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Mendeleev Commun., 2024, **34**, 198–200

Mendeleev Communications

Synthesis of furo[2,3-*c*]quinolinones *via* intramolecular C(3)–H arylation of furan core under Pd/NHC-catalysis

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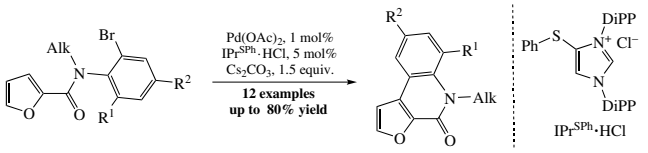
DOI: 10.1016/j.mencom.2024.02.012

An efficient procedure for the preparation of furo[2,3-*c*]-quinolin-4(5*H*)-ones from 2-furoic acid *N*-(*o*-bromoaryl)-amides *via* selective intramolecular C(3)–H arylation of the furan nucleus involves the catalysis by a Pd/NHC system generated *in situ* from $Pd(OAc)_2$ and readily available IPr^{SPh}·HCl proligand. A series of novel furo[2,3-*c*]quinolin-4(5*H*)-ones were prepared in 65–80% isolated yields.

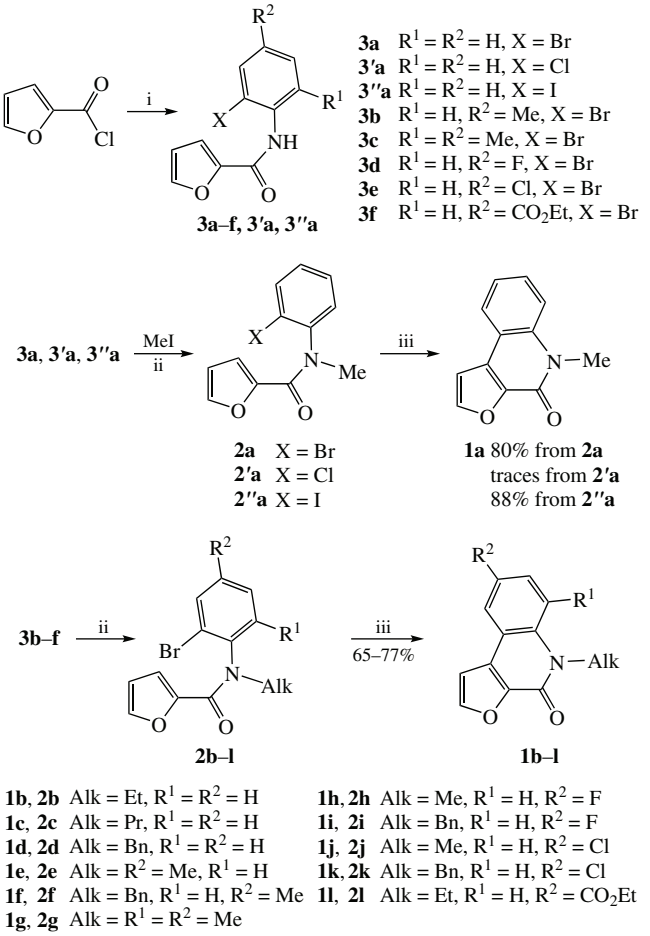


Keywords: palladium, C–H activation, arylation, N-heterocyclic carbene ligands, furo[2,3-*c*]quinolin-4(5*H*)-ones.

