Synthesis of 2,5-Disubstituted Furans via Palladium-Catalyzed Annulation of Alkyl 3-Oxo-6-heptynoates

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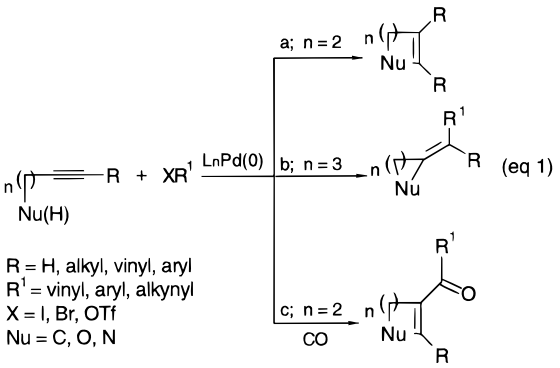
The reaction of the readily available alkyl 3-oxo-6-heptynoates with aryl halides in the presence of K_2CO_3 and catalytic amounts of $Pd(PPh_3)_4$ at 100 °C provides a valuable new route to 2,5-disubstituted furans **3**. Most probably, the furan ring is generated through an annulation reaction promoted by *σ*-arylpalladium complexes generated *in situ* and involving the nucleophilic attack of the ketonic oxygen across the carbon−carbon triple bond coordinated to palladium, followed by the base-catalyzed isomerization of the resultant stereoisomeric 2,5-dialkylidenetetrahydrofuran intermediates **4** and **5**. The reaction is highly chemoselective. No evidence was obtained of carboannulation products. The reaction temperature has proven to be crucial for the success of the methodology. The K_2CO_3:alkyne ratio also affects the reaction outcome. The highest yields of furan derivatives have been obtained with aryl halides containing electron-withdrawing substituents, very likely because the higher acidity of the methylene protons of **4** and **5** favors the isomerization step. Extension of the methodology to methyl 3-oxo-7-substituted-6-heptynoates leads to the formation of 2,5-disubstituted furans containing a branched side chain. The presence of an alkyl substituent on the C-2 of the staring alkyne, however, seems to prevent the isomerization step. Treatment of ethyl 2-methyl-3-oxo-6-heptynoate under our standard conditions produced in fact the 2,5-dialkylidene derivative **5p** in 42% yield, and no evidence of the corresponding furan derivative was attained.

Introduction

The annulation of alkynes containing nucleophiles close to the carbon−carbon triple bond, promoted by *σ*-vinyl-, *σ*-aryl-, and *σ*-alkynylpalladium complexes generated *in situ* from unsaturated triflates or halides, is emerging as a unique, powerful tool for the preparation of functionalized carbo-[1] and heterocycles.[2−8] This reaction, in fact, unlike from most nucleopalladations of alkynes promoted by Pd^{II} species not containing *σ*-carbon−palladium bonds (typically palladium dichloride or diacetate),[9] provides a straightforward approach to the construction of ring systems through the regio- and stereoselective addition of a nucleophile and of a vinyl, aryl, or alkynyl unit across the carbon−carbon triple bond (eqs 1a and 1b). One of its most remarkable features is that it enables the annulation process to combine with a rapid increase in molecular complexity. In this respect, the annulation carried out in the presence of carbon monoxide (leading to the addition of a nucleophile and of an acyl unit across the carbon−carbon triple bond)[6−8] takes on particular significance (eq 1c).



Our success in the utilization of this chemistry with acetylenic building blocks such as pentynoic acids,[2] *o*-alkynyltrifluoroacetanilides,[3,6] 2-propargyl-1,3-dicarbonyl compounds,[4] and *o*-alkynylphenols[7] encouraged us to investigate a possible extension to alkyl 3-oxo-6-heptynoates **1** in order to develop a new synthesis of 2,5-disubstituted furans **3** (eq 2). On the other hand, furan derivatives constitute one of the most important classes of heteroaromatic compounds. They are widely diffused among natural substances[10] and important pharmaceu-

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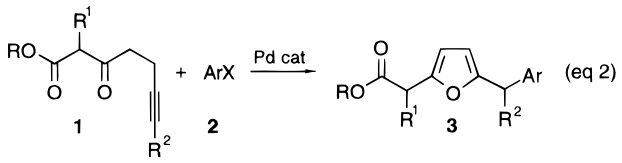


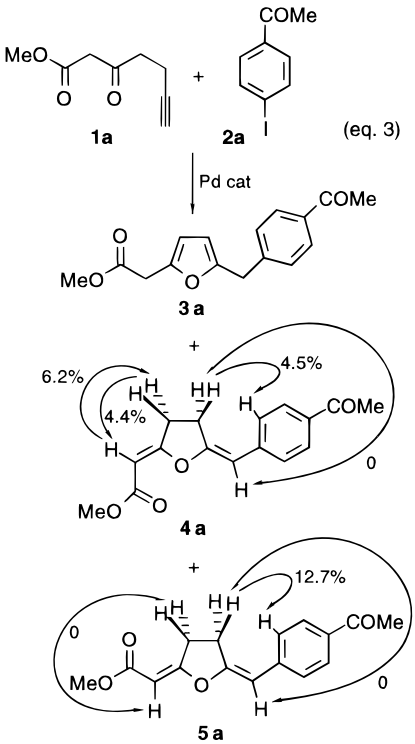
R = Me, Et; R^1 = H, alkyl; R^2 = H, aryl
Ar = aryl, heteroaryl; X = Br, I

ticals.[11] Additionally, polysubstituted furans serve as useful building blocks in organic synthesis.[12] This justifies the continued, considerable effort in the development of novel approaches to this class of compounds,[13] particularly when they use readily available starting materials, accommodate considerable functionalities, and are simple to carry out.

