Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2353–2356

Utility of Japp–Klingemann reaction for the preparation of 5-carboxy-6-chloroindole via Fischer indole protocol

Yihui Chen,[a] Masayuki Shibata,[b] Manju Rajeswaran,[c] Thamarapu Srikrishnan,[d] Sundeep Dugar[e] and Ravindra K. Pandey[a,*]

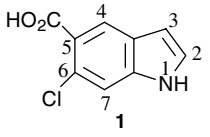
[a]*Chemistry Division, PDT Centre, Roswell Park Cancer Institute, Buffalo, NY 14263, USA*
[b]*Biomedical Informatics, UMDNJ-School of Health Related Professions, Department of Health Informatics, Newark, NJ 07107, USA*
[c]*Kodak Research and Development Laboratories, Eastman Kodak Company, Rochester, NY 14650-2106, USA*
[d]*Tumor Biology, Roswell Park Cancer Institute, Buffalo, USA*
[e]*Scios Pharmaceuticals, a subsidiary of Johnson and Johnson, Palo Alto, CA, USA*

Received 26 December 2006; revised 23 January 2007; accepted 24 January 2007
Available online 1 February 2007

Abstract—5-Carboxy-6-chloroindole, a precursor for p38 kinase inhibitor, was prepared from 4-amino-2-chloro-3-iodobenzoicacid by following the Japp–Klingemann synthetic approach. The structures of the key intermediates were also confirmed by X-ray analyses. Computational analysis was helpful in understanding the importance of the substituents at the cyclization step of the synthesis.

The indole nucleus is probably the most widely distributed heterocyclic ring system found in nature.[1] Due to the existence of a vast array of structurally diverse and biologically active indoles, it is not surprising that the indole nucleus is an important feature in many medicinal agents. The synthesis and reactivity of indole derivatives have been a topic of research interest for well over a century. Reports of several thousand individual indole derivatives appear annually in the chemical literature. The primary reason for this sustained interest is the wide range of biological activities found among indole analogs.[1] One of the most important biological activities of indole-based compounds is that these compounds can be used as inhibitors of p38 kinase.[2] These inhibitors are important in treating a variety of diseases: rheumatoid arthritis, osteoarthritis, sepsis, asthma, adult respiratory distress syndrome, cardiovascular disorders, and Alzheimer's disease. Among the indoles synthesized so far, compound **1** (Fig. 1) has also shown some promising p38 kinase inhibitory activity.[2]

In recent years, several synthetic methodologies have been reported for preparing indole analogs. For example, the Leimgruber–Batcho approach starts from the β-dialkylamino-*o*-nitrostyrene[3] or *o*-, β-nitrostyrene.[4]



1

Figure 1. 6-Chloro-5-indole carboxylic acid.

o-Amino- or *o*-nitro-phenylacetylenes can be cyclized to indoles by *endo*-dig addition.[5] Reductive cyclization of *o*-nitrostyrenes to indoles has also been reported.[6] The Nenitzescu reaction is another approach for indole synthesis.[7] The Watanabe indole synthesis deals with an oxidative cyclization.[8] It is the metal-catalyzed indole synthesis from anilines and glycols or ethanolamines with subsequent intramolecular cyclization of *o*-aminophenethyl alcohols to indole.[9] For all the metal-catalyzed indole synthesis approaches, palladium is the most widely used catalyst. The review articles by Gribble and Wolfe provide a detailed description on Pd mediated cyclization.[9,10] Other metals reported to catalyze indole synthesis include rhodium, ruthenium, titanium, zirconium, and copper.[9] The selection of the metal depends on the nature of the substrate(s).

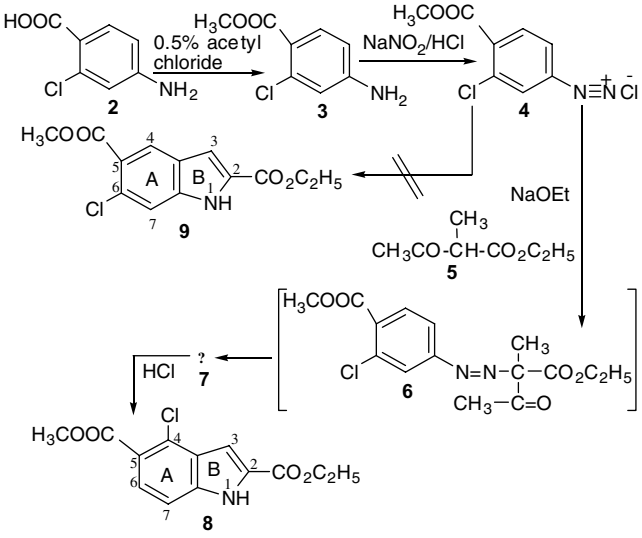
Among the synthetic methodologies reported so far for the preparation of the indole analogs, the Fischer indole synthesis still maintains its prominent role for large-scale production.[9] In particular, the Japp–Klingemann

