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Metal-free aerobic oxidation of benzazole derivatives†

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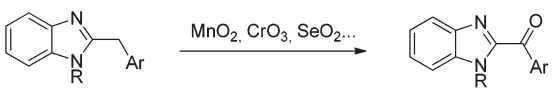
Aurélie Dos Santos,[a] Laurent El Kaïm*[a] and Laurence Grimaud*[b]

2-Benzyl benzothiazoles and benzimidazoles are easily oxidized under air and basic conditions to give the corresponding ketones in good yields. The use of palladium acetate as a catalyst has little effect and even gives, in some cases, much lower yields.

Introduction

The growing concern about environmental issues has led chemists to revise many synthetic processes that used one or several equivalents of reagents associated with waste disposal problems. In the case of oxidative processes, this trend has been associated with the substitution of stoichiometric oxidants such as chromium, lead or silver salts by oxygen or peroxides under the activation of metal catalysts.[1] Thus, recent years have seen a renewed interest in copper and palladium-catalyzed oxidations. Benzimidazoles substituted by benzyl groups at the 2-position are known to be easily oxidized into 2-keto analogues under treatment with stoichiometric amounts of chromium(VI) oxide,[2] manganese(IV) oxide,[3] or selenium dioxide (Scheme 1).[4]

Similar transformations were also reported with benzothiazoles, benzoxazoles as well as their related non-fused heterocycles.[5] Oxygen may be used in place of these toxic reagents but a metal salt such as $CoCl_2$ [6] or $RuCl_3$ [7] was added for the conversion into ketones. While working on alkylations of 2-benzylbenzimidazole derivatives, the ketone was frequently obtained as a side-product. To control this process, we decided to examine further the aerobic oxidation of benzazoles and the effect of metals (such as copper or palladium) known to trigger similar transformations.

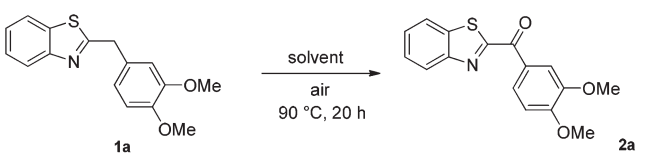


Scheme 1 Oxidation of 2-benzylbenzimidazoles.

Results and discussion

Benzothiazole **1a** possessing an electron-rich aryl group was selected as a probe to study the aerobic oxidation of the benzyl group. It was treated under air with a catalytic amount of palladium acetate under various conditions and the reactions stopped after 20 hours (Scheme 2). Moderate to good yields of ketone **2a** were obtained under both acidic and basic conditions. The optimized conditions turned out to be in DMF at 90 °C using 10% palladium acetate with cesium pivalate as a base. In a control experiment, **1a** was then treated with cesium carbonate without any palladium. To our surprise, **2a** was obtained within the same reaction time in almost the same yield showing that palladium had little influence on the process.[8] Potassium carbonate as well as sodium acetate gave lower yields and, in the absence of a base, the starting material was recovered quantitatively.

Simple aerobic oxidation of benzazoles is not unprecedented but usually associated with highly specific structures



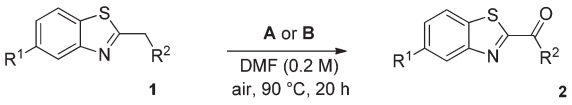
$Pd(OAc)_2$ 10%, DMA (0.2 M):	27%
$Pd(OAc)_2$ 10%, DMA (0.2 M), AcOH (4 equiv):	39%
$Pd(OAc)_2$ 10%, DMA (0.2 M), Cs_2CO_3 (1 equiv):	64%
$Pd(OAc)_2$ 10%, CH_3CN (0.2 M), Cs_2CO_3 (1 equiv):	79%
$Pd(OAc)_2$ 10%, DMF (0.2 M), Cs_2CO_3 (1 equiv):	73%
$Pd(OAc)_2$ 10%, DMF (0.2 M), CsOPiv (1 equiv):	85%
DMF (0.2 M), Cs_2CO_3 (1 equiv):	88%
DMF (0.2 M), K_2CO_3 (1 equiv):	78%
DMF (0.2 M), NaOAc (1 equiv):	50%

Scheme 2 Aerobic oxidation of benzothiazole **1a** to **2a**.