Hereafter we report the result of this study.

Results and Discussion

Methyl 2-oxo-6-heptynoate **1a** (R = Me; $R^1 = R^2 = H$) was used as the model starting alkyne. It was prepared in 70% yield through a one-pot procedure based on the acylation of Meldrum's acid with 4-pentynoic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine, followed by the methanolysis of the resultant crude 5-acyl derivative of Meldrum's acid. On the basis of the results obtained in our previous work, we initially examined the reaction of **1a** with *p*-acetylphenyl iodide **2a** in the presence of K_2CO_3 (5 equiv) and $Pd(PPh_3)_4$ (0.05 equiv) in DMF at 60 °C for 2 h (eq 3).



Under these conditions the 2,5-disubstituted furan derivative **3a** was isolated in a sparing 19% yield along with the stereoisomeric 2,5-dialkylidenetetrahydrofuran derivatives **4a** (38%) and **5a** (17%) (Table 1, entry 1). The stereochemistry of **4a** and **5a** was determined by NOE difference studies. Some of the significant NOE effects are quoted in the eq 3. As **4a** and **5a** were converted into **3a** (50% yield and almost quantitative yield, respectively) on treatment with K_2CO_3 in DMF at 60 °C for 1 h in the absence of palladium catalyst, suggesting that **3a** is generated from **4a** and **5a** through a base-catalyzed isomerization, the reaction of **1a** with **2a** was repeated [$Pd(PPh_3)_4$, K_2CO_3, DMF, 60 °C] prolonging the reaction time to 5 h as to favor the isomerization step. Although significant amounts of **4a** (20%) and **5a** (6%) were still obtained, the furan derivative **3a** was isolated in good yield (66%) (Table 1, entry 2).

Table 1. Solvents, Reaction Time, and Reaction Temperature in the Palladium-Catalyzed Annulation of Methyl 3-Oxo-6-heptynoate (1a) with *p*-Acetylphenyl Iodide (2a)[a]

entry	solvent	reaction temp (°C)	reaction time(h)	yield (%) of **3a**[b]	yield (%) of **4a**[b]	yield (%) of **5a**[b]
1	DMF	60	2	19	38	17
2	DMF	60	5	66	20	6
3	DMF	60	15	40	–	–
4	DMF[c]	60	15	54	–	–
5	DMSO[c]	60	15	40	9	–
6	MeCN[c]	60	15	28	54	12
7	DMF	80	6.5	59	–	–
8	DMF	100	3	67	–	–
9	DMF	100[d]	3	76	–	–

[a] Unless otherwise stated, reactions were carried out under an argon atmosphere using the following molar ratios: **1a**:**2a**:K_2CO_3:$Pd(PPh_3)_4$ = 1.2:1.0:5:0.05. [b] Yields are for pure isolated products. [c] Anhydrous. [d] **1a**:**2a**:K_2CO_3:$Pd(PPh_3)_4$ = 1.5:1.0:1.5:0.05.

Unfortunately, apart from *m*-nitrophenyl iodide (Table 2, entry 15), a variety of aryl halides failed to give the corresponding 2,5-disubstituted furans in satisfactory yield under these conditions. The intermediates **4** and **5** were always isolated in significant amount or as the main products (Table 2, entries 3, 9, 11, 13, 21, 23). Further extension of the reaction time (to 15 h) to bring the isomerization process to an end resulted in the isolation of **3a** in lower yield (Table 1, entry 3), most probably because of the instability of the furan derivative. This view seems to be supported by the recovery of **3a** in only 36% yield when it was subjected to reaction conditions in the absence of the palladium catalyst for 7.5 h. The use of anhydrous DMF, DMSO, and MeCN did not produce better results (Table 1, entries 4, 5, and 6).

A simple solution to the problem was found by increasing the reaction temperature to 100 °C and decreasing

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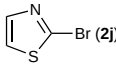
Table 2. Palladium-Catalyzed Annulation of Aryl Halides 2 with Methyl 3-Oxo-6-heptynoate (1a)[a]

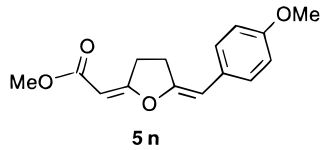
entry	aryl halide **2**	reaction temp (°C)	reaction time (h)	yield (%) of **3**[b]	yield (%) of **4**[b]	yield (%) of **5**[b]
1	*m*-F_3C-C_6H_4-I (**2b**)	100[c]	5.5	87	–	–
2	*m*-F_3C-C_6H_4-I (**2b**)	80[c]	20	76	–	–
3	*m*-F_3C-C_6H_4-I (**2b**)	60[d]	5.0	47	6	21
4	*p*-OHC-C_6H_4-Br (**2c**)	100[c]	1.75	57	–	–
5	*p*-OHC-C_6H_4-Br (**2c**)	60[d]	5.5	38	–	–
6	*m*-OHC-C_6H_4-Br (**2d**)	100[c]	5.0	43	–	–
7	*m*-OHC-C_6H_4-Br (**2d**)	60[d]	2.5	–	–	–
8	*m*-MeCO-C_6H_4-Br (**2e**)	100[c]	3.5	89	–	–
9	*m*-MeCO-C_6H_4-Br (**2e**)	60[d]	4.5	8	22	49
10	*p*-MeOOC-C_6H_4-I (**2f**)	100[c]	5.0	80	–	–
11	*p*-MeOOC-C_6H_4-I (**2f**)	60[d]	7.0	29	–	10
12	*m*-MeOOC-C_6H_4-I (**2g**)	100[c]	5.0	77	–	–
13	*m*-MeOOC-C_6H_4-I (**2g**)	60[d]	7.0	6	25	45
14	*m*-O_2N-C_6H_4-I (**2h**)	100[c]	1.75	82	–	–
15	*m*-O_2N-C_6H_4-I (**2h**)	60[d]	5.0	66	–	–
16	*p*-O_2N-C_6H_4-Br (**2i**)	100[c]	2.5	50	–	–
17	 Br (**2j**)	100[c]	6.0	73	–	–
18	*m*-F-C_6H_4-I (**2k**)	100[c]	5.0	39	14	–
19	*p*-F-C_6H_4-I (**2l**)	100[c]	5.0	12	49	–
20	PhI (**2m**)	100[c]	3.0	9	–	21
21	PhI (**2m**)	60[d]	7.0	–	30	51
22	*p*-MeO-C_6H_4-I (**2n**)	100[c]	6.0	–	25	–
23	*p*-MeO-C_6H_4-I (**2n**)	60[d]	17	–	19	57

