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Unexpected Oxidative Ring-Opening of Electron-Rich 3-Aminobenzofurans into α-Ketoimines Derivatives

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Abstract: An unexpected ring-opening of 3-aminobenzofurans promoted by NaOtBu in hot toluene, leading to a variety of α-ketoimines is described. In the presence of 3-iodobenzofurans, NaOtBu mediates the 3-aminobenzofurans ring-opening via a possible radical pathway without the help of any external radical sources.

INTRODUCTION

Combretastatin A-4 (CA-4, Figure 1) is a natural microtubule destabilizing drug, able to damage the vasculature cancer tumors causing central necrosis. Recently, Food and Drug Administration (FDA) has granted orphan drug designation to its prodrug CA-4 phosphate (CA-4P) for the treatment of glioblastoma multiform and neuroendocrine tumors.

Although effective in antitumor therapy, CA-4 is not stable since its Z-double bond isomerizes during storage and administration leading to a 100-fold less active E-stilbene. This problem was solved in our group by the discovery of isoCombretastatin A-4 (isoCA-4), and other analogues including, azaisoerianin and various quinoline derivatives as isoCoQuin. For instance, isoCoQuin in which a quinaldine replaced the 3,4,5-trimethoxyphenyl A-ring of isoCA-4 has demonstrated low nanomolar potency against diverse tumor models and displayed antivascular properties identical to those of CA-4 and isoCA-4. Our studies around isoCoQuins were furthered to design, synthesize, and evaluate a novel panel of compounds of type I containing a benzofuran as B-ring encountered in BNC105, a potent tubulin polymerization inhibitor.

Initially, we applied efficient Buchwald-Hartwig coupling conditions, for the coupling reaction of 4-aminoquinoline 2a with 3-iodobenzofuran 3a (R = Ph) to provide 4a using Pd2dba3 as the catalyst, XPhos as the ligand, NaOtBu as the base in hot toluene (Scheme 1). Surprisingly, the desired 4a was not detected and, instead, (Z)-α-ketoimine 5a, was obtained in 70% yield and evidenced by 1H-NMR and mass spectrometry. However by replacing sodium tert-butoxide (NaOtBu) by cesium carbonate (Cs2CO3), we were pleased to observe the formation of 4a, which turned out to be unstable and was rapidly N-methylated, using NaNH and CH3I providing 1a in 47% yield (two steps). Using these experimental conditions, targeted compounds 1b and 1c were synthesized and their antiproliferative activity was investigated against HCT116 human colon tumor cell lines. However, biological results revealed that compounds 1a-c exhibited a micromolar level of cytotoxicity, which was not sufficient to consider other structural modifications in this chemical series (see SI).
Next, we focused our attention on the intriguing formation of α-ketoimines of type 5. Although being interesting intermediates in synthetic organic reactions, the synthesis of α-ketoimines is, however, poorly documented and in particular those of compounds 5, which has never been reported. In this article we report the first 3-amino benzofuran ring-opening leading to α-ketoimines 5 under Buchwald-Hartwig coupling conditions.

RESULTS AND DISCUSSION

We began our investigations to increase the chemical yield in α-ketoimine 5b (Table 1) using p-ansidine 2b and 3-iodobenzofuran 3b as model substrates (47%, entry 1). A total conversion was observed and compound 5b was isolated in 85% yield (entry 2) using an excess of NaOrBu (5 equiv), demonstrating that the base played a major role in the benzofuran ring-opening. We noted that replacing NaOrBu by LiOrBu and KOOrBu (10 equiv) furnished 5b but with lower yields (25 and 60%, resp., entries 6 and 7), probably because the Buchwald coupling reaction was less efficient using these bases. Subsequently, the screening reaction conditions with respect to the phosphate ligand was investigated and revealed that, on the contrary to BINAP (L3), Xphos (L2) gave a comparable result with the one obtained with the bulky bidentate phosphine Xphos (L1) providing 5b in 92% yield (entry 11). Finally, after screening other conditions (solvent, temperature and reaction time), our optimal conditions were found to require 2b (1 equiv), 3b (1.1 equiv), Pd$$_{db}$$ (5 mol %), Xphos (10 mol %), NaOrBu (5 equiv), in toluene in a sealed Schlenk tube at 140 °C for 16 h.