[a]*DCSO-UMR 7652: CNRS-ENSTA-Ecole Polytechnique, Laboratoire Chimie et Procédés, Ecole Nationale Supérieure de Techniques Avancées, 828 Bd des Maréchaux, 91762 Palaiseau Cedex, France.*
E-mail: laurent.elkaim@ensta-paristech.fr; Tel: +33181872020
[b]*Ecole Normale Supérieure, Département de chimie, CNRS-UMR 8640-UPMC, 24 rue Lhomond, 75231 Paris Cedex 05, France. E-mail: laurence.grimaud@ens.fr*

†Electronic supplementary information (ESI) available: Preparation of starting materials **1** and **3** as well as proton and carbon NMR spectra for all compounds. See DOI: 10.1039/c3ob27404g

Table 1 Aerobic oxidation of 2-benzylbenzothiazole derivatives



Entry	R^1	R^2	2	Yield (**A**, %)	Yield (**B**, %)
1	Cl	3,4-$(MeO)_2C_6H_3$	**2b**	48	71
2	H	Ph	**2c**	58[a]	67
3	Cl	Ph	**2d**	46	73
4	H	2-Thiophenyl	**2e**	54	19
5	H	4-FC_6H_4	**2f**	49	0[b]

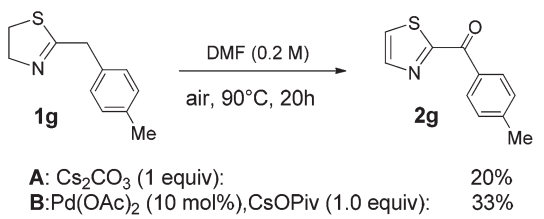
[a] The same reaction performed with *t*BuOK (1 equiv.), DBU (1 equiv.) and Cs_2CO_3 (0.2 equiv.) as bases gave **2c** in 20%, 56% and 76% isolated yields. [b] A substitution of the fluorine atom by a dimethylamino group was observed in the final ketone (obtained in 26% isolated yield).

such as methylpyridinium substituted derivatives.[9] In order to test the generality of the process, a variety of benzothiazoles were treated under air in DMF with cesium carbonate. The same reactions were performed with palladium acetate as a catalyst to confirm the behaviour observed with **1a**. The results are displayed in Table 1. If the palladium catalysed process gave slightly better yields, the trend is not general as observed for the thiophenyl substituted benzothiazole **2e** (Table 1, entry 4). In the case of 4-fluoroaryl derivatives the difference is even more pronounced as different compounds were formed under both sets of conditions (Table 1, entry 5). The palladium catalyzed formation of a dimethylamino derivative may be explained by an S_NAr process between intermediate **2f** and dimethylamine formed through fragmentation of DMF.

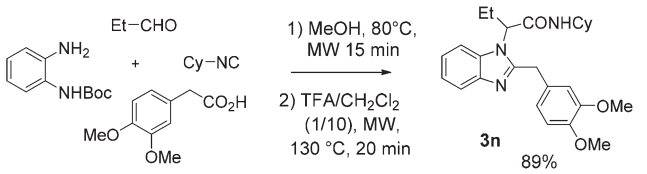
The same reactions may be observed for simple thiazole derivatives as shown by the oxidation of dihydrothiazole **1g** to thiazole **2g** formed in moderate yield (Scheme 3).

The study was then extended to benzimidazole derivatives. The starting materials were prepared according to standard procedures from phenylenediamine derivatives except for benzimidazoles **3n**, **3o** and **3p** which were prepared through an Ugi reaction involving *N*-Boc protected phenylenediamine (Scheme 4 for **3n**).[10]

The aerobic oxidations were performed under basic conditions with and without palladium. In the latter case, $PdCl_2(CH_3CN)_2$ was preferred over $Pd(OAc)_2$ as it gave slightly higher yields with benzimidazoles. For most benzimidazoles



Scheme 3 Aerobic thiazole oxidation.



Scheme 4 Ugi-deBoc-Cyclize strategy for the preparation of benzimidazole **3n**.

tested, the addition of palladium has a detrimental effect on yields. This could be explained by a competing CH activation pathway of the benzyl group leading to fused indolobenzimidazole derivatives *via* C–N bond formation. However, we could not isolate any compound that could support such a mechanistic pathway.

The yields are in general much better for *N*-alkyl substituted derivatives under both sets of conditions (Table 2, entries 9–11 and 14–16). This observation, together with the need for a base, suggests that the reaction probably proceeds through deprotonation of the CH_2 benzylic group (or its enamine tautomer) to form an electron-rich enamine which is easily oxidized. N–H benzimidazole derivatives should be preferentially deprotonated at the N–H position making the base-induced conversion into enamine more difficult to achieve under these moderately basic conditions. Tosyl or carboethoxy groups on the N atom of the benzimidazole (Table 1, entries 12 and 13) are not tolerated under these conditions, the NH deprotected oxidized derivatives **4a** and **4b** being recovered in moderate yields. The high yields obtained with Ugi–benzimidazole adducts (Table 1, entries 14–16) are interesting as even more complex fused benzimidazoles may be obtained through further cyclizations. Such ketones might be difficult to form directly from an Ugi reaction with ketocarboxylic acid due to potential competition in both Ugi step and benzimidazole cyclization.

