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5-Chloroindole계 화합물의 Large Scale 합성

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Highly Convenient and Large Scale Synthesis of 5-chloroindole and its 3-substituted Analogues

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요 약. CuCl과 *N*-methyl-2-pyrrolidone을 이용하여 5-bromoindole을 halogen - halogen 교환반응을 통하여 5-chloroindole계 화합물을 합성하는 one-pot대량합성방법을 개발하였다.

주제어: 5-haloindoles, 염화 구리 (I) , N-methyl-2-pyrrolidone, halogen-halogen 교환반응

ABSTRACT. A large scale and commercially feasible synthesis of 5-chloroindole and its 3-substituted analogues has been described *via* a halogen - halogen exchange reaction from 5-bromoindole and its derivatives using cuprous chloride and dipolar aprotic solvent *N*-methyl-2-pyrrolidone in one pot with good yields.

Keywords: 5-haloindoles, copper (I) chloride, *N*-methyl-2-pyrrolidone, halogen-halogen exchange.

INTRODUCTION

The synthesis of nitrogen-containing heterocycles continues to attract both synthetic and medicinal chemists, especially indole derivatives due to their excellent biological activities.[1] Indole and its derivatives are important intermediates in organic synthesis and exhibit various properties and pharmacological activites.[2] In connection with our on-going project for the large-scale industrial production of 5-chloroindole, we were interested in a method that can have high commercial viability and which can utilize very cheap and commercially available starting materials.

Literature survey revealed that there are several methods available for the synthesis of 5-chloroindole such as the general one being the classical decarboxylation[3] of 5-chloroindole-2-carboxylic acid, ortho chloroacetylation of anilines[4] following by cyclization and oxidation, or from substituted N-aryl-1-alkenylsulfinamides,[5] by direct chlorination of 1-acetylindoline followed by saponification,[6] from the direct oxidation of 5-chloroindoline with chloranil[7] etc. Other recent methods include palladium assisted cyclization from 2-bromoanilines with enamines,[8] vinylstannanes[9] etc. Ruthenium catalysed reactions have also been reported for the synthesis of 5-chloroindoles, which include, a sequence of acylation, chlorination, deacylating, and oxidation of indoline,[10] *via* indole-ruthenium complexes,[11] from anilines and ethylene glycol through a combination of ruthenium and tin catalysis.[12] Similarly, ruthenium-catalyzed heteroannulation of anilines with alkanolammonium chlorides[13] or thermal cyclization of 4-chloroaniline with 1,2-dibromoethane[14] have also been reported. Recently, rhodium catalysed cycloisomerisation of 4-chloroanilines with trimethylsilyl acetylenes to obtain 5-chloroindoles was reported.[15] Although the above methods are good to some extent for the small scale synthesis of 5-chloroindole, but they suffer from one or other disadvantages such as either low yields or use of expensive starting materials and reagents which limits the

applicability of the above methods for the scale up and production at an industrial scale.

RESULTS AND DISCUSSION

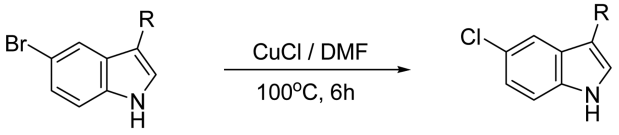
Looking at the above literature cited method's, we envisaged that a direct one step method that can utilize cheap raw materials could address the problem and which in turn would be of high commercial feasibility. However, direct synthesis of 5-chloroindole by the single step process from 5-bromoindole is not known in the literature so far.

In this regard, we thought of using a halogen - halogen exchange reaction[16-17] as this could be the best method to obtain 5-chloroindole in a single step starting from commercially available and cheap raw material 5-bromoindole[18] and the present paper deals with our efforts in this direction.

Initially, we have carried out the reaction of 5-bromoindole with cuprous chloride in presence of N, N-dimethylformamide at 100 ºC and obtained the halogen exchanged product as expected in only 57% yield after 6 h. Increasing the heating time of the reaction to 12-24 h did not improve the reaction yield (*Scheme* 1).

Therefore, we decided to screen a set of solvents as well as refluxing times for the reactions to see if we can obtain better yields and the results are summarised in *Table* 1 and best condition for the reaction is depicted in *Scheme* 2. The screening results indicate that among all the solvents tested for the reaction NMP was found to be the superior choice for the reaction with good to excellent yields.

Having succeeded the synthesis of required 5-chloroindole starting from 5-bromoindole in good yields, we have then extended the applicability of the present method to see if we can do this transformation on some other substituted indoles and the results are summarized in *Table* 2.

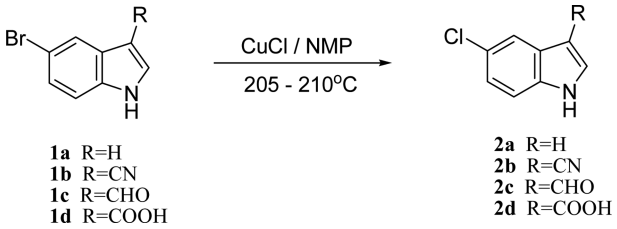


***Scheme* 1.**

***Table* 1.** Formation of **2a** under a range of solvents and temperatures

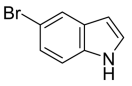
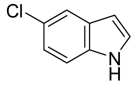
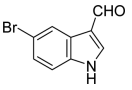
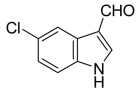
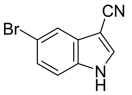
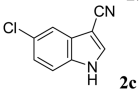
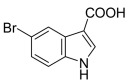
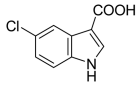
S. No.	Solvent	Time (h)*	Isolated yield (%)
1	DMF	6	57
2	DMF	12	63
3	NMP	12	76
4	NMP	15	85
5	DMA	15	43
6	DMSO	15	47
7	HMPA	15	59