Furo[2,3-*b*]quinoline represents a medicinally demanded scaffold that can be found in various alkaloids and other natural compounds.[1–4] Furo[2,3-*b*]quinoline derivatives exhibit antifungal,[5] antibacterial,[6] antitumor,[7] and antimicrobial[8] activities. However, isomeric furo[2,3-*c*]quinolines are still remain poorly studied due to difficulties of their synthesis. Previously developed approaches to the synthesis of furo[2,3-*c*]-quinolin-4(5*H*)-ones **1** (Scheme 1) were based on Pd/phosphine-catalyzed cyclization (intramolecular C–H arylation) of 3-iodo-2-furoic acid *N*-arylamides[9] or 2-furoic acid *N*-(*o*-haloaryl)-amides.[9–11] The second approach seems more attractive due to the higher availability of starting compounds obtained *via* acylation of *o*-haloanilines with furoic acid derivatives. However, Pd/phosphine cyclization of thus obtained 2-furoic acid *N*-(*o*-iodoaryl)amides afforded the desired products only in moderate yields (up to 59%) and required reflux in DMA at high Pd loading (30 mol%),[9] while the cyclization of *N*-(*o*-bromoaryl) amides suffered from the formation of spirooxindoles as byproducts.[10] A more convenient procedure is based on the cyclization of 2-furoic acid *N*-(*o*-chlorophenyl)-*N*-methylamide catalyzed by the $Pd(OAc)_2/PCy_3$ system at 3 mol% Pd loading in DMA at 130 °C, however the scope of the reaction was limited to only one example.[11] The problems with the cyclization of furan-2-carboxamides can be attributed to the general reluctance of the C(3)–H of furan nucleus in C–H functionalization reactions.[12–14]

N-Heterocyclic carbene (NHC) ligands often show excellent efficiency in various transition metal-catalyzed C_{sp^2}–H arylation reactions,[15–17] including heterocyclizations.[18,19] We supposed that the use of NHC ligands may facilitate the Pd-catalyzed cyclization of *N*-(*o*-haloaryl)furan-2-carboxamides with the selective formation of the desired furo[2,3-*c*]quinolinones. Herein, we report an efficient procedure for the preparation of furo[2,3-*c*]quinolin-4(5*H*)-ones **1** *via* cyclization of 2-furoic acid *N*-(*o*-bromoaryl)amides **2** under Pd/NHC catalysis.

The starting compounds **2a–l** used in the study (see Scheme 1) were obtained by the acylation of *ortho*-halogenated anilines with 2-furoyl chloride and subsequent alkylation of amides **3a–f**.



Scheme 1 *Reagents and conditions*: i, *o*-haloarylamine, NEt_3, CH_2Cl_2, 25 °C, 4 h; ii, **3a–f**, **3′a**, **3″a**, AlkI or BnBr, KOBu^t, THF, 25 °C, 12 h; iii, **2a–l**, **2′a**, **2″a** (0.25 mmol), $Pd(OAc)_2$ (0.0025 mmol, 1 mol%), IPr^{SPh}·HCl (0.0125 mmol, 5 mol%), Cs_2CO_3 (0.375 mmol), toluene (2 ml), 110 °C, 16 h.

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

Entry	[Pd] (mol%)	Ligand (mol%)	Yield of **1a** (%)[c]
1	$Pd(OAc)_2$ (5)	none	trace
2	$Pd(OAc)_2$ (5)	PPh_3 (15)	trace
3	$Pd(OAc)_2$ (5)	IMes·HCl (15)	trace
4	$Pd(OAc)_2$ (5)	IPr^{*OMe}·HCl (15)	trace
5	$Pd(OAc)_2$ (5)	IPr·HCl (15)	83
6	$Pd(OAc)_2$ (2)	IPr·HCl (5)	75
7	$Pd(OAc)_2$ (1)	IPr·HCl (5)	33
8	$Pd(OAc)_2$ (5)	IPr^{SPh}·HCl (15)	89
9	$Pd(OAc)_2$ (2)	IPr^{SPh}·HCl (5)	87
10	$Pd(OAc)_2$ (1)	IPr^{SPh}·HCl (5)	86
11	$Pd(OAc)_2$ (0.5)	IPr^{SPh}·HCl (5)	20
12	$Pd(OAc)_2$ (1)	IPr^{SPh}·HCl (15)	89
13	$Pd(OAc)_2$ (1)	IPr^{SPh}·HCl (3)	44
14	$Pd(OAc)_2$ (1)	IPr^{SPh}·HCl (1)	trace
15	**4** (1)	none	49

[a] *Reagents and conditions*: **2a** (0.25 mmol), [Pd] (0.0025–0.0125 mmol), ligand (0–0.025 mmol), Cs_2CO_3 (0.75 mmol), toluene (2 ml), 110 °C, 16 h. [b] For extended experimental data, see Online Supplementary Materials, Table S1. [c] The yield was determined by GC-MS.

