

Improved Process for Preparation of 6-Chloro-5-(2-Chloroethyl)oxindole

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Experimental Section

All ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively with solvent as an internal standard. High-resolution mass spectrum was obtained on Thermo LTQFTMS Ultra mass spectrometer using infusion via electrospray ionization technique. HPLC chromatography was performed with Zorbax-SB-CN column (15 cm X 4.6 mm I.D.) using following conditions: column temperature 35 °C, UV detector (254 nm), flow rate 1mL/min, mobile phase (75:15:10 v/v/v) 0.05 M aqueous KH_2PO_4 buffer solution (pH = 6.0): acetonitrile: methanol.

Compounds **1**¹ and **6**² were prepared by previously reported procedures.

Data for 6-chloro-5-(2-chloroacetyl) indolin-2-one (**1**):

^1H NMR (DMSO): δ 3.53 (s, 2H), 4.98 (s, 2H), 6.89 (s, 1H), 7.69 (s, 1H), 10.79 (s, 1H).

^{13}C NMR (DMSO): δ 35.81, 49.78, 111.70, 125.72, 126.81, 128.04, 131.86, 148.81, 177.17, 192.47.

Data for 6-chloro-5-(2-chloro-1-hydroxyethyl) indolin-2-one (**6**):

¹H NMR (DMSO): δ 3.46 (s, 2H), 3.55 (dd, 1H, J = 11.2 Hz, J = 7.47 Hz), 3.68 (dd, 1H, J = 11.2 Hz, J = 3.7 Hz), 5.02 (dd, 1H, J = 3.7 Hz, J = 7.47 Hz), 5.95 (br, 1H), 6.77 (s, 1H), 7.40 (s, 1H), 10.48 (s, 1H).

¹³C NMR (DMSO): δ 36.11, 49.67, 69.83, 109.87, 124.59, 125.86, 130.37, 132.35, 144.97, 177.05.

Preparation of 6-chloro-5-ethylindolin-2-one (5):

To a 250 mL round-bottomed flask equipped with a mechanical stirrer, reflux condenser and a thermocouple were charged methylene chloride (30 mL) and aluminum chloride (26.24 g, 3.3 eq., 0.197 moles). The mixture was stirred and cooled to 0 - 5 °C under nitrogen. To this mixture were added slowly chloroacetyl chloride (10.78 g, 1.6 eq., 0.0955 moles). The reaction mixture was stirred for 20 minutes at that temperature. To this mixture 6-chlorooxindole (10 g, 1 eq., 0.0597 moles) was added as slurry in methylene chloride (10 mL). The reaction mixture was heated under nitrogen atmosphere to 29 °C. The reaction was monitored by HPLC assay. At the end on reaction period (~ 20 h), the reaction mixture was cooled to – 20 °C. Triethylsilane (27.76 g, 0.239 moles, 4 eq.) was added to the reaction mixture dropwise by maintaining the temperature below 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 12 hours. The mixture was quenched with 200 mL of water at 0 – 5 °C. The reaction mixture was distilled at atmospheric pressure until most of the methylene chloride was removed from the reaction mixture. The mixture was cooled to 35 °C and tetrahydrofuran (THF) (400 mL) was added. The slurry was stirred at 45 °C for 30 minutes to dissolve all the solids. The solution was allowed to settle at 45 °C. The aqueous layer was separated and discarded. The organic layer was concentrated under reduced pressure. The

precipitated solid product was filtered, washed with small amount of THF and partially dried in a vacuum oven. The crude product was suspended in 25 % v/v of THF in isopropanol and stirred at 35 °C for 30 min. The slurry was filtered and the product was washed with isopropanol. The product was dried under high vacuum at 25 °C for 16 h.

¹H NMR (DMSO): δ 1.09 (t, 3H, *J* = 7.47 Hz), 2.60 (q, 2H, *J* = 7.47 Hz), 3.41 (s, 2H), 6.76 (s, 1H), 7.13 (s, 1H), 10.36 (s, 1H).

¹³C NMR (DMSO): δ 15.16, 26.43, 36.06, 110.18, 125.93, 126.35, 131.53, 133.86, 143.58, 176.94.

HRMS: m/z Calcd for C₁₀H₁₁N₁O₁Cl₁ (M⁺ + H) 196.0529; found: 196.0523.

General procedure for Design of Experiments (DOE):

All the experiments in this experimental design were performed in random order. Each experiment in this set was performed as follows:

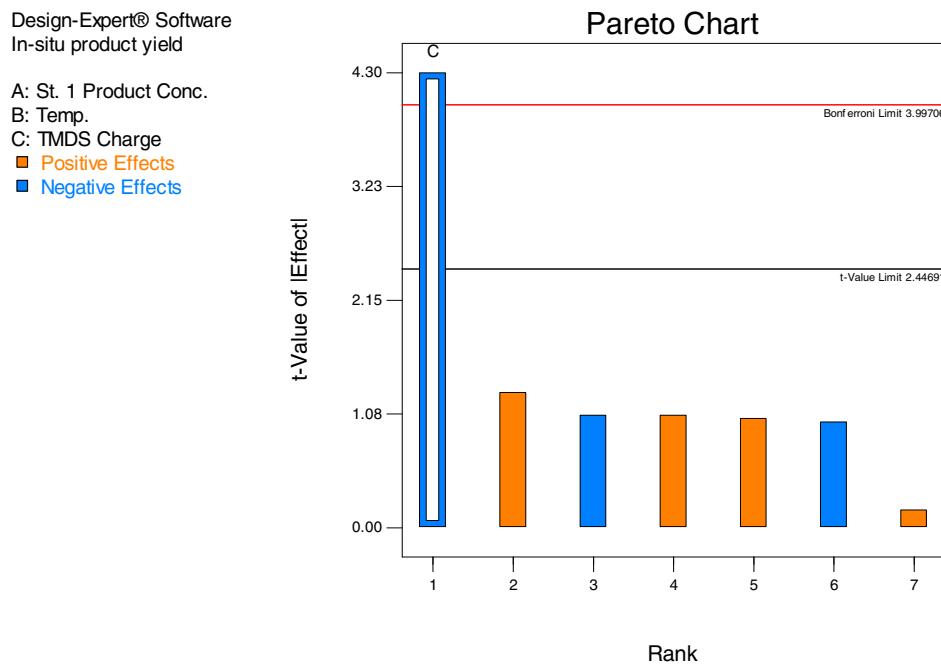
To a solution of aluminum chloride (39.37 g, 3.3 eq., 0.295 moles) and chloroacetyl chloride (16.17 g, 1.6 eq., 0.143 moles) in 45 mL of methylene chloride was added 6-chlorooxindole (15 g, 0.0895 moles, 1 eq.) as a solid at 0 - 5 °C. The mixture was heated to 29 °C under nitrogen atmosphere until the reaction was complete (~ 18 - 20 h). At the end of reaction the reaction mixture was diluted with methylene chloride as needed. The temperature of the reaction mixture was adjusted to the desired value. Appropriate amount of 1,1,3,3 tetramethyldisiloxane was added to the reaction mixture very slowly in a dropwise manner by maintaining the reaction mixture temperature at the desired limit (CAUTION: reaction is exothermic). At end of the reaction period (3 - 4 h) the reaction mixture was sampled. The reaction completion end point and in-situ yields were

determined by HPLC assay using external reference standard of the intermediate chloro alcohol **6** and product **2** respectively.

Statistical analysis of the data:

The statistical analysis was performed using Design-Expert software (version 7.1.3) from Stat-Ease, Inc 2021, East Hennepin Ave., Suite 480, Minneapolis, MN 55413.

Pareto Chart:



Response		In Situ Yield							
ANOVA for selected factorial model									
Analysis of variance table [Partial sum of squares - Type III]									
Source	Sum of Squares	df	Mean Square	F Value	p-value				
Model	1556.82	1	1556.82	18.50	0.0051				
C-TMDS	1556.82	1	1556.82	18.50	0.0051				
Curvature	177.98	1	177.98	2.11	0.1961				
Residual	504.92	6	84.15						
Cor Total	2239.72	8							
Std. Dev.	9.17		R-Squared	0.7551					
Mean	83.92		Adj R-Squared	0.7143					
C.V. %	10.93		Pred R-Squared	N/A					
PRESS	N/A		Adeq Precision	5.306					

Analysis of the results clearly indicate that this model is significant (p-value = 0.0051).

The variable of TMDS charge was found to be the only significant factor that had a major effect on product yields.

Reduction of **1** with Pentamethyldisiloxane:

To a solution of aluminum chloride (26.24 g, 3.3 eq., 0.1969 moles) and chloroacetyl chloride (10.79 g, 1.6 eq., 0.0955 moles) in 20 mL of methylene chloride was added 6-chlorooxindole (10 g, 0.0597 moles, 1 eq.) as a solid at 0 - 5 °C. The mixture was heated to 29 °C under nitrogen atmosphere until the reaction was complete (~ 18 - 20 h). At the end of the reaction the reaction mixture was cooled to 0 - 5 °C and appropriate amount of pentamethyldisiloxane (4 eq.) was slowly added to the reaction mixture. The mixture was stirred at that temperature for 12 -16 h. Analysis of the reaction mixture sample by HPLC indicated presence of mixture of products containing **2**, **6** and other impurities.

Reduction of **1** with Triethylsilane:

The step 1 acylation reaction was performed as above. At end of the reaction triethylsilane (2 eq.) was added to the reaction mixture at 0 - 5 °C. After 2 h at that temperature, analysis of the reaction mixture sample after by HPLC indicated presence of

2, small amount of alcohol **6** and some unchanged **1**. Addition of extra 2 equivalents of triethylsilane to the reaction mixture resulted in complete conversion to **5**.

Reduction of **1 with dimethylethoxysilane:**

The step 1 acylation reaction was performed as above. At the end of the reaction the reaction mixture was cooled to 0 - 5 °C and appropriate amount of dimethylethoxysilane (4 eq.) was slowly added to the reaction mixture. The mixture was stirred at that temperature for 12 -16 h. Analysis of the reaction mixture sample by HPLC indicated presence of mixture of products containing **2**, **6** and other impurities.

Reduction of **1 with chlorodimethylsilane:**

The step 1 acylation reaction was performed as above. At the end of the reaction the reaction mixture was cooled to 0 - 5 °C and chlorodimethylsilane (2 eq.) was slowly added to the reaction mixture. The mixture was stirred at that temperature for 12 - 16 h. Analysis of the reaction mixture sample by HPLC indicated presence of mixture of products containing **2**, **6** and other impurities.

References:

1. Busch, F. R.; Grobin, A. W.; Howard, H. R. Jr.; Leeman, K. R. PCT Int. Appl. WO 2003070246, 2003, *Chem. Abstr.* 139:214489
2. Zanon, J.; Martini, O.; Ciardella, F.; Gregori, L.; Sbrogio, F.; Castellin, A. EP 1787990A2, 2007; *Chem. Abstr.* 146:521828.