* Corresponding author. Tel.: +1 716 845 3203; fax: +1 716 845 8920; e-mail: ravindra.pandey@roswellpark.org

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.148

reaction[11,12] is quite efficient and deals with the preparation of intermediate hydrazones from the aryl diazonium salts derived from arylamines and β-keto-acids (or β-keto-esters). We were interested to investigate the utility of this approach for the synthesis of the desired 5-carboxy-6-chloroindole. The amino group in **3** was converted into the corresponding aryldiazonium analog **4**. It was treated with ethyl 2-methyl-acetoacetate **5** under basic conditions to produce intermediate **6**, which on subsequent acid rearrangement gave indole **8** (instead of **9**), formed by the intramolecular cyclization at the *ortho*-position of the chlorine atom. The formation of **8** without producing indole **9** even in traces was surprising. If steric hindrance is considered to be a determining factor for the cyclization of intermediate **4**, then compared to the *ortho*-position of the chlorine atom, the *para*-position is less sterically hindered, and one can expect that the cyclization would occur at the less hindered *para*-position. However, the cyclization in fact occurred at the more sterically hindered position (*ortho*-position). This observation suggests that at the cyclization step the steric hindrance is not a dictating factor (Scheme 1).

The other possibility that we looked at was the energy level for the formation of both indoles **8** and **9** calculated by semi-empirical MO, PM3, as well as more sophisticated ab initio RHF/6-31G**. However, the calculated values for the formation of both the indoles were quite close and did not help in determining the factors responsible for generating the undesired indole (see Supplementary data for details). In another set of experiments, intermediate **7** was isolated and characterized by X-ray analysis before subjecting it to cyclization. As can be seen from Figure 2, in compound **7,** the acetyl group that was present in **6** is gone and the nitrogen–nitrogen bond is now linked with a single bond, while the adjacent nitrogen–carbon single bond was converted into a double bond. A sigmatropic rearrangement of **7** under acid-catalyzed conditions afforded compound **8** as a sole product (Scheme 2).



Scheme 1. Preparation of indole **8** from 2-chloro-4-aminobenzoic acid **2**.

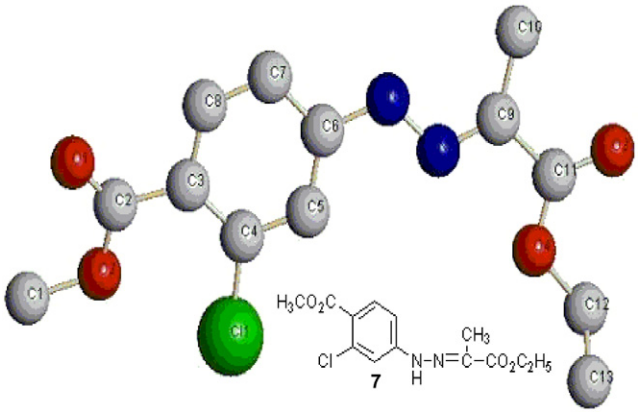
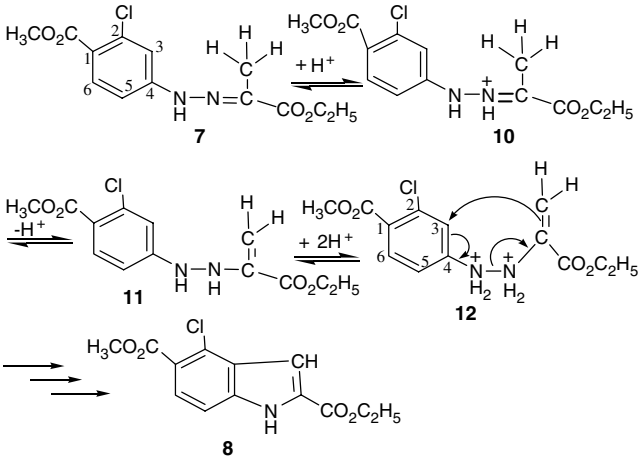


Figure 2. Single crystal X-ray structure of intermediate **7**.

