Tetrahedron Letters No. 10, pp 919 - 922, 1978. Pergamon Press. Printed in Great Britain.

PALLADIUM CATALYZED THIENYLATION OF α-METHALLYL ALCOHOL WITH 5-SUBSTITUTED 2-BROMOTHIOPHENES AND ITS APPLICATION TO SYNTHESIS OF QUEEN SUBSTANCE

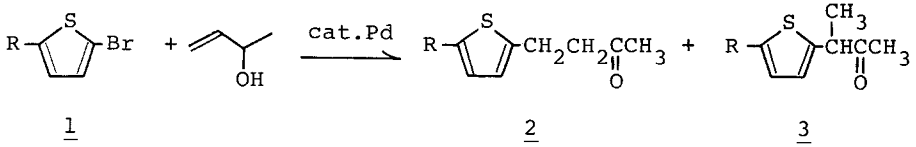
Yoshinao Tamaru, Yoshimi Yamada and Zen-ichi Yoshida*

Department of Synthetic Chemistry, Kyoto University,
Yoshida, Kyoto 606, Japan

(Received in Japan 26 December 1977; received in UK for publication 16 January 1978)

Recently the heterocyclic aromatics have been evaluated as the useful synthons for the synthesis of natural and unnatural products. As the extension of the palladium catalyzed phenylation of allylic alcohols[1] to the heterocyclic aromatics, we have reported that palladium catalyzes efficiently the reactions of allylic alcohols and 2-bromo- or 3-bromothiophene to give 3-(2-thienyl)- or 3-(3-thienyl)carbonyl compounds[2] selectively in excellent to fairly good yields depending on the structure of allylic alcohols. In this communication we wish to report the ability of this reaction to accomodate a wide variety of functionalities and its application to the synthesis of 9-oxo-2-*trans*-decenoic acid 10[3] (queen substance, a honey bee pheromone), taking advantage of the characteristics of thiophene as a template for the four-carbon homologation reaction.[4]

The palladium catalyzed reaction of 5-substituted 2-bromothiophenes (1a∿1e) with α-methallyl alcohol proceeded to give β-thienyl ketones (2a∿2e) selectively, together with small amounts of α-thienyl ketones (3a∿3e) (eq 1). The reaction conditions and results were summarized in the Table. Especially rewarding here is that the apparent ease of this reaction is not affected by these substituents. With 1b[5], reduction to give methyl (2-thienyl)acetate



(1)

1,2,3a ; R= CH_3
b ; R= $CH_2CO_2CH_3$
c ; R= H
d ; R= $COCH_3$
e ; R= CO_2CH_3

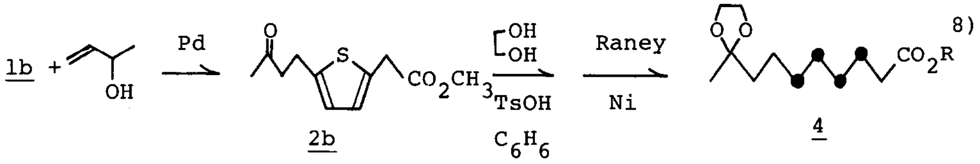
Table Palladium Catalyzed Thienylation of α-Methallyl Alcohol with 5-Substituted 2-Bromothiophene[a]

Entry	Thiophene	Solvent	Base	Temp (°C)	Time (hr)	Conv.[b] (%)	Product distribution[c] (%) 2	3	others
1	1a	HMPA	$NaHCO_3$	120	25	93	85.7(75)	8.4	6.2[d]
2	1b	HMPA	$NaHCO_3$	120	8.5	100	70.1(44)	6.2	23.6[e]
3	1b	DMF	K_2CO_3	100	5	100	90.2(61)	2.9	6.9[e]
4	1c	HMPA	$NaHCO_3$	120	7	94	90.6(80)	6.8(5)	2.6[f]
5	1c	DMF	$NaHCO_3$	120	16	96	90.9(82)	0.5	8.6[f]
6	1d	HMPA	$NaHCO_3$	120	5	91	86.4(80)	—	13.6[d]
7	1e	HMPA	$NaHCO_3$	120	9	100	∿100 (60)	—	—

