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Regioselective methylation of indazoles using methyl 2,2,2-trichloromethylacetimidate

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ABSTRACT

An efficient and regio selective synthesis of substituted 2-methyl-2*H*-indazoles using a methyl 2,2,2-trichloroacetimidate is described.

The indazole ring is one of the intensively exploited templates in the medicinal chemistry.[1] In addition to this, the indazole ring and its derivatives are found to exhibit analgesic,[2] antitumor,[3] anticancer,[4] anti-inflammatory,[5] and anti-fertility activities.[6] Surprisingly, 2*H*-indazoles are much less explored than 1*H*-indazoles.[7]

Considering therapeutic potential of this class of the molecules, it becomes extremely important to devise an efficient regioselective methylation of substituted 2-methyl-2*H*-indazoles. Indazoles are found to undergo unselective alkylation under basic conditions to afford corresponding mixture of *N*-1 and *N*-2 products, respectively whereas, under mild acidic conditions, regio selective alkylation at *N*-2 position takes place. *N*-1 alkylated products are thermodynamically controlled and the *N*-2 was favored under kinetic conditions. Cheung[8] and Luo[9] suggest that the *N*-2 lone pair is more kinetically accessible than the *N*-1 lone pair for neutral indazoles. Cheung's work features one of the best methods for regioselective methylation by employing trimethyloxonium tetrafluoroborate (Meerwein's reagent).[8] In general, Catalan[10] showed that the 1*H* tautomer is more stable than the 2*H* tautomer of indazoles.

Morel et al.[11a] and Boyer et al.[11b] reported that the methylation of 6-nitro-1*H*-indazole **1** by employing dimethyl sulfate in the presence of potassium hydroxide at 45 °C affords the products approximately in 1:1 mixture of 1-methyl-6-nitro-1*H*-indazole (42% yield) and 2-methyl-6-nitro-2*H*-indazole (44% yield). Auwers et al.[12] reported a regioselective methylation at *N*-2 position of 6-nitro-1*H*-indazole by heating with methyl iodide (4 equiv) at 100 °C in a sealed tube for 4 h; however, no yield was mentioned in the report. Jaffari et al.[13a] also reported the regioselective methylation of 6-nitro-1*H*-indazole using alkylating agents such as methyl iodide, methyl toluene-*p*-sulfonate, or diazomethane. Recently, Bernard et al.[13b] reported regioselective *N*-ethylation by using K_2CO_3/DMF/EtBr.

Interestingly, the regioselectivity of the indazoles was highly dependent on the nature of the methylating agents. For example, methylation of **1** (Scheme 1) using methyl iodide resulted in mixtures of 2-methyl-6-nitro-2*H*-indazole **2** in 50%, 1-methyl-6-nitro-1*H*-indazole **3** 10%, and dimethylated product in 17% yields. Methylation of 6-nitro-1*H*-indazole using methyl toluene-*p*-sulfonate resulted in 50% yield of 2-methylated product with 25% yield of recovered starting material. On the contrary, methylation of 6-nitro-1*H*-indazole using diazomethane in the presence of BF_3 (CH_2N_2, $BF_3{\cdot}Et_2O$, 70 °C, 6 h) resulted in a product with 75% yield of 1-methylated product. In order to develop a methylating reagent that has potential to afford regioselective product, we employed methyl 2,2,2-trichloroacetimidate for the series of indazoles bearing electron donating and electron with drawing groups.

It is well understood that there are many reagents that have been shown to afford *N*-1 and *N*-2 alkylated products in moderate to good yields but poor regioselectivity has always been observed.

In our endeavor, we attempted to develop a reliable method that may address regioselectivity issue in indazole class of molecules. In our initial exploration of the synthesis of substituted 2-methyl-2*H*-indazoles by using literature procedures, the *N*-alkylation afforded products with poor *N*-regioselectivity in minuscule yields. We understood that the regioselectivity of the indazoles is highly dependent on the nature of the alkylating agents thus we turned our attention to other unexplored alkylating agents.

