Water Facilitation of Palladium-Mediated Coupling Reactions

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Summary: Water-containing solvent systems are more effective than conventionally used organic reaction solvents for palladium-mediated coupling reactions of iodo derivatives of nitrogen heterocycles with cyclic enol ethers and furanoid glycals.

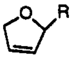
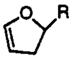
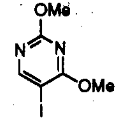
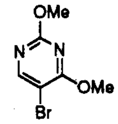
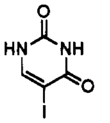
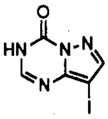
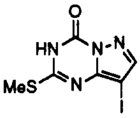
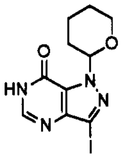
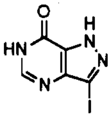
Water has been used as a reaction medium for organometallic reactions[1] to simplify separation and recovery of catalyst and to take advantage of the safety and economy of water. These considerations are of special importance for industrial-scale reactions. Tueting and co-workers[2] have reported that, in palladium-catalyzed reactions of organostannanes with vinyl epoxides, addition of water to the organic reaction medium increased yields and affected reaction regio- and stereochemistry. We now report what is, to our knowledge, the first successful palladium-mediated coupling reactions carried out in water-containing media which do not take place under more conventional reaction conditions employing organic media.

Recently, we have investigated palladium-mediated coupling reactions involving several nitrogen heterocyclic systems[3] which have proved to be especially challenging, owing to the potential of nitrogen-rich systems to inactivate the catalyst by complexation. After extensive experimentation, we succeeded in finding reaction conditions which permit coupling of certain nitrogen heterocyclic iodo derivatives with cyclic enol ethers.[3] We now report that, in water-containing media, these palladium-catalyzed coupling reactions occur readily and, more critically, we have achieved coupling reactions in aqueous media which we have been unable to accomplish in nonaqueous solvents.

Reactions carried out in water alone gave very low yields of coupled products owing to limited solubility of reactants. Therefore, varying ratios of an organic cosolvent were used. Dimethylformamide, acetonitrile, and ethanol were equally effective cosolvents. We found it convenient for this preliminary study to use a standard mixture of water and ethanol (1:1) as the reaction medium. Key results obtained using this reaction medium are summarized in Table I. It is noteworthy that use of absolute ethanol as reaction solvent was ineffective.

Coupling of 2,3-dihydrofuran with 2,4-dimethoxy-5-iodopyrimidine[4] mediated by catalytic palladium(II) acetate in dimethylformamide (DMF) (Table I, entry 1) is facile and yields a double-bond isomer[5] mixture. This coupling reaction in water and ethanol (1:1) (entry 2) was equally effective but resulted in a significantly different ratio of isomeric products. The less reactive bromo derivative[6] did not undergo coupling in DMF solution (entry 3) but produced a modest yield of the primary coupled product (without double-bond migration[5]) in the aqueous medium. Similar results (entries 5 and 6) were

Table I. Palladium-Mediated Coupling Reactions of Nitrogen Heterocyclic Halo Derivatives with 2,3-Dihydrofuran (10 Equiv)

entry no.	RX	procedure[a]	temp (°C)	time (h)	product (% yield)	
						
1		A[b]	25	5	25	57
2		C	25	5	61	25
3		A	50	10		
4		C	50	10	28	
5		B[c]	50	3	35	23
6		C	50	3	53	
7		A, B	50	10		
8		C	50	10	70	
9		C[d]	50	10	59	
10		C[d]	50	12	80	
11		C[d]	60	12		

[a] Procedures: (A) $Pd(OAc)_2$ (0.1 equiv), n-Bu_4NCl (1 equiv), NaOAc (1 equiv), Et_3N (3 equiv), dimethylformamide; (B) $Pd(OAc)_2$ (0.1 equiv), $AsPh_3$ (0.2 equiv), Et_3N (3 equiv), acetonitrile; (C) $Pd(OAc)_2$ (0.1 equiv), n-Bu_4NCl (1 equiv), $NaHCO_3$ (1 equiv), Et_3N (3 equiv), H_2O:EtOH (1:1). [b] A similar reaction has been reported.[3] [c] Taken from ref 3. [d] No coupling was observed using procedure A or B.

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(1) (a) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990,** *112,* 4324–4330. (b) Safi, M.; Sinou, D. *Tetrahedron Lett.* **1991,** *32,* 2025–2028. (c) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988,** *110,* 7542–7543. (d) Wallow, T. I.; Novak, B. M. *J. Chem. Soc.* **1991,** *113,* 7411–7412. (e) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991,** *32,* 7017–7020. (f) Bumagin, N. A.; Sukhomlinova, L. I.; Tolstaya, T. P.; Vanchikov, A. N.; Beletskaya, I. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990,** 2665–2666. (g) Vicente, J.; Abad, J.-A.; Jones, P. G. *Organometallics* **1992,** *11,* 3512–3517.

(2) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. *Tetrahedron* **1989,** *45,* 979–992.

(3) Zhang, H.-C.; Daves, G. D., Jr. *J. Org. Chem.* **1992,** *57,* 4690–4696.