[a] Reactions were carried out in DMF under an argon atmosphere. [b] Yields are for pure isolated products. [c] **1a**:**2**:K_2CO_3:Pd$(PPh_3)_4$ = 1.5:1.0:1.5:0.05. [d] **1a**:**2**:K_2CO_3:Pd$(PPh_3)_4$ = 1.2:1.0:5:0.05.

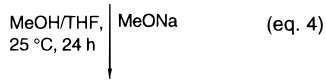
the base:alkyne ratio from 5:1 to 1.5:1. Under these conditions the starting alkyne disappears very quickly, and the isomerization of the addition intermediates **4** and **5** to **3** is faster than the decomposition of the furan derivative. The yield of **3a** increased to 76% in 3 h, and only trace amounts if any of **4a** and **5a** were detected into the reaction mixture (Table 1, entry 7). Entries 7 and 8 (Table 1) illustrate the dominant effect on the reaction outcome of the temperature increase, and entries 8 and 9 (Table 1) illustrate the effect of decreasing the base:alkyne ratio. The study was next extended to include some other aryl halides. The preparative results are summarized in Table 2 (entries 1, 4, 8, 10, 12, 14, 16, 17, 18). The best results have been obtained with aryl halides bearing electron-withdrawing substituents, maybe because the higher acidity of the methylene protons of the 2,5-dialkylidenetetrahydrofuran intermediates favors the isomerization step. In the presence of electron-donating substituents in the aromatic ring, **4** and **5** showed a strong inertness to isomerize, even at 100 °C (Table 2, entries 22 and 23). The employment of stronger bases resulted in the formation of decomposition products. For example, treatment of **5n** with MeONa in an anhydrous 1:2 MeOH/THF mixture at 25 °C for 24 h produced **6n** as the main reaction product (eq 4) and none of the furan derivative was isolated. In the presence of KOBu-*t* (HOBu-*t*/THF 1:6; 60 °C; 3 h) a complex reaction mixture was obtained that was not investigated.

It may be worth mentioning that the organopalladium-promoted annulation has always been found to be fast and efficient, independently of the nature of the aryl halide. The low yields of **4** and **5** reported in Table 2 in the reactions run at 60 °C reflect our efforts to favor the isomerization step by prolonging reaction times. **4** and **5** can be isolated in high yields interrupting the reaction as soon as the annulation step is completed. For example, **4n** and **5n** were isolated in an overall 81% yield after 7 h (Table 2, entry 21), when **3n** was completely, or near, absent from the reaction mixture.

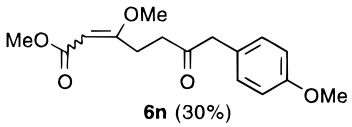
The extension of the procedure to alkyl 3-oxo-7-substituted-6-heptynoates provides an entry into 2,5-disubstituted-furans containing a branched side chain. As an example, exposure of **1b**, readily prepared from **1a** through the palladium-catalyzed coupling with *p*-acetylphenyl iodide, to *m*-carbethoxylphenyl iodide under usual conditions produced the corresponding furan derivative **3o** in high yield (eq 5). The presence of a substituent on the C-2 in the starting alkyne, however, appears to prevent the isomerization step. At least, this is the result we obtained with ethyl 2-methyl-3-oxo-6-heptynoate **1c**[14] (eq 6).



