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CH-alkylation of furan derivatives under photoinduced Pd catalysis

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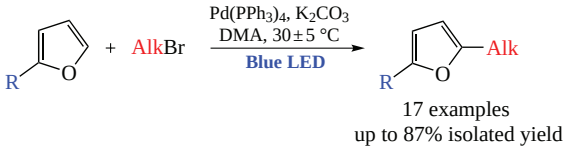
A new method for selective C(5)–H alkylation of 2-substituted furans with tertiary and secondary alkyl bromides under photoinduced by visible light (~460 nm) palladium catalysis has been developed. The method is relied on the use of available $Pd(PPh_3)_4$ catalyst under mild conditions (30 ± 5 °C, K_2CO_3 as base), tolerates to various functional groups in furanic substrates and provides from good to excellent yields of alkylated products.



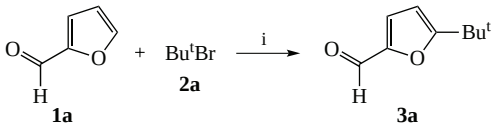
Keywords: furan, CH-alkylation, palladium, photoinduced metal catalysis, 2-hetarylfurans.

Furan derivatives which can be produced starting from carbohydrates of plant biomass are considered as renewable feedstocks for chemical industry.[1–4] Alkylated furan core may be found in numerous medicinal and bioactive compounds,[5–7] monomers,[3,8] plasticizers[9] and novel fuel additives.[10,11] Selective alkylation of furan core is attractive for the preparation of biologically active derivatives.[12,13] However, low stability of furan ring under typical conditions of the Friedel–Crafts reactions[14,15] stimulated the search for more selective methods for furan CH-alkylation.[12,13] Although new procedures for transition metal-catalyzed CH-alkylation of furan ring were developed,[16–25] they often suffer from limited scope of alkylating agents, or require to use specific expensive phosphine ligands.

Last years, many efforts have been devoted to developing new methods for CH-alkylation of various substrates with alkyl halides under photoinduced palladium catalysis.[26–30] Blue light (~460 nm) emitted by inexpensive light emitting diodes (LEDs) can excite Pd complexes and promote reactions with inactivated alkyl halides to give palladium-radical hybrid species active in CH-alkylation of various substrates.[30] However, potential of photoinduced Pd catalysis for CH-alkylation of furans with alkyl halides remains almost unexplored, only scarce examples of 3-formylfuran[31] and furfural[32] alkylation with 1-bromoadamantane were described. Herein we report a new simple method for selective C(5)H-alkylation of 2-substituted furans with secondary and tertiary alkyl bromides under conditions of visible light-induced Pd/PPh_3 catalysis.

Alkylation of furfural (**1a**) with *tert*-butyl bromide (**2a**) under blue light irradiation (two blue 40 W LED lamps) at 30 ± 5 °C was selected as a model reaction (Scheme 1). Initially, all potential precatalysts were tested in DMA in the presence of K_2CO_3 as base, because these conditions provided good efficiency for alkylation of alkenes with tertiary alkyl halides under photoinduced Pd catalysis (Table 1).[33]

It was found that $Pd(OAc)_2$ in the absence of ligands was almost inactive as precatalyst, even in the presence of $[Bu_4N]Br$ additive as Pd nanoparticles stabilizer (see Table 1, entries 1, 2). Effects of various NHC, phosphine and N-donor ligands were also studied (Figure S1). Addition of NHC-proligand IPr·HCl



Scheme 1 *Reagents and conditions*: i, **1a** (0.25 mmol), **2a** (0.5 mmol), [Pd] (0.0068–0.0250 mmol, 2.5–10 mol%), additive (0–20 mol%), base (0.5 mmol), solvent (1 ml), two blue 40 W LED lamps, 30 ± 5 °C, 24 h. For details, see Table 1.

Table 1 Optimization of the reaction conditions.[a,b]

Entry	[Pd] (mol%)	Additive (mol%)	*t*/h	NMR yield of **3a** (%)[c]
1	$Pd(OAc)_2$ (5)	none	24	trace
2	$Pd(OAc)_2$ (5)	$[Bu_4N]Br$ (20)	24	trace
3	$Pd(OAc)_2$ (5)	IPr·HCl (10)	24	trace
4	$Pd(OAc)_2$ (5)	XantPhos (10)	24	7
5	$Pd(OAc)_2$ (5)	PPh_3 (10)	24	12
6	$Pd(OAc)_2$ (5)	PPh_3 (20)	24	40
7	$Pd(PPh_3)_4$ (5)	none	24	71
8	$Pd(PPh_3)_4$ (5)	none	36	72
9	$Pd(PPh_3)_4$ (10)	none	36	71
10	$Pd(PPh_3)_4$ (5)	PPh_3 (15)	24	70
11	$Pd(PPh_3)_4$ (2.5)	none	36	40
12	$Pd(PPh_3)_4$ (5)	$[Bu_4N]Br$ (5)	24	71
13	$Pd(PPh_3)_4$ (5)	$[Bu_4N]I$ (5)	24	56
14	$Pd(PPh_3)_4$ (5)	IPr·HCl (10)	24	65
15	$Pd(PPh_3)_4$ (5)	none	24	trace[d]

