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Palladium-Catalyzed α-Arylation of Methyl Ketones Enables Modular Synthesis of 2,4,5-Trisubstituted Imidazoles

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A three-step synthesis of 2,4,5-trisubstituted imidazoles involving Pd-catalyzed α-arylation of aromatic methyl ketones, here represented by 4-acetyl pyridine, with 2-bromo-6-alkoxynaphtalenes, followed by *in situ* oxidation with selenium dioxide, featuring only two chromatographic purifications, provides the corresponding 1,2-diketones which underwent a Debus-Radziszewski condensation to furnish 2,4,5-trisubstitued imidazoles in moderate to good overall yields (30 examples). The methodology is particularly appropriate for the late-stage introduction of the substituent at C-2 in the imidazole ring and nicely complements previously described methods where the substituent at C-5 was incorporated at the end of the synthetic route.

Keywords: 2,4,5-trisubstituted imidazoles, Pd-catalyzed arylation, Debus-Radziszewski condensation

Introduction

Imidazole is a well-regarded structural motif since its first synthesis by Debus in 1858, particularly in the domain of medicinal chemistry.[1] Several drugs covering a range of pharmacological activities such as tripanocidal (benznidazole, **1**), antifungal (tioconazole, **2**), H2 blockers (cimetidine, **3**), angiotensin receptor blocker (losartan, **4**), muscarinic acetylcholine agonist (pilocarpine, **5**), and the basic scaffold for fluorophores for bioimaging (lophine, **6**), among others (Figure 1), display an imidazole ring as part of their structures.[2,3] Besides their therapeutic applications,[4] substituted imidazoles are also involved in functional applications such as in materials and polymer science and as ionic liquids,[5-8] being also found in natural products such as histidine, histamine, purines, theophylline, and marine natural products.[9]

In addition to their relevance as pharmacologically active ingredients, imidazoles play an important role in drug discovery with several representatives acting as enzyme inhibitors and chemical probes,[2,10,11] especially in the context of kinase targets.[12,13]

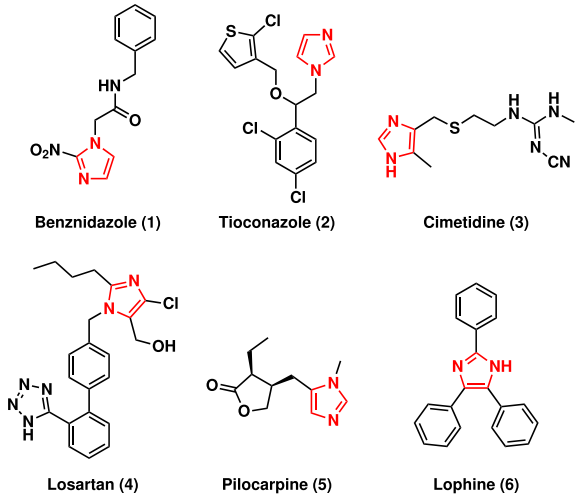

Figure 1. Chemical structures of some representative imidazoles.

Several methodologies have been developed to access differently substituted imidazoles[14-16] and, among them, the Debus-Radziszewski synthesis stands out as an attractive approach: a multicomponent reaction (MCR) featuring a four-bond formation strategy, involving a 1,2-dicarbonyl compound, an aldehyde, and ammonia or a primary amine, catalyzed by a plethora of catalysts.[17] Mostly, examples in the literature start with a diketo compound, such as benzil,

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or a hydroxyketone, such as benzoin, which in the presence of an oxidizing agent promptly undergoes reaction with an ammonium source, such as ammonium acetate or a primary amine.[18] The Debus-Radziszewski condensation has found use in industrial applications, including implementations using modern technologies such as continuous-flow processing, although issues such as poor selectivity, harsh reaction conditions, and low yields still remain significant limitations.[19]

Deng and co-workers[20] employed the dimethylsulfoxide-hydrobromic acid (DMSO-HBr) oxidation of methyl aryl (heteroaryl) ketones, followed by treatment of the glyoxal intermediate with aqueous ammonia to provide 2,4- and 2,5-aryloyl aryl imidazoles in combined moderate to good yields. The use of SeO_2 for the oxidation of acetophenones under reflux in 1,4-dioxane was described by Kuzu *et al.*[21] involving a two-step procedure for the synthesis of 2,4-disubstituted imidazoles while Jeena and Jayram described the one-pot, multicomponent preparation of derivatives of lophine (**6**) from α-benzyl arylketones which underwent benzylic oxidation in the presence of SeO_2, in acetic acid at 180 °C,[22] or catalytic amount of $CuCl_2$ in the presence of molecular oxygen in DMF to generate *in situ* the corresponding 1,2-diketone which underwent Debus-Radziszewski condensation to provide 2,4,5-triaryl imidazoles[23] as well as under treatment with iodine in DMSO at 100 °C.[24] Koch and co-workers[25] employed the strategy via Claisen condensation, followed by SeO_2 oxidation, to warrant the 1,2-diketone scaffold required for the Debus-Radziszewski condensation. Due to the harsh experimental conditions, the reports above only describe the use of ammonium acetate as the nitrogen source leading to di- or trisubstituted N*H*-imidazoles.

However, α-diketones are not usually commercially available, and their preparation process suffers from several drawbacks such as (*i*) high catalyst loading; (*ii*) harsh reaction conditions, (*iii*) low product yields and, (*iv*) tedious work-up procedures. Therefore, if readily available alkyl ketones could be employed instead of the more conventional α-diketones, it would broaden the scope of this methodology to prepare imidazoles. Previously, we have described a one-pot approach involving a sequential Kornblum oxidation, followed by Debus-Radziszewski imidazole condensation, to prepare 2,4-disubstituted imidazoles which could undergo a one-pot bromination, followed by Suzuki coupling, to produce 2,4,5-tribusbstituted imidazoles such as the kinase inhibitor GSK3037619A.[26,27]

Although our previously described methodology served well for the late-stage installation of the aryl moiety at C-5,[27] it did not provide acceptable yields when we aimed for the late-stage installation of the aryl substituent at C-2 position of the imidazole ring. Our evolving interest on inhibitors and chemical probes for understudied kinases, led us to develop a complementary approach to the synthesis of 2,4,5-N*H*-imidazoles.