As control experiments, when the reaction was achieved in the absence of NaOrBu (or Pd$$_{db}$$ or XPhos), no reaction occurred and starting materials 2b and 3b remained unchanged. One can note that after recrystallization of 5b in dichloromethane/diethyl ether mixture (10:90), the structure of the ketoamine product (Z)-5b was confirmed by X-ray analysis (Figure 2). With these optimized conditions in hands, we then proceeded to investigate the scope of this transformation using various 3-iodobenzofuran 3 and aromatic amines 2. As can be seen in Scheme 2, employing a variety of electron-rich anilines with 3-iodo-2-phenylbenzofurans 3a and 3b, α-ketoimines 5b-h were obtained in good to excellent yields ranging from 62 to 98% yield. An acceptable yield of 50% was obtained using the less nucleophilic p-nitroaniline to give the expected α-ketoamine 5i. Substituents on the aromatic ring on the C-2 position of the benzofuran nucleus were also permitted as it could be observed with α-ketoimines 5j,k (75 and 86%, respectively). However, when mixing 4-methoxaniline 2b with benzofurans having an electron-withdrawing group on C5 (CO$$_{Me}$$) or having an alkyl chain (n-Bu) on C2, starting materials were found unchanged suggesting that Buchwald coupling-reactions failed and were not optimized with these benzofurans. We further investigated the influence of various aromatic amines, and were pleased to observe that heterocyclic amines as 4-aminoquinoline, 9-methyl-9H-carbazol-3-amine and 1-methyl-1H-indol-5-amine reacted well under...
these conditions with 2-aryl-3-iodobenzofurans 3a, 3b and 3d to furnish the expected ketoimines 5i-o in good yields.

To gain some insight into the plausible mechanism of this unexpected ring-opening reaction, we next focused our attention on the role of NaOBut, which seemed to be responsible of the benzofurans ring-opening. As depicted in Scheme 3, our current hypothesis favors a radical pathway. Beside the formation of 4-aminobenzofuran 4a through Buchwald-Hartwig coupling, we hypothesized that catalytic amounts of the radical species $V^+$ and $t$BuO• were formed together with NaI from the reaction between NaOBut and 3-iodobenzofuran 3a. This hypothesis was assumed with regard to a previous report of Cuthbertson,10 which showed that reaction of an aryliodide with KOBut alone in high toluene generated $t$BuO• radicals. Note that the formation of $V^+$ is supported by the presence in the crude reaction of small amounts of 2-phenylbenzofuran, which was detected by LC/MS at the end of the reaction. Then, a hydrogen abstraction from 3-aminobenzofuran 4a by a $t$BuO• radical would occurr to give the resulting aminyl radical $W^+$.11 This hypothesis involving $W^+$ radicals is supported by the identification through LC/MS analysis of a dimeric hydrazine $W_2^{12}$ ($m/z$ of 819.3082 ([M + H]+) and 410.1577 ([M + 2H]+), see SI). In agreement with a recent report by Zhou et al.,13 radical $W^+$ would furnish a peroxy radical $X^+$ species by oxidation in the air. This latter, would then undergo oxidation of aminyl radical $W^+$ giving hemiketal radicals $Y^+$: A subsequent monoatomic ring-opening of $Y^+$ would furnish ketoimine $Z^+$, which after hydrogen traping from $t$BuOH led to ketoimine 5a and regenerated $t$BuO• radical. This mechanistic hypothesis is also supported by Lavanya and Yamuna’s works, which previously reported that 3-aminobenzofurans were excellent antioxidants agents able to trap free radicals.12

In order to determine the origin of the oxygen atom of ketoimine 5a, we then carried out the Buchwald coupling reaction of 2a with 3a in an oxygen-free glove box ($O_2$ <0.2 ppm) using NaOBut as the base. Under these conditions, the unstable diarylamino intermediate 4a was detected (NMR and LC/MS) as the main product in the crude mixture, and no trace of the ketoimine 5a was observed (absence of phenolic proton). This result demonstrated that the amount of $O_2$ (air atmosphere or dissolved in toluene) at the beginning of the Buchwald reaction in the Schlenk tube was enough to promote the benzofuran ring-opening of 4a.