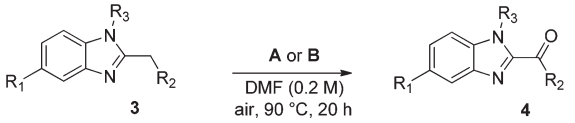
Experimental section

^1H NMR spectra were recorded on a 400 MHz spectrometer, using $CDCl_3$ solvent as a reference and/or an internal deuterium lock. ^{13}C NMR spectra were recorded on a 100.6 MHz spectrometer. Two-dimensional NMR spectroscopy [^1H–^1H COSY spectra, ^1H–^{13}C COSY spectra (HSQC) and long-range ^1H–^{13}C COSY spectra (HMBC)] was carried out to determine the correlation between ^1H and ^{13}C. The chemical shifts for all NMR spectra are expressed in parts per million to high frequency of TMS reference. Coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.1 Hz. The IR spectra were obtained using ATR accessories. High-resolution (HR) mass spectra were performed on a GC/MS system spectrometer. TLC was carried out using precoated plates of silica gel 60F254.

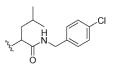
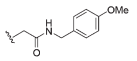
General procedure for the preparation of ketones 2a–2g

Procedure A: to a 0.2 M solution of benzothiazole (1.0 equiv.) in DMF was added Cs_2CO_3 (1.0 equiv.). The resulting mixture was

Table 2 Aerobic oxidation of 2-benzylbenzimidazole derivatives



A: Cs_2CO_3 (1 equiv)
B:$PdCl_2(CH_3CN)_2$ (10 mol%), CsOPiv (1.0 equiv)

Entry	R^1	R^2	R^3	2	Yield (**A**, %)	Yield (**B**, %)
1	H	3,4-$(MeO)_2C_6H_3$	H	**4a**	28	25
2	H	4-MeC_6H_4	H	**4b**	19	46
3	Cl	4-MeC_6H_4	H	**4c**	71	54
4	COPh	Ph	H	**4d**	73	37
5	NO_2	Ph	H	**4e**	29	20
6	H	CH_2Ph	H	**4f**	0	0
7	Me	2-Thiophenyl	H	**4g**	52	29
8	H	Ph	H	**4h**	21[a]	9
9	H	3,4-$(MeO)_2C_6H_3$	Et	**4i**	90	67
10	H	4-MeC_6H_4	4-*t*-$BuC_6H_4CH_2$	**4j**	84	74
11	H	3,4-$(MeO)_2C_6H_3$	Homoallyl	**4k**	76	65
12	H	3,4-$(MeO)_2C_6H_3$	CO_2Et	**4l**	0[b]	0[b]
13	H	4-MeC_6H_4	Tosyl	**4m**	0[c]	0[c]
14	H	3,4-$(MeO)_2C_6H_3$		**4n**	80	36
15	H	4-MeC_6H_4		**4o**	66	11
16	Cl	Ph		**4p**	73	39

[a] When the amount of $CsCO_3$ was lowered to 0.2 equiv. the yield dropped to 5%. [b] **4a** (28% with $Pd(OAc)_2$ and 37% without) was recovered instead of the expected **4l**. [c] **4b** (32% with $Pd(OAc)_2$ and 40% without) was recovered instead of the expected **4m**.

stirred at 90 °C for 20 h under air. After removal of the DMF by distillation with a Krugelrohr, the crude product was purified by flash chromatography on silica gel.

Procedure B: to a 0.2 M solution of benzothiazole (1.0 equiv.) in DMF were added $Pd(OAc)_2$ (10 mol%) and CsOPiv (1.0 equiv.). The resulting mixture was stirred at 90 °C for 20 h under air. After removal of the DMF by distillation with a Krugelrohr, the crude product was purified by flash chromatography on silica gel.