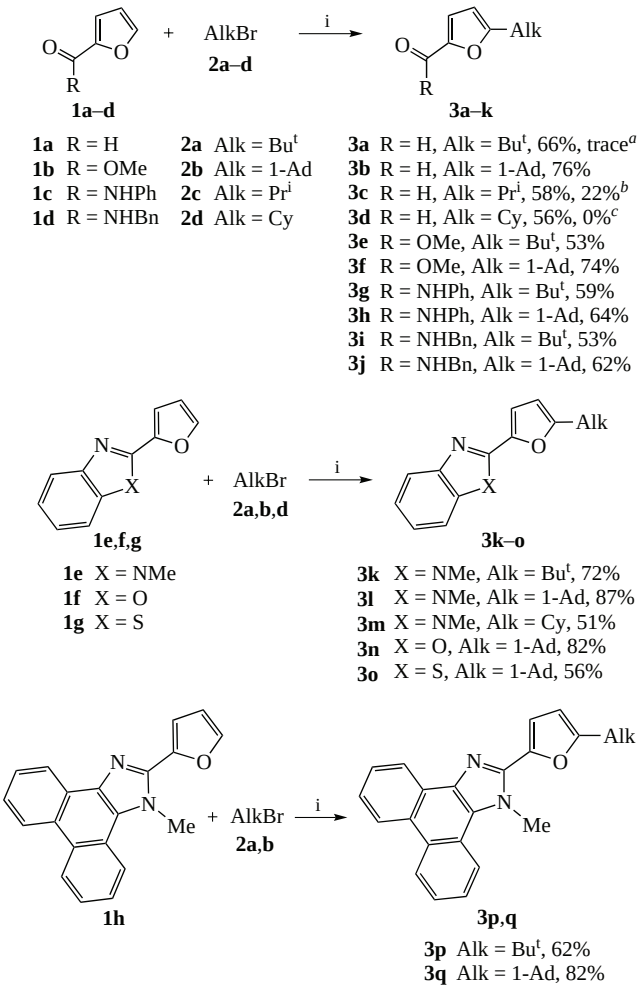
[a] *Reagents and conditions*: **1a** (0.25 mmol), **2a** (0.5 mmol), [Pd] (0.0068–0.0250 mmol, 2.5–10 mol%), additive (0–20 mol%), K_2CO_3 (0.5 mmol), DMA (1 ml), two blue 40 W LED lamps at 30 ± 5 °C, 24 h. [b] For extended experimental data, see Table S1 in Online Supplementary Materials. [c] The yield was determined by NMR. [d] In the dark.

(entry 3) as well as IMes·HCl and various N-donor ligands (see Online Supplementary Materials, Figure S1 and Table S1) did not result in appearance of CH-alkylation products in appreciable yields, only slow decomposition of *tert*-butyl bromide was observed by NMR. Better results were obtained with phosphine ligands such as XantPhos and PPh_3. Addition of XantPhos (10 mol%) often used in photoinduced Pd catalysis[26,29] resulted in formation of the desired alkylation product **3a** in 7% yield (see Table 1, entry 4), whereas addition of PPh_3 provided 12% yield at the same 10 mol% loading (entry 5) and significantly higher 40% yield at 20 mol% loading (entry 6). Further increasing PPh_3 loading and using other Pd^{II} salts combined with PPh_3 ligand did not improve significantly the reaction outcome (see Table S1, entries 9–11). However, employing $Pd(PPh_3)_4$ in 5 mol% loading instead of Pd^{II} salts and PPh_3 allowed us to increase the **3a** yield up to 71% (see Table 1, entry 7). Prolongation of the reaction time to 36 h (entry 8), raising $Pd(PPh_3)_4$ amount to 10 mol% (entry 9), or loading additional PPh_3 (entry 10) did not lead to increase in the yield, whereas reducing $Pd(PPh_3)_4$ loading to 2.5 mol% dropped this yield to 40% (entry 11).