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(5) Lee, T. D.; Daves, G. D., Jr. *J. Org. Chem.* **1983,** *48,* 399–402.

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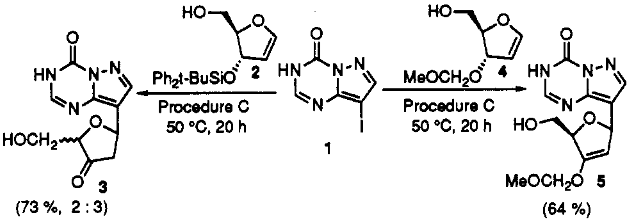
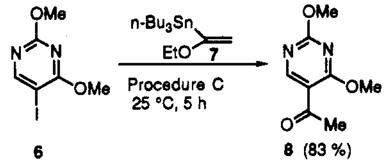
obtained in coupling reactions of 5-iodouracil,[7] which possesses unprotected NH functions.[3] The bicyclic nitrogen heterocycles 8-iodo-3*H*-pyrazolo[1,5-*a*]1,3,5-triazin-4-one[8a] (entries 7 and 8), 8-iodo-2-(methylthio)-3*H*-pyrazolo[1,5-*a*]1,3,5-triazin-4-one[8a] (entry 9), 3-iodo-1-(tetrahydropyranyl)pyrazolo[4,3-*d*]pyrimidin-7-one[8b] (entry 10), and 3-iodopyrazolo[4,3-*d*]pyrimidin-7-one[3] (entry 11) all failed to undergo palladium-mediated coupling with 2,3-dihydrofuran using procedures A and B, which employ nonaqueous solvents. The first three (entries 8–10) did, however, undergo coupling in aqueous media (procedure C) to yield, in each case, a single product in moderate to good yield. Only 3-iodopyrazolo[4,3-*d*]pyrimidin-7-one[3] (entry 11), which has an acidic pyrazole NH group, failed to afford a coupled product when the coupling reaction was carried out in aqueous media.

The palladium-mediated coupling reaction in aqueous media has been extended to the preparation of *C*-nucleosides.[9] Coupling of 8-iodo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazin-4-one[8a] (**1**) with 2 equiv of furanoid glycal **2**[10] did not occur using procedures A or B but was facile with procedure C. However, the isolated product **3** was a mixture of 3′-keto *C*-nucleosides isomeric at C-4′.[11] In the aqueous reaction media, the intermediate silyl enol ether was desilylated and the basic reaction conditions effected isomerization of the asymmetric center α to the 3′-keto function. When 3-O-silylated furanoid glycal **2**[10] was replaced with the methoxymethyl-protected glycal **4**,[12] coupling with iodo derivative **1** permitted isolation of the stereochemically intact *C*-nucleoside product **5**.[13]



Finally, procedure C was used for a palladium-mediated cross-coupling reaction between 2,4-dimethoxy-5-iodopyrimidine[4] (**6**) and 1-(ethoxyethenyl)-tri-*n*-butylstannane[14] (**7**, 2 equiv) to produce the corresponding pyrimidine derivative **8**[15] (formed by in situ hydrolysis of the intermediate enol ether).



The results obtained in this preliminary study demonstrate that water-containing solvent systems are effective for palladium-mediated coupling reactions with significant advantages for reactions involving complex nitrogen heterocycles. It is noteworthy that, by use of ethanol (or other water-miscible cosolvent), reactants which are essentially insoluble in water (e.g. glycal **2**) cause no difficulty.

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(8) (a) Prepared by iodination of the respective parent heterocycles (Kobe, J.; Robins, R. K.; O'Brien, D. E. *J. Heterocycl. Chem.* **1974**, *11*, 199–204) with *N*-iodosuccinimide in DMF. (b) Prepared by acid-catalyzed reaction of the 1-unsubstituted analog[3] with 3,4-dihydropyran (Zhang, H.-C.; Brakta, M.; Daves, G. D., Jr., unpublished results).

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(11) ^{1}H nuclear magnetic resonance (NMR) spectrum for **3** (two isomers, 3:2; δ $CDCl_3$): 2.60–3.10 (m, H-2″s), 3.65 (m, H-5″s), 3.95, 4.02 (2 t, *J* = 3.1, 3.0 Hz, H-4″s), 5.31 (dd, *J* = 10.5, 6.1 Hz), 5.60 (t, *J* = 7.3 Hz) (H-1″s), 7.73, 7.74, 7.77, 7.82 (4 s, H-2's, H-7's).

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(13) ^{1}H NMR spectrum for **5** (δ, $CDCl_3$): 3.45 (s, OCH_3), 3.94 (m, H-5″s), 4.81 (m, H-4′), 5.01 (m, H-2′, $-OCH_2O-$), 6.00 (m, H-1′), 7.99, 8.02 (2 s, H-2, H-7).

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(15) Wada, A.; Yammamoto, J.; Hamaoka, Y.; Ohki, K.; Nagai, S.; Kanatomo, S. *J. Heterocycl. Chem.* **1990**, *27*, 1831–1835.