Benzo[*d*]thiazol-2-yl(3,4-dimethoxyphenyl)methanone 2a. Procedure A was followed using the benzothiazole **1a** (50 mg, 0.18 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2). 46 mg (88%) of the desired adduct (yellow solid, M.p.: 170–171 °C) were isolated. R_f 0.9 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.55 (d, J = 8.6 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 8.05–8.02 (m, 2H), 7.61–7.53 (m, 2H), 7.03 (d, J = 8.6 Hz, 1H), 4.02 (s, 3H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 183.3, 167.8, 154.2, 153.8, 148.9, 136.8, 127.7, 127.4, 127.2, 126.8, 125.5, 122.1, 112.7, 110.2, 56.1, 56.0; IR (ν, cm^{-1}) 2936, 2838, 1632, 1593, 1583, 1513, 1489, 1461, 1419, 1300, 1273, 1231, 1182, 1150, 1115, 1025; HRMS calcd for $C_{16}H_{13}NO_3S$ 299.0616, found 299.0618.

(5-Chlorobenzo[*d*]thiazol-2-yl)(3,4-dimethoxyphenyl)methanone 2b. Procedure A was followed using the benzothiazole **1b** (50 mg, 0.16 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2). 25 mg (48%) of the desired adduct (yellow solid, M.p.: 167–168 °C) were isolated. R_f 0.7 (100% CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (d, J = 8.1 Hz, 1H), 8.19 (s, 1H), 8.02 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 4.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 182.7, 169.7, 154.5, 154.4, 148.9, 135.0, 132.8, 127.9, 127.4, 127.3, 125.0, 122.9, 112.6, 110.2, 56.1, 56.0; IR (ν, cm^{-1}) 3072, 3006, 2939, 2842, 1642, 1597, 1579, 1513, 1489, 1464, 1440, 1419, 1304, 1276, 1224, 1185, 1143, 1112, 1067, 1021; HRMS calcd for $C_{16}H_{12}ClNO_3S$ 333.0226, found 333.0227.

Benzo[*d*]thiazol-2-yl(phenyl)methanone 2c. Procedure A was followed using the benzothiazole **1c** (50 mg, 0.22 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2). 30 mg (56%) of the desired adduct (brown solid, M.p.: 103–104 °C) were isolated. R_f 0.9 (100% CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (d, J = 7.8 Hz, 2H), 8.25 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.68 (t, J = 7.8, 7.8 Hz, 1H), 7.61–7.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 185.4, 167.1, 153.8, 136.9, 134.9, 133.9, 131.2, 128.5, 127.6, 126.9, 125.7, 122.1; IR (ν, cm^{-1}) 3069, 1649, 1597, 1579, 1485, 1447, 1321, 1290, 1276, 1185, 1119, 1063, 1032; HRMS calcd for $C_{14}H_9NOS$ 239.0405, found 239.0405.

(5-Chlorobenzo[*d*]thiazol-2-yl)(phenyl)methanone 2d. Procedure A was followed using the benzothiazole **1d** (50 mg,

0.19 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2). 24 mg (46%) of the desired adduct (brown solid, M.p.: 133–134 °C) were isolated. R_f 0.9 (100% CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, J = 8.1 Hz, 2H), 8.23 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.68 (dd, J = 8.1, 6.8 Hz, 1H), 7.58–7.55 (m, 2H), 7.51 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 184.9, 168.9, 154.5, 135.2, 134.6, 134.1, 133.0, 131.3, 128.5, 128.2, 125.2, 122.9; IR (ν, cm^{-1}) 3072, 1646, 1593, 1489, 1436, 1286, 1234, 1192, 1122, 1070, 1056; HRMS calcd for $C_{14}H_8ClNOS$ 273.0015, found 273.0014.

Benzo[*d*]thiazol-2-yl(thiophen-2-yl)methanone 2e. Procedure A was followed using the benzothiazole **1e** (100 mg, 0.43 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2). 57 mg (54%) of the desired adduct (brown solid, M.p.: 108–109 °C) were isolated. R_f 0.8 (100% CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.77 (d, J = 4.3 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 4.3 Hz, 1H), 7.59 (dd, J = 8.1, 7.3 Hz, 1H), 7.53 (dd, J = 7.8, 7.3 Hz, 1H), 7.27–7.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 176.9, 166.5, 153.6, 139.6, 137.4, 136.9, 136.8, 128.5, 127.5, 126.9, 125.5, 122.2; IR (ν, cm^{-1}) 3100, 1621, 1506, 1489, 1408, 1360, 1321, 1297, 1276, 1234, 1119, 1067, 1039; HRMS calcd for $C_{12}H_7NOS_2$ 244.9969, found 244.9968.

