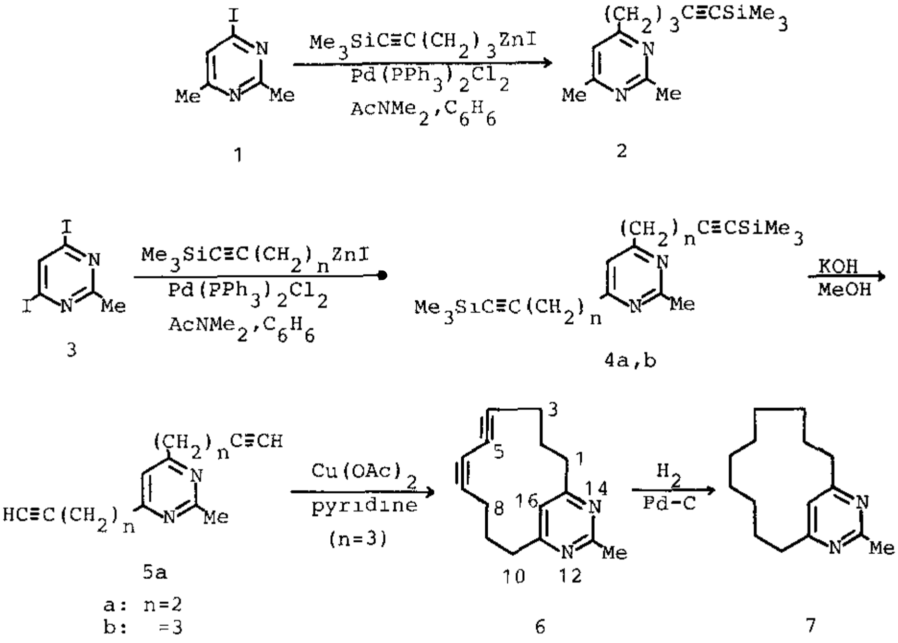
Although many cyclophanes with heteroaromatic nuclei are known, pyrimidinophanes have not yet been synthesized. For example, Hirano et al.[1] reported the reaction of 3-acetylcyclododecanone with phosphorus pentasulfide gave a thiophenophane in moderate yield, but they did not give any comment on the synthesis of pyrimidinophane by the condensation of the dione with amidine or with thiourea derivatives. Furthermore, it is reported that attempts of a pyrimidinophane from 1-acetoxy-13,13-dichlorobicyclo[10.1.0.]tridecane with guanidine were unsuccessful.[2]

On the other hand, the cross-coupling reactions of ary halides with ω-ethoxycarbonylalkylzinc iodides are prompted by the catalytic action of dichlorobis(triarylphosphine)palladium,[3] and the method can be applied to the carbon-carbon bond formation on N-heteroaromatic rings.[4]

In the present papar, we describe the synthesis of a pyrimidinophane from 4,6-bis-(pent-4-yn-1-yl)-2-methylpyrimidine which was derived by the palladium-catalyzed reaction of 4,6-diiodo-2-methylpyrimidine with 5-trimethylsilylpent-4-yn-1-ylzinc iodide.

When 4-iodo-2,6-dimethylpyrimidine (1) was allowed to react with 5-trimethylsilylpent-4-yn-1-ylzinc iodide which was prepared in situ from 5-trimethylsilylpent-4--yn-1-yl iodide and zinc-copper couple in N,N-dimethylacetamide (DMA) and benzene at 80°C, in the presence of dichlorobis(triphenylphosphine)palladium,[4] 2,6-dimethyl-4-(5-trimethylsilylpent-4-yn-1-yl)pyrimidine (**2**), bp 130°C/3 mmHg, was obtained in 65 % yield.

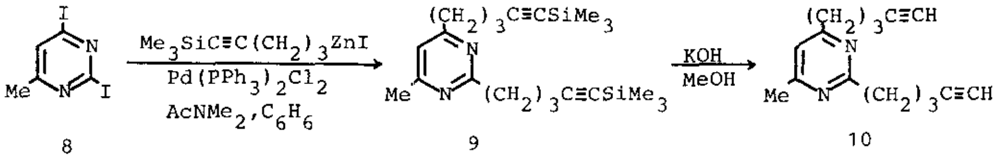
Based on the above results, 4,6-diiodo-2-methylpyrimidine (**3**) was treated with a small excess (2.5 equivalents) of the pentynylzinc iodide under the same conditions, and 4,6-bis(5-trimethylsilylpent-4-yn-1-yl)-2-methylpyrimidine (**4b**), bp 155°C/1 mmHg, was obtained in 48 % yield. Desilylation of **4b** with potassium hydroxide in methanol[5] gave 4,6-bis(pent-4-yn-1-yl)-2-methylpyrimidine (**5b**), bp 125°C/1 mmHg, in 98 % yield. Then, treatment of **5b** with cupric acetate in pyridine according to the method reported by Matsuoka et al.,[6] caused intramolecular oxidative coupling of the ethynyl group to give the pyrimidinophane (**6**), mp 148-149°C, in 37 % yield. Catalytic reduction of **6** over palladium-carbon gave 13-methyl[10](4,6)pyrimidinophane (**7**), bp 135°C/3 mmHg, in 83 % yield.



