Palladium-Catalyzed Furylation and Thienylation of Activated Alkenes with 2-Furoyl Chloride and 2-Thenoyl Chloride

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Received August 23, 1988

2-Furoyl or 2-thenoyl chlorides readily react with activated alkenes in the presence of a tertiary amine and a catalytic amount of palladium(II) acetate to give 2-furylated or 2-thienylated alkenes. Under similar conditions, 2-benzofuroyl chloride undergoes facile alkenylation to produce 2-alkenylated benzofurans. The reaction involves a highly efficient decarbonylation of furoyl or thenoyl-palladium species.

J. Heterocyclic Chem., **26**, 597 (1989).

Heterocyclic aromatics like furan and thiophene are important starting materials for synthesis of various biologically and physiologically active compounds. However, introduction of alkenyl groups to such heterocycles is difficult and no general method for this process is known. On the other hand, the palladium-catalyzed alkenylation of organic halides with alkenes (the Heck reaction) has become an important and general method for the preparation of arylalkenes. The alkene insertion is largely regiospecific, with organic halide adding to the least hindered position of the alkene [1]. In this context, the synthetically useful palladium-catalyzed arylation of alkenes has been extented to furan and thiophene rings [2].

Recently, Blaser and Spencer reported that aroyl chlorides serve as useful precursors to organo-palladium intermediates [3]. For example, benzoyl chloride reacts with ethyl acrylate in the presence of tertiary amine and a catalytic amount of palladium(II) acetate to result in the formation of ethyl cinnamate in moderate yield [3]. We have now successfully applied this modification to the furylation and thienylation of alkenes and wish to report

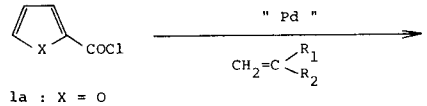
Table 1

Palladium-Catalyzed 2-Furoyl Chloride (**1a**) with Styrene (**2a**) under Various Conditions [a]

Entry	Base [b]	Catalyst (%) [c]	Yield of 2-Styrylfuran (**3a**) after different reaction times, % [d]			
			3 h	4 h	5 h	6 h
1	BDA	$Pd(DBA)_2$ (2)	20	22	23	
2	BDA	$Pd(OAc)_2$ (2)	22	26	26	
3	BDA	Pd/C (2)		11	12	
4	NEM	$Pd(DBA)_2$ (2)		24	28	28
5	NEM	$Pd(OAc)_2$ (1)	24	34	36	36
6	NEM	$Pd(OAc)_2$ (2)	26	38	42	38
7	NEM	$Pd(OAc)_2$ (3)	27	37	42	40
8	NEM	Pd/C (2)		14	16	15
9	EDA	$Pd(OAc)_2$ (2)	20	24	28	27

[a] A mixture of **1a** (10 mmoles), **2a** (20 mmoles), and amine (20 mmoles) was heated in *p*-xylene (40 ml) at 130° in the presence of the palladium catalyst for the time indicated. [b] BDA is *N*-benzyldimethylamine, NEM is *N*-ethylmorpholine, and EDA is ethyldiisopropylamine. [c] Mol % relative to **1a**. [d] Determined by glc.

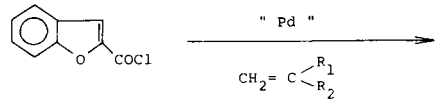
Scheme 1



1a : X = O
1b : X = S

2a : R_1 = Ph, R_2 = H
2b : R_1 = COOEt, R_2 = H
2c : R_1 = COOMe, R_2 = Me
2d : R_1 = COMe, R_2 = H
2e : R_1 = CN, R_2 = H

3a : X = O, R_1 = Ph, R_2 = H
3b : X = O, R_1 = COOEt, R_2 = H
3c : X = O, R_1 = COOMe, R_2 = Me
3d : X = O, R_1 = COMe, R_2 = H
3e : X = O, R_1 = CN, R_2 = H
4a : X = S, R_1 = Ph, R_2 = H
4b : X = S, R_1 = COOEt, R_2 = H
4c : X = S, R_1 = COOMe, R_2 = Me
4d : X = S, R_1 = $COCH_3$, R_2 = H
4e : X = S, R_1 = CN, R_2 = H