Among all the intermediates, the unstable intermediate **12** seems to be responsible for the formation of indole **8** over **9**. On the basis of the charge distribution study on compound **12** obtained with ab initio MO at MP2 level using the 6-31+G* basis set, the position 5 was found to be more electron dense (−0.32) than position 3 (−0.24) (Fig. 3). This characteristic could be responsible for the formation of indole **8**. In order to further confirm the rationality of the charge distribution at the intramolecular cyclization step, the chloro-substituent in compound **12** was replaced with a hydroxy group and the electron density of the possible intermediate **17** was calculated at the same level as chloro derivative discussed above. As expected, in contrast to compound **12**, intermediate **17** had a higher electron density at position 3 (−0.46) than at position 5 (−0.34). If charge density had been the determining factor the cyclization should have preferentially occurred at position 5 (instead of position 3) and indeed the position 5 cyclized indole compound **16** was isolated as a sole product (see Scheme 3).

In another approach, compound **19** in which position 3 was blocked by an iodo-group was first synthesized. It was then subjected to the reaction sequences depicted in Scheme 4 and the desired indole **1** was obtained in a moderate yield.



Scheme 2. A possible mechanism for the formation of indole **8** from intermediate **7**.

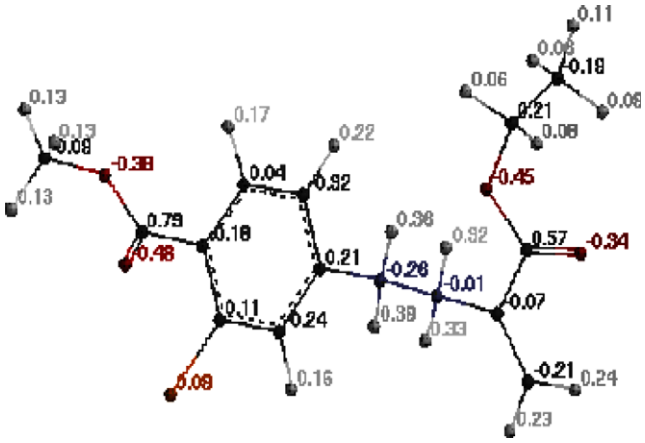
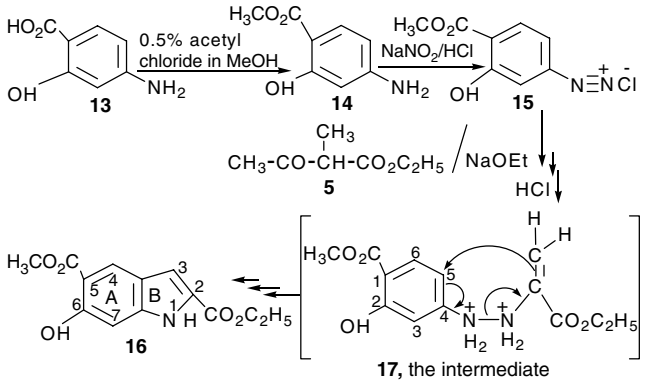
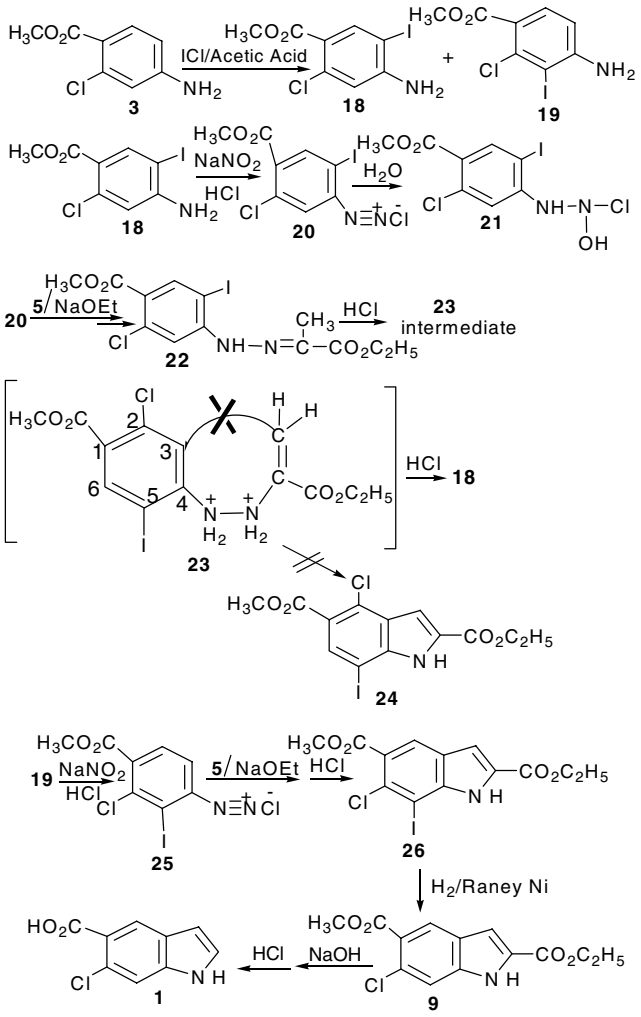


