SYNTHESIS OF PYRIMIDINE DERIVATIVES HAVING OLEFINIC SUBSTITUENTS BY PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF IODOPYRIMIDINES

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Abstract——— The palladium-catalyzed cross-coupling reactions of 2- and 4-iodopyrimidines with olefins were investigated on the stand-point of synthetic chemistry. The reaction was well catalyzed by use of palladium(II) acetate alone, palladium black, or palladium charcoal, and various olefinic pyrimidines were obtained in satisfactory yields.

The homo-coupling reaction of 4-iodopyrimidines caused by palladium(II) acetate with triphenylphosphine was resisted by removing triphenylphosphine from the catalyst-system.

Palladium catalyzed cross-coupling reaction of aryl halides (iodide, bromide) with monosubstituted ethylenes, is known to be a valuable method for the synthesis of various arylvinyl compounds.[1] Concerning this reaction, Heck et al.[2,3] have reported that the use of appropriate ligands such as triarylphosphines together with palladium(II) acetate is essential, when aryl bromides are employed as starting materials. The same authors[4] also described the use of palladium(II) acetate alone to be efficient enough in the reaction of aryl iodides with the ethylenes.

There are several papers[5,6] dealing with the application of the above coupling reaction to the synthesis of pyridine and quinoline derivatives, but poor results were obtained on the reaction of 2- and 4-bromopyridine with styrene by the catalytic action of palladium(II) acetate with tri(o-tolyl)phosphine. On the other hand, 3-bromo- and 3-iodo-pyridine, like bromobenzene, smoothly coupled with the same reagent under similar conditions to give 3-styrylpyridine in good yield.[5,6]

The present authors[6,7] tried the olefin cross-coupling reaction of halopyrimidines, as a part of their investigation on the synthesis of pyrimidine derivatives

containing a functionalized carbon substituent, and arrived at the following conclusion.

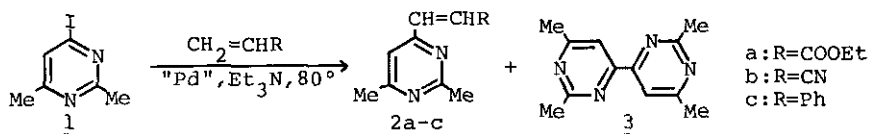
i) Among three positional isomers of iodopyrimidines, the 5-iodide, like 3-bromo- and 3-iodo-pyridine, afforded the desired 5-pyrimidinylolefins in satisfactory yields.

ii) The reaction of 2- and 4-iodopyrimidines, on the contrary, may not be expected as a valuable procedure for the synthesis of 2- and 4-pyrimidinylolefins, unless a fundamental improvement in the reaction conditions is worked out.

iii) In case of 4-iodopyrimidines having the free 5-position,[7] the homo-coupling reaction which gave 4,4'-bipyrimidinyl derivatives, is occurred rather than the desired cross-coupling reaction.

In order to open a way to a general procedure with experimental simplicity for the introduction of olefinic groups into the 2- and 4-position of pyrimidine ring, we reinvestigated the palladium-catalyzed reaction of 2- and 4-iodopyrimidines[8] with ethyl acrylate. First, the relation between the type of catalysts and the yield of products was examined on the reaction of 4-iodo-2,6-dimethylpyrimidine (1) with ethyl acrylate. As shown in Table 1, when palladium metal catalysts such as palladium black[9] and palladium on charcoal were used, ethyl pyrimidine-4-acrylate (2a) was obtained as a sole product, without the formation of the homo-coupling product (3). On the contrary, the reaction in the presence of triphenylphosphine, resulted in the recovery of 1 together with a poor yield of the cross-coupling product (2a), as reported previously.[6]

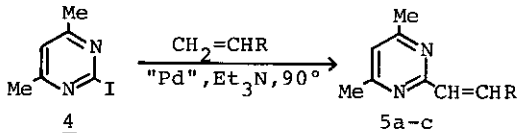
Table 1



"Pd" catalyst	R	Reaction time(hr)	Yield(%) 2	3	1(recovery)
$Pd(OAc)_2$-$2PPh_3$	COOEt	68	6	0	58
$Pd(OAc)_2$	COOEt	68	49	11	0
Pd black	COOEt	68	77	0	0
Pd-C(10%)	COOEt	77	73	0	0
Pd-C(10%)	CN	24	46	38	0
Pd-C(10%)	Ph	22	50	23	0

Then the reaction of 2-iodo-4,6-dimethylpyrimidine (4) with ethyl acrylate was similarly investigated. The results thus obtained were listed in Table 2, where the yields of the product (5a) did not vary significantly with changing catalysts, except palladium(II) acetate with triphenylphosphine.

