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PALLADIUM CATALYZED REACTION OF 4-BROMO-2,6-LUTIDINE WITH ALLYLIC ALCOHOLS

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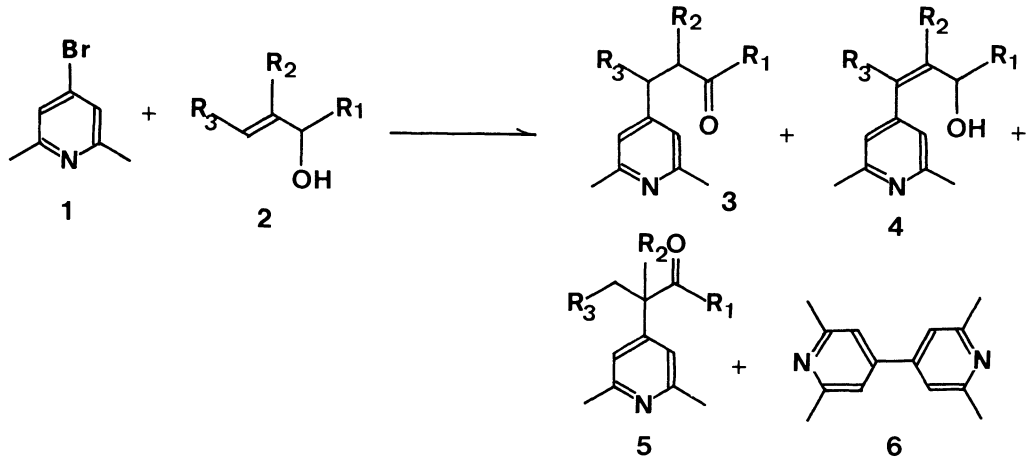
Palladium acetate catalyzed the reaction of 4-bromo-2,6-lutidine with allylic alcohols to give 4-(3'-oxo-alkyl)-2,6-lutidines selectively together with small amounts of 4-(2'-oxo-alkyl)-2,6-lutidines. Under the same conditions, 4-chloro- and 2-bromopyridines react to give 4,4'- and 2,2'-bipyridyls, respectively.

Heteroaromatics, accompanied by the current development of their ring opening procedures, have been evaluated as useful synthons for the synthesis of natural and unnatural products. In this context, the synthetically useful palladium catalyzed arylation of allylic alcohols[1] have been extended to heteroaromatics.

While palladium catalyzed thienylations of allylic alcohols proceed regardless of the reaction positions of thiophenes, i.e., alkylations at the 2- and 3-positions of thiophene using 2- and 3-bromothiophenes respectively,[2,3] the reaction of pyridine with allylic alcohols largely depends on the structures and reaction positions of pyridines. While 3-bromopyridine reacted with allylic alcohols to give 3-(3'-oxo-alkyl)pyridines,[4] 2-bromo- and 4-chloropyridines[5] were not alkylated, but dimerized to give 2,2'- and 4,4'-bipyridyls, respectively.[6] 4,4'-Bipyridyl (mp 113.5∿114.5°C)[7] was isolated in 38% yield by the reaction of 4-chloropyridine and α-methallyl alcohol in the presence of 1 mol% of $Pd(OAc)_2$ and 3 mol% of PPh_3 (120°C for 48 h, in HMPA).[8]

Interestingly, methyl-substituents at 2- and 6-positions changed the reaction dramatically; 4-bromo-2,6-lutidine[9] reacted with allylic alcohols to furnish the alkylation products (eq 1), accompanied by a small amount of dimelization product 6.



(1)

Table 1. Palladium Catalyzed Reaction of 4-Bromo-2,6-lutidine with Allylic Alcohols.

Entry	Alcohols			Reaction Conditions[a]				Product Distribution[c]				
	R^1	R^2	R^3	Solvents	Temp. (°C)	Time (hr)	Conv.[b] (%)	3	4	5	6	Others
1	H	CH_3	H	HMPA	100	23	92	87 (59)	---	---	5	8[d]
2	H	CH_3	H	DMF	100	48	98	95 (80)	---	---	1	4
3	CH_3	H	H	HMPA	120	6	100	80 (55)	12 (8)	4 (3)	3	2
4[e]	CH_3	H	H	HMPA	120	30	95	91	1	7	---	1
5	CH_3	H	H	DMF	120	7	100	82 (75)	14 (13)	3 (3)	---	1
6[e]	CH_3	H	H	DMF	120	30	70	95 (90)	2	3	---	
7	CH_3	H	CH_3	HMPA	120	24	100	66 (45)	---	14 (10)	9 (4)	11[d]
8	CH_3	H	CH_3	DMF	120	20	88	71 (68)	---	6 (4)	5 (4)	18[d]
9	Ph	H	H	HMPA	120	7	100	85 (76)	---	---	5 (3)	10[d]
10	Ph	H	H	DMF	120	9	100	90 (90)	---	---	4 (3)	6[d]