Figure 3. Charge distribution of compound **12**.



Scheme 3. Preparation of indole **16**.

For the preparation of iodinated derivative **19**, compound **3** was reacted with periodic acid and iodine,[13] which resulted in the formation of an undesired 5-iodo-substituted analog **18** as a sole product. However, reaction of **3** with iodine monochloride (ICl)[14] in acetic acid as the solvent gave a mixture of 3- and 5-iodinated derivatives **18** and **19**, respectively. The yields of the individual isomers were found to be temperature dependent. For example, at high temperature (>100 °C) **18** was isolated as a sole product, whereas at room temperature, both **18** and **19** were obtained, in the ratio of 2.5 to 1. Due to their close R_f values (similar lipophilicity), it was extremely difficult to separate the individual isomers in a reasonably large quantity by column chromatography. Although the R_f values of **18** and **19** were quite close, their NMR spectra were significantly different and it was easy to characterize the individual isomers. For compounds **18** and **19**, the resonance peak of amino group (–NH_2) was observed at 4.563 ppm and 4.743 ppm, respectively. The chemical shifts for the two aromatic protons were also quite different. For **18**, the resonances were observed at 8.231 and 6.733 ppm as singlets. On the other hand, for **19** these resonances as doublets were observed at 7.692 and 6.611 ppm, respectively, both protons *ortho*- to each other showed a strong interaction. The observed coupling constant value was 8.4 Hz. Both isomers on subjecting to cyclization gave some interesting results. For example, isomer



Scheme 4. Synthesis of indole **1**.

18 did not produce the expected indole **24** and the starting material was recovered quantitatively. However, the X-ray structure of intermediate **22** (Fig. 4) was found to be similar to intermediate **7** (Fig. 2). These results suggest that at the cyclization stage, due to a high steric hindrance caused by the substituents at positions 2 and 5 (Cl–, I–, respectively), the intermediate compound **23** was unable to cyclize and under acidic conditions decomposed to the starting material **18**.

After careful purification of all the compounds before HCl treatment, besides compound **22** a small amount of compound **21** was also isolated, which was possibly formed from **20** under aqueous reaction conditions. By following a similar synthetic approach, isomer **19** was successfully converted to indole **26** (Scheme 4). This result introduces another possibility that in addition to the charge distribution of the key intermediate discussed above, other factors such as HOMO/LUMO characteristics may be playing a significant role at the cyclization step of the synthesis. For example, a HOMO of compound **12** clearly showed that the C3 and C5 positions in the ring have an opposite polarity and a LUMO of the same compound shows a large population on the ethylene carbon (C=C) (see the Supplementary data

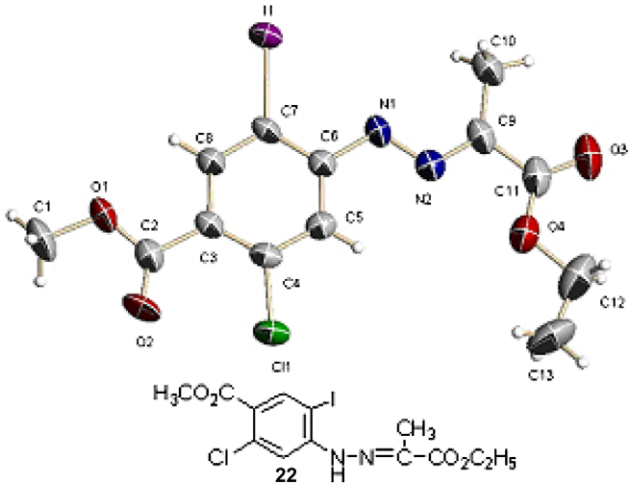


Figure 4. Single X-ray structure of compound **22**.

for HOMO/LUMO representation). Limited conformational flexibility through three bonds connecting the ethylene carbon and the ring may prevent the ethylene carbon for approaching the ring in the right orientation for cyclization to occur at C5 position. This provides a reasonable explanation for the quantitative recovery of the starting material **18**, without forming any cyclized product.