Benzo[*d*]thiazol-2-yl(4-fluorophenyl)methanone 2f. Procedure A was followed using the benzothiazole **1f** (50 mg, 0.21 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2). 26 mg (49%) of the desired adduct (yellow solid, M.p.: 108–109 °C) were isolated. R_f 0.9 (9 : 1 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.71–8.66 (m, 2H), 8.24 (d, J = 7.6 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.60 (dd, J = 8.1, 7.3 Hz, 1H), 7.56 (dd, J = 7.6, 7.3 Hz, 1H), 7.26–7.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 183.6, 166 (d, J_{C-F} = 251.7 Hz), 160.8, 153.8, 136.9, 134.2 (d, J_{C-F} = 9.5 Hz), 131.2 (d, J_{C-F} = 3.0 Hz), 127.7, 127.0, 125.7, 122.2, 115.7 (d, J_{C-F} = 20.5 Hz); IR (ν, cm^{-1}) 3069, 1642, 1590, 1485, 1457, 1422, 1290, 1272, 1238, 1161, 1122, 1105, 1018; HRMS calcd for $C_{14}H_8FNOS$ 257.0311, found 257.0320.

Thiazol-2-yl(*p*-tolyl)methanone 2g. Procedure A was followed using the thiazole **1g** (100 mg, 0.52 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2). 21 mg (20%) of the desired adduct (yellow solid, M.p.: 48–49 °C) were isolated. R_f 0.8 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40–8.37 (m, 2H), 8.09–8.07 (m, 1H), 7.71–7.69 (m, 1H), 7.34–7.31 (m, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 183.7, 168.2, 144.7, 132.5, 131.2, 129.7, 129.1, 126.0, 21.8; IR (ν, cm^{-1}) 3114, 3082, 3037, 2925, 2863, 1642, 1607, 1569, 1482, 1415, 1387, 1328, 1293, 1189, 1164, 1112, 1060, 1025; HRMS calcd for $C_{11}H_9NOS$ 203.0405, found 203.0403.

General procedure for the preparation of ketones 4a–4p

To a 0.2 M solution of benzimidazole (1.0 equiv.) in DMF was added Cs_2CO_3 (1.0 equiv.). The resulting mixture was stirred at 90 °C for 20 h under air. After removal of the DMF by distillation with a Krugelrohr, the crude product was purified by flash chromatography on silica gel.

(1*H*-Benzo[*d*]imidazol-2-yl)(3,4-dimethoxyphenyl)methanone 4a. The general procedure was followed using the benzimidazole **3a** (100 mg, 0.37 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2–AcOEt). 29 mg (28%) of the desired adduct (yellow solid, M.p.: 169–170 °C) were isolated. R_f 0.8 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.02 (br s, 1H), 8.75 (d, J = 8.6 Hz, 1H), 8.14 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.43–7.34 (m, 2H), 7.00 (d, J = 8.6 Hz, 1H), 4.00 (s, 3H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 182.0, 154.2, 148.8, 148.1, 143.9, 133.1, 128.3, 127.5, 126.1, 123.5, 122.0, 112.5, 111.9, 110.2, 56.1, 56.0; IR (ν, cm^{-1}) 3309, 3292, 2936, 2835, 1628, 1597, 1576, 1510, 1492, 1454, 1426, 1325, 1272, 1234, 1143, 1025; HRMS calcd for $C_{16}H_{14}N_2O_3$ 282.1004, found 282.0993.

(1*H*-Benzo[*d*]imidazol-2-yl)(*p*-tolyl)methanone 4b. The general procedure was followed using the benzimidazole **3b** (100 mg, 0.45 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2). 20 mg (19%) of the desired adduct (white solid, M.p.: 256–257 °C) were isolated. R_f 0.8 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.51 (br s, 1H), 8.63 (d, J = 7.8 Hz, 2H), 7.98 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.45 (dd, J = 8.1, 7.1 Hz, 1H), 7.40–7.36 (m, 3H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 183.4, 147.9, 145.0, 143.9, 133.0, 132.8, 131.4, 129.3, 126.3, 123.7, 122.2, 111.8, 21.9; IR (ν, cm^{-1}) 2915, 2866, 1656, 1607, 1489, 1419, 1391, 1318, 1265, 1178, 1140, 1122, 1035, 1014; HRMS calcd for $C_{15}H_{12}N_2O$ 236.0950, found 236.0951.