To get more insight into the radical-involving reaction pathway, control experiments were achieved in order to trap any radical species. To this end, 2a and 3a were reacted under standard conditions in the presence of radical traps (TEPOM or galvinoxyl, Scheme 4). Unfortunately, the presence of TEMPO or galvinoxyl shut down completely the Buchwald coupling reaction as starting materials were recovered unchanged. We then asked ourselves whether an external $t$BuO• radical source could (i) accelerate the formation of 5a when the reaction was conducted in the presence of NaOBut or (ii) allow obtaining 5a when the reaction was carried out in the presence of Cs$_2$CO$_3$. As depicted in Scheme 4, by adding in the mixtures dibutylperoxide (DTBP, 5 equiv) again, the Buchwald coupling reaction did not occur as starting
materials 2a and 3a were mainly found unchanged. All these experiments indicate that additives such as radical traps or external sources of tBuO• are not welcome in the Schlenk tube at the beginning of the coupling reaction.15 To demonstrate that 5a was formed from 4a in this novel process, a series of assays (reagents in blue, Scheme 4) were next performed from 4a, previously prepared using Cs₂CO₃ as the base. First, to determine if molecular oxygen was able to promote the benzofuran ring-opening of 4a, this latter was stirred under an O₂ atmosphere in hot toluene (TLC control). Accordingly, 4a was slowly and totally consumed after 16 h of stirring in the Schlenk tube to furnish 5a but with a low yield of 28% together with many unidentified by-products. This result shows that molecular oxygen is not the only one responsible for the opening of benzofuran ring.

Since the source of bases played a crucial role in this process, diarylamine 4a was mixed with NaOrBu (5 equiv) in hot toluene. After 16 h of reaction at 140 °C, no trace of 5a was detected, clearly indicating that NaOrBu alone is not able to transform 4a into 5a. Next, we were interested to examine the behaviour of benzofuran 4a in the presence of DTPB. We were very pleased to observe, after only 3 h of reaction, the transformation of 4a into 5a in a good 65% yield by employing only 5 mol% of DTPB. This last result clearly supports that the mechanism described in Scheme 3 involving tBuO• radicals (generated from NaOrBu and 3-iodobenzofurans) is plausible.

SCHEME 4. Mechanistic Investigations
CONCLUSION

In summary, ring-opening of 3-aminobenzofuran derivatives 4 promoted by NaOrBu and O2 has been described. 3-Aminobenzofurans were prepared from the N-arylation reaction between aromatic amines and 3-iodobenzofurans in the presence of Pd2dba and Cs2CO3 in toluene at 140 °C. When NaOrBu was used as the base, 3-aminobenzofuran derivatives 4 were not isolated because they rapidly reacted with tBuONa and O2 to give, after benzofurans ring-opening, a series of novel α-ketoamines 5 difficult to access by alternative routes. We believe that the ability of NaOrBu to promote in hot toluene, 3-aminobenzofuran ring-opening is of significant importance for the scientific community.

EXPERIMENTAL SECTION

General Information and Method. All reactions were carried out under an air atmosphere in dried glassware. When needed, non-aqueous reagents were transferred via syringe and dried prior to use. Toluene anhydrous (99.8%) from Sigma-Aldrich (244511) was used and sodium tert-butoxide was flame dried under high vacuum for 5 minutes prior to use and stored under argon. Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230-400 mesh) plates and analyzed by UV light or by staining upon heating with vanillin solution. For silica gel chromatography on column, the chromatography technique was used, with Merck silica gel 60 (230-400 mesh) and p.a. grade solvents.

The 1H NMR and 13C NMR spectra were recorded in either CDCl3 or Bruker Avance 300 spectrometer. The chemical shifts of 1H NMR spectra are reported in ppm relative to the solvent residual peak in CDCl3 (δ 7.26) for 1H NMR. For the 13C NMR spectra, the solvent signals of CDCl3 (δ 77.16) were used as the internal standard. IR spectra were measured on a Bruker Vector 22 spectrophotometer. MS were recorded on a Micromass Quadrupole. Analytical TLC was performed on Merck pre-coated silica gel 60F plates. Merck silica gel 60 (0.015-0.040 mm) was used for column chromatography. Melting points were recorded on a Büchi B-450 apparatus and were uncorrected. High resolution mass spectra (HR-MS) were recorded on a MicroMass LCT Premier Spectrometer, using ESI or APCI with methanol as the carrier solvent.

