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A Facile and Practical Process for the Synthesis of Polysubstituted Furans from Alkynes Using Atmospheric Oxygen as a Terminal Oxidant

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We present here a facile and practical procedure for the synthesis of tetrasubstituted furans from alkynes catalyzed by palladium acetate together with cupric acetate in acetic acid, using atmospheric oxygen as a terminal oxidant. Various internal aromatic alkynes afforded the target furans in satisfactory yield.

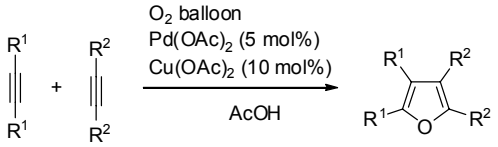
Keywords furan, alkyne, palladium, copper, oxygen

Introduction

From the viewpoint of green and sustainable chemistry, molecular oxygen is reputed to be an ideal oxidant due to its natural, inexpensive, and environmentally friendly characters, and therefore offers attractive academic and industrial prospects.[1] On the other hand, transition-metal catalyzed reactions are considered as the most attractive tools to construct heterocycles because they can regioselectively produce highly functionalized heterocyclic motifs from readily available feedstock under mild conditions.[2] Therefore, transition-metal-catalyzed transformations with molecular oxygen as a terminal oxidant are more attractive by combining the advantages of both molecular oxygen as an oxidant and the catalysis of transition-metal.

Furan derivatives, as featured moieties, occur in a number of plants and marine organism, such as furodysinin,[3] kallolide,[4] pinguisone,[5] and methyl vouacapenate.[6] These heterocyclic molecules also have a wide range of industrial applications in pharmaceuticals, fragrances, insecticides, dyes and so on.[7] Moreover, functionalized furans are widely employed as versatile building blocks to fabricate complicated natural products, and as privileged scaffolds in drug discovery due to their diverse biological activities.[8] Although a number of strategies have been developed for the synthesis of furan derivatives,[9] the development of novel procedures for the synthesis of highly functionalized furans remains appealing to organic chemist.

It is known that the oxidation of alkynes could afford furans under the catalysis of palladium.[10] The reported procedures could be conducted in an autoclave,[11] or in fluorous media,[12] using molecular oxygen as an oxidant. Although these processes could provide an alternative approach to furan derivatives, they are less practical because of operability and cost. We present herein that tetrasubstituted furan compounds could be synthesized from alkynes under the catalysis of $Pd(OAc)_2$ and $Cu(OAc)_2$ using atmospheric oxygen as a terminal oxidant in acetic acid (Eq. 1). This transformation could be performed in common solvent connected to an oxygen balloon, which established a more practical procedure for furan synthesis.



(1)

Results and Discussion

Our studies began by optimizing the reaction conditions for the synthesis of tetrasubstituted furans, choosing diphenylethyne as model substrate. The results are tabulated in Table 1. When this reaction was carried out in *N,N*-dimethylacetamide (DMA) at 100 ℃ for 12 h, using 5 mol% $Pd(OAc)_2$ as the catalyst, in the presence of 20 mol% $ZnCl_2$, under 101 kPa of pressure of dioxygen, no desired tetraphenyl furan was obtained (Table 1, Entry 1). The investigation on the effect of acid suggested that Brønsted acids could promote this reaction against Lewis acids (Table 1, Entries 2—5). The possible reason was that the recycling of catalyst necessitated proton under normal pressure. After screening common polar solvents, AcOH was found to be the best medium, which acted as proton source as well (Table 1, Entries

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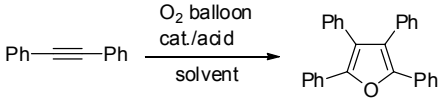
6—8). To our delight, the addition of cupric salt greatly improved the oxidative cyclization reaction and we found that $Cu(OAc)_2$ was a superior co-catalyst (Table 1, Entries 9—11). As shown in Table 1, the yield of target tetraphenylfuran decreased when the transformation proceeded under the catalysis of other palladium agent such as $PdCl_2$, $Pd(NCMe)_2Cl_2$, $Pd_2(dba)_3$ (Table 1, Entries 12—14).