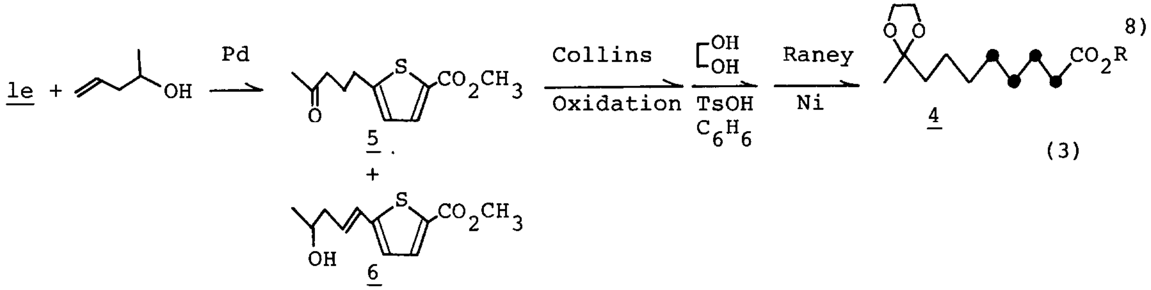
a. The usual scale is 1 (4.0 mmol), α-methallyl alcohol (6.0 mmol), $Pd(OAc)_2$ (0.04 mmol), NaI (0.14 mmol), base (4.8 mmol), triphenylphosphine (0.12 mmol) in 3 ml of solvent. For entry 3, see text. b. Based on 1 consumed.
c. Determined by the area intensities on vpc (SiDC 550, He). The values in parentheses refer to the isolated yields. The structures of 2a∿2e and 3a∿3e were determined by nmr, ir, and mass spectra and 2a∿2e gave satisfactory analytical data. d. unspecified product. e. Methyl (2-thienyl)acetate.
f. 2,2'-Bithienyl.

took place appreciably. This undesirable side reaction could be markedly suppressed by using DMF as a solvent and K_2CO_3 as a base and setting the reaction temperature lower (entry 3). Generally, DMF was the best choice of solvents for the regio-selectivities and the isolated yields.[6]

In order to illustrate the scope and utility of the catalytic reaction, the synthetic intermediate 4 for the synthesis of queen substance 10 was prepared independently according to eqns. 2 and 3, which also show that thiophene serves as the template for the construction of the desired molecules. The carbons originated from thiophene are indicated by black spots on the structural formula of 4. Thienylation of α-methallyl alcohol (60 mmol) with 1b (40 mmol) in 30 ml of DMF at 100°C for 5 hr in the presence of $Pd(OAc)_2$ (0.4 mmol), K_2CO_3 (24 mmol), and triphenylphosphine (1.2 mmol) gave a mixture of 2b and 3b (68% crude yield, 2b/3b=97/3), after ether extraction and the subsequent distillation (155°C/2 mmHg). Analytically pure 2b[7] was obtained in 61% yield by column chromatography (Silica gel, benzene-hexane). Ketalization of 2b (ethylene glycol, cat. TsOH, in refluxing benzene for 17 hr, 97% isolated yield) and the subsequent desulfurization with Raney nickel W-7[9] (in refluxing ethanol for 16 hr, 84% isolated yield) gave 4[8] (as $R=C_2H_5$, $\delta_{CCl_4}^{TMS}$ 1.09∿1.96 (m, 18H), 2.03∿2.39 (m, 2H), 3.83 (S, 4H), 4.08 (q., 7Hz, 2H).



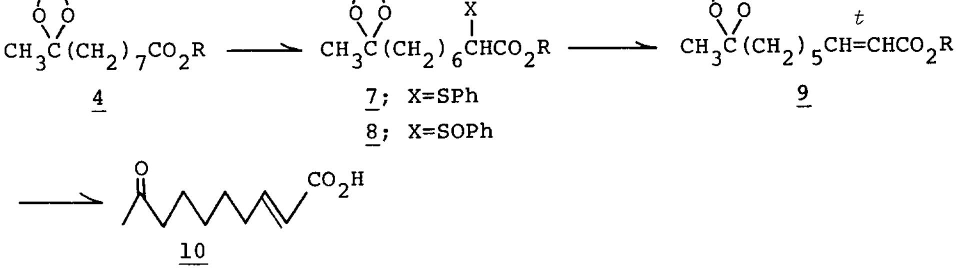
(2)



(3)

ν_{neat}^{max} (cm^{-1}). 2940(m), 1740(s), 1085(m), 1065(m), 1045(m). Calcd for $C_{14}H_{26}O_4$: C; 65.09, H; 10.14. Found: C; 64.98, H; 10.27).