General Procedure for the synthesis of 3a-e and characterization data

Suitable o-methoxydiarylalkyne (2 mmol, 1 equiv) was dissolved in dichloromethane (30 mL). To this solution was added iodine (3 mmol, 1.5 equiv), and the mixture was stirred at room temperature for 1 hour. The mixture was treated with saturated aqueous sodium thiosulfate (30 mL) and the product was extracted with dichloromethane (2x30 mL). The combined organic extracts were washed with water and dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solvent was removed in vacuo leaving a crude solid. The solid was purified on silica gel chromatography (cyclohexane/ethyl acetate = 1/10) to afford the corresponding product 3.

3-Iodo-6,7-dimethoxy-2-phenylbenzofuran (3a):
1.56 g, 88% yield, light brown solid; mp 92.7 - 93.5°C; 1H NMR (300 MHz, CDCl3) δ 8.17 (d, J = 7.3 Hz, 2H), 7.49 (t, J = 7.3 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 4.24 (s, 3H), 3.95 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 152.3, 149.7, 145.6 134.1, 130.0 (2), 129.1, 128.5 (2), 127.2 (2), 114.9, 110.0, 61.2, 61.0, 57.3; HRMS (ESI-TOF) m/z [M + H]+ calculated for C18H14O2I 380.9988, found 380.9982; IR film vmax/cm-1 : 3057, 2979, 2932, 1622, 1591, 1503, 1485, 1463, 1485, 1446, 1304, 1292, 1253, 1090.

General Procedure for the synthesis of 5a-o and characterization data

Benzofuran 3 (0.550 mmol, 1.10 equiv), aniline 2 (0.500 mmol, 1.00 equiv), Pd2dba (0.025 mmol, 0.05 equiv), Xyphos (0.050 mmol, 0.10 equiv), sodium tert-butoxide (2.50 mmol, 5.00 equiv) and toluene (5 mL) were added to a dried Sealed tube (30 mL) under air atmosphere. After the mixture was heated to 140°C and stirred for 16 hours, it was cooled to room temperature. The mixture was diluted with ethyl acetate (10 mL), filtered through a celite pad and concentrated. The solid was purified on silica gel chromatography (cyclohexane/ethyl acetate = 1/1) to afford the corresponding product 5.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-((2-methylquinolin-4-yl)imino)-1-phenylethanone (5a):
175 mg, 82% yield, yellow solid; mp 153.7 - 154.9 °C; 1H NMR (300 MHz, CDCl3) δ 13.31 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 7.3 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.23 (t, J = 7.7 Hz, 2H), 7.01 (d, J = 9.0 Hz, 1H), 6.72 (s, 1H), 6.49 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 4.24 (s, 3H), 3.95 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 152.3, 149.7, 145.6 134.1, 130.0 (2), 129.1, 128.5 (2), 127.2 (2), 114.9, 110.0, 61.2, 61.0, 57.3; HRMS (ESI-TOF) m/z [M + H]+ calculated for C18H14O2I 380.9988, found 380.9982; IR film vmax/cm-1 : 3057, 2979, 2932, 1622, 1591, 1503, 1485, 1463, 1485, 1446, 1304, 1292, 1253, 1090.
4.02 (3H), 3.94 (s, 3H), 2.57 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 192.9, 171.54, 159.2, 157.8, 156.6, 150.3, 148.4, 137.2, 135.0, 134.1, 130.0, 129.2 (2), 129.0 (2), 128.7, 127.5, 125.9, 123.2, 120.9, 117.2, 112.2, 103.8, 60.9, 56.3, 25.5; HRMS (ESI-TOF) m/z [M + H]+ calcld for C39H49NO2 719.3219, found 719.3219; IR film v(cm-1) : 3324, 2928, 2844, 1735, 1671, 1501, 1467, 1467, 1290, 1234, 1125, 1085.

(Z)-2-(2-Hydroxyphenyl)-2-((4-methoxyphenyl)limino)-1-phénylanéthane (5b):
152 mg, 92% yield, yellow solid; mp 157.2-158.4 °C; 1H NMR (300 MHz, CDCl3) δ 13.73 (s, 1H), 7.81 (d, J = 7.4 Hz, 2H), 7.54 (t, J = 8.4 Hz, 1H), 7.39 (m, 3H), 7.16 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.9 Hz, 2H), 6.80 (t, J = 8.4 Hz, 1H), 6.72 (d, J = 8.9 Hz, 2H), 3.72 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 195.3, 169.4, 161.8, 157.8, 138.9, 134.7, 134.2, 133.5, 130.3, 129.3 (2), 129.0 (2), 123.4 (2), 118.9, 112.2, 117.4 (2), 55.3; HRMS (ESI-TOF) m/z [M + H]+ calcld for C29H28O2N 432.1827, found 432.1820; IR film v(cm-1) : 3372, 2928, 2851, 1735, 1671, 1601, 1512, 1476, 1467, 1290, 1234, 1125.