Experimental

Reagents, solvents and glassware

All reactions were carried out with freshly distilled solvents, using anhydrous conditions unless otherwise noted. Dichloromethane (DCM) and triethylamine (Et_3N) were distilled over calcium hydride. *tert*-Butanol (*t*-BuOH) was distilled over calcium hydride and stored over 4 Å molecular sieves. Pyridine was dried over NaOH, distilled and stored over 4 Å molecular sieves. K_3PO_4 and K_2CO_3 were ground with a pestle and mortar to a fine powder and dried for at least 12 h in an oven at 200 °C. Tetrahydrofuran (THF) was distilled over metallic sodium (Na) and benzophenone. *N,N*-Dimethylformamide (DMF) and

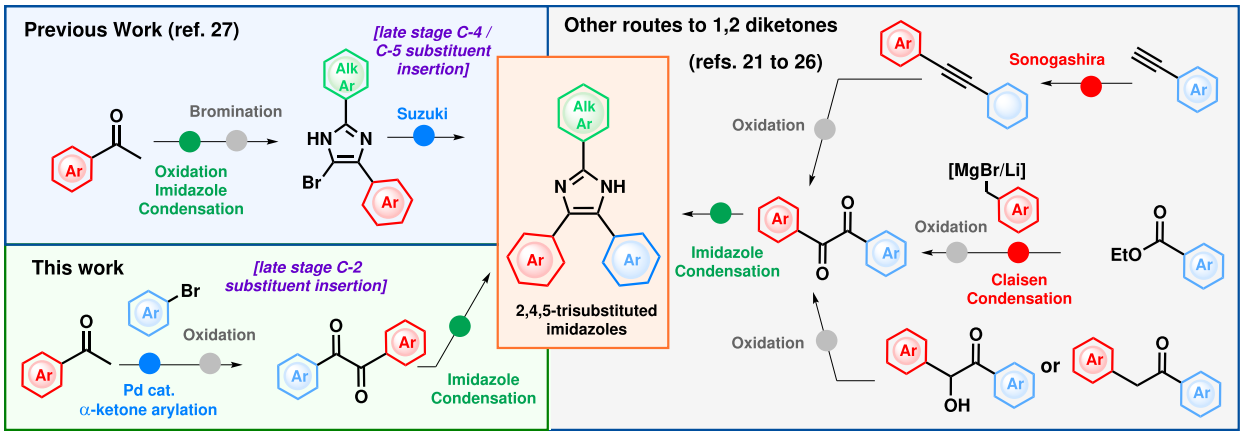


Figure 2. Some previous methodologies reported for the preparation of NH-2,4,5-trisubstituted imidazoles using the Debus-Radziszewski condensation and the one reported in this work.

dimethylsulfoxide (DMSO) were obtained in anhydrous grade and were used without previous treatment. The anhydrous solvents were transferred by oven-dried syringes. The sealed tubes used in the cross-coupling reactions were previously dried at 120 ºC in an oven for at least 3 h. Other reagents were obtained from commercial sources and were used without prior purification. Aryl bromide **8a** was prepared according to literature procedure.[28] Aldehydes **12a**, **12e**, **12f**, **12h**, **12i**, **12j** and **12k** are commercially available and were used as received.

Purification and chromatography

The reactions were monitored by thin-layer chromatography (silica gel 60 F254 in aluminum foil, Merck). Silica gel 200-400 mesh was used for flash column chromatography and was carried out using Biotage Isolera One flash column chromatography system or in open glass columns.

Spectroscopy, spectrometry and data acquisition

Nuclear magnetic ressonance (NMR) spectra were recorded on a Bruker Avance III HD 250 MHz, Bruker Avance III 400 MHz, Bruker Avance III 500 MHz or Bruker Avance III 600 MHz and processed using Topspin 4.3.0 or MestreNova 12.0.4 software. The chemical shifts are reported in parts *per* million (ppm) on a delta (δ) scale. The following residual solvent peaks were used as reference values for ^{1}H NMR: $CHCl_3$ - 7.26 ppm, CH_3OH - 3.31 ppm, and $(CH_3)_2SO$ - 2.50 ppm; and for ^{13}C NMR: $CDCl_3$ - 77.16 ppm, CD_3OD - 49.00 ppm, and $(CD_3)_2SO$ - 39.52 ppm. Signal multiplicity was reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint.), sextet (sext.), and multiplet (m). High-resolution mass spectra (HRMS) were acquired on an Orbitrap Thermo QExactive Mass Spectrometer, using electrospray ionization (ESI). Infrared (IR) spectra were recorded using a Thermo Scientific Nicolet IS5 spectrometer using Thermo Scientific ID3 or ID5 ATR, and the absorption frequencies are reported in cm^{-1}. The melting points (MP) of the compounds were measured using the MP50 equipment (Metler Toledo) with a heating ramp starting at 40 °C and ending at 350 °C, with a heating rate of 5 °C min^{-1}.

2-(6-Ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**9a**)

An oven-dried culture tube equipped with a magnetic stirring bar was charged with 4-acetylpyridine (**7**, 63 mg, 0.50 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 2 mol%), Xantphos (12 mg, 0.02 mmol, 4 mol%), 2-bromo-6-ethoxynaphthalene (**8a**, 152 mg, 0.60 mmol, 1.2 equiv.), and K_3PO_4 (325 mg, 1.50 mmol, 3.0 equiv.) under nitrogen. Then, THF (1.50 mL, 0.33 M) was added, the culture tube was sealed, and the mixture was stirred at 80 ºC for 18 h. After consumption of the starting material, indicated by thin layer chromatography (TLC) analysis, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and filtered through a short pad of silica gel which was washed with EtOAc (ca. 50 mL) until all the product has eluted. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluted with acetone in DCM (18 cm × 20 mm, gradient elution, from 2 to 6% acetone/DCM, 2% increases, 70 mL runs, 7 mL fractions), to afford **9a** (66 mg, 45%) as a yellow solid; R_f = 0.43 (50% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (dd, *J* 4.5 and 1.5 Hz, 2H), 7.78 (dd, *J* 4.4 and 1.6 Hz, 2H), 7.70 (d, *J* 8.9 Hz, 1H), 7.67 (d, *J* 9.1 Hz, 1H), 7.62 (s, 1H), 7.31 (dd, *J* 8.4 and 1.6 Hz, 1H), 7.14 (dd, *J* 8.8 and 2.4 Hz, 1H), 7.10 (d, *J* 2.4 Hz, 1H), 4.40 (s, 2H), 4.14 (q, *J* 7.0 Hz, 2H), 1.47 (t, *J* 6.9 Hz, 3H); note: reported signals refer to the ketone tautomer in the mixture. Approximately 8:2 (ketone:enol) ratio; ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.4, 157.3, 151.1, 142.6, 133.8, 129.6, 129.2, 129.1, 129.0, 128.4, 128.2, 127.8, 127.6, 121.7, 121.6, 119.6, 106.6, 63.6, 46.0, 14.9; note: minor peaks observed are due to the presence of the enol tautomer in the mixture; IR (thin film, ATR) ν_{max} / cm^{-1} 3444 (br), 2983 (w), 2931 (w), 1694 (s), 1631 (w), 1606 (m), 1556 (w), 1506 (w), 1479 (w), 1405 (m), 1396 (m), 1373 (w), 1336 (m), 1265 (s), 1215 (s), 1207 (s), 1194 (m), 1179 (m), 1162 (w), 1113 (w), 1065 (w), 1039 (m), 1012 (m), 972 (w), 952 (w), 927 (w), 893 (w), 863 (w), 848 (w), 823 (w), 810 (s), 793 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{18}NO_2$: 292.1332; found 292.1330. MP: 126.4-128.4 °C (DCM/acetone).

