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Ruthenium(II)-catalyzed C(3)–H arylation of furan moiety in fuberidazole derivatives

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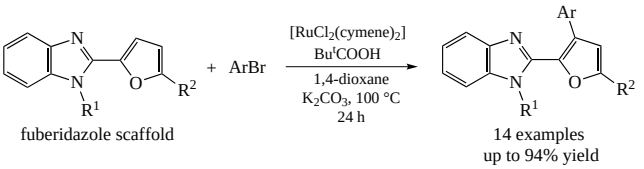
An efficient selective C(3)–H arylation of furan ring in 2-(furan-2-yl)benzimidazoles, derivatives of fuberidazole fungicide, with aryl bromides catalyzed by $[RuCl_2(cymene)]_2$/pivalic acid system has been accomplished. High selectivity of the process may be accounted for by the action of benzimidazol-2-yl substituent as the directing group.



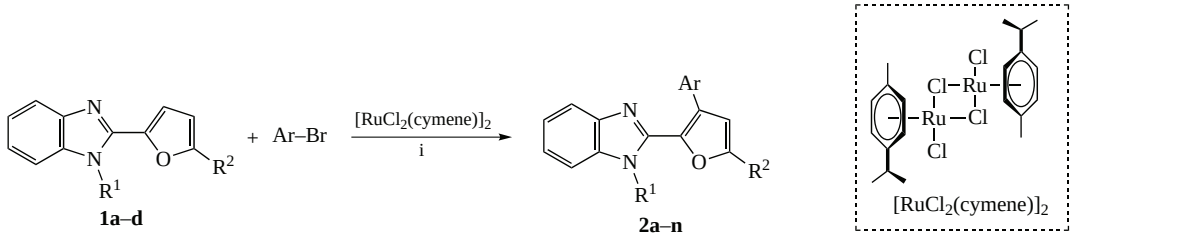
Keywords: furans, CH-functionalization, arylation, ruthenium complexes, carboxylate assistance, 2-hetarylfurans, benzimidazoles.

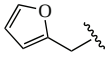
2-Heteroaryl substituted furans are used in medicine, agriculture and materials science.[1–3] Among them, anticancer drug lapatinib,[4] adenosine A_{2A} receptor antagonist preladenant,[5] antibiotic roseophilin[6] and fungicide fuberidazole (2-furylbenzimidazole, parent compound of type **1** with $R^1 = R^2 = H$, Scheme 1)[7,8] can be mentioned as the most important examples. Fuberidazole is also considered as the promising scaffold for searching new medicaments. Its derivatives are intensively studied as potential anticancer,[9–12] antiviral[13] and anti-inflammatory[14] agents, and are explored as multidentate ligands and chemosensors for metal cations[15,16] and components of organic light-emitting diodes.[17]

The search for new medicaments, pesticides and functional materials among 2-heteroarylfurans often needs selective functionalization of furan moiety. Most of developed approaches enable selective functionalization of 2-heteroarylfurans at the C(5) atom of the furan core *via* electrophilic substitution[18–20] or Pd and Ni-catalyzed C–H activation.[21,22] However, methods for C(3)–H or C(4)–H functionalization are still very limited.[23] It should be noted that functionalization of less active C(3)–H and C(4)–H bonds is a general problem for furan chemistry.[24,26]

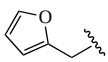
Within two last decades, ruthenium-catalyzed C–H activation has received wide application for benzene derivatives with directing groups.[27,28] Recently, furan compounds containing imine,[29] amide,[30,31] and quinoline-type[23] directing groups were also introduced into selective C–H functionalization of furan core. However, to the best of our knowledge, 2-benzimidazolyl moiety is still poorly studied as potential directing group in benzene compounds,[32,33] whereas derivatives of fuberidazole were not studied yet in Ru-catalyzed C–H functionalization. In this communication, we report on the results of C–H arylation of fuberidazole derivatives **1a–d** with the use of commercially available ruthenium precatalyst $[RuCl_2(cymene)]_2$ (see Scheme 1).

