A Novel Practical Synthesis of Pazopanib: An Anticancer Drug

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Abstract: This paper reports a novel approach to synthesize pazopanib. In our synthetic route, the potently mutagenic alkylating agents such as dimethyl sulfate and methyl iodide are avoided. A novel regioselective methylation of the 2-position of 3-methyl-6-nitro-1*H*-indazole was reported. This novel route is one step shorter than the previously reported route.

Keywords: Anticancer drug, pazopanib, regioselective methylation, synthesis, trimethyl orthoformate.

INTRODUCTION

Angiogenesis, the formation of new blood vessels from existing vasculature, plays an essential role in tumor progression and metastasis [1-3]. Vascular endothelial growth factor (VEGF) is a key mediator of neovascularization and research has intensely focused on interfering with the VEGF receptor (VEGFR) signaling system in order to modulate angiogenesis. Pazopanib (**1**) is a multikinase inhibitor with targets that include vascular endothelial growth factor receptors. Pazopanib was approved by the US FDA for the treatment of advanced renal cell carcinoma [4, 5].

Pazopanib (**1**) was earlier prepared by a route described in Scheme **1** [5]. The synthesis involves cyclization of 2-ethyl-5-nitroaniline (**2**) which was used as a diazotizing reagent *tert*-butyl nitrite to give 3-methyl-6-nitro-1*H*-indazole (**3**). Regioselective methylation of **3** provided intermediate **4** which was used as a methylating reagent trimethyl oxonium tetraflouroborate. The nitro functionality of **4** was reduced using tin(II) chloride to produce 6-amino-2,3-dimethyl-2*H*-indazole (**5**) and subsequent attachment of a 2,4-dichloropyrimidine to the arylamines **5** afforded **6**. Methylation of **6** with methyl iodide yielded *N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine (**7**). Finally, condensation of *N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine (**7**) and 5-amino-2-methylbenzenesulfonamide in the presence of a catalytic amount of HCl was carried out to afford pazopanib (**1**) in six steps overall.

This process suffers from disadvantages such as (a) The use of the potently mutagenic alkylating agent methyl iodide; (b) The use of trimethyl oxonium tetraflouroborate is expensive; (c) A highly flammable and light sensitive diazotizing reagent *tert*-butyl nitrite was used. All of which on large scale manufacturing process, may have induced environmental damage.

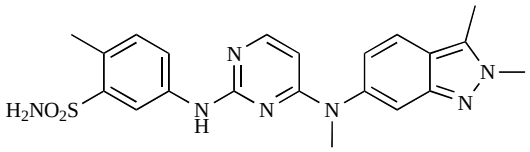

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Fig. (1). The structure of pazopanib.

Several other methods are available for the synthesis of pazopanib. Arundathy *et al.* [6, 7] used 3-methyl-6-nitro-1*H*-indazole sulfuric acid salt refluxing with dimethyl sulfate within DMSO and methylene chloride obtained the intermediate 2,3-dimethyl-6-nitro-2*H*-indazole (**4**) that could be used for the next step. Dimethyl sulfate as an alkylating agent is especially dangerous since this reagent is an extremely hazardous liquid and vapor (causes delayed burns to lungs and tissues, may be fatal if inhaled).

RESULTS AND DISCUSSION

On the basis of the above limitations, we devised a safe, economically competitive and environmentally benign synthetic route for **1**, which was obtained from **2** in five steps using inexpensive and commercially available raw materials and reagents (Scheme **1**). To the best of our knowledge, this novel route is environmentally advantageous over the earlier described methods owing to avoid using the potently mutagenic alkylating agents such as dimethyl sulfate and methyl iodide and one step shorter than previously reported. In addition, this new method is less expensive because of the much cheaper material used.

Process for 3-methyl-6-nitro-1*H*-indazole (3) without using *tert*-butyl nitrite

We opted sodium nitrite as a key raw material because the diazotizing reagent *tert*-butyl nitrite is a highly flammable and light sensitive liquid. 2-ethyl-5-nitroaniline (**2**) is reacted with sodium nitrite in acetic acid to obtain the 3-methyl-6-nitro-1*H*-indazole (**3**) in 93.9% yield [8].