The thienylation of 2-hydroxy-4-pentene with 1e gave a mixture of 5 and 6[9] in a ratio of 69:31 in 40% yield. Collins oxidation[10] of the mixture and the subsequent ketalization and desulfurization in the similar procedures to eq. 2 gave rise to 4 in 22% overall yield from 1e. Queen substance 10 was prepared according to eq 4, which essentially consisted of the α,β-unsaturation of ester by the method of Trost,[11] i.e., the sulfenylation (7, 92% isolated yield by the inverse quenching[11]) and oxidation with $NaIO_4$ in 60% aq. methanol at r.t. for 24 hr (8, 85% conversion), followed by the thermal dehydrosulfenylation (in refluxing toluene, 20 min) gave rise to *trans*-9 exclusively (85% from 7, after purification by preparative layer chromatography). 9; as $R=C_2H_5$, $\delta_{CCl_4}^{TMS}$ 1.20 (s, 3H), 1.25 (t, 7Hz, 3H), 1.2∿1.8 (br.m, 8H), 2.0∿2.43 (br.m, 2H), 3.83 (s, 4H), 4.14 (q, 7Hz, 2H), 5.74 (d, 16Hz, 1H), 6.90 (d.t, 16 and 7 Hz, 1H). ν_{neat}^{max}(cm^{-1}) 1720 (s), 1655 (m), 980 (w). m/e 256.1723 (calcd for $C_{14}H_{24}O_4$: 256.1673). The hydrolysis[12] of 9 (dil. HCl in aq. acetone, then KOH, in refluxing aq. methanol) gave queen substance 10 in a quantitative yield, with the identical spectral data to the reported ones.[3]



(4)

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, Chemistry Letters, 423 (1977). (b) Y. Tamaru, Y. Yamada, and Z. Yoshida, Tetrahedron Letters, 3365 (1977)
3. (a) B. M. Trost and K. Hiroi, J. Am. Chem. Soc., 98, 4314 (1976). (b) J. Tsuji, K. Masaoka, and T. Takahashi, Tetrahedron Letters, 2267 (1977) and references cited therein.
4. A. I. Meyers, "Heterocyclics in Organic Chemistry," John Wiley & Sons, Inc., 1974.
5. J. H. Ford, G. C. Prescott, and D. R. Colingsworth, J. Am. Chem. Soc., 72, 2109 (1950).
6. Other solvents, such as acetic acid, dimethyl sulfoxide, and dioxane, were also examined only to obtain the unsatisfactory results.
7. $\delta^{TMS}_{CCl_4}$ 2.10 (s, 3H), 2.52-3.17 (m , 4H), 3.69 (br.s, 5H), 6.51-6.74 (m, 2H) ν^{max}_{neat} (cm^{-1}) 3075 (w), 2960 (m), 1740 (s), 1720 (s), 807 (s). m/e 226. Anal. Calcd. for $C_{11}H_{14}O_3S$: C; 58.38, H; 6.24, S; 14.17. Found: C; 58.09, H; 6.25, S; 13.90.
8. During desulfurization, the exchange of alcohol part of ester occurred to give a mixture of methyl and ethyl ester of 4 (1:3.5).
9. While the mechanism of this reaction is not clear at present, the isolation of 6 suggests that the double bond migration of 6 to 5 through the sequential addition-elimination of hydridopalladium did not proceed effectively due to the conjugation with thiophene ring.
10. (a) J. C. Collins, W. W. Hess, and F. J. Frank, Tetrahedron Letters, 3363 (1968). (b) R. Ratchiffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).
11. B. M. Trost and T. N. Salzmann, J. Am. Chem. Soc., 95, 6840 (1973).
12. O. P. Vig, A. K. Vig, M. S. Grewal, and K. C. Gupta, J. Indian Chem. Soc., 52, 543 (1975).