Scheme 1

Similarly, the palladium-catalyzed cross-coupling reactions of **3** with 4-trimethylsilylbut-3-yn-1-ylzinc iodide and of 2,4-diiodo-6-methylpyrimidine (**8**) with the pentynylzinc iodide gave 4,6-bis(4-trimethylbut-3-yn-1-yl)-2-methylpyrimidine (**4a**), bp 155°C/3 mmHg and 2,4-bis(5-trimethylsilylpent-4-yn-1-yl)-6-methylpyimidine (**9**), bp 165°C/5 mmHg, in 60 and 27 % yields, respectively. Although the desilylation of **4a** and **8** proceeded smoothly to give **5a**, bp 125°C/4 mmHg and **10**, bp

145°C/5 mmHg, in 95 and 97 % yields, respectively, the oxidative cyclization of **5a** and **10** resulted in the formation of resinous substances, and no pyrimidinophane was obtained.



Scheme 2

EXPERIMENTAL

4,6-Bis(5-trimethylsilylpent-4-yn-1-yl)-2-methylpyrimidine (**4b**)

A mixture of Zn-Cu couple (1.8 g) and 5-trimethylsilylpent-4-yn-1-yl iodide (3.98 g, 15 mmol) in dry C_6H_6 (30 ml) and dry DMA (2 ml) was stirred at 80°C for 4 h. To this solution, $Pd(PPh_3)_2Cl_2$ (0.3 g, 0.04 mmol) and 4,6-diiodo-2-methylpyrimidine (**3**) (2.08 g, 6 mmol) were added, and the mixture was stirred at 80°C for 48 h. The mixture was washed with H_2O and dried over $MgSO_4$. The residue obtained from the C_6H_6 layer, was purified by silica gel column chromatography using $CHCl_3$-AcOEt (9:1 v/v) as an eluent. Bulb-to-bulb distillation of the product obtained from the eluate afforded a colorless liquid.

13-Methyl[10](4,6)pyrimidinophane-4,6-diyne (**6**)

A solution of 4,6-bis(pent-4-yn-1-yl)-2-methylpyrimidine (**5b**) (0.88 g, 3.9 mmol) in ether (1 l) was slowly added to a mixture of $Cu(OAc)_2$ (12.6 g, 69.4 mmol) and pyridine (260 ml) at 100-105°C during 28 h with stirring, and the mixture was heated at the same temperature for additional 1 h. After removal of the solvent in vacuo, the residue was partitioned between C_6H_6 and H_2O. The residue obtained from the C_6H_6 layer was purified by silica gel colunm chromatography using hexane-Et_3N (20:1 v/v) as an eluate. The product obtained from the eluate was recrystallized from cyclohexane to give colorless needles.

Table Spectral and Analytical Data for the Newly Synthesized Compounds

No.	Ir cm^{-1} ($CHCl_3$)	^{1}H-Nmr δ (ppm) ($CDCl_3$)	Formulae	Analysis (%) Calcd(Found)		
				C	H	N
2	2180	0.15(9H,s),1.7-3.0(6H,m),2.46 (3H,s),2.67(3H,s),6.85(1H,s)	$C_{14}H_{22}N_2Si$	68.24 (68.02)	9.00 (9.23)	11.37 (11.22)
4a	2170	0.13(18H,s),2.4-3.1(8H,m) 2.67(3H,s),6.93(1H,s)	$C_{19}H_{30}N_2Si_2$	66.61 (66.57)	8.82 (8.96)	8.18 (8.28)
4b	2170	0.15(18H,s),1.7-2.5(8H,m) 2.6-3.0(4H,m),2.67(3H,s) 6.85(1H,s)	$C_{21}H_{34}N_2Si_2$	68.04 (68.13)	9.24 (9.26)	7.56 (7.56)
9	2170	0.15(18H,s),1.7-3.1(12H,m) 2.43(3H,s),6.80(1H,s)	$C_{21}H_{34}N_2Si_2$	68.04 (67.75)	9.24 (9.49)	7.56 (7.34)
5a	3300 2120	1.95(2H,t,J=3Hz),2.3-3.1(8H,m) 2.67(3H,s),6.97(1H,s)	$C_{13}H_{14}N_2$	78.75 (78.89)	7.12 (7.09)	14.13 (14.05)
5b	3110 2120	1.7-2.5(10H,m),2.68(3H,s) 2.6-3.0(4H,m),6.83(1H,s)	$C_{15}H_{18}N_2$	79.61 (79.33)	8.02 (8.02)	12.38 (12.26)
10	3300 2110	1.6-3.2(14H,m),2.47(3H,s) 6.83(1H,s)	$C_{15}H_{18}N_2$	79.61 (79.41)	8.02 (8.31)	12.38 (12.06)
6	2170 2255	1.6-2.5(8H,m),2.66(3H,s) 2.7-3.0(4H,m),6.87(1H,s)	$C_{15}H_{16}N_2$	80.32 (80.14)	7.19 (7.19)	12.49 (12.43)
7	——	0.7-1.4(2H,m),1.6-2.0(4H,m) 2.66(3H,s),2.6-2.9(4H,m) 6.96(1H,s)	$C_{15}H_{24}N_2$	77.53 (77.68)	10.41 (10.71)	12.06 (11.89)

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