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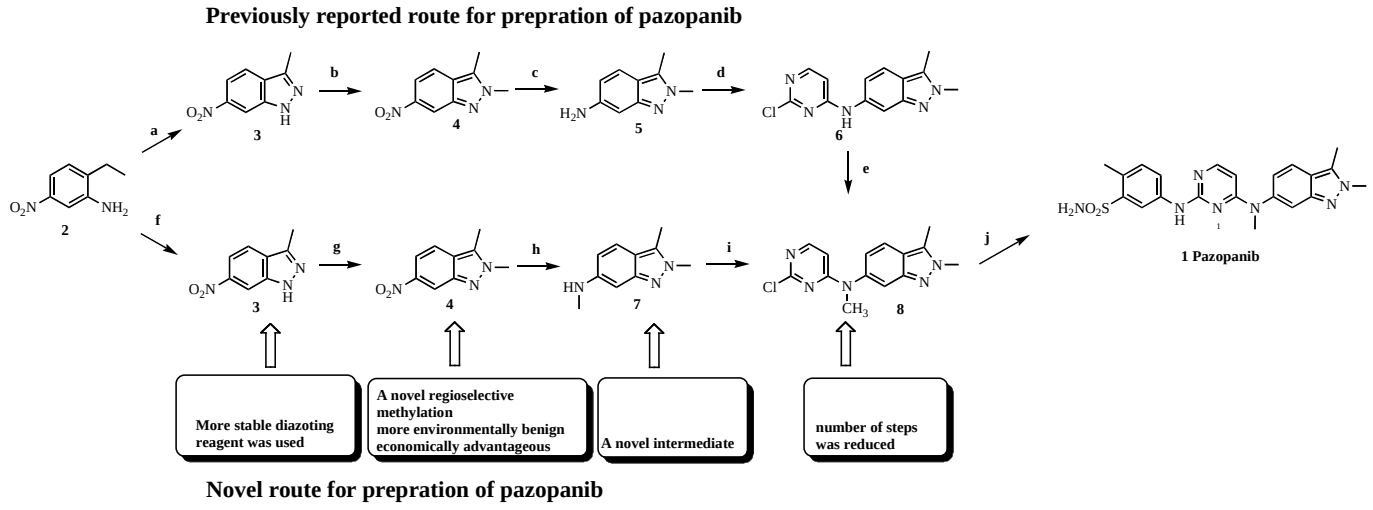


Scheme 1. Synthesis of pazopanib. Reagents and conditions: (**a**) *t*-BuONO, acetic acid; (**b**) trimethyl oxonium tetraflouroborate; (**c**) tin(II) chloride; (**d**) 2,4-dichloropyrimidine; (**e**) MeI, rt; (**f**) sodium nitrite, acetic acid; (**g**) trimethyl orthoformate, DMF, sulfuric acid, toluene, reflux; (h) MeOH, Pd/C, H_2, paraformaldehyde, NaH, $NaBH_4$; (i) 2,4-dichloropyrimidine; (**j**) 5-amino-2-methylbenzenesulfonamide, reflux.

Process for 2,3-dimethyl-6-nitro-2*H*-indazole (4) *via* a novel regioselective methylation method

A novel method for the preparation of 2,3-dimethyl-6-nitro-2*H*-indazole was developed. We have chosen the trimethyl orthoformate as methylating reagent due to its commercial availability and low cost, since the indazole ring has two nitrogen atoms and presents annular tautomerism with regards to the position of the NH hydrogen atom (Fig. **2**). The alkylation of N-H indazoles generally yielded a mixture of N-alkyl 1*H*-indazoles and N-alkyl 2*H*-indazoles regioisomers [9, 10] (Scheme **2**).

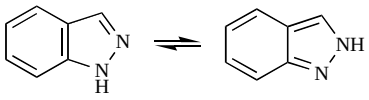


Fig. (2). Tautomeric forms of indazole.

The trimethyl orthoformate was reported as potent alkylating reagent that has been used to methylate many different functional groups [11]. We found that in the presence of sulfuric acid, the trimethyl orthoformate can regioselect methylate at N-2 position of the 3-methyl-6-nitro-1*H*-indazole. The workup is simple and it involves that once the reaction is completed, the reaction is cooled to room temperature followed by filtration and washing the product.

