CROSS-COUPLING REACTION OF 5-SUBSTITUTED 4-IODOPYRIMIDINES WITH OLEFINS IN THE PRESENCE OF PALLADIUM COMPLEX

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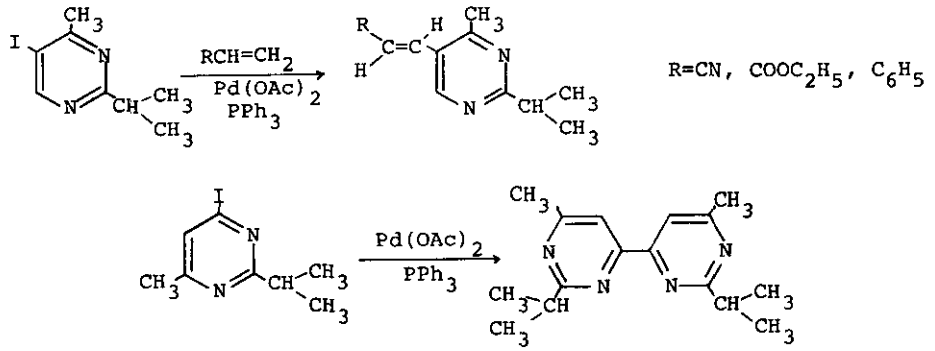
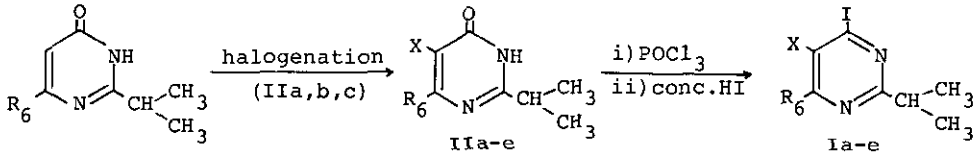
Abstract —— On the olefinic coupling reaction of halopyrimidines, the presence of a 5-substituent was found to facilitate the coupling at the 4-position. Namely, 5-substituted (X=I, Br, Cl, C_2H_5O, C_2H_5) 4-iodo-2-isopropylpyrimidines (Ia-e) reacted with styrene to give the corresponding 4-styryl derivatives in 46, 46, 40, 87, and 51 % yields, respectively. The syntheses of the starting material, 4-iodopyrimidines (Ia-e) are also described.

We have recently reported the following result on the cross-coupling reaction of *monoiodo(or bromo)pyrimidines with olefins.*[1] In the presence of a palladium-triphenylphosphine complex, olefins such as acrylonitrile, ethyl acrylate, and styrene reacted with 5-iodo(or bromo)pyrimidines to give the cross-coupled products. In contrast with this observation, the same olefins did not coupled with 2- and 4-*iodopyrimidines*. For instance, the reaction of 4-iodo-2-isopropyl-6-methylpyrimidine resulted in the formation of 2,2'-diisopropyl-6,6'-dimethyl-4,4'-bipyrimidine independent of the presence of olefins.



Scheme 1

In this communication, we wish to report the coupling reaction of 4,5-diiodo-2-isopropyl-6-methylpyrimidine (Ia) and its related compounds (Ib-e) with styrene affording the result which seemed to conflict with the above description.
The pyrimidines (Ia-e) employed in the investigation were prepared from the 5-substituted 4-pyrimidinones (IIa-e), which were obtained by the halogenation of the corresponding 4-pyrimidinones or by ring-closing reactions, through 4-chloro derivatives as illustrated in Scheme 2.



	Ia	Ib	Ic	Id	Ie
X	I	Br	Cl	C_2H_5O	C_2H_5
R_6	CH_3	CH_3	CH_3	H	CH_3
bp(mmHg) or mp(°C)	78-79	78	83-85	145(20)	45-47
Yield*(%)	80	70	63	70	57

*) The over-all yields from II to I were recorded.