Table 2



4 5a-c

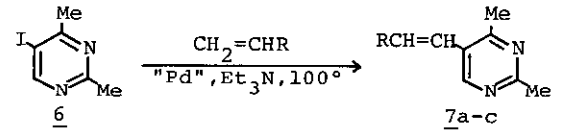
a:R=COOEt
b:R=CN
c:R=Ph

"Pd" catalyst	R	Reaction time(hr)	Yield(%) 5	Yield(%) 4(recovery)
$Pd(OAc)_2$-$2PPh_3$	COOEt	24	0	55
$Pd(OAc)_2$	COOEt	24	57	0
$PdCl_2$	COOEt	20	57	0
Pd black	COOEt	24	57	0
Pd-C(10%)	COOEt	24	60	0
$PdCl_2$	CN	32	61[a)]	0
$Pd(OAc)_2$	Ph	12	52	0
$PdCl_2$	Ph	7	53	0
Pd black	Ph	12	31	21

a) cis isomer, 37 %; trans isomer, 24 %.

Furthermore, the use of palladium catalysts without triphenylphosphine appeared to be effective for the preparation of ethyl 2,4-dimethypyrimidine-5-acrylate (7a) from the corresponding iodide (6).[10)]

Table 3



6 7a-c

a:R=COOEt
b:R=CN
c:R=Ph

"Pd" catalyst	R	Reaction time(hr)	Yield(%) 7	Yield(%) 6(recovery)
$Pd(OAc)_2$	COOEt	24	71	0
Pd black	COOEt	24	49	14
$Pd(OAc)_2$	CN	24	68[a)]	0
$Pd(OAc)_2$	Ph	48	45	0

a) cis:trans=7:3 by GLC.

On the basis of these results, styrylpyrimidines and pyrimidineacrylonitriles were successfully synthesized under the above devised conditions, although the formation of the homo-coupling product (3) was inevitable in the case of 4-iodide (1). These data were also listed in the lower parts of Table 1, 2, and 3. Spectral data of the products were summerized in Table 4 together with their melting points.

Table 4 Melting Points and Spectral Data of Olefinic Pyrimidines (2, 5, and 7)

No.	mp (°C)	IR($CHCl_3$) cm^{-1}	NMR($CDCl_3$) ppm	
			-CH=CH-(d) [J,Hz]	other protons
2a	67-69	1715,1645 1590	7.10 7.50 [16]	1.34(3H,t,J=7Hz), 2.50(3H,s) 2.70(3H,s), 4.29(2H,q,J=7Hz) 7.03(1H,s)
2b	70-72	2225,1590	6.72 7.33 [16]	2.51(3H,s), 2.69(3H,s), 6.86(1H,s)
2c	57-58	1652,1595	7.02 7.80 [16]	2.48(3H,s), 2.71(3H,s) 7.00(1H,s), 7.30-7.67(5H,m)
5a	54-56	1720,1645 1598	7.10 7.78 [16]	1.32(3H,t,J=7Hz), 2.48(6H,s) 4.30(2H,q,J=7Hz), 6.97(1H,s)
5b	74-75 (trans)	2230,1605	6.80 7.56 [16]	2.53(6H,s), 7.08(1H,s)
	82-83.5 (cis)	2230,1605	5.87 7.29 [12]	2.58(6H,s), 7.07(1H,s)
5c	47-48	1645,1595	7.27 8.00 [16]	2.48(6H,s), 6.85(1H,s) 7.30-7.75(5H,m)
7a	66	1715,1645 1586	6.40 7.85 [16]	1.37(3H,t,J=7Hz), 2.63(3H,s) 2.73(3H,s), 4.32(2H,q,J=7Hz) 8.70(1H,s)
7b	91-92[a] (trans)	2285,1625 1590	5.83 7.54 [16]	2.56(3H,s), 2.70(3H,s), 8.58(1H,s)
7c	72-73	1640,1582		2.63(3H,s), 2.75(3H,s), 7.09(2H,s) 7.20-7.76(5H,m), 8.75(1H,s)

a) Trans isomer was purified by recrystallization from hexane.

In coclusion, in the iodopyrimidine series, the use of palladium(II) or palladium metal catalysts alone is superior to that of palladium(II) catalyst with ligand (triphenylphosphine) in respect to the yield of the desired cross-coupling products.

References and Notes

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10) The synthesis of 5-iodopyrimidines including that of 2,4-dimethyl-5-iodopyrimidine (6) from 2,6-dimethyl-4-pyrimidinone will be reported in the near future.

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