1-(6-Ethoxynaphthalen-2-yl)-2-(pyridin-4-yl)ethane-1,2-dione (**10a**)

Starting from 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl) ethanone (**9a**)

A culture tube was charged with 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**9a**, 88 mg, 0.30 mmol, 1.0 equiv.) and a magnetic stirring bar under nitrogen. Then, AcOH (1.50 mL, 0.2 M) was added, followed by SeO_2 (50 mg, 0.45 mmol, 1.5 equiv.) and the resulting mixture was heated to 70 °C for 3 h. After consumption of the starting material, indicated by TLC analysis, the reaction mixture was cooled to room temperature, the solution was filtered over a pad of Celite® which was washed with EtOAc (20 mL). The filtrated was concentrated under reduced

pressure and dissolved in EtOAc (20 mL), washed with satd. aq. $NaHCO_3$ (1 × 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (Biotage Isolera, SNAP KP-Sil 10 g, from 10% to 30% EtOAc/hexanes, 15 mL fractions) to afford **10a** (79 mg, 86%) as a bright yellow solid.

Starting from 4-acetylpyridine (**7**) and 2-bromo-6-ethoxynaphthalene (**8a**)

An oven-dried pressure tube equipped with a magnetic stirring bar was charged with 2-bromo-6-ethoxynaphthalene (**8a**, 1.60 g, 6.30 mmol, 1.00 equiv.), $Pd(OAc)_2$ (29 mg, 0.13 mmol, 2 mol%), Xantphos (150 mg, 0.252 mmol, 4 mol%), 4-acetylpyridine (**7**, 1.57 g, 12.6 mmol, 2.00 equiv.), and K_3PO_4 (4.09 g, 18.9 mmol, 3.00 equiv.) under nitrogen. Then, THF (21.0 mL, 0.3 M relative to **8a**) was added, the pressure tube was sealed, and the mixture was stirred at 80 ºC for 18 h. After cooling to room temperature, the pressure tube was open and rapidly diluted with EtOAc (20 mL) and filtered through a short pad of silica gel, which was washed with EtOAc (ca. 50-100 mL) until all the product has eluted. The filtrate was concentrated under reduced pressure, and the residue was transferred to a 50 mL round-bottom flask. AcOH (31.5 mL, 0.18 M) was added, followed by addition of SeO_2 (1.19 g, 10.7 mmol, 1.70 equiv.) under nitrogen. The resulting mixture was heated to 70 °C and stirred for 3 h. After consumption of the starting material, indicated by TLC analysis (50% EtOAc/hexanes v/v), the reaction mixture was cooled to room temperature, filtered over a pad of Celite® which was washed with EtOAc (60 mL). The filtrated was concentrated under reduced pressure, dissolved in EtOAc (60 mL), washed with satd. aq. $NaHCO_3$ (1 × 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (Biotage Isolera, SNAP KP-Sil 25 g, from 10 to 30% EtOAc/hexanes, 15 mL fractions) to afford **10a** (1.44 g, 75%) as a bright yellow solid; R_f = 0.52 (50% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, *J* 5.6 Hz, 2H), 8.32 (s, 1H), 8.04 (dd, *J* 0.9 and 8.6 Hz, 1H), 7.85-7.79 (m, 4H), 7.21 (dd, *J* 9.0 and 2.1 Hz, 1H), 7.16 (d, *J* 1.8 Hz, 1H), 4.19 (q, *J* 7.0 Hz, 2H), 1.50 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.5, 192.6, 160.5, 151.3, 139.2, 138.8, 133.8, 131.8, 128.1, 127.7, 127.7, 124.5, 122.5, 120.7, 106.8, 64.0, 14.8; IR (thin film, ATR) ν_{max} / cm^{-1} 1685 (m), 1650 (m), 1614 (s), 1553 (w), 1475 (m), 1409 (w), 1393 (m), 1339 (w), 1327 (w), 1277 (w), 1263 (m), 1216 (w), 1182 (s), 1145 (w), 1109 (w), 1066 (w), 1041 (m), 991 (w), 973 (w), 907 (m), 868 (m), 851 (m), 836 (w), 827 (w), 813 (m), 800 (m), 762 (m), 753 (m), 731 (w), 712 (m), 670 (s); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{16}NO_3$: 306.1130; found 306.1130; MP 134.1-136.4 °C (EtOAc).

1-(Pyridin-4-yl)-2-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl) ethane-1,2-dione (**10b**)