5a : R_1 = Ph, R_2 = H
5b : R_1 = COOEt, R_2 = H
5c : R_1 = COOMe, R_2 = Me
5d : R_1 = CN, R_2 = H

Table 2

Products from Reactions of 2-Furoyl **1a**, 2-Thenoyl **1b**, and 2-Benzo[*b*]furoyl **1c** Chlorides with Alkenes **2**

Entry	Reactants	Product	Yield %	Bp (mm/Hg)° or mp°
1	**1a** + **2a**	(*E*)-2-Styrylfuran (**3a**)	42	54-55 (mp) [a]
2	**1a** + **2b**	(*E*)-Ethyl 3-(2-furyl)acrylate (**3b**)	45	121-124 (15) [b]
3	**1a** + **2c**	(*E*)-Methyl 3-(2-furyl)methacrylate (**3c**)	34	110-112 (6) [c]
4	**1a** + **2d**	(*E*)-4-(2-Furyl)-3-buten-2-one (**3d**)	37	102-104 (5) [d]
5	**1a** + **2e**	(*E*)- and (*Z*)-3-(2-Furyl)acrylonitrile (**3e**)	28	[e]
6	**1b** + **2a**	(*E*)-2-Styrylthiophene (**4a**)	38	111-112 (mp) [f]
7	**1b** + **2b**	(*E*)-Ethyl 3-(2-thienyl)acrylate (**4b**)	43	120-122 (3) [g]
8	**1b** + **2c**	(*E*)-Methyl 3-(2-thienyl)methacrylate (**4c**)	35	102-104 (3) [h]
9	**1b** + **2d**	(*E*)-4-(2-Thienyl)-3-buten-2-one (**4d**)	38	35-36 (mp) [i]
10	**1b** + **2e**	(*E*)- and (*Z*)-3-(2-Thienyl)acrylonitrile (**4e**)	30	[j]
11	**1c** + **2a**	(*E*)-2-Styrylbenzo[*b*]furan (**5a**)	45	120-122 (mp) [k]
12	**1c** + **2b**	(*E*)-Ethyl 3-(2-benzo[*b*]furyl)acrylate (**5b**)	46	76-78 (mp) [l]
13	**1c** + **2c**	(*E*)-Methyl 3-(2-benzo[*b*]furyl)methacrylate (**5c**)	38	98-100 (mp) [m]
14	**1c** + **2e**	(*E*)- and (*Z*)-3-(2-benzo[*b*]furyl)acrylonitrile (**5d**)	33	[n]