(5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(*p*-tolyl)methanone and (6-chloro-1*H*-benzo[*d*]imidazol-2-yl)(*p*-tolyl)methanone 4c. the procedure L was followed using the benzimidazole **3c** (95 mg, 0.37 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2). 71 mg (71%) of the desired adduct (white solid, M.p.: 209–210 °C) were isolated as a 4 : 6 inseparable mixture of two isomers. R_f 0.8 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.75 (br s, 0.4H), 10.70 (br s, 0.6H), 8.61 (d, J = 7.8 Hz, 2H), 7.95 (s, 0.4H), 7.88 (d, J = 8.6 Hz, 0.6H), 7.58 (s, 0.6H), 7.52 (d, J = 8.6 Hz, 0.4H), 7.41–7.33 (m, 3H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 183.2, 183.1, 148.9, 148.6, 145.4, 145.3, 142.5, 133.5, 132.6, 132.5, 131.5, 131.4, 129.3, 129.2, 126.9, 124.7, 123.1, 121.7, 112.8, 111.8, 21.9; IR (ν, cm^{-1}) 3295, 2925, 1632, 1604, 1503, 1410, 1311, 1252, 1189, 1067, 1014; HRMS calcd for $C_{15}H_{11}ClN_2O$ 270.0560, found 270.0559.

(1*H*-Benzo[*d*]imidazole-2,6-diyl)bis(phenylmethanone) 4d. The general procedure was followed using the benzimidazole **3d** (100 mg, 0.32 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2–AcOEt). 76 mg (73%) of the desired adduct (yellow solid, M.p.: 206–207 °C) were isolated. R_f 0.8 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.05 (m, 1H), 8.71 (dd, J = 8.6, 8.3 Hz, 2H), 8.41 (s, 1H), 8.06 (dd, J = 9.6, 9.1 Hz, 1H), 7.85 (d, J = 7.3 Hz, 2H), 7.72–7.66 (m, 2H), 7.62–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 196.4, 183.6, 149.3, 143.1, 137.9, 135.9, 135.0,

134.2, 133.4, 132.3, 131.3, 130.0, 128.6, 128.3, 128.0, 126.1, 125.5, 121.9, 115.1, 112.2; IR (ν, cm^{-1}) 3296, 3075, 1653, 1618, 1597, 1576, 1506, 1478, 1450, 1398, 1321, 1266, 1245, 1227, 1185, 1116, 1014; HRMS calcd for $C_{21}H_{14}N_2O_2$ 326.1055, found 326.1045.

(5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)(phenyl)methanone 4e. The general procedure was followed using the benzimidazole **3e** (100 mg, 0.39 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2). 31 mg (29%) of the desired adduct (yellow solid, M.p.: 256–257 °C) were isolated. R_f 0.9 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR (DMSO, 400 MHz) δ 14.17 (s, 1H), 8.70 (br s, 1H), 8.56 (d, J = 7.1 Hz, 2H), 8.26 (d, J = 8.3 Hz, 1H), 7.90 (br s, 1H), 7.78 (dd, J = 7.6, 7.3 Hz, 1H), 7.65 (dd, J = 7.3, 7.1 Hz, 2H); ^{13}C NMR (DMSO, 100.6 MHz) δ 138.3, 151.5, 144.0, 135.0, 134.2, 131.0, 128.6, 119.8, 116.5, 116.0; IR (ν, cm^{-1}) 3267, 2151, 2022, 1963, 1635, 1590, 1572, 1534, 1346, 1332, 1265, 1018; HRMS calcd for $C_{14}H_9N_3O_3$ 267.0644, found 267.0653.

(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)(thiophen-2-yl)methanone and (6-methyl-1*H*-benzo[*d*]imidazol-2-yl)(thiophen-2-yl)methanone 4g. The general procedure was followed using the benzimidazole **3g** (100 mg, 0.44 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2). 61 mg (57%) of the desired adduct (yellow solid, M.p.: 174–175 °C) were isolated as an inseparable 4 : 6 mixture of 2 isomers. R_f 0.7 (100% CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.74 (br s, 0.4H), 10.67 (br s, 0.6H), 8.93–8.91 (m, 1H), 7.84–7.82 (m, 1.6H), 7.74 (s, 0.4H), 7.49 (d, J = 8.3 Hz, 0.4H), 7.38 (s, 0.6H), 7.28–7.26 (m, 1.4H), 7.20 (d, J = 8.3 Hz, 0.6H), 2.52 (s, 1.8H), 2.51 (s, 1.2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.9, 175.8, 147.3, 146.9, 144.2, 142.1, 140.5, 140.4, 137.8, 137.7, 136.9, 136.8, 136.5, 136.4, 133.7, 133.6, 128.6, 128.3, 125.8, 121.5, 121.4, 111.6, 111.5, 22.1, 21.7; IR (ν, cm^{-1}) 3281, 1611, 1527, 1412, 1356, 1325, 1269, 1053, 1001; HRMS calcd for $C_{13}H_{10}N_2OS$ 242.0514, found 242.0507.