Table 1 Optimizing the reaction conditions for the synthesis of furans from alkynes[a]

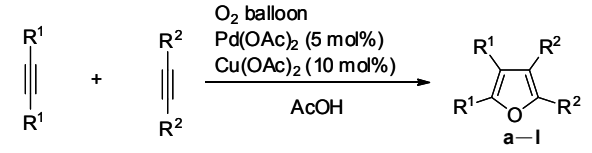


Entry	Catalyst	Co-catalyst	Acid	Solvent	Yield[b]/%
1	$Pd(OAc)_2$	—	$ZnCl_2$	DMA	N.P.
2	$Pd(OAc)_2$	—	$Zn(OTf)_2$	DMA	N. P.
3	$Pd(OAc)_2$	—	HCl	DMA	17
4	$Pd(OAc)_2$	—	PTSA[d]	DMA	25
5	$Pd(OAc)_2$	—	AcOH	DMA	26
6	$Pd(OAc)_2$	—	—	AcOH	39
7	$Pd(OAc)_2$	—	AcOH	DMF	25
8	$Pd(OAc)_2$	—	AcOH	DMSO	20
9[c]	$Pd(OAc)_2$	$CuCl_2$	—	AcOH	87
10[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	—	AcOH	95
11[c]	$Pd(OAc)_2$	$Cu(OTf)_2$	—	AcOH	95
12[c]	$PdCl_2$	$Cu(OAc)_2$	—	AcOH	57
13[c]	$Pd(NCMe)_2Cl_2$	$Cu(OAc)_2$	—	AcOH	55
14[c]	$Pd_2(dba)_3$	$Cu(OAc)_2$	—	AcOH	23

[a] Reaction conditions: 1,2-diphenylacetylene (1.0 mmol), catalyst (5 mol%), acid (20 mol%), solvent (2 mL), 100 ℃, O_2 balloon (101 kPa), 12 h. [b] Determined by GC. [c] Co-catalyst (10 mol%). [d] PTSA=*p*-toluenesulfonic acid.

The scope of the method was then examined after establishing the optimal reaction conditions, and the results are listed in Table 2. The homo-coupling reactions of alkynes were firstly tested. Symmetrical 4-substituted diphenylethynes could all go through the reaction efficiently and provided the target furans in good to excellent yield (Table 2, Entries 1—5). In comparison, electron-withdrawing groups favored the reaction more than electron-donating groups. It is noteworthy that this procedure for the preparation of polysubstituted furan tolerates aryl bromides which allow further functionalization (Table 2, Entry 6). Symmetrical 3-substituted diphenylethynes produced the corresponding furans in a lower yield than 4-substituted ones (Table 2, Entries 7—9), but in a higher yield than 2-substituted one (Table 2, Entry 10). The cross-coupling reaction of diverse alkynes was then explored and we found that a mixture of cross-coupled product and homo-coupled one was obtained when bis(4-butylphenyl)ethyne reacted with bis(4-(trifluoromethyl)phenyl)-ethyne or diphenylethyne under the optimized reaction conditions. The cross-coupled furan product was isolated in the yields of 60% and 52% respectively (Table 2, Entries 11, 12).

Table 2 Scope of alkynes for the synthesis of furans[a]



Entry	R^1	R^2	Product	Yield[b]/%
1	C_6H_5	C_6H_5	**a**	92
2	4-*n*-BuC_6H_4	4-*n*-BuC_6H_4	**b**	78
3	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**c**	71
4	4-$(CF_3)C_6H_4$	4-$(CF_3)C_6H_4$	**d**	96
5	4-FC_6H_4	4-FC_6H_4	**e**	85
6	4-BrC_6H_4	4-BrC_6H_4	**f**	90
7	3-MeC_6H_4	3-MeC_6H_4	**g**	70
8	3-ClC_6H_4	3-ClC_6H_4	**h**	76
9	3-FC_6H_4	3-FC_6H_4	**i**	72
10	2-FC_6H_4	2-FC_6H_4	**j**	50
11	4-*n*-BuC_6H_4	4-$(CF_3)C_6H_4$	**k**	60
12	C_6H_5	4-*n*-BuC_6H_4	**l**	52

[a] Reactions were carried out using alkyne (R^1) (0.5 mmol), alkyne (R^2) (0.5 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (10 mol%), AcOH (2 mL), 100 ℃, O_2 balloon (101 kPa), 12 h. [b] Isolated yields.

In order to justify the practicability of this method, a gram-scale synthesis was carried out. 1.0712 g of diphenylethyne was allowed to react for 12 h in a 50 mL round bottom flask charged with 0.0683 g $Pd(OAc)_2$, 0.1252 g $Cu(OAc)_2$ and 20 mL AcOH connected to an oxygen balloon, under magnetic stirring at 100 ℃. After the reaction was completed, the reaction solution was transferred into a separatory funnel and then 60 mL water was added. The aqueous solution was extracted with ethyl acetate (30 mL×3) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was vacuumed and the crude product was isolated by silica gel column chromatography with light petroleum ether/CH_2Cl_2 as eluent to give the pure product. The product 2,3,4,5-tetraphenylfuran (**a**), in the amount of 0.9850 g, was obtained in 88% yield.