a) The usual scale is as follows: 4-bromo-2,6-lutidine (4 mmol), allylic alcohol (6 mmol), $Pd(OAc)_2$ (0.04 mmol), $NaHCO_3$ (4.8 mmol), and PPh_3 (0.12 mmol) in 3 ml of anhydrous solvent. Bath temperature was controlled within ± 0.5°C. b) Based on 4-bromo-2,6-lutidine consumed. c) Determined by VPC (SiDC 550, He). The values in parentheses refer to the isolated yields. d) Unknowns consist of more than one product in less than 5%. e) Without PPh_3.

Pyridylation at the 3-position of allylic alcohols to give 3 and 4 predominated over pyridylation at the 2-position to give 5. The results of the pyridylation reaction with 4 kinds of allylic alcohols, with variations of solvents and additives, are summarized in Table 1. Dimethylformamide (DMF) showed the higher regioselectivity (3+4 vs. 5) than hexamethylphosphoric triamide (HMPA); there was not observed any significant difference in the reactivity between the reactions in these solvents. Especially for the practical purpose, DMF is the solvent of choice, i.e., for the reactions undertaken in DMF, the products can be isolated without aqueous workup by the direct distillation of the filtrate (of the reaction mixture through a Florisil or cellurose column). By aqueous workup, which cannot be omitted for the reaction in HMPA owing to the difficulty in separation of products and HMPA, the isolated yields

fall to half owing to the high solubility of the products in water.

Triphenylphosphine raised the reactivity, though it sometimes made the reaction complex (entries 3 and 5). Omission of triphenylphosphine remarkably suppressed the formation of pyridine-substituted allylic alcohol 4 (entries 4 and 6).

A typical experiment is as follows (entry 5): an argon purged mixture of $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), PPh_3 (31.5 mg, 0.12 mmol), and $NaHCO_3$ (404 mg, 4.8 mmol) was added a solution of 4-bromo-2,6-lutidine (744 mg, 4.0 mmol) and α-methallyl alcohol (432 mg, 6 mmol) in 3 ml of anhydrous DMF (dried over CaH_2) by means of a syringe through a rubber septum. The slurry brown reaction mixture was stirred and heated at 120°C for 7 h. After allowing to cool to ambient temperature, the reaction mixture was diluted with 30 ml of ether and filtered through a Florisil column (mesh 100 ∿200, 3 g). Evaporation of the solvent and subsequent distillation (150∿160°C/5 mm Hg, Kugel rohr) gave a colorless oil (645 mg, 91% isolated yield), which consisted of 82% of 3 (R^1= CH_3, R^2= R^3= H), 14% of 4 (R^1= CH_3, R^2= R^3= H), 3% of 5 (R^1= CH_3, R^2= R^3 = H), and 1% of unknown. These products were separated and purified by preparative VPC[10] (SiDC 550; column temperature was gradually raised from 170°C to 240°C).

Experiments to clarify the effects of substituents and leaving groups on the course of reactions are under way.[11]

References and Notes

1. (a) J. B. Melpolder and R. F. Heck, J. Org. Chem., 41, 265 (1976); (b) A. J. Chalk and S. A. Magennis, ibid., 41, 273, 1206 (1976).
2. (a) Z. Yoshida, Y. Yamada, and Y. Tamaru, Chem. Lett., 423 (1977); (b) Y. Tamaru, Y. Yamada, and Z. Yoshida, Tetrahedron Lett., 3365 (1977); (c) Y. Tamaru, Y. Yamada, and Z. Yoshida, ibid., 919 (1978).
3. 2,2'- and 3,3'-Bithienyls were obtained as minor products, the former being formed in larger amount than the latter under the similar conditions.
4. Y. Tamaru, Y. Yamada, and Z. Yoshida, J. Org. Chem., 43, in press (1978).
5. 2- and 4-Halopyridines, especially bromopyridines, readily dimerize at room temp: H. E. Mertel,"The Chemistry of Heterocyclic Compounds", E. Klingsberg, Ed., Chapter VI, Part II, Interscience, New York, N. Y., 1961. Freshly distilled halopyridines were used for all experiments. 4-Bromo-2,6-lutidine is rather stable at room temperature, but some decomposition is observed during a long shelf storage.
6. For the palladium(II) catalyzed dimerization of aryliodides, see F. R. S. Clark, R. O. C. Norman, and C. B. Thomas, J. Chem. Soc., Perkin I, 121 (1975) and references cited therein.
7. C. R. Smith, J. Am. Chem. Soc., 46, 414 (1924).
8. Similarly 2,2'-bipyridyl was obtained in 40∿50% yield.
9. (a) H. Matsumura, T. Hirooka, and K. Imagawa, Nippon Kagaku Zasshi, 82, 616 (1961); (b) R. F. Evans and H. C. Brown, J. Org. Chem., 27, 1665 (1962); J. Suszko and M. Szafran, Roczniki. Chem., 39, (7/8), 1045 (1965). CA., 64, 12637g (1966).
10. The spectral, physical and analytical data of the new compounds obtained in this study are as follows: 3 (R^1= H, R^2= CH_3, R^3= H) bp 150∿155°C/ 5 mm Hg; NMR (CCl_4) 1.07 (d, 6.8Hz, 3H), 2.42 (s, 6H), 2.3∿3.1 (m, 3H), 6.67 (s, 2H), and 9.61 (s, 1H);