5n



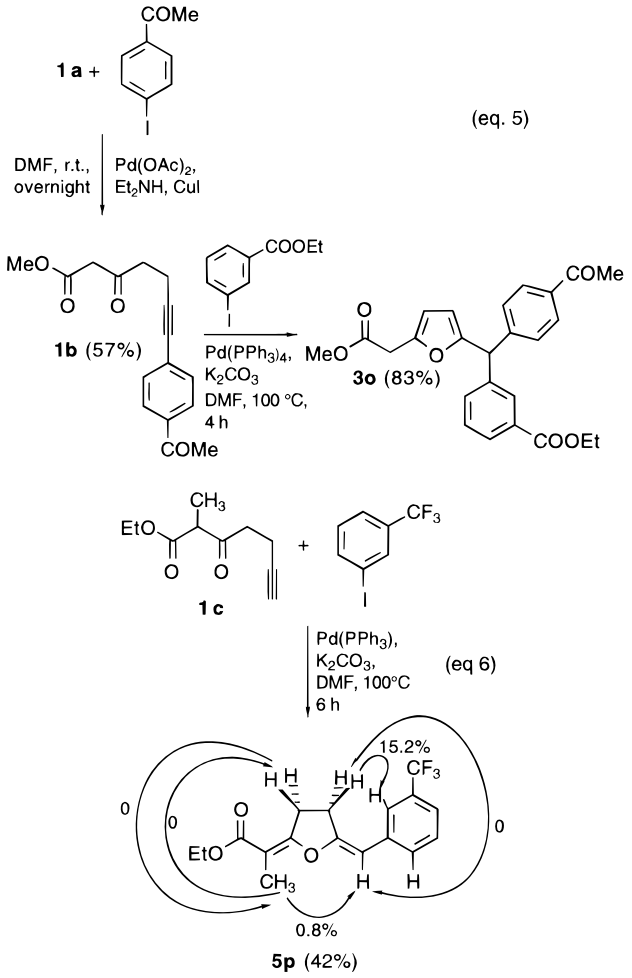
(eq. 4)



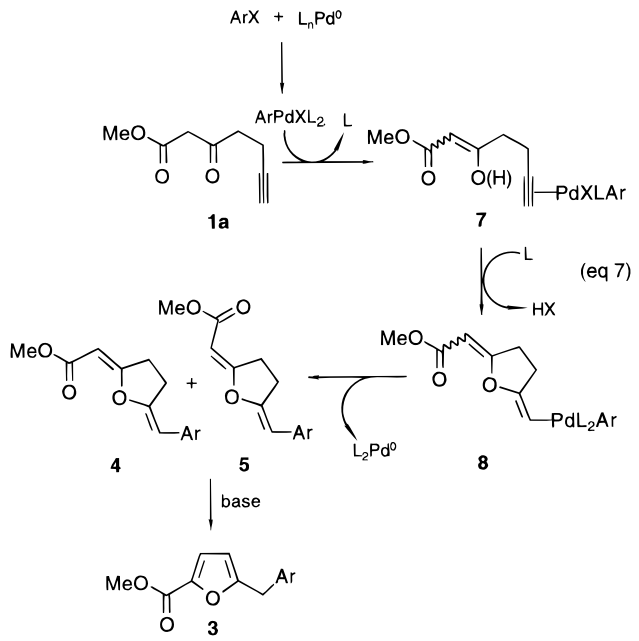
6n (30%)

Mechanistically, the present reaction may proceed through the following basic steps (illustrated by **1a** in eq 7): (a) formation of the η^2-palladium complex **7**, (b) generation of the σ-vinylpalladium complex **8** via regioselective *trans* addition of the oxygen and palladium across the carbon−carbon triple bond (no evidence was attained of annulation products arising from the nucleophilic attack of the carbon terminus of the putative enolate intermediate), (c) reductive elimination of Pd^0 species to give the stereoisomers **4** and **5**, and (d)

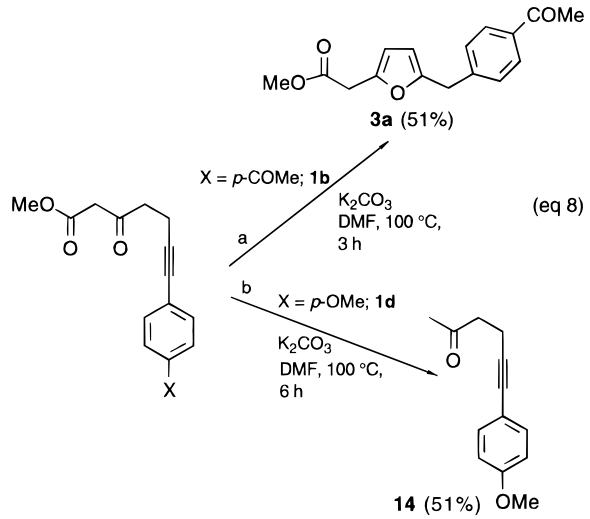
(14) **1c** was prepared through a malonate method involving the preparation of a magnesium-malonate complex from the potassium salt of the malonate monoethyl ester, followed by its reaction with the imidazolide of 4-pentynoic acid prepared *in situ* from pentynoic acid and carbonyl diimidazolide: Clay, R. C.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290.

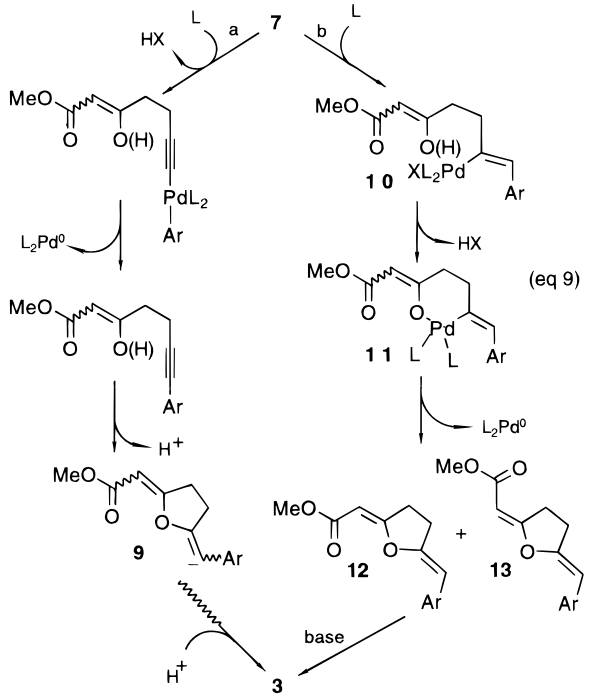


isomerization of **4** and **5** to **3** (very likely through a base-catalyzed process; **4a** was recovered essentially unchanged when warmed at 60 °C in DMF for 6 h in the absence of base).



