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PALLADIUM CATALYZED THIENYLATION OF ALLYLIC ALCOHOLS WITH 3-BROMOTHIOPHENE

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One of the remarkable features of thiophene chemistry is that electrophilic substitution and metallation take place selectively at 2-position of thiophene ring. Therefore 3-substituted thiophenes are relatively difficultly available compounds.[1]

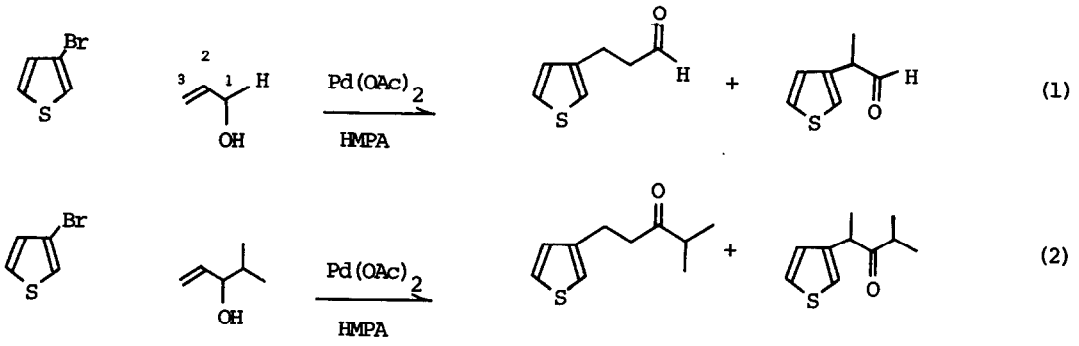
There have been reported a few devices to overcome this difficulty by making use of relatively easily available 3-bromothiophene[2] as a key compound. Among them, the reaction with 3-thienyllithium[3] has been widely applied to prepare 3-substituted thiophenes. However, this reagent is unstable over -70°C and does not react with the less reactive electrophiles such as alkyl iodide, but decomposes at higher temperature to give a ring-opening product.[4]

In this context, it seems to be valuable to explore a convenient method to introduce alkyl substituent to 3-position of thiophene.

Herein we wish to report the palladium catalyzed alkylation of thiophene at 3-position, which is accomplished by adopting the method recently developed by Heck et al.[5a] and Chalk et al.[5b] for the phenylation of allylic alcohols. That is, in the presence of a catalytic amount of palladium acetate 3-bromothiophene reacted with allylic alcohols to give 3-(3-thienyl)aldehydes and ketones in the excellent to fairly good yields depending on the structure of allylic alcohols (eqs. 1 and 2). As was expected, the reaction of 3-bromothiophene with allylic alcohols was relatively slower than that of 2-bromothiophene.[6]

The reaction conditions and product distributions of the thienylation of

eight kinds of allylic alcohols with 3-bromothiophene are summarized in the Table. By examination of the Table, it becomes evident that there are



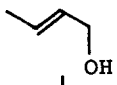
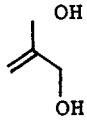
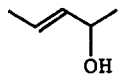
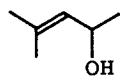
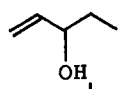
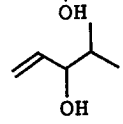
remarkable differences in the product distributions and isolated yields between the reactions which give aldehydes and ketones. The thienylation to give ketones takes place selectively at 3-position of allylic alcohols (except for entry 6) and shows a good agreement between vpc. and isolated yields.

On the other hand, in the reaction giving aldehydes a comparable amount of isomeric mixture is obtained in the low isolated yield. It seems premature at present to give some explanations to the differences in the regioselectivities in these two types of reactions.

Interestingly, alkyl substituents at 1-position of allyl alcohol accelerate the reaction independently to the bulkiness of alkyl groups,[7] though alkyl substituents at 2- or 3-position of allyl alcohol decelerate and in the case of isobutenyl methyl carbinol (entry 6) the reaction becomes unacceptably slow and 3,3'-bithienyl formation becomes the main course of reaction.