The search for a suitable catalytic system and the optimization of the reaction conditions were carried out using cyclization of the model *N*-(2-bromophenyl)-*N*-methylfuran-2-carboxamide **2a** to compound **1a** (Tables 1 and S1).

Attempts to cyclize compound **2a** under catalysis with $Pd(OAc)_2$ (5 mol%) in the absence of ligand, or in the presence of PPh_3, were unsuccessful (see Table 1, entries 1 and 2). Therefore, various imidazolium salts as NHC proligands were screened (Figure 1). The use of IMes·HCl and IPr^{*OMe}·HCl was inefficient, only trace yields of product **3a** were detected by GC-MS. Meantime, IPr·HCl and recently[20] developed novel NHC proligand IPr^{SPh}·HCl gave 83 and 89% yields of **1a**, respectively (entries 5 and 8). Remarkably, at the same Pd and ligand loadings, the IPr^{SPh}·HCl proligand (entries 8–10) exhibited higher catalytic efficiency than IPr·HCl (entries 5–7). Therefore, the IPr^{SPh}·HCl proligand was employed for further optimization of the reaction conditions. Cesium carbonate was found to be an optimal base. The use of other bases such as K_2CO_3, Na_2CO_3 or $KOBu^t$ resulted in a decrease in **1a** yield, while the use of KOH or NEt_3 was completely inefficient (Table S1). Other solvents such as DMA, 1,4-dioxane, and acetonitrile were less efficient than toluene (see Table S1). The molar ratio of IPr^{SPh}·HCl/$Pd(OAc)_2$ was also optimized (entries 8–14). The ratio of IPr^{SPh}·HCl/$Pd(OAc)_2$ equal to 5 : 1 at 1 mol% Pd loading was accepted as an optimal one (entry 10). A significant excess of NHC proligand is apparently required to compensate for NHC losses in side R-NHC coupling reactions of *in situ* formed Pd/NHC complexes with aryl halide, substrate, and base.[16,21,22] Higher loading did not significantly improve the **1a** yield (entry 12), while lower loading led to a decrease in yield (entries 13, 14). We also evaluated the efficiency of the well-defined complex **4**[20] (see Figure 1) with the same IPr^{SPh} ligand (entry 15), however no improvement of **1a** yield was achieved compared to the *in situ* generated catalytic system (entry 10). Therefore, considering the simplicity of the preparation of IPr^{SPh}·HCl compared to complex **4**,[20,23] the conditions of the entry 10 were accepted as optimal ones.

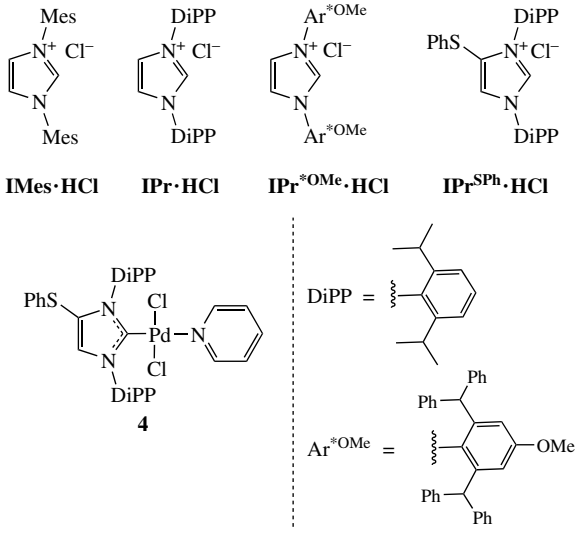


Figure 1 Structures of NHC proligands and complex **4** used in the study.

Substrates **2′a** (X = Cl) and **2′′a** (X = I) were also tested under the optimized conditions. Aryl chloride **2′a** was almost inert under the conditions studied, whereas aryl iodide **2′′a** afforded 88% yield of compound **1a** (see Scheme 1 and Table S1). Considering the higher availability of aryl bromides over aryl iodides, further studies were carried out with aryl bromides.