An oven-dried 20 mL culture tube equipped with a magnetic stirring bar was charged with **8b** (320 mg, 1.05 mmol, 1.00 equiv.), $Pd(OAc)_2$ (4.8 mg, 0.021 mmol, 2 mol%), Xantphos (25 mg, 0.042 mmol, 4 mol%), 4-acetylpyridine (**7**, 259 mg, 2.10 mmol, 2.0 equiv.), and K_3PO_4 (682 mg, 3.15 mmol, 3.0 equiv.) under nitrogen. Then, THF (3.5 mL, 0.3 M) was added, the culture tube was sealed, and the mixture was stirred at 80 ºC for 18 h. After cooling to room temperature, the culture tube was open, rapidly diluted with EtOAc (18 mL) and filtered through a short pad of silica gel, which was washed with EtOAc (ca. 50-100 mL or until all the product eluted). The filtrate was concentrated under reduced pressure, and the residue was transferred to a 10 mL round-bottom flask. AcOH (5.2 mL, 0.18 M) was added, followed by addition of SeO_2 (233 mg, 2.10 mmol, 2.00 equiv.) under nitrogen. The resulting mixture was heated to 70 °C and stirred for 3 h. After consumption of the starting material, indicated by TLC analysis (50% EtOAc/hexanes), the reaction mixture was cooled to room temperature, the solution was filtered over a pad of Celite® which was washed with EtOAc (60 mL). The filtrate was concentrated under reduced pressure, dissolved in EtOAc (60 mL) and partitioned into satd. aq. $NaHCO_3$ (1 × 40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with EtOAc in hexanes (Biotage Isolera, SNAP KP-Sil 25 g, stepped gradient elution from 10 to 30% EtOAc/hexanes v/v, 15 mL fractions) to afford **10b** (288 mg, 76%) as a bright yellow solid; R_f = 0.45 (30% EtOAc/hexanes, UV); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.89 (d, *J* 6.0 Hz, 2H), 8.37 (s, 1H), 8.09 (dd, *J* 8.7 and 1.7 Hz, 1H), 7.93-7.85 (m, 2H), 7.83 (d, *J* 6.0 Hz, 2H), 7.30 (dd, *J* 9.0 and 2.5 Hz, 1H), 7.21 (d, *J* 2.4 Hz, 1H), 4.52 (q, *J* 8.0 Hz, 2H); ^{19}F NMR (235 MHz, $CDCl_3$) δ –73.64; ^{13}C NMR (63 MHz, $CDCl_3$) δ 193.2, 192.4, 158.4, 151.3, 139.1, 138.1, 133.6, 132.4, 128.7, 128.6, 128.4, 125.0, 123.2 (q, *J* 277.7 Hz), 122.5, 120.0, 107.7, 65.8 (q, *J* 36.1 Hz); IR (thin film, ATR) ν_{max} / cm^{-1} 1686 (w), 1661 (m), 1622 (m), 1558 (w), 1477 (w), 1409 (w), 1342 (w), 1291 (w), 1259 (s), 1216 (w),

1180 (s), 1153 (s), 1068 (w), 971 (w), 903 (w), 870 (w), 854 (w), 841 (w), 811 (w), 794 (w), 763 (w), 754 (w), 714 (w), 667 (s), 634 (w); HRMS (ESI(+)-TOF) *m/z* calcd. for $C_{19}H_{13}F_3NO_3$ 360.08420; found 360.08411; MP 113.0-115.2 °C (DCM).

General procedure A for imidazole condensation

Reactions performed on a 0.10 mmol scale

A 21 mL culture tube (16 cm × 150 mm) was charged with the diketone (0.1 mmol, 1.0 equiv.), aldehyde (0.13 mmol, 0.30 mmol, 1.3, 3.0 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and a magnetic stirring bar. The culture tube was sealed with a polytetrafluoroethylene (PTFE) septum screw cap under nitrogen atmosphere and *t*-BuOH (1.0 mL, 0.1 M) was added. The PTFE septum screw cap was changed for an unpierced one by quickly opening the culture tube. The reaction mixture was heated to 50 ºC and stirred for 1 to 24 h (depending on the substrate). After consumption of the starting material, indicated by TLC analysis [50% EtOAc:EtOH (3:1 v/v)/hexanes], the reaction mixture was cooled to room temperature and diluted with H_2O:brine (1:1 v/v, 1 × 4 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (4 × 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was adsorbed on silica gel for loading and purified by silica gel column chromatography.

General procedure B for Boc deprotection

A 5 mL vial was charged with the corresponding *N*-Boc imidazole (1.0 equiv.) obtained in the previous step and a magnetic stirring bar. Then, DCM (1 mL, 0.1 M) was added, the solution was cooled to 0 °C in an ice-water bath and stirred for 5 min before the dropwise addition of trifluoroacetic acid (TFA) (20 equiv.). In most cases, addition of TFA led to a change to bright yellow or orange color. The reaction mixture was left to warm to room temperature and stirred for 30 min to 5 h (depending on the substrate) at room temperature. After consumption of the starting material, indicated by TLC analysis [10% MeOH:NH_4OH (9:1 v/v)/DCM), the reaction mixture was quenched by the addition of 10% MeOH:NH_4OH [(9:1 v/v)]/DCM (2-3 mL) and the resulting mixture was transferred to a 25 mL round-bottom flask and enough 10% MeOH:NH_4OH (9:1 v/v)/DCM was added until the yellow/orange color dissipated (ca. 15-20 mL). The volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography with the residue dissolved in 10% MeOH/DCM for column loading (adsorbed into silica or alumina).

General procedure C for sequential Boc deprotection and reductive amination

A 5 mL vial was charged with the *N*-Boc piperidine imidazole (1.0 equiv.) obtained in the previous step and a magnetic stirring bar. Then, DCM (1 mL, 0.1 M) was added, the solution was cooled in an ice-water bath and stirred for 5 min before the dropwise addition of TFA (20.0 equiv.). The reaction mixture was left to warm to room temperature and stirred for 1 h. After consumption of the starting material, indicated by TLC analysis [10% MeOH:NH_4OH (9:1 v/v)/DCM], the volatiles were removed under reduced pressure and the residue was dissolved in MeCN (0.025 M). Then, Et_3N (1.5 equiv.) was added, followed by the addition of aqueous 37% formaldehyde solution (6.9 equiv.). The reaction mixture was left to stir at room temperature for 1 h, and then, $Na(OAc)_3BH$ (2.5 equiv.) was added in one portion. The reaction mixture was left to stir at room temperature for 18 h and after consumption of the deprotected intermediate, indicated by TLC analysis [10% MeOH:NH_4OH (9:1 v/v)/DCM], the reaction mixture was concentrated under reduced pressure, diluted with [10% MeOH:NH_4OH (10:1 v/v)/DCM] (ca. 1 mL) and filtered through a silica gel pad (1 cm × 15 mm), which was washed with [10% MeOH:NH_4OH (9:1 v/v)/DCM] until complete elution of the product (ca. 20 mL). The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography. The residue was adsorbed in silica gel or dissolved in DCM for column loading.

tert-Butyl 4-(4-(6-ethoxynaphthalen-2-yl)-5-(pyridin-4-yl)-1*H*-imidazol-2-yl)piperidine-1-carboxylate (**13a**)

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.); *tert*-butyl 4-formylpiperidine-1-carboxylate (**12a**, 28 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.); *t*-BuOH (1.00 mL, 0.1 M). The reaction mixture was left to stir for 1 h at 50 °C.