Process for N,2,3-trimethyl-2*H*-indazole-6-amine (7)

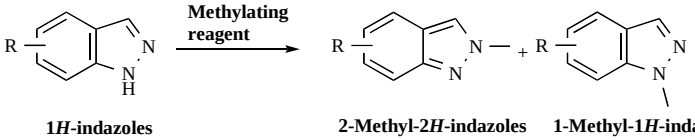
The N,2,3-trimethyl-2*H*-indazol-6-amine (**7**) was prepared by hydrogenation, followed by introduction of the methyl group using the Eschweiler-Clarke methylation reaction [12], providing a novel intermediate **7**.

EXPERIMENTAL SECTION

All purchased starting materials were used without further purification. Melting points were determined in open capillary tubes on a MelTemp II apparatus which were uncorrected. ^{1}H NMR and ^{13}C NMR were run on a Bruker 300 MHz spectrophotometer using DMSO-d_6 as solvent with tetramethylsilane as internal standard. Chemical shift data are reported in parts per million (δ in ppm) where s, br, d, dd, t, and m designate singlet, broad, doublet, doublet of doublet, triplet, and multiplet, respectively. Coupling constants are in units of hertz (Hz).

3-methyl-6-nitro-1*H*-indazole (3)

To a solution of 2-ethyl-5-nitroaniline (20.0 g, 120 mmol) in glacial AcOH (500 mL) a solution of sodium nitrite (11.1g 132 mmol) in water (24 mL) was added all at once. During this addition, the temperature was not allowed to rise above 35℃. After the nitrite solution had been added, stirring was maintained for 30 min. The solution was evaporated in vacuo. Cold water was added to the orange residue and the contents of the flask were washed into a beaker where they were stirred. The product was filtered, rinsed with saturated aqueous $NaHCO_3$ and dried to afford 3-methyl-6-nitro-1*H*-indazole (20.0 g, 93.9% yield); mp 176-178℃; ^{1}H NMR (300 MHz DMSO-d_6): δ 13.50 (br, 1H), 8.38 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.88 (dd, J' = 8.7 Hz, J'' = 1.8 Hz, 1H), 2.56 (s, 3H); MS: *m/z* 178.1 $[M + H]^+$



Scheme 2. Methylation of 1-*H* indazoles

2,3-dimethyl-6-nitro-2*H*-indazole (4)

Concentrated sulfuric acid (1.5 g, 14.9 mmol) was added to a solution of 3-methyl-6-nitroindazole (**3**) (2.6 g, 14.7 mmol) in trimethyl orthoformate (10 mL) , toluene (10 mL) and DMF (1 mL) at room temperature. The solution was refluxed for 3 hr. The solution was cooled and filtration gave a yellow solid, which was washed with petroleum ether and saturated aqueous $NaHCO_3$ to yield the crude product. The crude product was recrystallized from the ethanol to give 2,3-dimethyl-6-nitro-2*H*-indazole (**4**) (1.77 g, 63.0% yield). mp 183-184℃; ^{1}H NMR (300 MHz DMSO-d_6): δ 8.49 (d, *J* = 1.8 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.70 (dd, *J'* = 9.0 Hz, *J''* = 1.8 Hz 1H), 4.15 (s, 3H), 2.67 (s, 3H); MS: *m/z* 192.1 $[M + H]^+$.

N,2,3-trimethyl-2*H*-indazole-6-amine (7)