[a] Ir (potassium bromide): 1600, 1580, 760, 690 (monosub Ar-H), 1630, 960 (*trans* -CH=CH-), 880 cm^{-1} (furan ring); ^{1}H-nmr (deuteriochloroform/TMS): δ 6.48 (d-d, 1H, C_4-H), 6.62 (d-d, 1H, C_3-*H*), 6.88 (d, 1H, J = 17 Hz, -C=C*H*-Ph), 7.18-7.40 ppm (m, 7H, -C*H*=C-Ph + Ar-*H* + C_5-*H*); lit [o] mp 54-55°. [b] Ir (neat): 1720 (-COOEt), 1640, 965 (*trans* -CH=CH-), 880 cm^{-1} (furan ring); ^{1}H-nmr (deuteriochloroform/TMS): δ 1.30 (s, 3H, -CH_3), 4.22 (q, 2H, -CH_2), 6.30-6.60 (m, 3H, -C=C*H*-COOEt + C_3-*H* + C_4-*H*), 7.40 (d, 1H, J = 17 Hz, -C*H*=C-COOEt), 7.49 ppm (d-d, 1H, C_5-*H*); lit [b] bp 118-119° (11 mm/Hg). [c] Ir (neat): 1720 (-COOMe), 1640, 810 (-CH=C-), 880 cm^{-1} (furan ring); ^{1}H-nmr (deuteriochloroform/-TMS): δ 2.01 (s, 3H, -C=C-CH_3), 3.73 (s, 3H, -COOCH_3), 6.42 (d-d, 1H, C_4-*H*), 6.96 (d-d, 1H, C_3-*H*), 7.41 ppm (m, 2H, C_5-*H* + -C*H*=C-COOMe); lit [q] bp 103-104° (4 mm/Hg). [d Ir (neat): 1690 (-CO), 1610, 970 (*trans* -CH=CH-), 880 cm^{-1} (furan ring); ^{1}H-nmr (deuteriochloroform/TMS): δ 2.32 (s, 3H, -COCH_3), 6.50 (d-d, 1H, C_4-*H*), 6.62 (d, 1H, J = 16 Hz, -C=C*H*-CO-), 6.70 (6.70 (d-d, 1H, C_3-H), 7.30 (d, 1H, J = 16 Hz, -C*H*=C-COMe), 7.50 ppm (d-d, 1H, C_5-*H*); lit [r] bp 116° (10 mm/Hg). [e] Mixture of 28% *Z* and 72% *E* isomer which was separated by silica gel column chromatography (benzene-hexane). *Z*-isomer: colorless oil, ir (neat): 2220 (-CN), 1620, 710 (*cis* -CH=CH-), 880 cm^{-1} (furan ring); ^{1}H-nmr (deuteriochloroform/TMS): δ 5.13 (d, 1H, J = 12 Hz, *cis* -C=C*H*-CN), 6.30-7.55 ppm (m, 4H, furan ring protons + -C*H*=C-CN); *Anal.* Calcd. for C_7H_5NO: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.48; H, 4.16; N, 11.70. *E*-isomer; colorless oil: ir (neat): 2220 (-CN), 1620, 970 (*trans* -CH=CH-), 880 cm^{-1} (furan ring); ^{1}H-nmr (deuteriochloroform/TMS): δ 5.60 (d, 1H, J = 17 Hz, *trans* -C=C*H*-CN), 6.36-7.50 ppm (m, 4H, furan ring protons + -C*H*=C-CN). *Anal.* Calcd. for C_7H_5NO: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.50; H, 4.18; N, 11.68. [f] Ir (potassium bromide): 1640, 970 (*trans* -CH=CH-), 1600, 1580, 750, 690 cm^{-1} (monosubt Ar-H); ^{1}H-nmr (deuteriochloroform/TMS): δ 6.93-7.60 ppm (m, 11H, -C*H*=C*H* + Ar-*H* + thiophene ring protons); lit [o] mp 112-13°. [g] Ir (neat): 1720 (-COOEt), 1620, 965 cm^{-1} (*trans* -CH=CH-); ^{1}H-nmr (deuteriochloroform/TMS): δ 2.30 (t, 3H, -CH_3), 4.17 (q, 2H, -CH_2), 6.13 (d, 1H, J = 17 Hz, -C=C*H*-COOEt), 6.95-7.30 (m, 3H, thienyl ring protons), 7.65 ppm (d, 1H, J = 17 Hz, -C*H*=C-COOEt); lit [p] bp 138-139° (6 mm/Hg). [h] Ir (neat): 1720 (-COOMe), 1620, 820 cm^{-1} (-CH=C-); ^{1}H-nmr (deuteriochloroform/TMS): δ 2.27 (d, 3H, -C=C-CH_3), 3.84 (s, 3H, -COOCH_3), 7.06-7.37 (m, 3H, thienyl ring protons), 7.83 ppm (q, 1H, -C*H*=C-COOMe); lit [q] bp 110-112° (6 mm/Hg). [i] Ir (potasium bromide): 1690 (-CO), 1610, 970 cm^{-1} (*trans* -CH=CH-); ^{1}H-nmr (deuteriochloroform/TMS): δ 2.31 (s, 3H, -COCH_3), 6.24 (d, 1H, J = 17 Hz, -C=C*H*-COMe), 7.03-7.38 (m, 3H, thienyl ring protons), 7.45 ppm (d, 1H, J = 17 Hz, -C*H*=C-COMe); lit [q] mp 34-35°. [j] Mixture of 31% *Z* and 69% *E* isomers which was separated by silica gel column chromatography (benzene-hexane 1:2); *Z*-isomers: colorless oil, ir (neat): 2220 (-CN), 1630, 810 cm^{-1} (*cis* -CH=CH-); ^{1}H-nmr (deuteriochloroform/TMS): δ 5.42 (d, 1H, J = 12 Hz, *cis* -C=C*H*-CN), 6.91-7.14 ppm (m, 4H, -C*H*=C-CN + thienyl ring protons). *Anal.