Conclusions

In conclusion, we have developed a procedure for the synthesis of highly substituted furans from alkynes catalyzed by palladium using atmospheric oxygen as a terminal oxidant. This protocol could be carried out in

common solvent connecting to an oxygen balloon, which was more facile and practical.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-400 spectrometer using indicated deuterated solvents and TMS as an internal standard. Mass spectra were obtained with a SHIMADZU model GCMS-QP5000 spectrometer. TLC was performed by using commercially prepared 100－400 mesh silica gel plates (GF_{254}) and visualization was effected at 254 nm.

Typical procedure

Alkyne (1 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (10 mol%) and AcOH (2 mL) were added into a test tube attached to an oxygen balloon (101 kPa). The system was stirred magnetically and heated at 100 ℃ with an oil bath for 12 h. And then the reaction was quenched by the addition of 10 mL water. The aqueous solution was extracted with ethyl acetate (10 mL×3) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was vacuumed and the crude product was isolated by TLC with light petroleum ether/CH_2Cl_2 as eluent to give the pure product.

2,3,4,5-Tetraphenylfuran (**a**):[11,12] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53－7.46 (m, 4H), 7.28－7.18 (m, 12H), 7.17－7.11 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.7, 133.2, 130.9, 130.4, 128.4, 128.4, 127.3, 127.2, 125.9, 125.1; MS (EI, 70 eV) *m/z* (%): 372 (M^+, 100), 267 (34), 165 (19), 77 (11).

2,3,4,5-Tetrakis(4-butylphenyl)furan (**b**):[11b,12] ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.45－7.35 (m, 4H), 7.14－7.01 (m, 12H), 2.57 (td, J=7.8, 2.8 Hz, 8H), 1.64－1.48 (m, 8H), 1.33 (hd, J=7.3, 3.3 Hz, 8H), 0.90 (td, J=7.4, 1.8 Hz, 12H); ^{13}C NMR (101 MHz, acetone-d_6) δ: 148.1, 142.9, 142.5, 131.5, 131.0, 129.3, 129.2, 126.2, 125.6, 35.8, 34.2, 22.9, 14.2; MS (EI, 70 eV) *m/z* (%): 596 (M^+, 100), 553 (64), 539 (11), 213 (23), 161 (55), 133 (28), 57 (10), 44 (15).

2,3,4,5-Tetrakis(4-methoxyphenyl)furan (**c**):[11,12] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40－7.27 (m, 4H), 7.13－7.01 (m, 4H), 6.92－6.77 (m, 8H), 3.72 (s, 6H), 3.71 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 132.6, 132.5, 132.4, 132.3, 132.3, 129.9, 114.2, 113.9, 113.8, 113.6, 55.4, 55.2, 29.7; MS (EI, 70 eV) *m/z* (%): 492 (M^+, 28), 318 (100), 275 (32), 135 (45).

2,3,4,5-Tetrakis(4-(trifluoromethyl)phenyl)furan (**d**):[11a,12] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60－7.54 (m, 12H), 7.30－7.23 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.0, 135.6, 133.0, 131.2, 130.5, 130.1, 129.8, 129.5, 128.0, 126.2, 125.9, 125.9, 125.7, 125.7, 125.3, 125.1, 122.6; MS (EI, 70 eV) *m/z* (%): 644 (M^+, 46), 471 (13), 173 (100), 145 (33).

2,3,4,5-Tetrakis(4-fluorophenyl)furan (**e**):[11,12] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52－7.40 (m, 4H), 7.27－7.05 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.2, 134.7, 134.5, 133.9, 131.6, 130.1, 130.0, 129.8, 128.4, 128.1, 128.0, 125.8, 124.5, 124.0; MS (EI, 70 eV) *m/z* (%): 444 (M^+, 100), 321 (73), 123 (69), 95 (55).

2,3,4,5-Tetrakis(4-bromophenyl)furan (**f**):[11b,12] ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.57－7.50 (m, 8H), 7.48－7.42 (m, 4H), 7.21－7.13 (m, 4H); ^{13}C NMR (101 MHz, acetone-d_6) δ: 148.0, 133.0, 132.9, 132.7, 132.6, 132.4, 130.0, 128.2, 125.4, 122.5, 122.3, 120.4; MS (EI, 70 eV) *m/z* (%): 484 (100), 441 (32), 161 (14), 105 (29).

