Synthesis of Asthma Drug Zafirlukast (Accolate) Using Intramolecular Oxidative Coupling via $sp^3$ C–H Bond Activation

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Supporting Information

ABSTRACT: The FDA-approved drug for the treatment of asthma, zafirlukast, is synthesized engaging multiple catalytic reactions including a new method for the construction of 3-aroylindoles via oxidative cyclization. The highlights include transition-metal and peroxide free C–H bond activation using the stoichiometric amount of sodium persulfate as an oxidizing agent in the construction of 3-aroylindole, avoiding transition metal, with over 28% overall yield. The complete process has a turnaround time of 28 h to get the target molecule starting from substituted aniline, with practically no protecting groups.

INTRODUCTION

Substituted indoles play a pivotal role in drug discovery, culminating in launch of several drugs, and many molecules are in clinical pipeline.1–5 The discovery and development of drugs to treat allergic conditions and asthma has been of paramount importance in the pharmaceutical industry.6 The success rate in this area of research has been significant because the human intralobar airways have a single receptor for peptido leukotrienes.6–8 There has been a great progress reported in identifying selective peptide leukotriene antagonists.9 Indole and indazole compounds have been extensively studied as selective antagonists of the leukotriene pathway.10–13 These efforts have culminated in launching zafirlukast (1) as the oral leukotriene receptor antagonist for the maintenance treatment of asthma, prescribed in combination with bronchodilators and steroids.14–23 Other marketed products which have indole skeleton are panobinostat (2),24 roxindole (3),25,26 tropisetron (4),27,28 etc (Figure 1).

Zafirlukast attracted our attention owing to its biological profile along with our own interest to develop new strategies to build heterocyclic scaffolds for ongoing medicinal chemistry programmes.29–31 Traditionally, these classes of compounds are synthesized from prefabricated indole which offers lesser flexibility in substitutions in the benzene ring of indole.1

Thus, a nonconventional strategy engaging indole construction as the key step of synthesis, unlike using substituted indoles as starting materials, was envisaged, thereby avoiding Fischer indole synthesis. In this regard, we aimed at the synthesis of 3-aroylindoles owing to easy manipulation of its carbonyl functionality. Few literature representative methods for the synthesis of 3-aroylindoles have been shown in Scheme 1.32–38 Recently, Patel et al. have reported an intramolecular copper-catalyzed $sp^3$ C–H activation followed by C–C and C–O bond formation reactions to construct indole scaffold from alkylnyl aniline.36,37 Simultaneously, Liang and co-workers reported a palladium–copper-catalyzed 3-aroylindole synthesis.38 We desired a peroxide-free and preferably transition metal-free cyclization protocol which prompted us to explore various oxidants to trigger the cyclization process of alkylnyl N-methyl anilines to substituted indoles, which could in turn be transformed to zafirlukast.

Initially, easily accessible N,N-dimethyl-2-(phenylethynyl)-aniline 5a39 was subjected to sodium persulfate catalyzed oxidation to produce the indole 6a in 75% yield. The optimum

Figure 1. Representative drugs with 3-substituted indoles.
yields were obtained with three equivalents of sodium persulfate (see Table 1). After establishing the optimized conditions, we studied the scope and generality of the reaction with substituted N,N-dimethyl-2-(phenylethynyl)anilines and obtained corresponding 3-aroylindoles (6a−e, Table 2) in good yields (68−91%). In general, aryl rings substituted with electron-withdrawing groups gave higher yields (6d, 91% yield) compared to electron-donating groups. The procedure is also applicable to electron-rich aniline 5e to give required product 6e in 60% yield. The scalability of this reaction is proved by the preparation of 3-aroylindole 6d in a large scale.

The synthesis of substituted indoles gave us the confidence to choose molecules containing indole skeleton and we narrowed down our search to zafirlukast. A retrosynthetic analysis of zafirlukast gave the key intermediate 6f, which can be synthesized from the alkyne 5f by extending our methodology. The alkyne can in turn be synthesized from 2-bromoaniline 7 (Scheme 2).

To add value to this reaction, appropriately substituted alkylnl aniline derivative 5f was prepared in a one-pot three-step process. 2-bromoaniline 7 was subjected to Sonogashira coupling with trimethylsilyl-acetylene using palladium catalyst, followed by desilylation with the addition of K2CO3 and subsequent Sonogashira coupling in the same flask with methyl 4-iodo-3-methoxybenzoate 10 furnished 5f in 58% overall yield over three steps (Scheme 3). To our satisfaction, sodium persulfate in hot dimethyl sulfoxide (DMSO), in absence of any external catalyst, facilitated the entire sequence of sp3 C−H activation of N−Me group and formation of two new covalent C−C and C−O bonds in excellent yield (88%), to generate key intermediate 6f.