We also studied effect of tetraalkylammonium salt additives, the well-known stabilizers of nanosized Pd species.[34] It should be noted that remarkable promoting effect of tetrabutylammonium salt additives on the CH-alkylation of (benz)oxazoles with tertiary alkyl chlorides under close conditions was reported recently.[35] However, addition of $[Bu_4N]Br$ did not increase the **3a** yield (see Table 1, entry 12), whereas addition of $[Bu_4N]I$ even decreased it (entry 13). Apparently, stabilizing effect of tetraalkylammonium salts is less pronounced in reactions with more reactive alkyl bromides. Inhibiting effect of $[Bu_4N]I$ may be explained by the formation of stable $Pd(PPh_3)_2I_2$ complexes which are more slowly reduced to active Pd^0L_x complexes than Pd species with bromide ligands.[36] Addition of IPr·HCl, which can serve both as Pd nano-species stabilizer and NHC proligand,[34] did not result in appreciable variation of the **3a** yield (entry 14).

Other solvents and bases were also tested, however no increase in **3a** yield was achieved (see Online Supplementary Materials, Table S1, entries 21–28). The reaction proceeded neither in the absence of Pd catalyst (entry 30) nor in the dark (see Table 1, entry 15). On the basis of these experimental data, conditions of the entry 7 in Table 1 were accepted as optimal.

With the optimal conditions in hand, we studied possibilities for extending scope of furan substrates and alkylating reagents. Derivatives containing electron-withdrawing groups such as furfural **1a**, methyl 2-furoate **1b**, 2-furoic acid amides **1c**,**d** and 2-hetaryl-substituted furans, the fuberidazole fungicide derivative **1e**[37,38] and medicinally oriented compounds **1f**–**h**[39–42] reacted smoothly with tertiary and secondary alkyl bromides affording 5-alkylated furans **3a**–**q** in good to excellent yields (Scheme 2). Remarkably, despite the presence of potential O-donor and N-donor directing groups, CH-alkylation of compounds **1a**–**h** proceeded selectively affording the only alkylation products **3a**–**q**. However, electron-rich unsubstituted furan and 2-methylfuran (Figure S2), according to NMR and GC-MS data, did not react with *tert*-butyl bromide and other alkyl halides. Decrease in reactivity of heteroaromatic substrate toward alkylation under photoinduced Pd catalysis with decrease in their electron deficiency was mentioned in the literature.[31,35] Taking into account the proposed reaction mechanism based on previous reports,[31,35] the decreased reactivity of furan and 2-methylfuran may be explained by the lowered rate of slightly nucleophilic alkyl radical addition, or, alternatively, by decreased CH-acidity of heterocyclic radical intermediates reacting with base to give a final product (see Online Supplementary Materials, Scheme S1). However, this question deserves a special mechanistic study which is beyond the scope of this



Scheme 2 *Reagents and conditions*: i, furan derivative **1a**–**h** (0.25 mmol), alkyl bromide **2a**–**d** (0.5 mmol), $Pd(PPh_3)_4$ (0.0125 mmol, 5 mol%), K_2CO_3 (0.5 mmol), DMA (1 ml), Blue light (460 nm, two 40 W LEDs), 24 h. [a]Reaction with Bu^tCl. [b]Reaction with Pr^iI. [c]Reaction with CyCl.

communication. Attempts to use primary alkyl bromides and various alkyl chlorides were unsuccessful (Figure S2 and Table S2). For example, using *n*-butyl bromide for the alkylation of **1a** led to corresponding alkylated product in 25% yield, whereas attempts to use benzyl bromide, *n*-heptyl chloride, cyclohexyl chloride and *tert*-butyl chloride resulted in zero or trace yields of the alkylated products. Low reactivity of these alkyl halides may be explained by lower rates of C–Cl bond homolysis and lower stability of primary alkyl radicals, the factors responsible for insufficient concentration of palladium-radical active species involved to the catalytic cycle.[30] The use of primary alkyl iodides also resulted in low yields. Secondary alkyl iodides were sufficiently less efficient than bromides, probably due to their lower stability and inhibiting effect of iodide anion releasing during reaction. Overall, furan derivatives **1a**–**d** demonstrated significantly lower reactivity in the alkylation reaction under conditions of photoinduced Pd catalysis compared to 1,3-oxazole derivatives which smoothly reacted with tertiary alkyl chlorides.[35]

Structures of compounds **3a**–**q** were confirmed by HRMS, ^1H and ^{13}C NMR spectra, including 2D techniques. For example, NOESY experiment unequivocally supported structure of compound **3k** and excluded alternative structure of an isomer which could form through C(3)–H alkylation of furan ring owing to directing influence of benzimidazole ring in starting 2-(2-furyl)-1-methylbenzimidazole **1e** (Figure S27).[43]

In conclusion, a new method for C(5)H-alkylation of 2-substituted furans with secondary and tertiary alkyl bromides

enabled by visible light-induced catalysis with $Pd(PPh_3)_4$ in the presence of K_2CO_3 as base has been developed. The method may be useful for last stage modification of biologically active furan compounds because mild reaction conditions tolerate well to various functional groups present in the position 2 of the furan ring, including formyl, carboxylate and amide groups as well as strongly coordinating N-containing heterocyclic rings.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.06.017.

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