(Z)-2-((3,5-Dimethoxyphenyl)limino)-2-(2-hydroxyphenyl)-1-phénylanéthane (5c):
125 mg, 69% yield, yellow solid; mp 153.3 - 153.9 °C; 1H NMR (300 MHz, CDCl3) δ 13.37 (s, 1H), 7.84 (d, J = 7.5 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.24 (m, 3H), 7.28 (s, 1H) 7.19 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.15 (s, 2H), 3.66 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 194.3, 170.6, 161.83, 160.9, 147.7, 142.1, 143.1, 134.6, 134.0, 130.7, 129.4 (2), 129.0 (2), 119.0, 118.3, 117.0, 100.3 (2), 98.5, 55.3 (2); HRMS (ESI-TOF) m/z [M + H]+ calcld for C38H37O3N 575.2643, found 575.2645; IR film v(cm-1) : 3061, 2960, 2936, 1678, 1592, 1425, 1259, 1140.

(Z)-2-((3,5-Dimethoxyphenyl)limino)-2-(2-hydroxyphenyl)-1-phénylanéthane (5d):
112 mg, 62% yield, brown solid; mp 147.8 - 148.5 °C; 1H NMR (300 MHz, CDCl3) δ 13.68 (s, 1H), 7.83 (d, J = 7.3 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.40 (m, 3H), 7.16 (dd, J = 8.2 Hz, J = 1.3 Hz, 1H), 7.11 (dd, J = 8.2 Hz, J = 1.3 Hz, 1H), 6.80 (t, J = 7.6 Hz, 1H), 6.68 (d, J = 9.1 Hz, 1H), 6.60 (m, 2H), 3.79 (s, 3H), 3.74 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 195.3, 169.6, 161.8, 148.9, 147.3, 139.2, 134.8, 134.3, 133.6, 130.4, 129.3 (2), 129.0 (2), 118.9, 118.3, 117.2, 114.3, 111.1, 106.3, 55.9 (2); HRMS (ESI-TOF) m/z [M + H]+ calcld for C38H37O3N 575.2643, found 575.2645; IR film v(cm-1) : 3320, 2934, 2840, 1671, 1564, 1513, 1443, 1416, 1399, 1225, 1159.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-(4-nitrophenyl)limino)-1-phénylanéthane (5i):
102 mg, 50% yield; yellow cristal, mp 162.3 - 162.9 °C; 1H NMR (300 MHz, CDCl3) δ 12.95 (s, 1H), 8.06 (d, J = 8.9 Hz, 2H), 7.79 (d, J = 7.3 Hz, 2H), 7.60 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.8 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 9.0 Hz, 1H), 6.47 (d, J = 9.0 Hz, 1H), 3.99 (s, 3H), 3.93 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 193.5, 172.0, 158.4, 156.9, 152.6, 145.6, 137.7, 135.9, 134.6, 130.0 (2), 129.8 (2), 127.9, 125.2 (2), 123.0 (2), 112.4, 104.3, 61.3, 56.7; HRMS (ESI-TOF) m/z [M + H]+ calcld for C43H37NO3 677.2817, found 677.2815; IR film v(cm-1) : 3334, 2936, 2849, 1624, 1523, 1448, 1340, 1292, 1247, 1217, 1197, 1171.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-(4-nitrophenyl)limino)-1-phénylanéthane (5j):
181 mg, 86% yield, yellow solid; mp 210.4 - 211.9 °C; 1H NMR (300 MHz, CDCl3) δ 14.29 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 9.0 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.39 (d, J = 9.0 Hz, 1H), 3.97(s, 3H), 3.89 (s, 3H), 3.82
(s, 3H), 3.71 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 193.2, 169.1, 164.7, 157.6, 156.5, 147.9, 138.9 (2), 131.9 (2), 127.4, 126.3, 123.4 (2), 114.3 (2), 114.1 (2), 112.6, 102.8, 60.7, 56.0, 55.5, 55.3; HRMS (ESI-TOF) m/z [M + H]+ calc for C16H13NO2 242.1064, found 242.1062; HRMS (ESI-TOF) m/z [M + H]+ calc for C16H13NO2 242.1062, found 242.1064.