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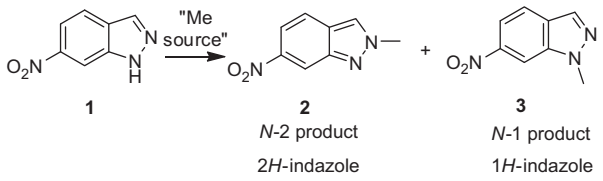


Scheme 1. *N*-Alkylated, *N*-1, and *N*-2 indazoles.

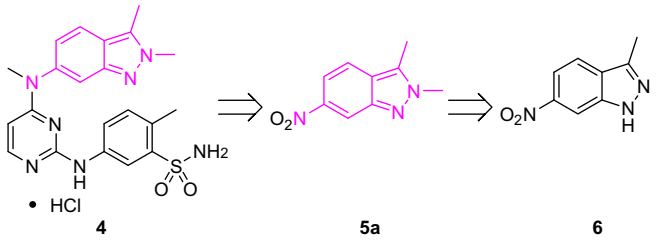


Figure 1. Retro synthetic analysis of Pazopanib hydrochloride.

Table 1
Screening of solvents for the synthesis of **2**

Entry	Screening solvents	Yield %	Remarks
1	Dichloromethane	87	Reaction completed in 16–18 h
2	Ethyl acetate	80	Reaction completed in 12–13 h
3	Acetonitrile	52	20–30% of starting material were unreacted
4	Tetrahydrofuran	—	Reaction did not proceed

Considering the requirement of sterically hindered methyl source which would provide regioselective product we employed methyl 2,2,2-trichloroacetimidate. This reagent is used for alkylation of other functional group other than amines.[14]

We exploited the potential of this reagent to synthesize one of the key starting materials **5a** of Pazopanib hydrochloride **4** as shown in Figure 1 (Votrient™, made by GlaxoSmithKline). This compound **4** is a tyrosine kinase inhibitor (TKI). It has been approved for renal cell carcinoma by the US Food and Drug Administration (FDA).

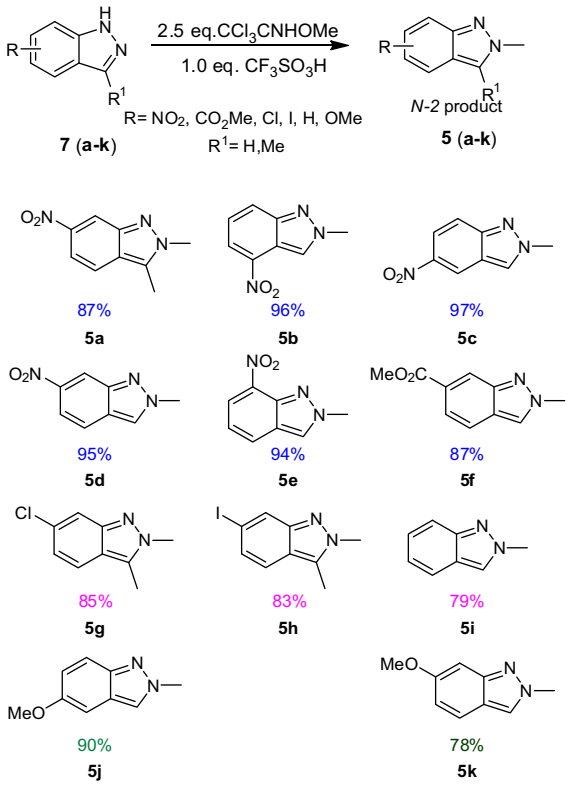
As part of a process development program, it is required to prepare a large quantity of 2,3-dimethyl-6-nitro-2*H*-indazole **5a** for the synthesis of Pazopanib hydrochloride **4**.

Regioselective methylation on 3-methyl-6-nitro-1*H*-indazole **6** was extensively optimized with regard to combinations of reagent, solvent, time, temperature as well as stoichiometry of reagent. In our approach, the regioselective methylation on 3-methyl-6-nitro-1*H*-indazole **6** was carried out in the following selected solvents such as dichloromethane, ethyl acetate, acetonitrile, and tetrahydrofuran. Among these, dichloromethane and ethyl acetate were found to be effective solvents of choice in terms of complete reaction conversion; in ethyl acetate rate of reaction was faster than the dichloromethane but there were a few impurities that have been observed and incomplete reaction conversion was observed in acetonitrile. Attempts to perform this reaction in tetrahydrofuran solvent were futile. Eventually, dichloromethane was opted as choice of solvent as shown in Table 1.

