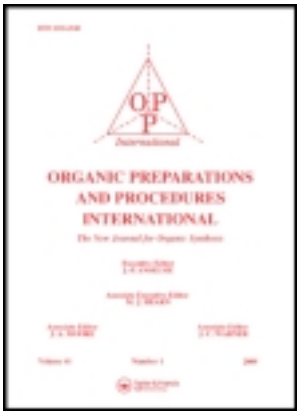

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An Improved Preparation of 4-Chloro-1H-indazole

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An Improved Preparation of 4-Chloro-1*H*-indazole

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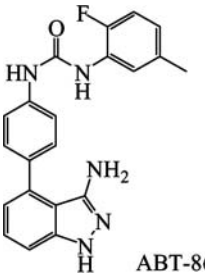
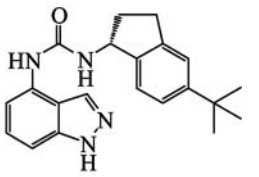
Increasing attention has been paid to the synthesis of heterocyclic compounds bearing the indazole motif because of their broad pharmacological activities,[1] including antidepressant activity,[2] antineoplastic activity,[3–10] anti-inflammatory and analgesic activity,[11,12] liver carbonyl reductase inhibitive activity,[13] antiplatelet activity,[14] antitrypanocidal activity,[15] VR-1 inhibitive activity,[16] *etc*. Recently, many pharmacologically important compounds with substituents at the 4-position of indazole have been developed for pre-clinical testing, such as ABT-869[17] and ABT-102.[18,19]



ABT-869



ABT-102

Reliable and efficient syntheses of these indazoles were required to provide access to large quantities of bulk drug for further studies. Therefore, various methods have been devised to obtain these 4-substituted indazoles.[20–24] Thus, 4-chloro-l*H*-indazole (**1**) is an important building block for the synthesis of these biologically active 4-substituted indazole derivatives. Until now, quite limited synthetic methods of **1** have been reported from either 3-chloro-2-methylaniline (**2**)[25,26] or 2-chloro-6-fluorobenzaldehyde (**3**)[27] (*Scheme 1*).

Unfortunately, these methods cannot be considered practical for multi-kilogram preparations for the following reasons. *Method A* requires the addition of expensive and toxic crown ether catalyst and deprotection step to recover the indazole.[28,29] In our hands, *Method B* has turned out to be unreliable with relatively lower overall yields than the reported

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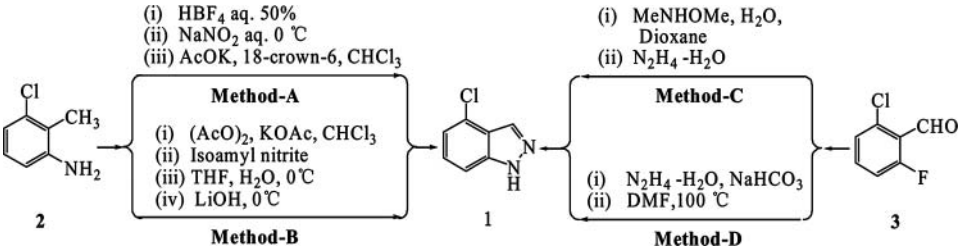
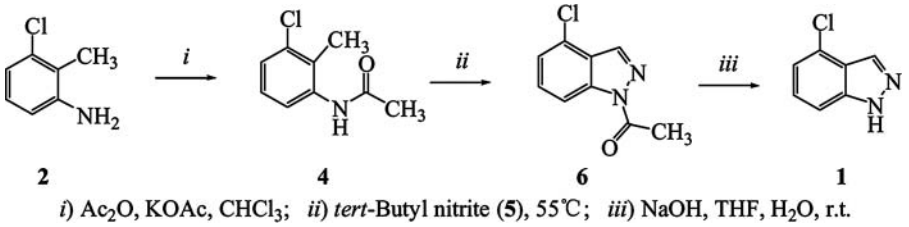


Scheme 1
Reported Syntheses of Compound 1

literature,[26] due to the tedious work-up of intermediates and final product as well as the incomplete hydrolysis of the unpurified intermediate **6** to **1** by using LiOH. *Method C* requires the expensive fluoro compound **3** and *N*-methoxymethanamine as the starting materials, which leads to the high cost of production of **1**. Apart from the use of the expensive fluoro compound, the Wolff-Kishner reduction of the intermediate hydrazone in *Method D* does lead to the formation of 2-chloro-6-fluorotoluene as a side-product.

Therefore, an efficient and economic synthesis of **1** is still needed. By contrasting and analyzing the above methods, we therefore choose the commercially available 3-chloro-2-methylaniline (**2**) as an inexpensive starting material. Acetylation of NH_2 group of **2** provided *N*-acetyl-3-chloro-2-methylaniline (**4**), which reacted with *tert*-butyl nitrite, which was prepared just prior to use, to give *N*-acetyl-4-chloro-1*H*-indazole (**6**) without further separation of **4**. The final hydrolysis of purified **6** under basic condition of NaOH result in **1** in the 99% overall yield based on **2**. The whole efficient and economic process is suitable for large scale synthesis of **1** (*Scheme 2*).

In summary, there are three main aspects in this improved industrial adapted synthesis procedure of **1** compared with reported *Method B*[26]: 1) *tert*-Butyl nitrite was used instead of expensive *iso*-amyl nitrite. 2) Intermediate **6** was separated and purified before the removal of the carbonyl group at the *N*-1 position to ensure the complete reaction. 3) NaOH was used for the hydrolysis instead of expensive LiOH.