With the optimized conditions in hand, the reaction scope was evaluated using various amides **2a–l** (see Scheme 1). It was found that *N*-alkyl substituents in the starting amides **2b–d** had an insignificant effect on the yields of the cyclized products **1b–d**. Starting compounds containing F (**1h**,**i**), Cl (**1j**,**k**) and CO_2Et (**1l**) substituents in the benzene moiety were tolerated under the reaction conditions. Unfortunately, the NH-unprotected amides **3a–f** could not be cyclized under the conditions studied, only starting compounds were isolated from the reaction mixtures, which was also shown in the previous works.[9,10]

The structures of the obtained furo[2,3-*c*]quinolin-4(5*H*)-ones **1a–l** were confirmed by ^1H and ^{13}C NMR and ESI-MS spectra. The representative structures **1g**,**j** were established by single crystal X-ray studies† (Figure 2; for details, see Online Supplementary Materials).

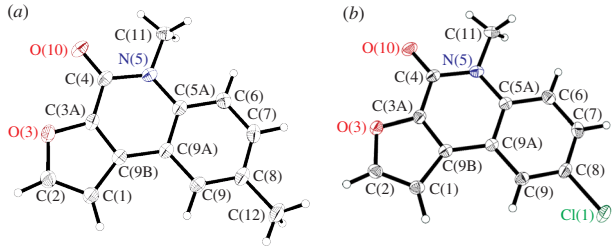


Figure 2 General view of (*a*) compound **1g** and (*b*) compound **1j** in the representation of atoms *via* thermal ellipsoids at the 50% probability level.

† *Crystal data for* **1g**. $C_{13}H_{11}NO_2$ (M = 213.23), monoclinic, space group $P2_1/c$, at 100(2) K, a = 7.29862(7), b = 10.87970(8) and c = 13.26532(11) Å, β = 05.5334(9)°, V = 1014.882(15) Å^3, Z = 4, d_{calc} = 1.396 g cm^{-3}, μ(CuKα) = 0.771 mm^{-1}, F(000) = 448. Total of 15852 reflections were collected [2202 independent reflections, R_{int} = 0.0211] and used in the refinement, which converged to $wR(F^2)$ = 0.0969, GOOF 1.064 for all independent reflections [R_1 = 0.0347 was calculated for 2152 reflections with $I > 2\sigma(I)$].

Crystal data for **1j**. $C_{12}H_8ClNO_2$ (M = 233.64), triclinic, space group $P2_1/c$, at 100(2) K, a = 7.84250(10), b = 10.07480(10) and c = 13.03250(10) Å, β = 100.5590(10)°, V = 1012.282(18) Å^3, Z = 4, d_{calc} = 1.533 g cm^{-3}, μ(CuKα) = 3.203 mm^{-1}, F(000) = 480. Total of 13518 reflections were collected [2190 independent reflections, R_{int} = 0.0276] and used in the refinement, which converged to $wR(F^2)$ = 0.0886, GOOF 1.042 for all independent reflections [R_1 = 0.0326 was calculated for 2169 reflections with $I > 2\sigma(I)$].

CCDC 2300119 and 2300120 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

In conclusion, a novel efficient procedure for the synthesis of furo[2,3-*c*]quinolin-4(5*H*)-ones *via* intramolecular cyclization of 2-furoic acid *N*-(*o*-bromoaryl)amides involving activation of the reluctant C(3)–H bond of the furan nucleus under Pd/NHC catalysis has been developed. The use of N-heterocyclic carbenes allows the palladium loading to be significantly reduced (by up to 1 mol%) compared to previously reported methods. The developed catalytic system is also tolerant to Cl, F and carboxylate functions in the substrate *N*-aryl moiety and, therefore, allows one to obtain functionalized furo[2,3-*c*]-quinolin-4(5*H*)-ones which are potentially suitable for further functionalization.

This work was supported by the grant of the President of the Russian Federation (no. MK-171.2022.1.3). The authors are grateful to Academician of the Russian Academy of Sciences Professor V. P. Ananikov for a fruitful discussion of the results of this work and valuable comments. The authors also thank the Shared Research Center 'Nanotechnologies' of the Platov South-Russian State Polytechnic University for NMR and GC-MS services, and the Shared Research Center of Zelinsky Institute of Organic Chemistry for mass-spectrometry and X-ray analyses.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.012.

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Received: 23rd October 2023; Com. 23/7280