Thereafter, a systematic approach was adopted toward optimization of reaction conditions that involve mole equivalence of acid reagent and methyl 2,2,2-trichloroacetimidate, reaction time, and temperature. We were able to identify the optimum conditions featuring dichloromethane as a solvent, temperature; 25–35 °C and time about 16–18 h.

Table 2
Screening of acid for synthesis of **2**

Entry	Acid reagent	Yield %
1	Trifluoromethanesulfonic acid	87
2	Sulfuric acid	48
3	Pyridinium *p*-toluenesulfonate	35



Scheme 2. Synthesis of 2-alkyl-substituted 2*H*-indazole.

Different acid reagents were screened for methylation on indozole moiety; for example, sulfuric acid (H_2SO_4), trifluoromethanesulfonic acid (CF_3SO_3H), and pyridinium *p*-toluenesulfonate. Among these, trifluoromethanesulfonic acid afforded best results. Finally, optimum mole equivalent of trifluoromethanesulfonic acid was found to be 1.0 equiv for methylation of **7** (**a–k**) as shown in Table 2.

Initial experiments were begun with 1.25, 1.75, 2.1, and 2.5 mol equiv of methyl 2,2,2-trichloroacetimidate. These screening efforts reveal that 2.5 equiv is the optimum quantity for regioselective methylation of **7** (**a–k**). The quantity of solvent, dichloromethane was adjudged to be 25 vol with respect to starting material.

The electronic effects on the methylation of indazoles were studied. In general, the electron withdrawing group favors the formation of *N*-1 product whereas the electron donating group helps to afford *N*-2 selective product. In our endeavor, regioselective methylation was explored by using different types of indazoles **7** (**a–k**), containing either electron donating (e.g., methoxy, etc.) or electron withdrawing (e.g., nitro, ester, etc.) groups and without substituent in the aromatic system (**7i**). As shown in Scheme 2, irrespective of substituent in the reactant, 2-alkyl-substituted 2*H*-indazole (*N*-2-methyl) compounds **5** (**a–k**) were preferentially isolated in the range of 75–97% yields.[15]

In conclusion, we have developed an efficient and regio selective synthesis of substituted 2-methyl-2*H*-indazoles using methyl 2,2,2-trichloroacetimidate as a methylating agent. This

methodology can be applied to one of the key intermediates of Pazopanib hydrochloride and various substituted indozole ring systems of pharmaceutical significance.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.030.

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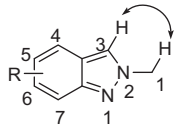
15. Regiochemistry of the products was determined by observing a correlation between H-1 and H-3 from the 1D-NOE- NMR spectroscopic experiments.



5 (a-k)

General procedure for the synthesis of 2-methylsubstituted 2H-indazoles: Preparation of 2-methyl-6-nitro-2H-indazole (**5d**). To a stirred mixture of 6-nitro-1*H*-indazole (1.0 g, 0.0061 mmol) in dichloromethane (25.0 mL) was added trifluoromethanesulfonic acid (0.54 mL, 0.0061 mmol), stirred for 5–10 min at 25–35 °C. To this mixture was added methyl 2,2,2,-trichlroacetimidate (2.69 g, 0.015 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16–18 h under N_2. After reaction completion, chilled saturated $NaHCO_3$ solution was added. The aqueous and organic phases were separated. Aqueous phase was extracted with dichloromethane 10 mL. Combined organic layers were washed with DM water (2×10 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated completely under vacuum to obtain 2-methyl-6-nitro-2*H*-indazole (1.03 g, 95.0%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.683 (s, 1H), 8.03 (s, 1H), 7.91 (d, 1H), 7.89 (d, 1H), 4.31 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) 146.93, 146.46, 124.52, 121.24, 115.70, 115.27, 41.06; MS (+ve ES) 178 (M+H).