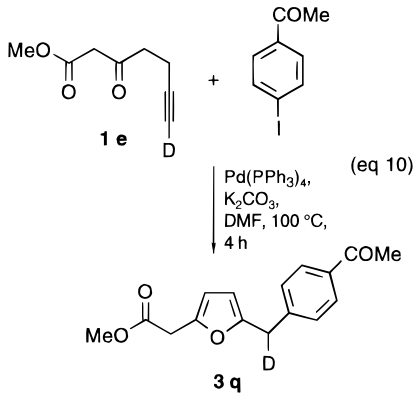
In effect, the isolation of the furan derivative **3a** in 51% yield upon treatment of **1b** under our standard conditions, omitting the aryl halide and the palladium catalyst (eq 8a), appears to suggest that an alternative mechanism might be operating. Compound **3a** could in fact arise from the base-catalyzed annulation of the coupling intermediate possibly generated from the η^2-acetylene-palladium complex **7** (eq 9a). This pathway, however, seems to be flawed by the absence of the arylalkyne **1b** as intermediate in the palladium-catalyzed reaction of **1a** with **2a** (none of **1b** was in fact discernible monitoring the reaction) and by the lower reaction rate for the base-catalyzed annulation of **1b** (compare eq 8a with Table 1, entry 9). In addition, no cyclization derivative (**3**, **4**, or **5**) was isolated when methyl 3-oxo-7-(*p*-methoxyphenyl)-6-heptynoate (**1d**) was treated with K_2CO_3 in the absence





of palladium. The main reaction product was the ketone **14** (51% yield) resulting from the decarboxylation of **1d**. The starting alkyne was recovered in 25% yield (eq 8b). These results suggest that the efficiency of the base-catalyzed annulation depends strongly on the nature of the substituent on the aromatic ring. Conversely, annulation promoted by σ-arylpalladium complexes is a very efficient reaction, both with electron-donating and electron-withdrawing substituents. The formation of **3o** in the reaction of *m*-carbethoxyphenyl iodide with **1b**, in which the absence of a C_{sp}−H bond prevents any coupling reaction (eq 5), also argues in favor of an annulation reaction promoted by σ-arylpalladium complexes.

The most convincing evidence confirming the validity of a mechanism producing the furan ring without requiring the cleavage of the C_{sp}−H bond (eq 7) and ruling out the possible formation of **3** through a coupling/cyclization sequence (eq 9a) is the isolation of the deuterio derivative **3q** from the reaction of methyl 3-oxo-7-deuterio-6-heptynoate **1e** with *p*-acetylphenyl iodide (eq 10).



Another possible mechanism for the generation of **3**, which would meet the requirement of producing the furan ring without involving the C_{sp}−H bond, might be considered (eq 9b). This involves the (a) *syn* addition of the σ-arylpalladium complex to the carbon−carbon triple bond to give the σ-vinylpalladium complex **10**, (b) nucleophilic attack of the oxygen on the palladium atom to give the six-membered ring, oxygen-containing palladacycle **11**, (c) reductive elimination of Pd^0 species, and (d) base-catalyzed isomerization of the stereoisomeric alkylidene furan derivatives **12** and **13**. This mechanism, however, may be safely excluded because it predicts the wrong stereochemistry for the carbon−carbon double bond bearing the added aryl unit in the intermediates **12** and **13**.

In conclusion, we have shown that the present synthesis of 2,5-disubstituted furans from readily available alkyl 3-oxo-6-heptynoates and 3-oxo-7-substituted-6-heptynoates is quite efficient with aryl halides bearing electron-withdrawing substituents. The poor results achieved with aryl halides bearing electron-donating substituents depends on the requirements of the base-catalyzed isomerization step (the annulation step produces good results with aryl halides bearing both electron-withdrawing and electron-donating substituents). In spite of this limitation, the reaction can accommodate a variety of considerable functionalities, amenable of further functionalization, and may represent a useful method for the preparation of this class of compounds.

Experimental Section

Melting points were determined with a Büchi apparatus and are uncorrected. All of the starting materials, catalysts, ligands, bases, and solvents (anhydrous solvents included) are commercially available and were used as purchased, without further purification. Reaction products were purified on axially compressed columns (packed with SiO_2, 25−40 nm, Macherey Nagel) connected to a Gilson solvent delivery system and to a Gilson refractive index detector and eluting with *n*-hexane/EtOAc mixtures. ^{1}H NMR spectra ($CDCl_3$, unless otherwise stated; TMS as internal standard) were recorded at 200 MHz. ^{13}C NMR spectra were recorded at 50.3 MHz.