Purification by silica gel chromatography, eluted with EtOAc in hexanes, and then, with EtOAc:EtOH (3:1 v/v) in hexanes (Biotage Isolera, SNAP KP-Sil 10 g [from 50 to 70% EtOAc/hexanes, then, from 30 to 100% EtOAc:EtOH (3:1 v/v)/hexanes], 18 mL fractions) to afford **13a** (46 mg, 92%) as a white solid; R_f = 0.40 (7% EtOH/$CHCl_3$, UV, Dragendorff Stain); R_f = 0.31 (50% EtOAc:EtOH(3:1)/hexanes, UV, Dragendorff Stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (br s, 1H), 8.42 (s, 2H), 8.04-7.62 (m, 3H), 7.58-7.29 (m, 3H), 7.22-7.08 (m, 2H), 4.16 (q, *J* 6.9 Hz, 2H), 4.30-4.12 (m, 2H), 2.99 (tt, *J* 11.6, 3.4 Hz, 1H), 2.94-2.75 (m, 2H), 2.10-1.97 (m, 2H), 1.77 (dq, *J* 12.2 and

3.4 Hz, 2H), 1.49 (t, *J* 6.9 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 154.8, 151.3, 149.8, 142.8, 134.5, 133.5, 129.6, 128.9, 127.7, 127.1, 126.8, 121.5, 120.1, 106.6, 79.9, 63.7, 36.5, 31.1, 29.8, 28.6, 25.0, 14.9; note: due to slow relaxation, some ^{13}C{^{1}H} NMR signals were not identified in the spectra; specifically, the ^{13}C{^{1}H} NMR data for compound **13a** lack one of the 24 expected signals; IR (thin film, ATR) ν_{max} / cm^{-1} 2975 (w), 2920 (br), 2852 (w), 1691 (s), 1629 (s), 1535 (w), 1469 (w), 1423 (s), 1392 (m), 1365 (m), 1272 (m), 1249 (m), 1232 (w), 1207 (m), 1169 (s), 1123 (m), 1043 (w), 993 (w), 931 (w), 857 (w), 832 (m); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{30}H_{35}N_4O_3$: 499.2704; found 499.2717; MP 212.0 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(piperidin-4-yl)-1*H*-imidazol-4-yl)pyridine (**14a**)

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.); *tert*-butyl 4-formylpiperidine-1-carboxylate (**12a**, 28 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.); *t*-BuOH (1.00 mL, 0.1 M). The reaction mixture was left to stir for 1 h at 50 °C.

Purification by silica gel chromatography, eluted with EtOAc in hexanes, and then, with EtOAc:EtOH (3:1 v/v) in hexanes (Biotage Isolera, SNAP KP-Sil 10 g [from 50 to 70% EtOAc/hexanes, then, from 30 to 100% EtOAc:EtOH (3:1 v/v)/hexanes], 18 mL fractions) to afford **13a** (46 mg, 92%) as a white solid.

General procedure B (Boc deprotection)

Amounts employed: *tert*-butyl 4-(4-(6-ethoxynaphthalen-2-yl)-5-(pyridin-4-yl)-1*H*-imidazol-2-yl) piperidine-1-carboxylate (**13a**, 50 mg, 0.10 mmol, 1.0 equiv.); TFA (154 µL, 2.0 mmol, 20 equiv.); DCM (1.0 mL, 0.1 M). The reaction mixture was left to stir for 1 h at room temperature.

Purification by silica gel chromatography, eluted with MeOH:NH_4OH (9:1 v/v) in DCM [14 cm × 15 mm, gradient elution, from 10 to 20% MeOH:NH_4OH (10:1 v/v)/DCM, 1% increases, 20 mL runs, 5 mL fractions] to afford **14a** (32 mg, 80%) as a white solid; R_f = 0.08 (10% MeOH:NH_4OH [9:1]/DCM); ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (dd, *J* 4.7 and 1.6 Hz, 2H), 7.87 (s, 1H), 7.79 (d, *J* 8.5 Hz, 1H), 7.74 (d, *J* 9.0 Hz, 1H), 7.49 (dd, *J* 4.8 and 1.5 Hz, 2H), 7.42 (dd, *J* 8.5 and 1.6 Hz, 1H), 7.26 (d, *J* 2.3 Hz, 1H), 7.16 (dd, *J* 8.9 and 2.4 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.27-3.21 (m, 2H), 3.04 (tt, *J* 11.9 and 3.7 Hz, 1H), 2.83 (dt, *J* 12.5 and 2.6 Hz, 2H), 2.11-2.03 (m, 2H), 1.90 (dq, *J* 12.6 and 3.7 Hz, 2H), 1.47 (t, *J* and 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 154.1, 150.0, 136.0, 130.5, 130.3, 128.6, 128.5, 127.8, 127.7, 123.0, 120.8, 107.6, 64.6, 46.4, 37.1, 31.7, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 3 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 3199 (br), 1603 (s), 1536 (w), 1501 (w), 1469 (m), 1424 (m), 1393 (m), 1258 (m), 1209 (m), 1183 (m), 1153 (w), 1126 (w), 1042 (w), 992 (w), 961 (w), 857 (w), 833 (s), 744 (w), 691 (w), 631 (m); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{25}H_{27}N_4O$: 399.2179; found 399.2178; MP 244 °C (decomp.) (MeOH/DCM).

4-(4-(6-Ethoxynaphthalen-2-yl)-2-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl)pyridine (**15a**)

Imidazole condensation – general procedure A

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.); *tert*-butyl 4-formylpiperidine-1-carboxylate (**12a**, 28 mg, 0.13 mmol, 1.3 equiv.); NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.); *t*-BuOH (1.00 mL, 0.1 M). The reaction mixture was left to stir for 1 h at 50 °C.

General procedure C (sequential Boc deprotection and reductive amination)

Amounts employed: *tert*-butyl 4-(4-(6-ethoxynaphthalen-2-yl)-5-(pyridin-4-yl)-1*H*-imidazol-2-yl) piperidine-1-carboxylate (**13a**, 13 mg, 0.025 mmol, 1.0 equiv.); TFA (39 µL, 0.50 mmol, 20 equiv.); DCM (0.25 mL, 0.1 M). The reaction mixture was left to stir for 1 h at room temperature.

Amounts employed: Et_3N (5.3 µL, 0.038 mmol, 1.5 equiv.), aqueous 37% (w/w) formaldehyde solution (13 µL, 0.17 mmol, 6.9 equiv.), $Na(OAc)_3BH$ (14 mg, 0.063 mmol, 2.5 equiv.) and MeCN (1 mL, 0.025 M).