Methanol (20 mL) and THF (60 mL) was added to a flask containing 10% Pd/C (0.3 g, 0.27 mmol). The 2,3-dimethyl-6-nitro-2*H*-indazole (**4**) (2.0 g, 10.5 mmol) was added, and the reaction mixture was stirred in an H_2 atmosphere until the hydrogen was no longer absorbed. After completion of the reaction, the Pd/C catalyst was filtered off on celite and the solvent was removed by rotary evaporation, the residue was dissolved in methanol (30.0 mL); paraformaldehyde (1.6 g, 53.3 mmol) was added to the solution and stirred at room temperature. NaH (0.5 g, 22.1 mmol) was added carefully. The reaction solution was stirred at room temperature overnight. Then $NaBH_4$ (1.6 g, 42.3 mmol) was added. And the reaction solution was stirred at room temperature for 3 hours. the solvent was removed by rotary evaporation. The residue was diluted with EtOAc and washed with water. The organic phase was dried with anhydrous $NaSO_4$, and then concentrated by rotary evaporation. Yield N,2,3-trimethyl-2*H*-indazole-6-amine (**7**) as a pink solid (1.6 g, 85.8% yield). ^{1}H NMR (300 MHz DMSO-d_6): δ 7.27 (d, *J* = 8.7 Hz, 1H), 6.43 (d, *J'* = 8.7 Hz 1H), 6.14 (s, 1H), 5.61 (br, 1H), 3.87 (s, 3H), 2.67 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz DMSO-d_6): 9.70, 30.38, 36.89, 89.96, 114.95, 115.16, 120.24, 131.23, 148.47, 149.38; MS: *m/z* 176.1 $[M + H]^+$.

N-(2-chloropyrimidin-4-yl)-N,2,3-trimethyl-2*H*-indazol-6-amine (8)

DMF (6.0 mL) was added to a flask containing N,2,3-trimethyl-2*H*-indazole-6-amine (0.6 g, 3.4 mmol), $NaCO_3$ (0.6 g, 5.7 mmol), 2,4-dichloropyrimidine (0.6 g, 4.03 mmol). The reaction mixture was warmed to 100℃ under N_2. The reaction was stirred for 3 hours. The reaction solution was cooled and water (100 mL) was added. The solution was extracted by EtOAc and washed with saturated aqueous $NaHCO_3$ and water, dried with anhydrous $NaSO_4$, then concentrated by rotary evaporation. Yield N-(2-chloropyrimidin-4-yl)-N,2,3-trimethyl-2H-indazol-6-amine (**8**) as a pale yellow solid (0.9 g, 88.4% yield). mp 164-165℃; ^{1}H NMR (300 MHz DMSO-d_6): δ 8.14 (d, *J* = 6.3 Hz, 1H), 7.93 (d, *J* = 6.3 Hz 1H), 7.64 (s, 1H), 6.86 (dd, *J'* = 8.7 Hz, J'' = 0.9 Hz 1H), 6.24 (d, *J* = 6.0 Hz 1H), 4.07 (s, 3H), 3.43 (s, 3H), 2.63 (s, 3H); MS: *m/z* 288.1 $[M + H]^+$.

Pazopanib (Free Base). (1)

To a solution of N-(2-chloropyrimidin-4-yl)-N,2,3-trimethyl-2*H*-indazol-6-amine (2.0 g, 6.9 mmol) and 5-amino-2-methylbenzenesulfonamide (1.2 g 6.9 mmol) in *i*-PrOH (45 mL) was added 3 drops of conc HCl and the mixture heated to reflux for 5 hr. The mixture was cooled at room temperature. The resulting precipitate was collected *via* filtration and washed with diethyl ether to yield pazopanib hydrochloride. The salt was suspended in water, triethyl amine was added to adjust the pH to 9, the precipitate was filtered and dried resulting a white solid. (2.5 g, 76.0% yield) ^{1}H NMR (300 MHz DMSO-d_6 free base) δ 9.37 (s, 1H), 8.60 (d, *J* = 2.1 Hz, 1H), 7.92 (d, *J* = 5.7 Hz, 1H), 7.71-7.84 (m, 2H), 7.45 (s, 1H), 7.23 (s, 2H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.87 (dd, *J'* = 8.71 Hz, *J''* = 1.5 Hz, 1H), 5.75 (d, *J* = 6.0 Hz, 1H), 4.06 (s, 3H), 3.50 (s, 3H), 2.63 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz DMSO-d_6 free base) 9.86, 19.59, 37.82, 38.50, 97.11, 114.39, 117.77, 119.95, 120.08, 121.90, 122.30, 127.59, 132.50, 132.64, 139.68, 142.29, 142.38, 147.45, 156.17, 159.87, 162.88; MS: *m/z* 438.2 $[M + H]^+$.

CONFLICT OF INTEREST

Declared none.

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