(1*H*-Benzo[*d*]imidazol-2-yl)(phenyl)methanone 4h. The general procedure was followed using the benzimidazole **3h** (100 mg, 0.48 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2). 22 mg (21%) of the desired adduct (white solid, M.p.: 218–219 °C) were isolated. R_f 0.8 (9 : 1 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.76 (br s, 1H), 8.71 (d, J = 7.1 Hz, 2H), 7.98 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 7.3 Hz, 1H), 7.62–7.55 (m, 3H), 7.45 (dd, J = 8.1, 7.1 Hz, 1H), 7.38 (dd, J = 7.3, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 184.0, 147.7, 143.9, 135.3, 133.9, 133.1, 131.3, 128.5, 126.5, 123.8, 122.3, 112.0; IR (ν, cm^{-1}) 3302, 3065, 1646, 1600, 1579, 1510, 1489, 1422, 1321, 1262, 1182, 1147, 1039, 1021; HRMS calcd for $C_{14}H_{10}N_2O$ 222.0793, found 222.0796.

(3,4-Dimethoxyphenyl)(1-ethyl-1*H*-benzo[*d*]imidazol-2-yl)methanone 4i. The general procedure was followed using the benzimidazole **3i** (50 mg, 0.17 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2–AcOEt). 47 mg (90%) of the desired adduct (yellow solid, M.p.: 82–83 °C) were isolated. R_f 0.9 (100% CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.86 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.45 (dd, J = 8.1, 6.8 Hz, 1H), 7.38 (dd, J = 8.3, 6.8 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 4.60 (q, J = 7.1 Hz, 2H), 3.98 (s, 6H), 1.56 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 184.7, 153.9, 148.8, 146.6, 141.9, 135.4, 129.7, 127.3, 125.3, 123.4, 121.9, 112.3, 110.4, 110.1, 56.2, 56.0, 40.5, 15.6; IR (ν, cm^{-1}) 2974, 2936, 2842, 1642, 1593, 1579, 1517, 1482, 1468, 1419, 1335, 1297, 1262, 1238, 1210, 1178, 1133, 1025, 1004; HRMS calcd for $C_{18}H_{18}N_2O_3$ 310.1317, found 310.1316.

(1-(4-(*tert*-Butyl)benzyl)-1*H*-benzo[*d*]imidazol-2-yl)(*p*-tolyl)methanone 4j. The general procedure was followed using the benzimidazole **3j** (100 mg, 0.27 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2). 87 mg (84%) of the desired adduct (white solid, M.p.: 146–147 °C) were isolated. R_f 0.6 (100% CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.42–7.27 (m, 6H), 7.15 (d, J = 7.8 Hz, 2H), 5.82 (s, 2H), 2.45 (s, 3H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 186.1, 150.5, 146.6, 144.5, 141.9, 136.0, 134.3, 133.6, 131.3, 129.0, 126.5, 125.6, 123.6, 122.0, 111.1, 48.2, 34.4, 31.2, 21.8; IR (ν, cm^{-1}) 2964, 2866, 1642, 1607, 1520, 1478, 1450, 1398, 1335, 1269, 1175, 1011; HRMS calcd for $C_{26}H_{26}N_2O$ 382.2045, found 382.2047.

(1-(But-3-en-1-yl)-1*H*-benzo[*d*]imidazol-2-yl)(3,4-dimethoxyphenyl)methanone 4k. The general procedure was followed using the benzimidazole **3k** (96 mg, 0.30 mmol). The crude product was purified using silica gel column chromatography (CH_2Cl_2–AcOEt). 76 mg (76%) of the desired adduct (yellow oil) were isolated. R_f 0.8 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.82 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.44 (dd, J = 8.1, 7.1 Hz, 1H), 7.36 (dd, J = 8.1, 7.1 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 5.80 (ddt, J = 16.9, 10.1, 7.1 Hz, 1H), 5.02 (d, J = 16.9 Hz, 1H), 4.99 (d, J = 10.1 Hz, 1H), 4.62 (t, J = 7.1 Hz, 2H), 3.97 (s, 6H), 2.68–2.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 184.9, 153.9, 148.8, 146.8, 141.8, 135.6, 134.0, 129.7, 127.4, 125.3, 123.4, 121.9, 117.9, 112.3, 110.6, 110.0, 56.1, 56.0, 44.6, 34.6; IR (ν, cm^{-1}) 3058, 3009, 2939, 2915, 2838, 1642, 1593, 1583, 1513, 1478, 1461, 1419, 1336, 1266, 1234, 1175, 1133, 1021; HRMS calcd for $C_{20}H_{20}N_2O_3$ 336.1474, found 336.1483.