Purification by silica gel chromatography, eluting with MeOH:NH_4OH (10:1 v/v) in $CHCl_3$ [3 cm × 15 mm, isocratic elution, 10% MeOH:NH_4OH (10:1 v/v)/$CHCl_3$, 20 mL run, 1 mL fractions] yielded a white solid which was triturated with Et_2O:hexanes (2:8 v/v, 3 × 1 mL) to afford **15a** as a white solid (7 mg, 71% yield); R_f = 0.45 [10% MeOH:NH_4OH (10:1 v/v)/$CHCl_3$, UV, Dragendorff stain]; ^{1}H NMR (250 MHz, CD_3OD) δ 8.36 (d, *J* 5.6 Hz, 2H), 7.87 (d, *J* 1.4 Hz, 1H), 7.80 (d, *J* 8.5 Hz, 1H), 7.74 (d, *J* 9.0 Hz, 1H), 7.49 (d, *J* 6.3 Hz, 2H), 7.42 (dd, *J* 8.4, 1.8 Hz, 1H), 7.26 (d, *J* 2.2 Hz, 1H), 7.16 (dd, *J* 9.0, 2.5 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.05-2.99 (m, 2H), 2.87 (tt, *J* 12.0, 4.0 Hz, 1H), 2.34 (s, 3H), 2.19 (dt, *J* 11.9, 2.3 Hz, 2H), 2.09-2.03 (m, 2H), 1.96 (dq, *J* 12.5, 3.4 Hz, 2H), 1.47 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz,

CD_3OD) δ 159.1, 154.1, 150.0, 136.0, 130.5, 130.3, 128.6, 128.5, 127.8, 123.0, 120.8, 107.6, 64.6, 56.4, 46.4, 36.9, 31.7, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 4 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2942 (w), 2846 (w), 2781 (w), 1629 (w), 1602 (s), 1537 (w), 1505 (w), 1471 (w), 1391 (w), 1379 (w), 1269 (m), 1208 (m), 1186 (w), 1040 (w), 1019 (w), 995 (m), 930 (w), 891 (m), 861 (m), 832 (m), 769 (w), 694 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{29}N_4O$: 413.2341; found 413.2338; MP 250 °C (dec.)

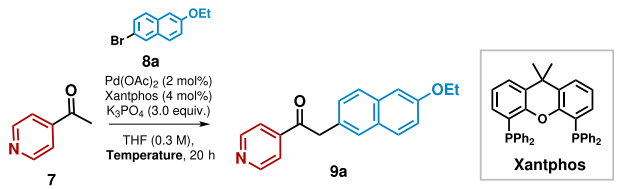
Results and Discussion

To enable expeditious library construction of the trisubstituted imidazole series to be evaluated as STK10 kinase inhibitors in structure-activity relationship (SAR) studies[27] involving late stage modifications at C-2 position, we planned to use a palladium-catalyzed α-monoarylation of 4-acetyl pyridine (**7**) to provide the required α-methylene ketone which would, then, enter in the pipeline of α-methylene oxidation and Debus-Radziszewski imidazole condensation, as shown below. For that, the palladium-catalyzed ketone arylation, a reaction discovered by Palucki and Buchwald,[29] would be key to the success in our proposal (Scheme 1).

We started our investigation with the α-monoarylation of 4-acetyl pyridine (**7**) with 2-bromo-6-ethoxynaphtalene (**8a**) but a literature search for precedents employing **7** resulted in no matches. However, Desai *et al.*[30] reported that closely related heteroaromatic ketones could be employed in such coupling. Both palladium:ligand ratio and heteroatom ring pattern played an important role in this transformation under the conditions investigated. Moreover, Tartaggia *et al.*[31] also reported that a very similar heteroaromatic methyl ketone could undergo α-monoarylation. Both conditions overlapped regarding the ligand (Xantphos) and base (K_3PO_4) selection but diverged in terms of solvent [THF:PhMe:dioxane (1:1:1, v:v:v) *vs.* NMP], the methyl ketone:aryl bromide molar ratio (2:1 *vs.* 1:1.2) and the palladium source [$Pd(OAc)_2$ *vs.* $Pd(acac)_2$].

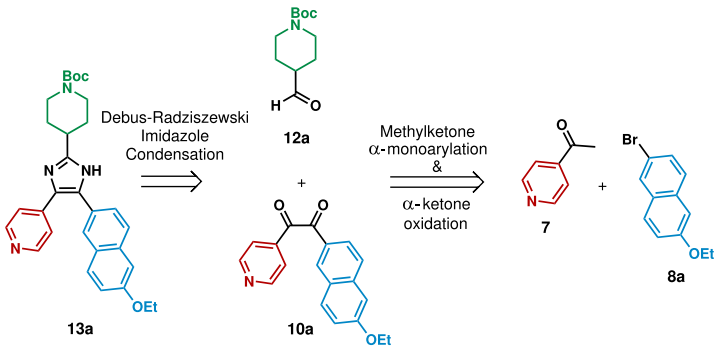
We decided to probe $Pd(OAc)_2$/Xantphos catalyst, K_3PO_4 in THF and 20 h of reaction time under different **7**:**8a** molar ratios and temperatures. Employing the molar ratio described by Tartaggia *et al.*[31] (**7**:**8a** = 1:1.2), we screened three different reaction temperatures to find that the reaction did not proceed at 65 °C (Table 1, entry 1) but provided complete conversion of 4-acetyl pyridine (**7**) and low yield of the desired coupling product **9a** at 100 °C (Table 1, entry 2; 34% yield determined by ^1H NMR using tetrachloroethane as internal standard). Surprisingly, the reaction run at 80 °C (Table 1, entry 3) provided the desired product in 45% isolated yield which was reasoned as due to thermal decomposition of the limiting reagent **7** above 80 °C. A slight excess of **7** (molar ratio **7**:**8a** = 1.2:1,

Table 1. Optimization of the preparation of ketone **9a** via α-arylation of 4-acetylpyridine (**7**)



entry	**7** (equiv.)	**8a** (equiv.)	Temperature / °C	Yield[a] /%
1	1.0	1.2	65	0[b]
2	1.0	1.2	100	(34)
3	1.0	1.2	80	(45)
4	1.2	1.0	80	64 (66)
5[c]	1.2	1.0	80	69
6	1.6	1.0	80	82
7	2.0	1.0	80	88 (71)

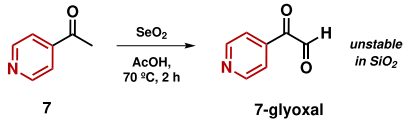
[a]Yield after work-up as determined by ^1H nuclear magnetic resonance (NMR) of the crude reaction mixture. Tetrachloroethane (δ 5.95 ppm) was used as internal reference for yield calculation. Yield in parenthesis indicates the yield after purification by silica gel column chromatography. [b]No conversion of the starting materials. [c]$Pd(OAc)_2$ (5 mol%) and Xantphos (10 mol%) were employed instead of $Pd(OAc)_2$ (2 mol%) and Xantphos (4 mol%).