The task of converting 6f to zafirlukast was accomplished following four easy synthetic transformations (Scheme 3). Initially, 6f was hydrogenated with Pd/C and H2 which under acidic workup provided the indole acid 8 in 76% yield. The

Table 1. Optimization of Conditions for sp3 C−H Bond Activation

| entry | Na2S2O8 (equiv) | time (h) | yield (%) |
|-------|----------------|---------|-----------|
| 1     | 0.1            | 4       | 10        |
| 2     | 0.2            | 4       | 18        |
| 3     | 0.3            | 4       | 24        |
| 4     | 0.4            | 4       | 32        |
| 5     | 0.5            | 4       | 42        |
| 6     | 1.0            | 4       | 51        |
| 7     | 2.0            | 4       | 63        |
| 8     | 2.5            | 4       | 68        |
| 9     | 3.0            | 5       | 75        |
| 10    | 4.0            | 4       | 48        |

“*The reaction was carried out with 5a (0.1 mmol) in DMSO (2 mL) under an inert atmosphere at 80 °C. Yield of the isolated product 6a.

Table 2. Synthesis of Various 3-Aroylindoles

|                        | Na2S2O8 | time (h) | yield (%) |
|------------------------|---------|----------|-----------|
|                        | DMSO    |          | 6a−d      |
| 6a−d                   | 5a−d    | 6a−d     | 5a−d      |
| 6b−d                   | 6b−d    | 6b−d     | 6b−d      |
| 6c−d                   | 6c−d    | 6c−d     | 6c−d      |
| 6d−d                   | 6d−d    | 6d−d     | 6d−d      |
| 6e−d                   | 6e−d    | 6e−d     | 6e−d      |

“The reaction was carried out with 5a (0.1 mmol) and Na2S2O8 (0.3 mmol) in DMSO (2 mL) under an inert atmosphere at 80 °C. Yield of the isolated product 6d.

Scheme 2. Retrosynthetic Analysis of Zafirlukast

Scheme 1. Representative Methods for 3-Aroylindoles

Scheme 3. Retrosynthetic Analysis of Zafirlukast

Indole formation via sp3 C−H activation

Sonogashira cross coupling
coupling of indole acid 8 with sulphonamide 11 in the presence of ZnCl2 catalyst afforded 9 in 92% yield. The reduction of the nitro group in 9 was accomplished with Ran−Ni under a H2 atmosphere in EtOAc to yield 5-amino indole derivative in quantitative yield. This was converted to zaflukast (1) by conjugating with cyclopentyl chloroformate 12 following reported procedure, using N-methyl morpholine, in excellent yield (89%).

On the basis of literature reports, a plausible mechanism has been proposed for this transformation (Scheme 4). The aminyl radical cation A is formed by a single electron transfer process from the nitrogen atom of the N,N-dimethyl-2-(phenylethynyl)aniline (5). Abstraction of a hydrogen radical from N−Me gives an iminium intermediate B. The intramolecular cyclization of intermediate B via nucleophilic attack of the alkynyl group at the iminium carbon and subsequent addition of sodium persulfate gave enolate intermediate C. Then, ketonization of C afforded ketone D, which underwent further oxidation to provide 3-aroylindole 6.

In summary, an FDA-approved drug zaflukast is synthesized in six steps starting from commercially available 2-bromo-N,N-dimethyl-4-nitroaniline engaging all catalytic transformations and almost with no protective groups. The key features are (i) one pot, three transformations to build biaryl alkynes, (ii) overall yield of 28%, and (iii) all the six steps requiring only 28 h overall for completing the process, which constitutes a very fast approach to the target.

### GENERAL DETAILS

**General Information.** All the reagents and solvents were of reagent grade and used without purification unless specified otherwise. All the dry reactions were performed under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring. For reactions carried out using dry solvents, dimethylformamide (DMF), DMSO, CH2Cl2, were freshly distilled over calcium hydride and methanol was dried over calcium oxide. Technical grade ethyl acetate and hexane used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60−120 and 100−200 mesh) packed in glass columns. 1H and 13C NMR spectra were recorded at 400, 500 and 100, 125 MHz, respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in CDCl3 (H: δ = 7.26 and C: δ = 77.16 ppm) as the internal standard, and coupling constants (J) are given in Hz. High-resolution mass spectra (HRMS) were obtained by electron spray ionization (ESI) using an ESI-TOF mass spectrometer in positive ion mode (M + H or M + Na) as indicated.