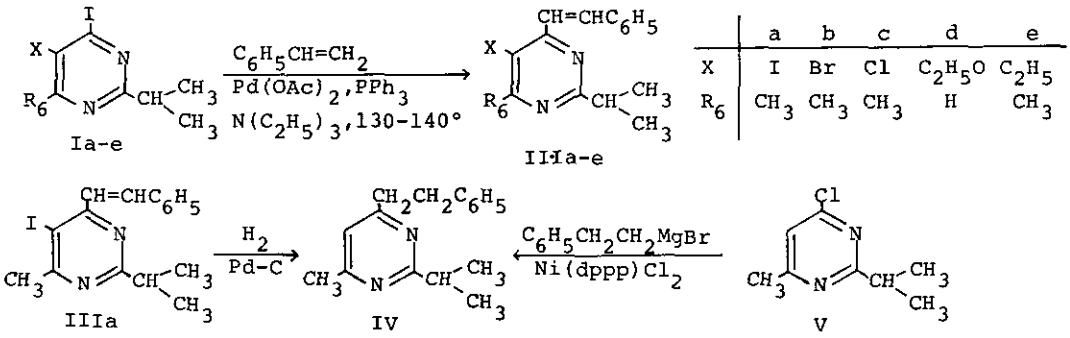
Scheme 2

When 4,5-diiodo-2-isopropyl-6-methylpyrimidine (Ia) was heated with styrene in triethylamine in the presence of a catalytic amount of palladium-triphenylphosphine complex,[2] 5-iodo-2-isopropyl-6-methyl-4-styrylpyrimidine (IIIa), mp 84-85°, $C_{16}H_{17}IN_2$, was obtained in 46 % yield, and the corresponding 5-styryl isomer was not isolated. Although the NMR spectrum ($CDCl_3$) of IIIa [1.35 ppm (6H, d, J=7.0 Hz), 2.68 ppm (3H, s), 2.80-3.40 ppm (1H, m), 7.00-7.80 ppm (5H, m), 7.52 ppm (1H, d, J=15.0 Hz), and 8.08 ppm (1H, d, J=15.0 Hz)] is consistent with its trans olefin structure, the spectrum gives no information on differentiation of IIIa from the 5-isomer. The catalytic reduction of IIIa over palladium-charcoal gave 2-isopropyl-6-methyl-4-phenethylpyrimidine (IV), bp 148° (2 mm Hg), which was identical with the authentic specimen prepared from 4-chloro-2-isopropyl-6-methylpyrimidine (V) according to the reported manner.[3] Thus it became apparent that Ia coupled with styrene in a fashion quite different from what might have been

anticipated by the reaction of the monoiodopyrimidines.

Further investigation was made to confirm the scope of this unusul reaction. Namely, 5-bromo-4-iodo-2-isopropyl-6-methyl- (Ib), 5-chloro-4-iodo-2-isopropyl-6-methyl- (Ic), 4-iodo-5-ethoxy-2-isopropyl- (Id), and 5-ethyl-4-iodo-2-isopropyl-6-methyl-pyrimidine (Ie) were allowed to react with styrene under identical conditions. In all the cases, the corresponding 4-styryl compounds (IIIb-e) were obtained in the following yields [IIIb: mp 69-70.5°, 46 %; IIIc: mp 77-79°, 40 %; IIId: bp 170° (2 mmHg), 87 %; and IIIe: bp 165° (1 mmHg), 51 %].

Based on the results of the elemental analysis and the mass spectra of the products [IIIb: $C_{16}H_{17}BrN_2$, m/e=316, 318 (M^+); IIIc: $C_{16}H_{17}ClN_2$, m/e=272, 274 (M^+); IIId: $C_{17}H_{20}N_2O$, m/e=268 (M^+); and IIIe: $C_{18}H_{22}N_2$, m/e=226 (M^+)], the olefinic coupling reaction was clearly demonstrated to occur at the 4-position of these pyrimidine derivatives (Ib-e).



Scheme 3

The superior activity of an iodo-(or bromo-)substituent at the β-position of N-heteroaromatics toward the olefinic coupling reaction has already reported not only on halopyrimidines but on halogenated pyridines, quinolines, and isoquinolines.[1,4] Accordingly, our present result forms striking contrast to the previous observations mentioned above, although the role of the neighbouring substituents in this reaction is still obscure.

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References

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2. According to the manner reported by Heck et al., as an experimental procedure, palladium acetate and triphenylphosphine were added to the reaction mixture in place of the previously prepared palldium complex [R. H. Heck and J. P. Nolley, J. Org. Chem., 1978, 43, 3396].
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