Scheme 1. A complementary route to 2,4,5-trisubstituted imidazole **13a** from 4-acetylpyridine (**7**).

Table 1, entry 4) led to the desired product **9a** in 64% isolated yield while increasing the catalyst load (Table 1, entry 5) provided only a minor increase in the yield (69% yield determined by ^{1}H NMR). Further increase of the **7**:**8a** molar ratio (Table 1, entries 6 and 7) was beneficial with the desired product being isolated in 71% yield when a 2:1 molar ratio was employed at 80 °C for 20 h (Table 1, entry 7).

In order to prepare for the Debus-Radziszewski imidazole condensation, the α-methylene ketone synthesized above needed to be converted to the corresponding 1,2-diketone. Kornblum oxidation which had served well for the previously described preparation of 2,4-disubstituted imidazoles[27] provided the corresponding imidazole in moderate yield (64%). In an attempt to improve yields, we evaluated the use of copper catalyzed aerobic oxidation[32] that provided even lower yields (48%) and SeO_2, in acetic acid at 80 °C, which afforded the desired 1,2-diketone **10a** in 86% yield.[33,34] Considering that the glyoxal intermediate formed in the SeO_2 oxidation of remaining 4-acetyl pyridine (**7**) is expected to be unstable to silica gel column chromatography,[35] we decided to implement the chromatographic separation only at the stage of the desired 1,2-diketone **10a**.



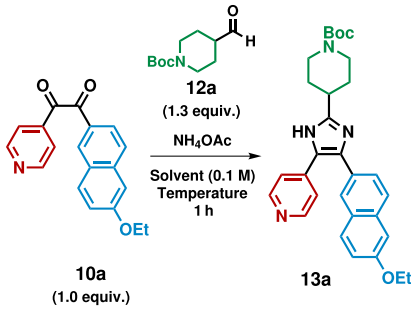
Scheme 2. 4-Acetyl pyridine (**7**) affords **7**-glyoxal under SeO_2 oxidation condition.

Therefore, after the α-monoarylation of 4-acetyl pyridine (**7**) under the optimized conditions shown in Table 1, entry 7, the crude reaction mixture, contaminated with remaining **7**, was just filtered through a plug of silica gel to remove inorganic salts and polar contaminants and the crude product was treated with SeO_2 in acetic acid at 70 °C, to afford the corresponding 1,2-diketone **10a** in 77% overall yield over 2 steps. Under this protocol, remaining **7** was converted to the corresponding glyoxal byproduct (**7**-glyoxal) by SeO_2, streamlining purification by silica gel column chromatography (Scheme 2). The procedure was scaled up 7-fold starting from 6.3 mmol of 4-acetyl pyridine (**7**) to provide 1,2-diketone **10a** in 75% yield (Scheme 3).

According to literature,[33,36] the formation of the corresponding 2,4,5-trisubstituted imidazole **13a** from *N*-Boc 4-formyl piperidine (**12a**) could be accomplish either in MeOH or acetic acid under heating, employing NH_4OAc as the ammonia source.

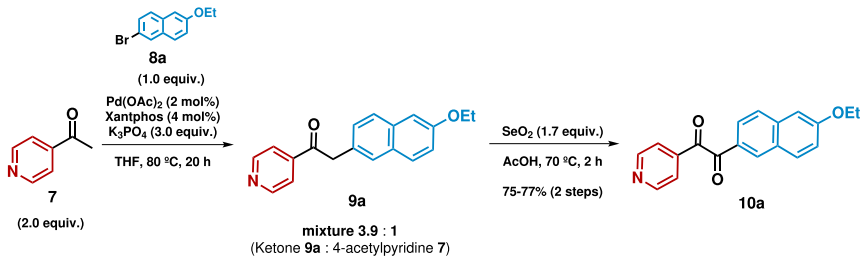
Employing a 1.0:1.3 molar ratio of 1,2-diketone **10a** and aldehyde **12a**, 15 equiv. of NH_4OAc in AcOH for 1 h at 50 °C, only traces of the desired product **13a** was formed (Table 2, entry 1) while at 100 °C and otherwise the same reaction conditions, a moderate yield could be isolated (60%, Table 2, entry 2). The use of alcohols as solvent provided much higher yields (76-92%, Table 2, entries 3-7) with *tert*-butanol performing best (Table 2, entry 5) and allowing reduction of the amount of NH_4OAc without compromising the yield (Table 2, entries 6 and 7).

Table 2. Optimization of the reaction conditions of the Debus-Radziszewski condensation for the preparation of 2,4,5-trisubstittued imidazole **13a**



entry	Solvent	NH_4OAc (equiv.)	Temperature / °C	Yield[a] /%
1	AcOH	15.0	50	traces
2	AcOH	15.0	100	60
3	MeOH	15.0	50	76
4	*i*-PrOH	15.0	50	88
5	*t*-BuOH	15.0	50	92
6	*t*-BuOH	10.0	50	92
7	*t*-BuOH (0.1 M)	5.0	50	92

Reactions performed in 0.30 mmol scale; [a]isolated yield after purification by silica gel column chromatography.