We revealed that heating 2-(furan-2-yl)-1-methylbenzimidazole **1a** with bromobenzene in the presence of $[RuCl_2(cymene)]_2$ and K_2CO_3 led to an arylated product **2a** in 7% yield (Table 1, entry 1). Encouraged by this result we studied



a R^1 = Me, R^2 = H
b R^1 = Bn, R^2 = Me
c R^1 = Me, R^2 = PhC(O)
d R^1 =  , R^2 = H

a R^1 = Me, R^2 = H, Ar = Ph, 94%
b R^1 = Me, R^2 = H, Ar = 4-MeC_6H_4, 78%
c R^1 = Me, R^2 = H, Ar = 3-MeC_6H_4, 84%
d R^1 = Me, R^2 = H, Ar = 4-$MeOC_6H_4$, 70%
e R^1 = Me, R^2 = H, Ar = 4-FC_6H_4, 82%
f R^1 = Me, R^2 = H, Ar = 4-$PhOC_6H_4$, 71%
g R^1 = Bn, R^2 = Me, Ar = Ph, 93%
h R^1 = Bn, R^2 = Me, Ar = 4-MeC_6H_4, 80%

i R^1 = Bn, R^2 = Me, Ar = 4-$MeOC_6H_4$, 67%
j R^1 = Bn, R^2 = Me, Ar = 4-FC_6H_4, 73%
k R^1 = Bn, R^2 = Me, Ar = 4-$PhOC_6H_4$, 75%
l R^1 = Me, R^2 = PhC(O), Ar = Ph, 71%
m R^1 = Me, R^2 = PhC(O), Ar = 4-$MeOC_6H_4$, 60%
n R^1 =  , R^2 = H, Ar = Ph, 66%

Scheme 1 *Reagents and conditions*: i, **1a–d** (0.25 mmol), ArBr (0.5 mmol), K_2CO_3 (0.5 mmol), $[RuCl_2(cymene)]_2$ (5 mol%), ButCOOH (30 mol%), 1,4-dioxane (2 ml), 100 °C, 24 h.

effect of carboxylic acid additives on the yield of product **2a** having in mind that metal-catalyzed CH-arylation reactions are often promoted by carboxylic acid anions *via* concerted metalation–deprotonation mechanism (CMD mechanism).[34] We observed that carboxylic acid additives (30 mol%) resulted in significant enhancement of the yields of **2a** (entries 2–5). Pivalic acid (Bu^{t}COOH) was found to be the most efficient promotor (entry 5), whereas acetic, benzoic or 2,4,6-trimethylbenzoic acids were less effective (entries 2–4). We also found that initially applied 30 mol% loading of pivalic acid can be accepted as the optimal loading (entry 5). Lower amounts of the promotor led to decrease in the yield, whereas higher loadings did not improve it.

Effects of other reaction conditions such as base, solvent and catalyst loading were also explored (see Table 1, entries 6–15). Among the bases studied, K_2CO_3 was found to be the most efficient (entries 5–9). The yields of **2a** in 1,4-dioxane (entry 5) were higher than in toluene, *N*-methylpyrrolidone (NMP) and water traditionally used for Ru-catalyzed C–H arylation (entries 12–14).[27,28,35] The catalyst loading of 5 mol% was accepted as optimal. Reducing Ru loading to 2.5 mol% led to decrease in the yield, however, raising this loading to 10 mol% did not improve the yield significantly. Lower yield of product **2a** was observed when PhI was used instead of PhBr, whereas only trace yield of **2a** was detected in case of PhCl. Therefore, bromoarenes were used in further studies.

With the optimal conditions in hand (see Table 1, entry 5), arylation of fuberidazole derivatives **1a**–**d** containing electron-withdrawing as well as electron-donating substituents in the position 5 of furan ring with various aryl bromides was investigated (see Scheme 1; for detailed experimental procedure and NMR studies, see Online Supplementary Materials). In all cases, the developed catalytic system provided selective C(3)–H arylation to give products **2a**–**n** in good and excellent yields, even in the case of substrate **1c** containing potential alternative directing benzoyl group in position 5 of the furan ring (structure of products **2l** and **2m** was confirmed by NOESY and HMBC experiments). Structures of the products were ultimately confirmed by single crystal X-ray analyses of compounds **2f** and **2i** (Figure 1).[†]

Table 1 Optimization of the reaction conditions.[a]