### EXPERIMENTAL PROCEDURES AND ANALYTICAL DATA

**General Procedure for Intramolecular Oxidative Coupling via sp2 C−H Bond Activation (6a−e).** To a stirred solution of 5a−e (0.1 mmol) in DMSO (3 mL), NaN3 (0.3 mmol) was added into this mixture, and finally, the mixture was heated at 80 °C for 4 to 5 h. After completion of the reaction monitored by thin-layer chromatography (TLC), the reaction mixture was quenched with water (5 mL) and the product was extracted with ethyl acetate (2 × 5 mL). The organic phase was dried over anhydrous sodium
sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 3-arylindole products (6a–e).

(1-Methyl-5-nitro-1H-indol-3-yl)(phenyl)methanone 6a. By following the general procedure, compound 6a was prepared (71 mg, 68%) as a yellow solid; Rf = 0.5 (silica, EtOAc/hexane = 1:9); mp = 134–136 °C; IR (neat): 3485, 2954, 2926, 2854, 1726, 1634, 1459, 1220, 894, 772, 688 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.29 (d, J = 2.6 Hz, 1H), 8.15 (dd, J = 9.2, 2.6 Hz, 1H), 7.57–7.51 (m, 2H), 7.42–7.36 (m, 3H), 6.58 (d, J = 9.2 Hz, 1H), 5.47 (s, 1H), 3.05 (d, J = 5.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 158.0, 139.0, 131.5, 131.3, 129.0, 127.0, 125.1, 121.1, 110.0, 111.0, 95.5, 88.0, 43.0; HRMS (ESI-TOF) (m/z): calc'd for [M + H]+ C₁₅H₁₃N₃O₅, 375.1293; found, 375.1304.

Experimental Procedures for the Total Synthesis of Zafrilukast. One-Pot Synthesis of Intermediate 5f. To a mixture of aryl bromides (7.5 g, 20.41 mmol), PdCl₂ (PPh₃)₂ (143 mg, 10 mol%), CuI (39 mg, 10 mol%), and Et₃N (4.3 mL, 30.61 mmol) was added in dry DMF (80 mL); then, trimethylsilyle acetylene (5.5 mL, 20.41 mmol) was added slowly at room temperature, and the resultant mixture was stirred for 2 h at 80 °C. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, and then, K₂CO₃ (3.9 g, 30.61 mmol) was added to this mixture then heating was continued until the silylated acetylene disappeared (monitored by TLC). Once again, the reaction was allowed to come to room temperature, then added with PdCl₂ (PPh₃)₂ (143 mg, 10 mol%), Et₃N (4.3 mL, 30.61 mmol), and CuI (39 mg, 10 mol%), and continued stirring for 30 min at room temperature. Finally, aryl iodide 10 (5.9 g, 20.41 mmol) in DMF (10 mL) was added dropwise in residual mixture, and then resultant mixture was heated for 3 h at 80 °C. The reaction mixture was re-cooled to room temperature and quenched with cold water (70 mL), and the solid was filtered using with EtOAc (150 mL). Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to provide the biaryl acetylene 5f (3.9 g, 58% in 3 steps) as a yellow solid; Rf = 0.7 (silica, EtOAc/hexane = 3:7); mp = 152–154 °C; IR (neat): 3476, 3226, 2951, 2925, 2850, 1723, 1622, 1582, 1435, 1293, 1108, 767 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.38 (d, J = 2.8 Hz, 1H), 8.05 (dd, J = 9.3, 2.8 Hz, 1H), 7.64 (dd, J = 7.9, 1.3 Hz, 1H), 7.57 (d, J = 1.0 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.67 (d, J = 9.4 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.29 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 167.0, 160.1, 157.4, 138.5, 133.0, 132.0, 131.2, 125.5, 122.0, 117.2, 115.0, 111.4, 110.1, 94.5, 91.3, 56.1, 52.5, 43.0; HRMS (ESI-TOF) (m/z): calc'd for [M + H]+ C₁₅H₁₄N₂O₅, 355.1294; found, 355.1299.

Methyl 3-Methoxyphenyl(1- methyl-5-nitro-1H-indol-3-yl) (2-nitrophenyl)methanone 6d. By following the general procedure, compound 6d was prepared (77 mg, 73%) as a yellow solid; Rf = 0.5 (silica, EtOAc/hexane = 3:7); mp = 142–144 °C; IR (neat): 3476, 2928, 2838, 1738, 1627, 1534, 1416, 1318, 1219, 894, 772, 685 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 9.25 (d, J = 1.9 Hz, 1H), 8.22 (dd, J = 9.0, 1.5 Hz, 1H), 7.85 (t, J = 5.5 Hz, 2H), 7.69 (s, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.02–6.98 (m, 2H), 3.93 (s, 3H), 3.90 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 189.0, 163.0, 144.0, 140.2, 139.1, 132.5, 131.1, 120.0, 120.9, 119.1, 117.5, 114.0, 110.0, 57.0, 34.1; HRMS (ESI-TOF) (m/z): calc'd for [M + H]+ C₁₅H₁₄N₂O₅, 311.1032; found, 311.1039.