*Temperatures are the best average with respect to yields obtained



***Scheme* 2.**

***Table* 2.** Synthesis of 5-chloroindole and its analogues

Sr. No.	Starting Material	Product	M.P. (ºC)	Yield (%)
1.		 **2a**	70-72	85
2.		 **2b**	212-215	83
3.		 **2c**	190-194	76
4.		 **2d**	240-246	79

EXPERIMENTAL

Melting points were obtained on a MP apparatus SP 62 and are un-corrected. Infrared spectra were recorded on a FT-IR, Perkin-Elmer Spectrum-I spectrometer and the NMR spectra on a Bruker at 400 M Hz instrument-using TMS as internal standard.

Synthesis of 5-chloroindole (2a)

A mixture of 5-bromoindole (1a, 100 g, 0.51 mmole, 1.0 eq), cuprous chloride (115 g, 1.28 mmole, 1.15 eq) were dissolved in N-methyl-2-pyrrolidone (400 mL). The reaction mixture was slowly heated to 205-210 ºC in an oil bath and maintained at the same temperature for 15 h (GC analysis). The reaction mixture was then cooled to room temperature and was added aq. ammonia (2 L, 20-25%), stirred for 30 min and extracted with chloroform (4 × 500 mL). The layers were separated and the organic layer was washed with water (2 × 400 mL) until basic to p^H. Evaporation of the solvent under reduced pressure resulted the crude compound as a brown viscous liquid, which upon high

vacuum distillation using an oil bath at vapor temperature 110-130 °C/1 mm/Hg yielded the pure product. The pure fraction was further crystallized in *n*-hexane yielding the pure product as white plates, 65.7 grams with GC purity of 99.8%.

I.R (KBr): 3386, 1446, 761 cm^{-1}; ^{1H}NMR (400 MHz, DMSO-d_6): δ 6.40 (s, 1H), 7.05 (dd, *J*=8.6, 2.0 Hz, 1H), 7.39 (d, *J*=9.4 Hz, 1H) 7.40 (d, *J*=3.12 Hz, 1H), 7.56 (d, *J*=2.0 Hz, 1H, 11.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6):134.74, 129.21, 127.38, 123.87, 121.25, 119.57, 113.23, 101.26; MS (ESI): m/z (%)=150.1 (M-H).

5-chloroindole-3-carboxyaldehyde (2b)

Following the general procedure for 2a from 5-bromoindole-3-carboxyaldehyde. The crude compound was dissolved in 8-volumes of water, adjusted the to p^H to 2.0 with conc. hydrochloric acid followed by carbon treatment and filtered. The p^H of the filtrate was then adjusted to between 9.0-9.5 using 50% aq. sodium hydroxide solution and stir for one hour at RT to obtain pure product as an off-white solid.

I.R (KBr): 3218, 1644 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 12.28 (bs, 1H), 9.92 (s, 1H), 8.34 (s, 1H), 8.06 (d, *J*= 2.0 Hz, 1H), 7.52 (d, *J*=8.6 Hz, 1H), 7.26 (dd, *J*=8.6Hz, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 185.1, 139.3, 135.5, 126.8, 125.2, 123.4, 119.9, 117.5, 114.1; MS (ESI): m/z (%)=180.2 (M+H).

5-Chloroindole-3-carbonitrile (2c)

Following the general procedure for 2a from 5-bromoindole-3-carbonitrile. The crude product was crystallized from methanol to obtain a cream color solid.

IR (KBr): 3253, 2226 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 7.28 (dd, *J*=8.72, 8.68Hz, 1H), 7.56 (d, *J*=8.72 Hz, 1H), 7.64 (d, *J*=1.88 Hz, 1H), 8.31 (d, *J*=3.04 Hz, 1H),12.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 84.48, 114.96, 116.06, 118.04, 123.94, 126.86, 128.14, 134.11, 136.39; EIMS: 175, 177 (M+1).

5-Chloroindole-3-carboxylic acid (2d)

Following the general procedure for 2a from 5-bromoindole-3-carboxylic acid. The crude compound was crystallized from isopropyl alcohol to obtain pure product as an off-white solid.

IR (KBr): 3399, 3324, 1613 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.72 (bs, 1H), 8.14 (d, *J*=2.0 Hz, 1H), 8.09 (s, 1H), 7.43 (d, *J*=8.6 Hz, 1H), 7.14 (dd, *J*=8.6, 2.1 Hz, 1H), 6.88 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 166.7, 135.0, 130.3, 127.8, 125.6, 122.2, 120.6, 113.7, 110.5; MS (ESI): m/z (%)=194.9 (M-H).

CONCLUSION

In conclusion, we have developed the best industrially scalable and commercially feasible method for the production of 5-chloroindole starting from commercially available and cheap 5-bromoindole. The protocol has been extended towards the synthesis of other substituted indole analogues in good yields. The advantage of the present method lies in its operational simplicity and yet very productive for producing 5-chloroindole and analogues, which are very useful and important intermediates in drug industry.

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