One-Flask Preparation of Methyl 3-Oxo-6-heptynoate (1a) from 4-Pentynoic Acid. A solution of dicyclohexylcarbodiimide (2.518 g, 12.23 mmol in 5 mL of CH_2Cl_2) was added dropwise, at 0 °C, to a solution of 4-pentynoic acid (1.000 g, 10.19 mmol), Meldrum's acid (2.203 g, 15.28 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (1.870 g, 15.28 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 24 h. Then the reaction mixture was filtered and washed five times with 30 mL of CH_2Cl_2. The organic phase was exctracted with 2 N HCl, washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was diluted with 15 mL of methanol and refluxed overnight. The solution was concentrated under reduced pressure, and the residue was chromatographed on silica gel, eluting with *n*-hexane/EtOAc (80/20 v/v) to afford **1a** (1.099 g, 70% yield): mp oil; IR (liquid film) 3288, 2123, 1745, 1721 cm^{-1}; ^{1}H NMR δ 3.75 (s, 3H), 3.50 (s, 2H), 2.82 (t, J = 6.9 Hz, 2H), 2.47 (dt, J = 6.9 Hz, J = 2.6 Hz, 2H), 1.99 (t, J = 2.6 Hz, 1H); ^{13}C NMR δ 200.52, 167.35, 82.50, 69.04, 52.40, 48.88, 41.57, 12.76; MS (CI) *m*/*e* (relative intensity): 155 (M^+ + 1, 100). Anal. Calcd for $C_8H_{10}O_3$: C, 62.31; H, 6.54. Found: C, 62.44; H, 6.55.

Typical Procedure for the Preparation of 2,5-Disubstituted Furans 3 from Methyl 3-Oxo-6-heptynoate (1a). 2-(Carbomethoxymethyl)-5-((*p*-acetylphenyl)methyl)-furan (3a). To a stirred solution of methyl 3-oxo-6-heptynoate (**1a**) (0.113 g, 0.73 mmol) and *p*-acetylphenyl iodide (**2a**) (0.120 g, 0.49 mmol) in DMF (3 mL) were added K_2CO_3 (0.101 g, 0.73 mmol) and $Pd(PPh_3)_4$ (0.028 g, 0.02 mmol). The reaction mixture was stirred at 100 °C for 3 h under argon. After cooling the mixture, ethyl acetate was added, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with *n*-hexane/EtOAc (85/15 v/v) to afford **3a** (0.151 g, 76% yield): mp oil; IR (liquid film) 1743, 1684 cm^{-1}; ^{1}H NMR δ 7.91 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 6.14 (d, J = 3.1 Hz, 1H), 5.96 (d, J = 3.1 Hz, 1H), 4.00 (s, 2H), 3.72 (s, 3H), 3.64 (s, 2H), 2.59 (s, 3H); ^{13}C NMR δ 197.83, 169.95, 152.89, 146.79, 143.70, 135.51, 128.87, 128.61, 108.84, 107.71, 52.24, 34.39, 33.90, 26.61; MS *m*/*e* (relative intensity) 272 (M^+, 53), 213 (100), 147 (63). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93. Found: C, 70.65; H, 5.91.

2(*Z*)-(Carbomethoxymethylidene)-5(*E*)-((*p*-acetylphenyl)methylidene)-3,4-tetrahydrofuran (4a): mp 178−180 °C; IR (KBr) 1708, 1683 cm^{-1}; ^{1}H NMR δ 7.84 (d, J = 10.0 Hz, 2H), 7.22 (d, J = 10.0 Hz, 2H), 6.34 (bs, 1H), 4.90 (t, J = 1.8 Hz), 3.67 (s, 3H), 2.91 (bs, 4H), 2.53 (s, 3H); ^{13}C NMR δ 197.26, 166.90, 165.15, 158.93, 140.25, 134.39, 128.57, 127.22, 104.75, 90.75, 50.90, 29.81, 26.39, 25.12; MS *m*/*e* (relative intensity) 272 (M^+, 100), 257 (61), 213 (69). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93. Found: C, 70.66; H, 5.95.

2(*E*)-(Carbomethoxymethylidene)-5(*E*)-((*p*-acetylphenyl)methylidene)-3,4-tetrahydrofuran (5a): mp 153−155 °C; IR (KBr) 1708, 1679 cm^{-1}; ^{1}H NMR δ 7.94 (d, J = 12.0 Hz, 2H), 7.27 (d, J = 12.0 Hz, 2H), 6.27 (t, J = 1.8 Hz, 1H), 5.56 (t, J = 1.8 Hz, 1H), 3.74 (s, 3H), 3.41 (td, J = 7.5 Hz, J = 1.8 Hz, 2H), 3.06 (td, J = 7.5 Hz, J = 1.8 Hz, 2H), 2.61 (s, 3H); ^{13}C NMR δ 197.43, 172.28, 168.20, 158.15, 140.49, 134.59, 128.80, 127.30, 104.15, 92.52, 51.11, 28.87, 26.55, 26.19; MS *m*/*e* (relative intensity) 272 (M^+, 100), 257 (79), 213 (33). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93. Found: C, 70.47; H, 5.91.

2(*E*)-(Carbomethoxymethylidene)-5(*E*)-((*p*-methoxyphenyl)methylidene)-3,4-tetrahydrofuran (5n): mp 128−131 °C; IR (KBr) 1700 cm^{-1}; ^{1}H NMR δ 7.14 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.17 (t, J = 1.7 Hz, 1H), 5.50 (t, J = 1.7 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.28 (td, J = 8.1 Hz, J = 1.7 Hz, 2H), 2.94 (td, J = 8.1 Hz, J = 1.7 Hz, 2H); ^{13}C NMR δ 172.93, 168.39, 158.01, 154.39, 128.56, 127.77, 114.11, 104.09, 91.47, 55.28, 50.90, 29.13, 25.42; MS *m*/*e* (relative intensity) 260 (M^+, 100), 221 (21), 121 (17). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.20; H, 6.20. Found: C, 69.31; H, 6.21.