(1-Methyl-5-nitro-1H-indol-3-yl)(2-nitrophenyl)methanone 6d. By following the general procedure, compound 6d was prepared (95 mg, 91%) as a yellow solid; Rf = 0.6 (silica, EtOAc/hexane = 2:8); mp = 188–190 °C; IR (neat): 3432, 3098, 2946, 1740, 1614, 1577, 1524, 1326, 1142, 1068, 855, 756, 670 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.58 (d, J = 2.2 Hz, 1H), 8.19–8.14 (m, 2H), 7.77 (td, J = 7.5, 3.1 Hz, 1H), 7.70 (td, J = 7.9, 1.5 Hz, 1H), 7.56 (dd, J = 7.5, 1.5 Hz, 1H), 7.38 (d, J = 9.1 Hz, 1H), 6.66 (d, J = 0.6 Hz, 1H), 3.60 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 149.5, 142.1, 140.4, 139.4, 133.0, 131.3, 130.2, 125.0, 118.1, 118.0, 110.0, 105.0, 31.2; HRMS (ESI-TOF) (m/z): calc'd for [M + H]+ C₁₅H₁₂N₂O₅, 326.1489; found, 358.1474.

(1-Methyl-1H-indol-3-yl)(phenyl)methanone 6e. By following the general procedure, compound 6e was prepared (64 mg, 60%) as a viscous liquid; Rf = 0.7 (silica, EtOAc/hexane = 1:9); IR (neat): 3479, 3392, 2926, 2856, 1642, 1523, 1459, 1220, 1065, 772, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.46–8.40 (m, 1H), 7.81–7.76 (m, 2H), 7.54–7.49 (m, 1H), 7.49–7.42 (m, 3H), 7.32 (dd, J = 5.7, 3.6 Hz, 3H), 3.78 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 190.9, 140.9, 138.1, 137.6, 131.1, 128.7, 128.3, 123.7, 122.7, 115.5, 109.7, 33.6; HRMS (ESI-TOF) (m/z): calc'd for [M + H]+ C₁₅H₁₃N₃O₅, 236.1075; found, 236.1063.
mol %) and concd HCl (0.2 equiv) sequentially. The flask was evacuated and pressurized with H₂ (balloon) atmosphere, and the reaction mixture was stirred for 6 h. After completion of the reaction, the solvent was removed under reduced pressure, and the pH value of the reaction mixture was adjusted to 2 withaq HCl (2.0 M) and then, cyclopentyl chloroformate was added under hydrogen balloon pressure at room temperature for 2 h. The reaction mixture was filtered using diethyl ether and dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure and purified by column chromatography to give compound 8 (1.4 g, 76%) as a yellow solid; Rf = 0.5 (silica, EtOAc/hexane = 7:3); mp = 183–185 °C; IR (neat): 3417, 2951, 2850, 1723, 1689, 1584, 1431, 1370, 1163, 1062, 1036, 872, 758 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 9.18 (s, 1H), 8.26 (dd, J = 8.0, 1.3 Hz, 1H), 7.51 (td, J = 7.5, 1.3 Hz, 2H), 7.40 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 1.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.16 (dd, J = 7.9, 1.6 Hz, 1H), 7.09 (d, J = 7.9 Hz, 2H), 6.77 (s, 1H), 6.51 (s, 1H), 5.18 (ddd, J = 8.9, 5.9, 2.6 Hz, 1H), 4.03 (s, 2H), 3.85 (s, 3H), 3.70 (s, 3H), 2.68 (s, 3H), 1.86 (s, 2H), 1.74 (d, J = 12.6 Hz, 4H), 1.60 (s, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 164.4, 158.0, 138.0, 137.0, 137.0, 134.1, 134.1, 133.0, 138.0, 130.1, 130.0, 128.4, 128.1, 127.0, 119.4, 115.2, 112.0, 110.0, 56.0, 33.0, 33.0, 25.4, 24.0, 21.0; HRMS (ESI-TOF) (m/z): calcd for [M + Na]^+ C₃H₁₅N₂O₅Na, 598.1988; found, 598.1975.

**ASSOCIATED CONTENT**

Supporting Information

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General details; experimental procedures and analytical data for biaryl alkynes; and ¹H and ¹³C NMR spectra of the obtained compounds (PDF).

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**Notes**

The authors declare no competing financial interest.

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