* Calcd. for C_7H_5NS: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.14; H, 3.64; N, 10.18; *E*-isomer: colorless oil, ir (neat): 2220 (-CN), 1620, 970 cm^{-1} (*trans* -CH=CH-); ^{1}H-nmr (deuteriochloroform/TMS): δ 5.20 (d, 1H, J = 17 Hz, *trans* -C=C*H*-CN), 6.98-7.58 ppm (m, 4H, -C*H*=C-CN + thienyl ring protons); *Anal.* Calcd. for C_7H_5NS: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.10; H, 3.58; N, 10.23. [k] Ir (potassium bromide): 1630, 960 (*trans* -CH=CH-), 1600, 1580, 760, 730, 690 cm^{-1} (Ar-H); ^{1}H-nmr (deuteriochloroform/TMS): δ 6.62 (s, 1H, furan ring proton), 6.87 (d, 1H, J = 17 Hz, -C=C*H*-Ph), 7.12-7.68 ppm (m, 10H, Ar-*H* + -C*H*=C-Ph); lit [s] mp 121-122°. [l] Ir (potassium bromide): 1720 (-COOEt), 1620, 980 (*trans* -CH=CH-), 1600, 1580, 740 cm^{-1} (*o*-disubst Ar-*H*); ^{1}H-nmr (deuteriochloroform/TMS): δ 1.34 (t, 3H, -CH_3), 4.26 (q, 2H, -CH_2-), 6.54 (s, 1H, J = 16 Hz, -C=C*H*-COOEt), 6.89 (s, 1H, furan ring proton), 7.03-7.58 ppm (m, 5H, Ar-*H* + -C*H*=C-COOEt); lit [s] mp 77-78°, compound **5b** was misnumbered in reference [s]. [m] Ir (potassium bromide): 1720 (-COOMe), 1640, 810 (-CH=C-COOMe), 1600, 1580, 740 cm^{-1} (*o*-disubst Ar-H); ^{1}H-nmr (deuteriochloroform/TMS): δ 2.14 (s, 3H, -C=C-CH_3), 3.82 (s, 3H, -COOCH_3), 6.68 (s, 1H, furan ring proton), 7.20-7.78 ppm (m, 5H, Ar-*H* + -C*H*=C-COOMe); lit [s] mp 99-100°, compound **5c** was misnumbered in reference [s]. [n] Mixture of 33% *Z* and 67% *E* isomers which was separated by silica gel column chromatography (benzene-hexane 1:3); *Z*-isomer, mp 88-90°, ir (potassium bromide): 2220 (-CN), 1620, 810 (*cis* -CH=CH-), 1600, 1580, 750 cm^{-1} (*o*-disubt Ar-*H*); ^{1}H nmr (deuteriochloroform/TMS): δ 5.52 (d, 1H, J = 12 Hz, -C=C*H*-CN), 7.18-7.52 ppm (m, 5H, Ar-*H* + -C*H*=C-CN), lit [t] mp 89-90°; *E*-isomer, mp 101-102°; ir (potassium bromide): 2220 (-CN), 1620, 970 (*trans* -CH=CH-), 1600, 1580, 740 cm^{-1} (*o*-disubst Ar-H); ^{1}H-nmr (deuteriochloroform/TMS): δ 6.02 (d, 1H, J = 17 Hz, -C=C*H*-CN), 6.90 (s, 1H, furan ring proton), 7.20-7.40 ppm (m, 5H, Ar-*H* + -C*H*=C-CN), lit [t] mp 102-103°. [o] E. J. Seus, *J. Heterocyclic Chem.*, **2**, 318 (1965). [p] C. C. Price and E. A. Dudley, *J. Am. Chem. Soc.*, **78**, 68 (1956). [q] A. Kasahara, T. Izumi, G. Saito, and T. Takeda, *Asahi Garasu Kogyou Gijutsu Shoreikai Kenkyu Hokoku*, **22**, 95 (1973); *Chem. Abstr.*, **81**, 135859e (1974). 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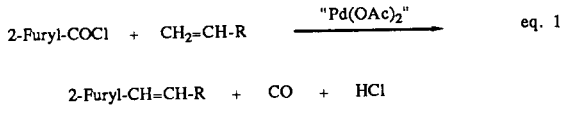
here a simple synthesis of 2-furyl- and 2-thienylalkenes from 2-furoyl chlorides (**1a**), 2-thenoyl chloride (**1b**), and 2-benzo[*b*]furoyl chloride (**1c**).