For a large-scale preparation of indole **1**, we started with a mixture of iodo-analogs **18** and **19**. Two major products isolated from the reaction mixture were characterized as the desired intermediate indole **26** and an unreacted isomer **18**. From the mixture, these compounds can easily be separated by column chromatography. Our next step was to selectively remove the iodo-group on **26** without removing the chloro substituent. Several approaches were tried to produce the desired compound and finally the hydrogenation with Raney nickel afforded **9** in a quantitative yield. At the final step of the synthesis, the ester functionalities were hydrolyzed on stirring in aqueous sodium hydroxide solution. The corresponding carboxylic acid on stirring in hot HCl preferentially decarboxylated the 2-carboxylic acid functionality and the desired indole **1** was obtained in 60% yield.[15]

In conclusion, starting from the readily available starting materials, the preparation of the desired 5-carboxy-6-chloroindole, a useful precursor for p38 kinase inhibitor, is discussed. Our study indicates that in Japp–Klingemann reaction, the position and nature of the substituents in the intermediate product(s) play an important role at the cyclization step of the synthesis. However, in our present study the reaction conditions for the preparation of the intermediates and the final products were not optimized.

The structures of the key synthetic intermediates were also confirmed by X-ray analysis. The computer modeling study suggested that the distribution of the electron density in the intermediate molecules plays an important role but other factors such as conformational flexibility and HOMO/LUMO may play additional roles at the cyclization step of the synthesis.

Acknowledgment

Support from the shared resources of the RPCI (P30CA16056) is appreciated.

Supplementary data

Experimental procedures, characterization data of compounds **1**, **3**, **7**–**9**, **14**, **16**, **18**, **19**, **21**, **22**, and **26**. Crystallographic file (cif) for compounds **7** and **22**. Molecular modeling calculations. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.148.

References and notes

1. Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005**, *70*, 504, and references cited therein.
2. Luedtke, G.; Tester R.; Dugar, S.; Lu, Q.; Perumattam, J.; Tan, X. United States Patent: US 200501711 83A1, 2005.
3. Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.
4. Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, *48*, 3347.
5. Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856.
6. Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375.
7. Landwehr, J.; Troschutz, R. *Synthesis* **2005**, *14*, 2414.
8. Shim, S. C.; Youn, Y. Z.; Lee, D. Y.; Kim, T. J.; Cho, C. S.; Uemura, S.; Watanabe, Y. *Synth. Commun.* **1996**, *26*, 1349.
9. Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
10. Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625.
11. Phillips, R. R. *Org. React.* **1959**, *10*, 143.
12. Gorlitzer, K.; Fabian, J.; Frohberg, P.; Drutkowski, G. *Pharmazia* **2002**, *57*, 243.
13. Panetta, C. A.; Fang, Z.; Mattern, D. L. *J. Org. Chem.* **1995**, *60*, 7953.
14. Hubig, S. M.; Jung, W.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 6233.
15. *Experimental*: In brief, compound **2** was converted into **3** in 90% yield by refluxing in methanol with catalytic amount of acetyl chloride. Compound **3** was then dissolved in acetic acid and reacted with iodine monochloride to afford a mixture of compounds **18** and **19** (the ratio of **18** to **19** was roughly 2.5 to 1) in 75% yield. At low temperature (<5 °C), compound **25** obtained by reacting **18** and **19** with sodium nitrite was treated with the sodium ethyl 2-methylacetoacetate (obtained by reacting **5** with sodium ethoxide). The resulting intermediate was reacted with HCl gas-saturated ethanol to give **26** in 19% yield, which on hydrogenolysis (Raney nickle/H_2) produced **9** in quantitative yield. At the final step of the synthesis, **9** was reacted with sodium hydroxide and the resulting carboxylic acid analog without any further purification was decarboxylated under acidic conditions (concd HCl) to produce the desired indole **1** in 60% overall yield (for details see the 'Supplementary data').