Entry	RCOOH	*T*/°C	Base	Solvent	Yield of **2a**[b] (%)
1	none	100	K_2CO_3	1,4-dioxane	7
2	MeCOOH	100	K_2CO_3	1,4-dioxane	43
3	PhCOOH	100	K_2CO_3	1,4-dioxane	20
4	MesCOOH	100	K_2CO_3	1,4-dioxane	41
5	Bu^{t}COOH	100	K_2CO_3	1,4-dioxane	96 (94[c]), 56,[d] trace[e]
6	Bu^{t}COOH	100	Cs_2CO_3	1,4-dioxane	66
7	Bu^{t}COOH	100	Na_2CO_3	1,4-dioxane	75
8	Bu^{t}COOH	100	KOH	1,4-dioxane	trace
9	Bu^{t}COOH	100	KOAc	1,4-dioxane	22
10	Bu^{t}COOH	80	K_2CO_3	1,4-dioxane	50
11	Bu^{t}COOH	120	K_2CO_3	1,4-dioxane	90
12	Bu^{t}COOH	100	K_2CO_3	toluene	59
13	Bu^{t}COOH	100	K_2CO_3	NMP	69
14	Bu^{t}COOH	100	K_2CO_3	H_2O	13
15	Bu^{t}COOH	100	K_2CO_3	1,4-dioxane	97,[f] 94,[g] 87,[h] 81[i]

[a] *Reagents and conditions*: **1a** (0.25 mmol), PhBr (0.4 mmol), $[RuCl_2(cymene)]_2$ (0.0125 mmol, 5 mol%), RCOOH (0.075 mmol), base (0.5 mmol), solvent (2 ml), 24 h. [b] The yield was determined by GCMS. [c] Isolated yield. [d] Reaction with PhI. [e] Reaction with PhCl. [f] $[RuCl_2(cymene)]_2$ (0.00625 mmol, 2.5 mol%). [g] $[RuCl_2(cymene)]_2$ (0.025 mmol, 10 mol%). [h] 16 h. [i] Bu^{t}COOH (15 mol%).

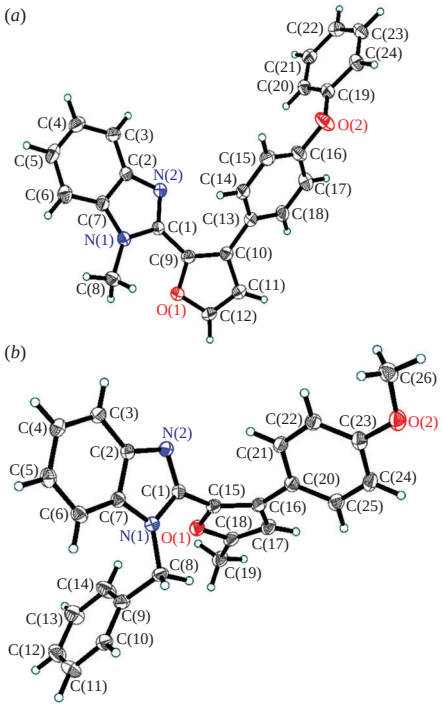


Figure 1 Molecular structures of (*a*) compound **2f** and (*b*) compound **2i**, *p* = 50%. Only one of four crystallographically inequivalent molecules of **2f** is shown. The disorder in **2i** is omitted.

In comparison with the recently reported procedure for the arylation of furans containing quinoline or quinoxaline directing groups,[23] our approach relies on the use of benzimidazol-2-yl moiety as a directing group, which does not require the application of phosphine ligands and operates under milder reaction conditions.

In conclusion, the effective use of benzimidazole moiety as directing group for the selective Ru-catalyzed C(3)–H arylation of furan ring was demonstrated for the first time. A series of previously inaccessible fuberidazole derivatives arylated in the position 3 of the furan core were prepared by the arylation of

[†] *Crystal data for* **2f**. $C_{24}H_{18}N_2O_2$, *M* = 366.40, triclinic, *P*1 at 100 K: *a* = 7.95355(7), *b* = 9.21984(6) and *c* = 24.96305(11) Å, α = 84.7922(4)°, β = 88.1032(6)°, γ = 88.5825(6)°, *V* = 1821.56(2) Å^3, *Z* = 4, d_{calc} = 1.336 g cm^{-3}, μ(CuKα) = 0.686 mm^{-1}, *F*(000) = 768. Total of 82483 reflections were measured and 14980 independent reflections (R_{int} = 0.0784) were used. The refinement converged to wR_2 = 0.1390 and GOF = 1.074 for all independent reflections [R_1 = 0.0495 was calculated against *F* for 14725 observed reflections with $I > 2\sigma(I)$].