Results and Discussion.

Initially, as a model system, **1a** was reacted with styrene (**2a**) in the presence of *N*-ethylmorpholine and a catalytic amount of palladium(II) acetate (2 mole %) in *p*-xylene at 130° for 5 hours. Analyses of the resulting mixture revealed that the desired (*E*)-styrylfuran (**3a**) was formed in 42% yield (Table 1, entry 6).



Although the reactions presented in eq 1 gave favorable regioselectivity, the yields were modest and the long reaction time was unsatisfactory from a preparative point of view. As catalyst, bis(dibenzylideneacetone)palladium(0) has also been used successfully. As bases, tri-*n*-butylamine and *N*-benzyldimethylamine can also be used, however, *N*-ethylmorpholine gave the best results (Table 1).

The reaction is also fairly general for activated alkenes such as ethyl acrylate (**2b**), methyl methacrylate (**2c**), methyl vinyl ketone (**2d**), and acrylonitrile (**2e**), with the exception of those derived from **2e**, where up to one third of the product has the *Z*-structure: the furylated isomer at the more hindered position of the alkenes were not observed (Table 2). Previously, Yosida and his co-workers reported formation of 2-(3-oxoalkyl)furan, accompanied by a small amount of 2-(2-oxoalkyl)furan, in a palladium-mediated reaction starting from methyl 5-bromofuroate and allylic alcohols [2b]. In the light of this, the high selectivity for furylation at the terminal carbon atom of alkenes reported here is remarkable. This difference may be due to the creation of an electron-deficient palladium center, under the conditions employed. On the other hand, no vinylation was observed with electron-rich substrates, such as ethyl vinyl ether, vinyl acetate, or isopropenyl acetate.

Under similar conditions, 2-thenoyl chloride (**1b**) and 2-benzo[*b*]furoyl chloride (**1c**) also reacted with activated alkenes to result in the formation of *E*-products. The preparative results of these investigations are summarized in Table 2. Although only moderate yields are obtained, it seems that this new palladium-catalyzed transformation is a useful route for the preparation of 2-alkenylfurans or -thiophenes from very simple and readily available starting materials.

The mechanism of alkenylation of **1** with **2** should proceed as suggested by Blaser and Spencer for aroyl chlorides [3]. This involves oxidative addition of the acid chloride **1** to the palladium species, migration of the furyl (or thienyl) group, and subsequent decarbonylation.

EXPERIMENTAL

Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected.

General Procedure for The Reaction of Furoyl, Thenoyl, and Benzo[*b*]furoyl Chloride with Activated Alkenes.

A mixture of acid chloride **1a**, **1b**, or **1c** (25 mmoles), *N*-ethylmorpholine (3.6 g, 31 mmoles), palladium(II) acetate (0.12 g, 0.54 mmole), and 31 mmoles of alkene in 70 ml of *p*-xylene was heated at 130° for 6 hours in a nitrogen atmosphere. After cooling, the reaction mixture was washed successively with 10% hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, and dried. The solvent was removed at reduced pressure and the products were isolated by column chromatography using silica gel and benzene-hexane (1:1) as eluent. The structures of the products were established by ^{1}H nmr and ir spectra, and by comparison with authentic samples. The results are given in Table 2.

REFERENCES AND NOTES

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