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-(1H-indol-5-yl)imino)-1-(p-tolylenethane (5k): 158 mg, 75% yield, yellow solid; mp 187.6 - 187.9 °C; 1H NMR (300 MHz, CDCl3) δ 14.19 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 9.0 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.39 (d, J = 9.0 Hz, 1H), 3.97s (3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 193.2, 169.1, 164.7, 157.6, 156.5, 147.9, 138.9 (2), 131.9 (2), 127.4, 126.3, 123.4 (2), 114.3 (2), 114.1 (2), 112.6, 102.8, 60.7, 56.0, 55.5, 55.3; HRMS (ESI-TOF) m/z [M + H]+ calc for C16H13NO2 242.1064, found 242.1062; HRMS (ESI-TOF) m/z [M + H]+ calc for C16H13NO2 242.1062, found 242.1064.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-(1H-indol-5-yl)imino)-1-(p-tolylenethane (5l): 158 mg, 75% yield, yellow solid; mp 187.6 - 187.9 °C; 1H NMR (300 MHz, CDCl3) δ 14.19 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 9.0 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.39 (d, J = 9.0 Hz, 1H), 3.97s (3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 193.2, 169.1, 164.7, 157.6, 156.5, 147.9, 138.9 (2), 131.9 (2), 127.4, 126.3, 123.4 (2), 114.3 (2), 114.1 (2), 112.6, 102.8, 60.7, 56.0, 55.5, 55.3; HRMS (ESI-TOF) m/z [M + H]+ calc for C16H13NO2 242.1064, found 242.1062; HRMS (ESI-TOF) m/z [M + H]+ calc for C16H13NO2 242.1062, found 242.1064.
84 mg, 39% yield, white solid; mp 248.2 - 248.6 °C; 'H NMR (300 MHz, CDCl₃) δ 7.90 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 4.0 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 4.0 Hz, 1H), 7.05 (t, J = 4.0 Hz, 1H), 7.00 (t, J = 7.7 Hz, 1H), 6.88 (s, 1H), 6.54 (d, J = 8.5 Hz, 1H), 6.31 (d, J = 8.5 Hz, 1H), 4.15 (s, 3H), 3.74 (s, 3H), 3.42 (s, 3H), 2.70 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 158.3, 153.6, 149.5, 148.0, 145.0, 144.3, 134.6, 130.6, 129.6, 127.8 (2), 126.8, 125.3, 125.1, 124.7, 123.5, 121.0, 116.2, 109.8, 107.4, 61.0, 57.0, 41.8, 25.1; HRMS (ESI-TOF) m/z [M + H]⁺ calc'd for C₂₃H₂₉N₆O₅S 431.4129, found 431.4132; IR film vmax/cm⁻¹: 2854, 2776, 1642, 1604, 1515, 1430, 1394, 1392, 1276, 1112, 1083; HPLC [H₂O, 0.1% ac. form. / ACN – gr 5-100% - 20 min.] r.t.: 12.13 min., purity: 96%.

SUPPORTING INFORMATION AVAILABLE: 'H and ¹³C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES


(2) http://www.mateon.com/


(7) All secondary diarylamines 4 turn out to be unstable in air and during purification on silica gel leading to ketoamines 5 in small amount together with many unidentified by-products (TLC multi-spots). For example, after 50 h under air, diarylamine 4a was totally transformed; ketoamine 5a was isolated in 20 % yield, the mass balance being constituted by unidentified by-products. Therefore, it is necessary to rapidly filter the diarylamines 4 on a pad of celite and engage them immediately in the N-methylation step, leading to isoCoquin derivatives 1.


(12) When achieving the reaction of 2a with 3a under optimized conditions using Cs₂Co₃ instead of NaOttBu, dimer W₂ was not detected.


(15) Under an O₂ atmosphere, no Buchwald coupling reaction of 2a and 3a took place.
Ar = phenyl, quinolines, carbazoles, indoles

R = H, OMe; R' = H, OMe, Me.

- Rapid "one pot" access to unsymmetrical α-keto-imines
- 15 examples (50 to 98%)
- Possibility to prepare separately Buchwald amines using Cs₂CO₃ in place of NaOtfBu