Methyl 3-Methoxy-6-oxo-7-(*p*-methoxyphenyl)-2-heptenoate (6n). A solution of sodium methoxide (0.019 g, 0.35 mmol) in anhydrous MeOH (1 mL) was added at room temperature to a stirred solution of **5n** (0.060 g, 0.23 mmol) in anhydrous THF (1.5 mL). The reaction mixture was stirred at room temperature for 24 h. After cooling the mixture, ethyl acetate was added, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with *n*-hexane/EtOAc (80/20 v/v) to afford **6n** (0.020

g, 30% yield): mp oil; IR (liquid film) 1710 cm^{-1}; ^1H NMR δ 7.12 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6Hz, 2H), 4.98 (s, 1H), 3.79 (s, 3H), 3.65 (s, 3H), 3.64 (s, 2H), 3.02 (t, J = 8.2 Hz, 2H), 2.67 (t, J = 8.2 Hz, 2H); ^{13}C NMR δ 207.24, 174.92, 167.86, 158.69, 130.52, 126.38, 114.18, 90.73, 55.61, 55.33, 50.91, 48.95, 38.91, 26.64; MS *m/e* (relative intensity) 292 (M^+, 8), 143 (30), 121 (100). Anal. Calcd for $C_{16}H_{20}O_5$: C, 66.03; H, 6.94. Found: C, 66.17; H, 6.93.

Preparation of Methyl 3-Oxo-7-(*p*-acetylphenyl)-6-heptynoate (1b). To a stirred solution of **1a** (0.400 g, 2.60 mmol) and Et_2NH (2.7 mL) in DMF (4 mL) were added *p*-acetylphenyl iodide (0.765 g, 3.11 mmol), $Pd(OAc)_2(PPh_3)_2$ (0.039 g, 0.05 mmol), and CuI (0.020 g, 0.10 mmol). The reaction mixture was stirred at room temperature overnight under argon. Ethyl acetate and 2 N HCl were added, and the organic layer was separated, neutralized with a saturated $NaHCO_3$ solution, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc 60/40 v/v) to give **1b** (0.403 g, 57% yield): mp oil; IR (liquid film) 2221, 1737, 1712 cm^{-1}; ^1H NMR δ 7.87 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 3.52 (s, 2H), 2.91 (dt, J = 7.2 Hz, J = 1.5 Hz, 2H), 2.72 (dt, J = 7.2 Hz, J = 1.5 Hz, 2H), 2.58 (s, 3H); ^{13}C NMR δ 197.43, 168.39, 135.96, 131.74, 128.47, 128.21, 91.78, 80.67, 52.52, 49.00, 41.68, 27.82, 26.65, 13.94; MS *m/e* (relative intensity) 272 (M^+, 24), 213 (26), 199 (100). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93. Found: C, 70.66; H, 5.95.

Methyl 3-Oxo-7-(*p*-methoxyphenyl)-6-heptynoate (1d): mp oil; IR (liquid film) 1745, 1721 cm^{-1}; ^1H NMR δ 7.31 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.51 (s, 2H), 2.86 (dt, J = 6.6 Hz, J = 1.1 Hz, 2H), 2.67 (dt, J = 6.6 Hz, J = 1.1 Hz, 2H); ^{13}C NMR δ 201.01, 167.54, 159.33, 133.03, 115.64, 113.95, 86.44, 81.11, 55.36, 52.55, 49.12, 42.15, 14.01; MS *m/e* (relative intensity) 260 (M^+, 23), 187 (100), 145 (75). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.20; H, 6.20. Found: C, 69.31; H, 6.18.

Preparation of 2-(Carbomethoxymethyl)-5-(*p*-acetylphenyl)-5-((*m*-carbethoxyphenyl)methyl)furan (3o). To a stirred solution of **1b** (0.177 g, 0.65 mmol) and *m*-carbethoxyphenyl iodide (0.120 g, 0.43 mmol) in DMF (3 mL) were added K_2CO_3 (0.090 g, 0.65 mmol) and $Pd(PPh_3)_4$ (0.025 g, 0.02 mmol). The reaction mixture was stirred at 100 °C for 4 h under argon. After cooling the mixture, ethyl acetate was added, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with *n*-hexane/EtOAc (60/40 v/v) to afford **3o** (0.151 g, 83% yield): mp oil; IR (liquid film) 1745, 1720 cm^{-1}; ^1H NMR δ 8.00−7.87 (m, 4H), 7.36 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 6.15 (d, J = 3.1 Hz, 1H), 5.83 (d, J = 3.1 Hz, 1H), 5.51 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.69 (s, 3H), 3.64 (s, 2H), 2.57 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 197.80, 169.85, 166.43, 154.60, 147.65, 146.68, 161.33, 135.89, 133.15, 130.93, 129.95, 129.02, 128.78, 128.70, 128.35, 109.99, 108.81, 61.12, 52.28, 50.60, 33.98, 26.66, 14.34; MS *m/e* (relative intensity) 420 (M^+, 22), 388 (100), 361 (38), 271 (36). Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.40; H, 5.76. Found: C, 71.31; H, 5.78.

Base-Catalyzed Annulation of Methyl 3-Oxo-7-(*p*-acetylphenyl)-6-heptynoate (1b). To a stirred solution of **1b** (0.100 g, 0.37 mmol) in DMF (3 mL) was added K_2CO_3 (0.051 g, 0.37 mmol). The reaction mixture was stirred at 100 °C for 3 h under argon. After cooling the mixture, ethyl acetate was added, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with *n*-hexane/ethyl acetate (85/15 v/v) to afford **3a** (0.051 g, 51% yield).