IR (neta film) 1718 (vs), 1605 (s), 1563 (s), and 734 (w) cm^{-1}; MS (m/e, rel. int.) 177(P^+, 90), 149(94), 121(100), and 91(59); Found: m/e 177.1153, Calcd for $C_{11}H_{15}NO$: 177.1153. 3 (R^1=CH_3, R^2= R^3= H) bp 150-160°C/5 mmHg (Kugel rohr); NMR (CCl_4) δ 2.06(s, 3H), 2.39(s, 6H), 2.67(s, 4H), and 6.65(s, 2H); IR(neat film) 1713(s), 1610(s), 1570(s), and 735(w) cm^{-1}; MS (m/e, rel. int.) 177(P^+, 100), 134 (100), 91(92), and 77(92); Found: 177.1159, Calcd for $C_{11}H_{15}NO$: 177.1153. 4 (R^1= CH_3, R^2= R^3= H) bp 150-160°C/ 5 mmHg (Kugel rohr); mp 81.3-82.0°C (from benzene-n-hexane); NMR (CCl_4) δ 1.30(d, 6.6Hz, 3H), 2.41(s, 6H), 3.55(s, 1H), 4.4 (m, 1H), 6.35(m, 2H), and 6.78(s, 2H); IR (KBr disc) 1605(s), 1557(m), 1141(s), 1075(m), and 968(s) cm^{-1}; MS (m/e, rel. int.) 177(P^+, 48), 134(100), and 91(26). 5 (R^1= CH_3, R^2= R^3= H) bp 150-160°C/5 mmHg (Kugel rohr); NMR(CCl_4) δ 1.38(d, 7Hz, 3H), 1.98(s, 3H), 2.46(s, 6H), 3.52(q, 7Hz, 1H), and 6.69(s, 2H); IR (neat film) 1712(s), 1603(s), 1569(s), 1173(s), and 860(w) cm^{-1}; MS (m/e, rel. int.) 177(16), 135(100), and 77(56). 3 (R^1= R^3= CH_3, R^2= H) bp 160-165°C/ 5 mmHg(Kugel rohr); NMR(CCl_4) δ 1.20(d, 7Hz, 3H), 2.02(s, 3H), 2.43(s, 6H), 2.60(d, 7Hz, 2H), 3.17(q, 7Hz, 1H), and 6.74(s, 2H); IR (neat film) 1718(s), 1612(s), 1573(s), and 740(w) cm^{-1}; MS(m/e, rel. int.) 191(P^+, 89), 149(78), 148(100), and 91(65); Found: 191. 1290, Calcd for $C_{12}H_{17}NO$: 191.1301. 5 (R^1= R^3= CH_3, R^2= H) bp 160-165°C/5 mmHg ; NMR(CCl_4) δ 0.82(t, 7.0Hz, 3H), 2.00(s, 3H), 2.46(s, 6H), 3.25(m, 2H), 3.34(t, 7.2Hz, 1H), and 6.71(s, 2H); IR (neat film) 1707(s), 1602(s), 1567(s), and 740(m) cm^{-1}; MS (m/e, rel. int.) 191(P^+, 25), 148(22), and 134(100). 3 (R^1= Ph, R^2= R^3= H) bp 180°C/1 mmHg; NMR(CCl_4) δ 2.49(s, 6H), 2.8-3.5(A_2B_2m, 4H), 6.83(s, 2H), and 7.4-8.1(m, 5H); IR (neat film) 1685(s), 1610(s), 1450(s), 1208(s), 774(s), and 690(s) cm^{-1}; MS (m/e, rel. int.) 239(P^+, 100), 134(38), 105(95), and 77(74); Found: C, 80.45; H, 7.29; N, 5.87; O, 6.39. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85; O, 6.69.

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