2,3,4,5-Tetram-tolylfuran (**g**):[11,12] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (s, 2H), 7.24 (s, 2H), 7.12 (t, J= 7.6 Hz, 4H), 7.06－6.92 (m, 8H), 2.30 (s, 6H), 2.23 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.6, 137.9, 137.7, 133.2, 131.1, 131.0, 128.1, 128.1, 128.0, 127.7, 127.5, 126.4, 125.1, 123.0, 21.6, 21.3; MS (EI, 70 eV) *m/z* (%): 428 (M^+, 100), 309 (21), 119 (65), 91 (18).

2,3,4,5-Tetrakis(3-chlorophenyl)furan (**h**):[12] ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.58－7.53 (m, 2H), 7.45－7.28 (m, 12H), 7.26－7.20 (m, 2H); ^{13}C NMR (101 MHz, acetone-d_6) δ: 147.8, 135.1, 135.0, 134.9, 132.6, 131.3, 131.3, 130.8, 129.7, 129.0, 128.8, 126.1, 125.8, 124.9, 124.0, 122.1; MS (EI, 70 eV) *m/z* (%): 510 (M^+, 100), 183 (40), 169 (56), 139 (80), 111 (65), 57 (48).

2,3,4,5-Tetrakis(3-fluorophenyl)furan (**i**):[12] ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.47－7.24 (m, 8H), 7.18－6.99 (m, 8H); ^{13}C NMR (101 MHz, acetone-d_6) δ: 164.8, 162.4, 147.7, 135.5, 135.4, 133.0, 132.9, 131.6, 131.5, 131.4, 127.2, 125.9, 122.3, 117.9, 117.7 115.8, 115.6, 115.6, 115.4, 113.0, 112.8; MS (EI, 70 eV) *m/z* (%): 444 (M^+, 100), 321 (70), 201 (28), 123 (60), 95 (29).

2,3,4,5-Tetrakis(2-fluorophenyl)furan (**j**):[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56－7.37 (m, 4H), 7.30－7.25 (m, 4H), 7.23－7.20 (m, 4H), 7.14－7.10 (m, 2H), 7.03－6.98 (m, 2H); ^{13}C NMR (101 MHz, acetone-d_6) δ: 162.2, 161.3, 159.7, 158.8, 146.7, 132.7, 131.6, 131.6, 130.8, 130.7, 130.7, 125.3, 125.2, 124.9, 121.7, 121.2, 121.1, 119.3, 119.1, 117.1, 116.9, 116.3, 116.1; MS (EI, 70 eV) *m/z* (%): 444 (M^+, 100), 321 (54), 201 (14), 123 (59), 95 (27).

2,3-Bis(4-butylphenyl)-4,5-bis(4-(trifluoromethyl)-phenyl)furan (**k**):[12] ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.74－7.61 (m, 1H), 7.51－7.37 (m, 1H), 7.19－7.03 (m, 1H), 2.60 (t, J=7.7 Hz, 1H), 1.67－1.49 (m, 1H), 1.38－1.28 (m, 1H), 0.90 (td, J=7.4, 0.8 Hz, 1H);^{13}C NMR (101 MHz, acetone-d_6) δ: 145.0, 146.7, 143.8, 143.2, 138.0, 134.8, 131.8, 131.0, 130.4, 129.7, 129.5, 129.4, 129.3, 128.5, 126.7, 126.5, 126.4, 126.3, 35.9, 35.8, 34.2, 34.2, 22.9; MS (EI, 70 eV) *m/z* (%): 620 (M^+, 100), 577 (31), 173 (66), 161 (96), 145 (23), 91 (26), 57 (27), 43 (44).

2,3-Bis(4-butylphenyl)-4,5-diphenylfuran (**l**):[12] ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.53－7.38 (m, 4H), 7.33－7.16 (m, 8H), 7.15－7.06 (m, 6H), 2.69－2.47 (m, 4H), 1.66－1.46 (m, 4H), 1.40－1.23 (m, 4H), 0.90 (td, J=7.3, 1.4 Hz, 6H); ^{13}C NMR (101 MHz, ace-

tone-d_6) *δ:* 148.6, 147.9, 143.1, 142.7, 134.2, 131.7, 131.1, 131.0, 129.2, 128.2, 126.3, 125.6, 35.9, 34.2, 22.9, 14.2; MS (EI, 70 eV) *m/z* (%): 484 (M^+, 100), 441 (31), 161 (24), 105 (46), 59 (28).

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