6-(*p*-Methoxyphenyl)hex-5-yn-2-one (14): mp oil; IR (Nujol) 1713 cm^{-1}; ^1H NMR δ 7.31 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 2.76−2.60 (m, 4H), 2.18 (s, 3H); ^{13}C NMR δ 206.81, 189.14, 132.87, 115.66, 113.79, 86.87, 80.68, 55.20, 42.57, 29.90, 13.97; MS *m/e* (relative intensity) 202 (M^+, 53), 187 (100), 145 (71). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.19; H, 6.98. Found: C, 77.30; H, 6.96.

Preparation of Ethyl 2-Methyl-3-oxo-6-heptynoate (1c). Solution A: 1,1′-carbonyldiimidazole (1.134 g, 10.74 mmol) was added to a solution of 4-pentynoic acid (0.500 g, 5.10 mmol) in anhydrous CH_3CN (5 mL). The reaction mixture was stirred at room temperature until the end of CO_2 development. Solution B: Et_3N (2.4 mL) and $MgCl_2$ (1.214 g, 12.76 mmol) were added to a solution of ethyl 2-methylmalonate potassium salt (1.939 g, 10.71 mmol) in anhydrous MeCN (5 mL). The reaction mixture was stirred at room temperature for 2 h. The solution A was added dropwise to the solution B maintained under stirring at room temperature. The reaction mixture was stirred overnight. Then, 6 N HCl (20 mL) was added and the reaction mixture was stirred for 1 h. Ethyl acetate and saturated $NaHCO_3$ were added, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with *n*-hexane/EtOAc (70/30 v/v) to afford **1c** (0.740 g, 80% yield): mp oil; IR (liquid film) 3279, 2123, 1737, 1721 cm^{-1}; ^1H NMR δ 4.20 (q, J = 7.3 Hz, 2H), 3.54 (q, J = 7.2 Hz, 1H), 2.89 (dt, J = 17.6 Hz, J = 6.7 Hz, 1H), 2.76 (dt, J = 17.6 Hz, J = 6.7 Hz, 1H), 2.48 (dt, J = 6.7 Hz, J = 1.7 Hz, 2H), 1.96 (t, J = 1.7 Hz, 1H), 1.36 (d, J = 7.2 Hz, 3H), 1.28 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 203.70, 170.31, 82.74, 68.87, 61.51, 52.77, 40.14, 14.11, 12.94, 12.64; MS (CI) *m/e* (relative intensity) (183 (M^+ + 1, 100). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.90; H, 7.75. Found: C, 65.81; H, 7.74.

2(*E*)-(1-Carbethoxypropylidene)-5(*E*)-((*m*-(trifluoromethyl)phenyl)methylidene)-3,4-tetrahydrofuran (5p): mp 89−91 °C; IR (nujol) 1704 cm^{-1}; ^1H NMR δ 7.55−7.30 (m, 4H), 6.27 (t, J = 2.1 Hz, 1H), 4.19 (q, J = 7.0 Hz, 2H), 3.29 (tq, J = 7.0 Hz, J = 1.6 Hz, 2H), 3.01 (td, J = 7.0 Hz, J = 2.1 Hz, 2H), 1.91 (t, J = 1.6 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 160.70, 165.80, 157.62, 136.60, 132.64, 131.22, 130.80 (q, J = 32.4 Hz), 130.37, 128.94, 124.10 (q, J = 272.8), 123.72 (q, J = 3.7 Hz), 122.32 (q, J = 3.7 Hz),102.75, 100.88, 61.05, 29.37, 26.54, 14.40, 11.53; MS *m/e* (relative intensity) 326 (M^+, 100), 281 (34), 252 (37). Anal. Calcd for $C_{17}H_{17}F_3O_3$: C, 62.56; H, 5.25. Found: C, 62.64; H, 5.23.

Preparation of Methyl 3-Oxo-7-deuterio-6-heptynoate (1e). To a stirred solution of methyl 3-oxo-6-heptynoate (**1a**) (0.500 g, 3.25 mmol) in anhydrous THF (4 mL) at −72 °C was added dropwise a solution of lithium diisopropylamide (2 M) in THF (8.1 mL); the reaction mixture was warmed at 0 °C for 45 min. Then the solution was cooled at −72 °C, and D_2O (2 mL) was added. Then the reaction mixture was warmed at room temperature for 1 h. Ethyl acetate and 2 N HCl were added, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with *n*-hexane/EtOAc (80/20 v/v) to afford the deuteriated and the undeuteriated product in 85% yield (0.378 g).

The methyl 3-oxo-6-heptynoate % D was determined by ^1H NMR and MS. From these analyses an abundance of D of approximately 76% was calculated.

2-(1-Carbomethoxy-1-deuteriomethylidene)-5-((*p*-acetylphenyl)methyl)furan (3q): mp oil; IR (liquid film) 1745, 1678 cm^{-1}; ^1H NMR δ 7.85 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.09 (d, J = 3.1 Hz, 1H), 5.92 (d, J = 3.1 Hz, 1H), 3.95 (s, 1.25H), 3.66 (s, 3H), 3.60 (s, 2H), 2.53 (s, 3H); ^{13}C NMR δ 197.82, 169.96, 152.92, 146.84, 143.73, 135.56, 128.89, 128.63, 108.86, 107.73, 52.26, 33.92, 33.90 (t, J = 19.6 Hz), 26.62; MS *m/e* (relative intensity) 273 (M^+, 58), 214 (100). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93. Found: C, 70.41; H, 5.94.

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Supporting Information Available: Characterization data for **3b**−**m** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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