Crystal data for **2i**. $C_{26}H_{22}N_2O_2$, *M* = 394.45, triclinic, $P\bar{1}$ at 100 K: *a* = 8.37238(8), *b* = 11.18203(13) and *c* = 12.01925(12) Å, α = 66.9764(10)°, β = 78.2678(8)°, γ = 84.5945(9)°, *V* = 1013.84(2) Å^3, *Z* = 2, d_{calc} = 1.292 g cm^{-3}, μ(CuKα) = 0.652 mm^{-1}, *F*(000) = 416. Total of 22636 reflections were measured and 4380 independent reflections (R_{int} = 0.0281) were used. The refinement converged to wR_2 = 0.0981 and GOF = 1.038 for all independent reflections [R_1 = 0.0389 was calculated against *F* for 4279 observed reflections with $I > 2\sigma(I)$].

The measurements were performed on a four-circle Rigaku Synergy-S diffractometer equipped with a HyPix-600HE area-detector (kappa geometry, shutterless ω-scan technique), using CuKα-radiation (λ = 1.54184 Å). The structures were solved by dual methods using SHELXT and refined by full-matrix least-squares on F^2 using SHELXL-2018 and OLEX2. All non-hydrogen atoms were refined with individual anisotropic displacement parameters. All hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters.

CCDC 2150291 and 2150292 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

1-alkyl-2-furylbenzimidazoles with aryl bromides using simple commercially available $[RuCl_2(cymene)]_2$ precatalyst and pivalic acid promotor. Further work is ongoing to expand the substrate scope to other 2-heteroaryl substituted furans and arylating agents.

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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.2022.07.018.