The reaction was carried out in the following procedure uniformally; A mixture of 3-bromothiophene (652 mg, 4 mmol), isopropyl vinyl carbinol (600 mg, 6 mmol), Pd $(OAc)_2$ (9.0 mg, 0.04 mmol), NaI (21 mg, 0.14 mmol), $NaHCO_3$ (404 mg, 4.8 mmol), and triphenylphosphine (32 mg, 0.12 mmol) in 3 ml of hexamethylphosphoric triamide was stirred and heated at 130°C under argon atmosphere for 8 hr. The black and almost homogeneous reaction mixture was poured into water and extracted with ether. After drying over magnesium

Table Palladium Catalyzed Thienylation of Allylic Alcohols with 3-Bromothiophene.[a]

Entry	Alcohols	Temp[b] (°C)	Time (hr)	Conv.[c] (%)	Product Distribution[d] (%) 3-(3-Thienyl)[e] carbonyl	2-(3-Thienyl)[e] carbonyl	Bi-thienyl[f]	Others
1		90	19	60	44.6 (25.7)	37.1 (16.3)	trace	18.3[g]
2		120	16	79	51.1 (23.3)	37.4 (17.3)	trace	11.5[g]
3		100	33	24	79.3	——	trace	6.3,[g] 14.4[h] (10.7)
4		120	10	96	90.5 (89.9)	9.5 (7.5)	trace	
5		120	10	86	70.0 (62.4)	18.0 (16.1)	trace	12.0[i] (9.3)
6		125	62	54	33.9 (21.9)	——	40.5 (22.0)	25.6[j] (17.2)
7		120	16	60	87.6 (79.7)	7.1 (6.4)	5.3	
8		130	8	92	87.5 (87.0)	3.1 (3.0)	9.4	

a) The usual scale is 3-bromothiophene (4.0 mmol), allylic alcohol (6.0 mmol), $Pd(OAc)_2$ (0.04 mmol), NaI(0.14 mmol), $NaHCO_3$(4.8 mmol), triphenylphosphine (0.12 mmol) in 3 ml of HMPA. b) Bath temperature controlled within ±0.5°C deviation. c) Based on 3-bromothiophene consumed. d) Determined by the area intensities on vpc (SiDC 550, He). The values in parentheses refer to the isolated yields. e) 3-(3-Thienyl) and 2-(3-thienyl) carbonyl refer to 3-(3-thienyl)ketones or aldehydes and 2-(3-thienyl)ketones or aldehydes, respectively. f) 3,3'-Bithienyl. g) Unspecified product. h) 3-(3-Thienyl)methacrolein. i) 4-(3-Thienyl)-pent-4-en-2-ol. j) 5-(3-Thienyl)-4-methyl-pentan-2-one.

sulfate and evaporation of solvent, the residue was subjected to Kugelrohr distillation to give a colorless oily distillate (160°-170°C/4-7 mmHg, 672 mg; 90 % of the isolated yield based on 3-bromothiophene, consumed), which consisted of 96.7 % of 2-methyl-5-(3-thienyl)pentan-3-one and 3.3 % of 2,4-dimethyl-4-(3-thienyl)butan-3-one.

2-Methyl-5-(3-thienyl)pentan-3-one; $\delta^{TMS}_{CCl_4}$ 1.02 (d, 7 Hz, 6 H), 2.48 (sept, 7 Hz, 1 H), 2.5∿3.0 (A_2B_2 multiplet, 4 H), 6.73∿7.25 (m, 3 H). ν^{max}_{neat} (cm^{-1}) 3100(w), 2970 (m), 1710 (v.s), 1385 (w), 1365 (w), 1080 (m), 1005 (m), 775 (s). m/e (%) 182 (53), 139 (19), 111 (99), 97 (100).

2,4-Dimethyl-4-(3-thienyl)butan-3-one; $\delta^{TMS}_{CCl_4}$ 0.91 (d, 7 Hz, 3 H), 1.03 (d, 7 Hz, 3 H), 1.33 (d, 7 Hz, 3 H), 2.65 (∿sept, 7 Hz, 1 H), 3.96 (quart. 7 Hz, 1 H), 6.80∿7.33 (m, 3 H). ν^{max}_{neat} (cm^{-1}) 3100 (w), 2975 (m), 1712 (v.s) 1385 (w), 1090 (w), 1020 (m), 768 (s). m/e (%) 182 (32), 111 (100), 77 (33), 71 (74).

Some applications to the preparation of physiologically active compounds and full details will be reported in due course.

References and Notes

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4. a) S. Gronowitz and T. Frejd, Acta Chem. Scand., 24, 2656 (1970).
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5. a) J. B. Melpolder and R. F. Heck, J. Org. Chem., 41, 265 (1976).
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7. Ethylvinyl carbinol reacted with 3-bromothiophene much slowly compared with methyl and isopropyl vinyl carbinols, though ethyl vinyl carbinol reacted with 2-bromothiophene in the similar magnitude of reactivities to methyl and isopropyl vinyl carbinols (Unpublished results). Concerning to this irregularity, we cannot give any rationale at present.