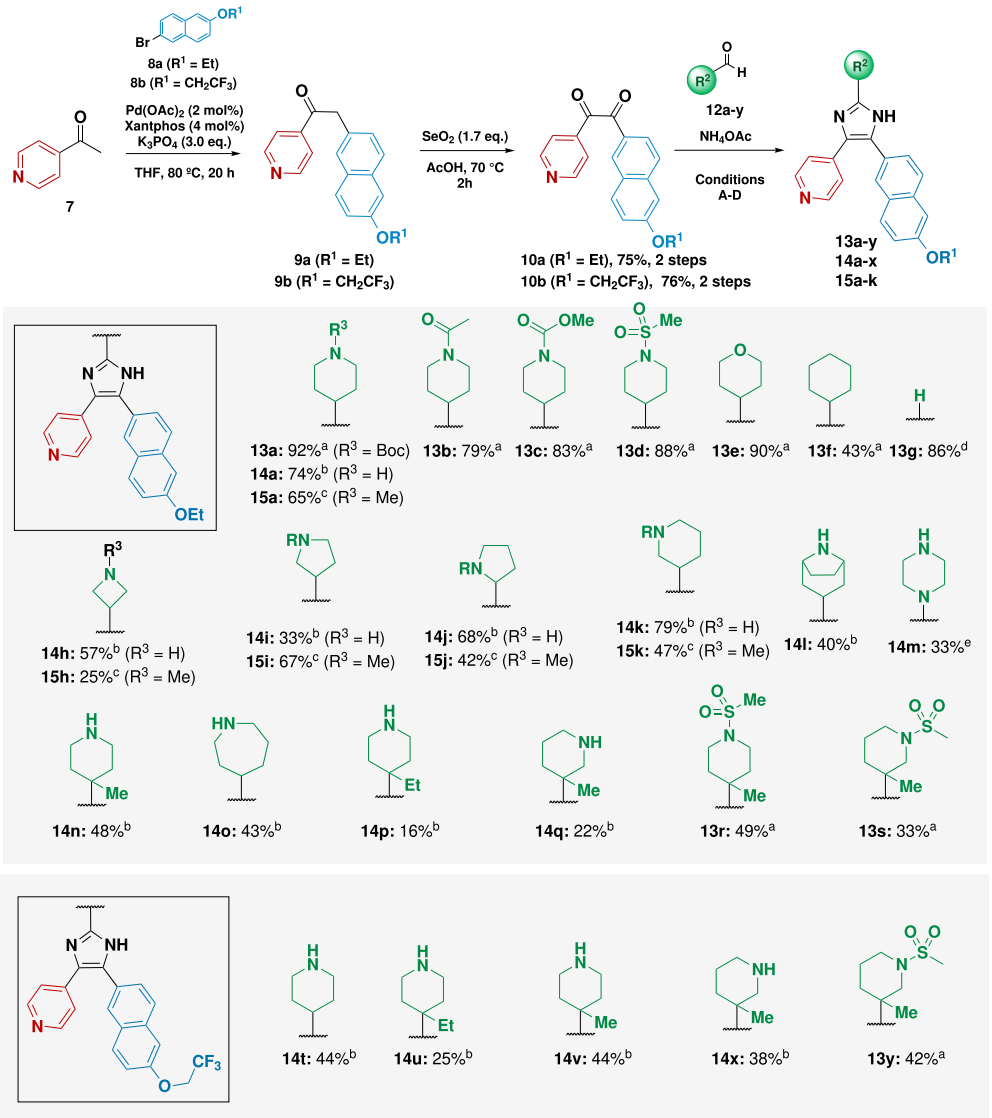
Scheme 3. Streamlining the chromatographic purification of 1,2-diketone **10a**.

The new protocol for implementation of a late-stage introduction of C-2 substituent was applied to the preparation of a series of 2,4,5-trisubstituted imidazoles as shown below.

As to the Debus-Radziszewski condensation scope, the reaction tolerates a wide range of cycloalkyl aldehydes, providing the trisubstituted imidazoles in good to excellent yields. However, when α-quaternary aldehydes were employed, a decrease in yield was observed (**14n**, **14p**, **14q**, **14u**, **14v**, **14x**, **13r**, **13s**, **13y**). This effect is even more pronounced when an ethyl group is present (**14p** and **14u**). This behavior might be due to an increase in steric bulk in the aldehyde which translates into an subsituent adjacent to the imidazole ring which can slow down the imidazole condensation allowing for side reactions to occur.

Conclusions

Herein, a new approach to trisubstituted 2,4,5-N*H*-imidazoles is described introducing the C-2 substituent at a late stage in the synthetic scheme, starting from readily available starting materials such as aryl methyl



[a]**Condition A:** 1,2-diketone (1.0 equiv.), aldehyde (1.3 equiv.), NH_4OAc (5 equiv.), *t*-BuOH, 50 °C, 1 h
[b]**Condition B**: same as Condition A; ii) TFA (20 equiv.), DCM (0.1 M), 0 °C to rt, 1-5 h
[c]**Condition C:** same as Condition B then 37% CH_2O aq. (6.9 equiv), $NaBH(OAc)_3$ (2.5 equiv.), Et_3N (1.5 equiv.), MeCN (0.025 M), rt, 18 h
[d]**Condition D:** 1,2-diketone (1.0 equiv.), paraformaldehyde (5.0 equiv.), NH_4OAc (20 equiv.), AcOH (0.05 M), 110 °C, 16 h
[e]**Condition E:** a) i) 1,2-diketone (1.0 equiv.), guanidine **12m** (1.10 equiv.), MeOH, rt, 30 min, ii) H_2 (1 atm), Pd/C (12.5 mol%), AcOH (2.5 equiv.), MeOH (0.22 M), rt, 2 h, b) TFA (20 equiv.), DCM (0.1 M), 0 °C to rt, 1 h

Scheme 4. Scope of the synthesis of 2,4,5-trisubstituted imidazoles **13a-g**, **13r,s**, **13y**, **14a**, **14h-q**, **14t-x**, and **15a**, **15h-k** via the protocol involving α-arylation of methylene ketones, oxidation the corresponding diketones and Debus-Radziszewski condensation. Overall yields shown are for final products isolated according to reaction conditions A-E and purification by column chromatography.

ketones and aryl bromides which provided access to 30 novel 2,4,5-trisubstituted imidazoles via a streamlined sequence which requires only two chromatographic purifications to obtain the final products. By optimizing the α-arylation and oxidation steps, purification is performed solely at the stage of the diketone intermediate, exploiting the chromatographic instability of the 4-pyridyl glyoxal by-product formed from the remaining 4-acetyl pyridine (**7**). The subsequent Debus-Radziszewski condensation proceeds efficiently, particularly when alcohols are used as solvents, most notably *tert*-butanol. Overall, the method affords moderate to excellent yields, except for reactions involving α-tertiary aldehydes which generally provide low to moderate yields (apart from compounds **14n** and **13r**).

The methodology is particularly appropriate for the late-stage introduction of the substituent at C-2 in the imidazole ring and nicely complements our previously disclosed methodology where the substituents at C-4 and C-5 were incorporated at the end of the synthetic route.

Considering the vast literature on the arylation of methylene ketones,[37-40] the methodology described herein should find general applications in the synthesis of 2,4,5-trisubstituted imidazoles, despite the limitation in the yields associated with the use of α-quaternary substituted aldehydes.

Supplementary Information

Supplementary Information is available free of charge at http://jbcs.sbq.org.br, as PDF file.

Data Availability Statement

All data are available in the text and supporting information.

Acknowledgments

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Author Contributions

I. T. was responsible for conceptualization, execution, analysis, validation, writing, review & editing; M. C. R. S. for execution, analysis, validation; M. A. M. for execution, analysis, validation; J. M. E. for conceptualization, validation, review; R. A. P. for conceptualization, supervision, analysis, validation, writing, review & editing.

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