References

1 L. V. Romashov, K. S. Kozlov, M. K. Skorobogatko, A. Yu. Kostyukovich and V. P. Ananikov, *Chem. – Asian J.*, 2021, **17**, e202101227.
2 R. Banerjee, H. K. S. Kumar and M. Banerjee, *Int. J. Rev. Life Sci.*, 2012, **2**, 7.
3 E. V. Verbitskiy, S. A. Baskakova, D. V. Belyaev, D. V. Vakhrusheva, N. I. Eremeeva, G. L. Rusinov and V. N. Charushin, *Mendeleev Commun.*, 2021, **31**, 210.
4 F. Petrelli, M. Ghidini, V. Lonati, G. Tomasello, K. Borgonovo, M. Ghilardi, M. Cabiddu and S. Barni, *Eur. J. Cancer*, 2017, **84**, 141.
5 P. A. LeWitt, S. D. Aradi, R. A. Hauser and O. Rascol, *Parkinsonism Relat. Disord.*, 2020, **80**, S54.
6 A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582.
7 N. F. Aftab, K. S. Ahmad and M. M. Gul, *Int. J. Environ. Anal. Chem.*, 2021, doi.org/10.1080/03067319.2021.1949586.
8 Y. Wen, J. Li, F. Yang, W. Zhang, W. Li, C. Liao and L. Chen, *Talanta*, 2013, **106**, 119.
9 A. Temirak, Y. M. Shaker, F. A. F. Ragab, M. M. Ali, H. I. Ali and H. I. El Diwani, *Eur. J. Med. Chem.*, 2014, **87**, 868.
10 M. A. Abdullaziz, H. T. Abdel-Mohsen, A. M. El Kerdawy, F. A. F. Ragab, M. M. Ali, S. M. Abu-Bakr, A. S. Girgis and H. I. El Diwani, *Eur. J. Med. Chem.*, 2017, **136**, 315.
11 H. T. Abdel-Mohsen, M. A. Abdullaziz, A. M. El Kerdawy, F. A. F. Ragab, K. J. Flanagan, A. E. E. Mahmoud, M. M. Ali, H. I. El Diwani and M. O. Senge, *Molecules*, 2020, **25**, 770.
12 L. Racané, I. Zlatar, N. Perin, M. Cindrić, V. Radovanović, M. Banjanac, S. Shanmugam, M. R. Stojković, K. Brajša and M. Hranjec, *Molecules*, 2021, **26**, 4935.
13 P. Peixoto, Y. Liu, S. Depauw, M.-P. Hildebrand, D. W. Boykin, C. Bailly, W. D. Wilson and M.-H. David-Cordonnier, *Nucleic Acids Res.*, 2008, **36**, 3341.
14 D. W. Dunwell, D. Evans and T. A. Hicks, *J. Med. Chem.*, 1975, **18**, 1158.
15 J. Kim, S. Lee, S. Kim, M. Jung, H. Lee and M. S. Han, *Dyes Pigm.*, 2020, **177**, 108291.
16 J.-H. Hei, Y.-X. Zhi, Y. Zhen, J. Li and F.-X. Zhang, *J. Coord. Chem.*, 2013, **66**, 1320.
17 Q.-F. Li, M.-J. Li, H.-X. Lin, P.-P. Xu, Z.-B. Gu and Y.-M. Cui, *Heterocycl. Commun.*, 2016, **22**, 21.
18 A. A. Aleksandrov, M. M. Elchaninov, D. A. Tishina, Yu. E. Tarakanova and M. L. Shmanovsky, *Russ. J. Org. Chem.*, 2021, **57**, 664 (*Zh. Org. Khim*., 2021, **57**, 583).
19 A. A. Aleksandrov, M. M. El'chaninov and D. A. Zablotskii, *Russ. J. Gen. Chem.*, 2019, **89**, 37 (*Zh. Obshch. Khim*., 2019, **89**, 45).
20 M. M. El'chaninov, A. M. Simonov and L. Ya. Oleinikova, *Chem. Heterocycl. Compd.*, 1983, **19**, 1041 (*Khim. Geterotsikl. Soedin*., 1983, **19**, 1311).
21 F. Abdellaoui, C. Youssef, H. Ben Ammar, J.-F. Soulé and H. Doucet, *Synthesis*, 2014, **46**, 3341.
22 O. V. Khazipov, K. E. Shepelenko, D. V. Pasyukov, V. V. Chesnokov, S. B. Soliev, V. M. Chernyshev and V. P. Ananikov, *Org. Chem. Front.*, 2021, **8**, 2515.
23 H. H. Al Mamari, U. Grošelj, F. Požgan and H. Brodnik, *J. Org. Chem.*, 2021, **86**, 3138.
24 B. Y. Karlinskii and V. P. Ananikov, *ChemSusChem*, 2021, **14**, 558.
25 F. A. Kucherov, L. V. Romashov, K. I. Galkin and V. P. Ananikov, *ACS Sustainable Chem. Eng.*, 2018, **6**, 8064.
26 B. Ya. Karlinskii, A. Yu. Kostyukovich, F. A. Kucherov, K. I. Galkin, K. S. Kozlov and V. P. Ananikov, *ACS Catal.*, 2020, **10**, 11466.
27 P. Nareddy, F. Jordan and M. Szostak, *ACS Catal.*, 2017, **7**, 5721.
28 R. Gramage-Doria and C. Bruneau, *Coord. Chem. Rev.*, 2021, **428**, 213602.
29 F. Siopa, V.-A. Ramis Cladera, C. A. M. Afonso, J. Oble and G. Poli, *Eur. J. Org. Chem.*, 2018, 6101.
30 P. Nareddy, F. Jordan, S. E. Brenner-Moyer and M. Szostak, *ACS Catal.*, 2016, **6**, 4755.
31 J. M. J. M. Ravasco, C. M. Monteiro, F. Siopa, A. F. Trindade, J. Oble, G. Poli, S. P. Simeonov and C. A. M. Afonso, *ChemSusChem*, 2019, **12**, 4629.
32 Y.-G. Li, Z.-Y. Wang, Y.-L. Zou, C.-M. So, F.-Y. Kwong, H.-L. Qin and E. A. B. Kantchev, *Synlett*, 2017, **13**, 499.
33 G.-F. Zha, H.-L. Qin and E. A. B. Kantchev, *RSC Adv.*, 2016, **6**, 30875.
34 L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315.
35 K. E. Shepelenko, K. A. Nikolaeva, M. A. Shevchenko, Yu. N. Tkachenko, M. N. Minyaev and V. M. Chernyshev, *Mendeleev Commun.*, 2022, **32**, 205.

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