Scheme 2
Efficient Synthesis of Compound 1

Experimental Section

Melting points were taken on an X-4 digital melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo-Elba 1106 elemental analyzer. IR spectra were recorded on a Nicolet FI-IR 360 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker AM-400(400 MHz) spectrometer with TMS as an internal standard. Chemical shifts are reported in δ. Mass Spetra were measured on a HP5988A instrument by direct inlet at 70 ev. All materials were obtained from commercial suppliers and used as received.

tert-Butyl Nitrite

To a 250 mL three neck flask was added with *tert*-butanol (37.0 g, 0.5 mol) and then an aqueous solution of sodium nitrite (38.0 g, 0.6 mol) in 150 mL of H_2O. The reaction mixture was cooled to 0°C and sulfuric acid (35%, 68.0 mL) was added to this mixture from the bottom of the reaction vessel for 2 h by using a glass inlet tube. The yellowish oily product rose above the aqueous layer; the gases evolved from the system were absorbed through an alkali solution (NaOH 10%). The oily product was separated and washed with water (50 mL × 3) and sodium bicarbonate aqueous solution (5%) (50 mL × 3) until pH 7, and then washed with water again. The yellow liquid obtained was dried over sodium sulfate and distilled to give the desired product (25.9 g, 50%), bp. 60–61°C. *lit*. 60–61°C.[29]

N-Acetyl-3-chloro-2-methylaniline (4)

To a 250 mL flask fitted with mechanical stirrer was added 3-chloro-2-methylaniline (**2**, 4.2 mL, 5.0 g, 35.3 mmol), potassium acetate (4.2 g, 42.4 mmol) and chloroform (60 mL). This mixture was cooled to 0°C with stirring, and then acetic anhydride (10.0 mL, 106.0 mmol) was added over 2 min. The reaction mixture was allowed to gradually warm up to room temperature and stirred for 1 h to give a chloroform solution containing KOAc, acetic acetic, acetic anhydride and *N*-acetyl-3-chloro-2-methylaniline (**4**). This solution was used in the next step without further purification. Pure **4** may be obtained by recrystallization from petroleum ether-ethyl acetate (2:1) as white prisms, mp. 158–159°C. *lit*. 159–160°C.[30]

N-Acetyl-4-chloro-1H-indazole (6)

The chloroform solution obtained containing **4** was heated to 55°C, *tert*-butyl nitrite (10.9 g, 105.8 mmol) was added and the reaction mixture was stirred for 7 hrs at 55°C until the reaction has completed (TLC, petroleum ether-ethyl acetate 2:1). After cooling to room temperature, the reaction mixture was washed with sodium bicarbonate aqueous solution (5%) to pH 7 and then washed with water again. The organic layer was dried over anhydrous sodium sulfate and then evaporated *in vacuo* to give *N*-acetyl-4-chloro-1*H*-indazole (**6**, 7.3g) as an orange-red solid, which was recrystallized from THF/H_2O (1:1.7) to give pure **6**, mp. 63–64°C.[31] The crude product could be directly used in next step without purification. ^{1}H NMR ($CDCl_3$, 400 MHz):δ 8.35 (d, J = 8.00 Hz, 1H, Ph-5-*H*), 8.21 (s, 1H, Pyrazole-3-*H*), 7.48 (t, J = 8.00 Hz, 1H, Ph-6-*H*), 7.33 (d, J = 8.00 Hz, 1H, Ph-7-*H*),

2.80 (s, 3H, CH_3-CO-); ^{13}C NMR ($CDCl_3$, 400 MHz):δ171.07 (*C*=O), 139.95 (Ph-*C*-N), 137.75 (Pyrazole-3-*C*H), 130.20 (Ph-6-*C*H), 126.41 (Ph-4-*C*-Cl), 125.41(Ph-4-CH-*C*-3-CH-Pyrazole), 124.16 (Ph-5-*C*H), 114.00 (Ph-7-*C*H), 23.02 (*C*H_3); MS (EI) *m/z* 196 (M^+).

Anal. Calcd for $C_9H_7ClN_2O$: C, 55.54; H, 3.63; Cl, 18.22; N, 14.39; Found: C, 55.52; H, 3.60; Cl, 18.25; N, 14.36.

4-Chloro-1H-indazole (1)

To the crude orange-red solid **6**[32] was added water (60 mL) and THF (150 mL) and the reaction mixture was cooled to 0°C. Sodium hydroxide (9.9 g, 247.5 mmol) was added and the reaction mixture was stirred at 0°C until the reaction was completed after 2 hrs (monitored by TLC, petroleum ether-ethyl acetate 2:1). After evaporation of THF *in vacuo*, the residue was extracted with ethyl acetate (50 mL × 3). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* to yield 4-chloro-1*H*-indazole (**1**, 5.3g, 99%) and may be purified by recrystallization from THF/H_2O (1:2) as orange crystals, mp. 155–157°C. *lit*. 155-157°C.[25-27]

Acknowledgment

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32. Although the purification of **6** is not necessary, compound **6** should be separated from the reaction mixture before the next step. If the next reaction was performed according to the literature[26] without separation of **6** from the crude reaction mixture, the hydrolysis process was not fully complete, which results in the lower overall yield of **1**.