***N*-Cyclohexyl-2-(2-(3,4-dimethoxybenzoyl)-1*H*-benzo[*d*]imidazol-1-yl)butanamide 4n.** The general procedure was followed using the Ugi adduct **3n** (100 mg, 0.23 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2–AcOEt). 83 mg (80%) of the desired adduct (colorless oil) were isolated. R_f 0.8 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 7.1 Hz, 1H), 7.79–7.77 (m, 2H), 7.40–7.34 (m, 2H), 6.99 (d, J = 8.6 Hz, 1H), 6.88 (s, 1H), 5.30–5.26 (m, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.80–3.75 (m, 1H), 2.34–2.20 (m, 2H), 1.97–1.94 (m, 1H), 1.70–1.62 (m, 2H), 1.52–1.51 (m, 2H), 1.39–1.20 (m, 4H), 0.98–0.90 (m, 1H), 0.62 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 185.8, 167.1, 154.8, 149.1, 148.3, 142.1, 134.1, 128.9, 128.2, 125.6, 123.8, 121.7, 113.6, 111.9, 110.2, 61.1, 56.2, 56.0, 48.4, 32.7, 32.5, 25.4, 24.6, 24.4, 21.8, 10.3; IR (ν, cm^{-1}) 2932, 2859, 1649, 1607, 1520, 1485, 1447, 1395, 1332, 1272,

1178, 1018; HRMS calcd for $C_{26}H_{31}N_3O_4$ 449.2315, found 449.2316.

***N*-(4-Chlorobenzyl)-4-methyl-2-(2-(4-methylbenzoyl)-1*H*-benzo[*d*]imidazol-1-yl)pentanamide 4o.** The general procedure was followed using the Ugi adduct **3o** (100 mg, 0.22 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2). 68 mg (66%) of the desired adduct (colorless oil) were isolated. R_f 0.9 (8 : 2 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, J = 7.1 Hz, 2H), 7.90 (d, J = 7.3 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.42–7.38 (m, 3H), 7.36 (d, J = 7.1 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 5.66–5.63 (m, 1H), 4.46 (dd, J = 14.9, 5.8, 1H), 4.36 (dd, J = 14.9, 5.8, 1H), 2.47 (s, 3H), 2.42–2.34 (m, 1H), 2.09–2.01 (m, 1H), 1.07–1.01 (m, 1H), 0.75 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 187.3, 168.5, 147.9, 146.0, 142.1, 136.4, 134.3, 133.2, 133.0, 131.6, 129.4, 28.7, 128.6, 126.0, 124.1, 122.0, 113.6, 57.5, 42.9, 36.8, 24.6, 22.9, 21.9, 21.3; IR (ν, cm^{-1}) 3054, 2960, 2933, 2873, 1649, 1608, 1531, 1486, 1443, 1391, 1332, 1259, 1213, 1182, 1095, 1021; HRMS calcd for $C_{28}H_{28}ClN_3O_2$ 473.1870, found 473.1874.

2-(2-Benzoyl-5-chloro-1*H*-benzo[*d*]imidazol-1-yl)-*N*-(4-methoxybenzyl)acetamide 4p. The general procedure was followed using the Ugi adduct **3p** (100 mg, 0.24 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2–AcOEt). 75 mg (73%) of the desired adduct (white solid, M.p.: 180–181 °C) were isolated. R_f 0.8 (9 : 1 CH_2Cl_2–AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.8 Hz, 1H), 7.67 (dd, J = 8.1, 7.3 Hz, 1H), 7.63 (s, 1H), 7.54 (dd, J = 8.1, 7.3 Hz, 2H), 7.37 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 7.3 Hz, 2H), 6.80–6.78 (m, 3H), 5.11 (s, 2H), 4.38 (d, J = 5.3 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 186.3, 166.0, 159.0, 146.9, 140.3, 136.7, 135.9, 134.2, 132.6, 131.4, 129.4, 128.9, 128.5, 125.4, 123.1, 114.0, 111.0, 55.2, 49.3, 43.2; IR (ν, cm^{-1}) 3285, 3069, 2932, 1656, 1558, 1517, 1482, 1450, 1276, 1248, 1175, 1060, 1039, 1014; HRMS calcd for $C_{24}H_{20}ClN_3O_3$ 433.1193, found 433.1195.

Conclusion

As a conclusion, we have disclosed a new aerobic oxidation of benzyl substituted azoles under simple conditions. A systematic study has been done to address the effect of a palladium catalyst in this transformation. If few improvements were observed, in most cases, the palladium salts had a detrimental effect on yields. These results contrast with previous studies suggesting the need for a metal catalyst.[6,7]

Notes and references

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