Condensation reaction of Indole and ketone

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INTRODUCTION:

The subject of this project is the study of condensation reaction of indole and ketone. Indole and indole derivatives are widely applied to material sciences, agrochemicals, and pharmaceuticals[1]. This research topic needs to be studied and supported by a large amount of date and hundreds of experiments, because the indole and ketone could be reacted in different solvents with different ratios and reaction conditions. For this limited-time UROP topic, which is also a small part of this huge project, two specific mole ratios are chosen for indole and ketones, which are 1:2 and 2:1 under acidic conditions. The emphasis is on the reaction of 2:1 indole and ketone reaction, in which the products are bisindolylmethanes (BIMs).

As an important class of indole derivatives, BIMs are “most active cruciferous substances for promoting beneficial estrogen metabolism and inducing apoptosis in human cancer cells” as written in *Green Protocol for the Synthesis of Bisindolylmethanes and Evaluation of Their Antimicrobial Activities*[2]. In this

UROP project, the most straightforward method is chosen to synthesize BIMs, which is the acid-catalyzed condensation reaction of indole and ketones.

RESULTS AND DISCUSSIONS

In the whole project, five reactions have been run with a total 100 hours. The reaction results are summarized in Table I.

In the first two reactions, indole (10mmol) reacted with cyclopentanone (20mmol) catalyzed by hydrochloric acid (20mmol). No desired products were synthesized from the two reactions. Thus, the reaction of 1:2 indole and cyclopentanone may need to be carried out under a weaker acid than hydrochloric acid.

In the third run, the target product 3, 3'-cycloheptenediindole was synthesized successfully catalyzed by a weaker acid—boric acid. The reaction was also heated from the very beginning. The crude product mixture was complex and after separation, the final product was relatively pure.

In the fourth and fifth runs, the reactions were catalyzed by a moderate acid—phosphate acid. In the fourth reaction, the reagents were not heated but just stirring at the beginning. It turned out that the final product was too complex to analyze. In the fifth run, same reagents with almost the same mole ratio were reacted under both heat source and stirring. Also, in the fifth reaction, the refluxing column was set up to

extract water so that the equilibrium of the reaction will move to the product direction further. However, after the analysis of crude products by NMR H^1, it was observed that no reaction was carried out after about 48 hours.

In summary, BIM product 3,3'-cycloheptenediindole could be synthesized successfully under Boric acid. Some physical properties of the product 3,3'-cycloheptenediindole are summarized in Table 2.

Table 1 Reaction Conditions

Reaction NO.	Reagents	Other reagents(solvent)	Condition	Conclusion
1	indole(10mmol),cyclopentanone(20mmol)	HCl (20mmol),triethylamine (15mmol),THF(3.2mL)	48hrs stirring at R.T.,then heat&refluxing for 24 hrs	no product
2	indole(10mmol),cyclopentanone(20mmol)	HCl(20mmol),triethylamine(15mmol),THF(3.2mL)	48hrs stirring at R.T.,then heat&refluxing for 24 hrs	no product
3	indole(20mmol),cycloheptanone(12mmol)	B(OH)3(4mmol),naphthalene(0.5mmol)	heat and keep at about 80 Celsius degree for 6 hrs,using MPLC for separation	total five fractions and fraction 3 is the product, 3,3'-cycloheptenediindole
4	indole(20mmol),cycloundecanone(12mmol)	H3PO4(4mmol),naphthalene(0.5mmol)	no heat just stirring	complex product mixtures
5	indole(40mmol),cycloundecanone(20mmol)	H3PO4(6mmol),isopropanol(10mL),benzene(30mL)	heat in oil bath keep at 80 Celsius degree for 5 hrs	no reaction

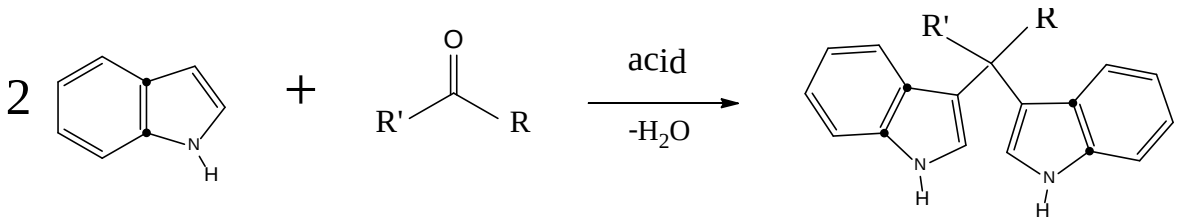
Table 2 Properties of Product

Product	Purity	Melting Point (^oC)	Appearance
3,3'-cycloheptenediindole	91wt%	181-182	White crystal

EXPERIMENTAL

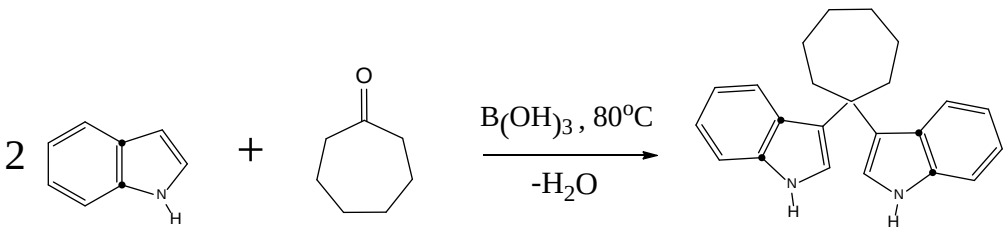
The general reaction scheme for the five reactions and the reaction scheme for the third run are shown below.

General reaction scheme:



Indole ketone 3,3'-alkylidenediindole

The third reaction scheme:



Indole cyclopentanone 3,3'-cycloheptenediindole

The melting point was measured in the open glass capillary tubes and was not corrected. The products were tested by TLC plate using silica gel as adsorbent and the spots were visualized under UV light. The solvents chosen for the transformation of products during the experiments were dichloromethane, ethyl acetate and water. ^{1}H NMR data and GC data was recorded for the final products.

GENERAL PROCEDURE

Indole and cycloketone initially reacted under acidic condition in 100ml round-bottomed flask with or without heat. To test the reaction process, TLC sample was taken at each half an hour. Generally, when the indole spots no longer appeared on the TLC plate, the reaction could be stopped. After the initial reaction, the product mixture was extracted by first dichloromethane or ethyl acetate and then the brine solution. The collected organic phase was then dried under drying agent. After drying, the product mixture was transferred to the round-bottomed flask and insert into Rotor-Vapor machine to evaporate the solvent. The next step was to separate the product mixture, which was finished by either MPLC (Medium Performance Liquid Chromatography) or a flash column. During the separation process, the product mixture was combined with silica thoroughly and then transferred to the separation column. After the separation, the product mixture was separated into different fractions and could be further analyzed by gas chromatograph or ^{1}H NMR.

3,3'-cycloheptenediindole

White solid, crystal; m.p. 181-182^{o}C; ^{1}H NMR($CDCl_3$) δ ppm:8.22(m,2H), 7.30(m,4H), 7.22(m,2H), 7.02(m,2H), 6.55(m,2H), 2.52(m,4H), 1.75(m,8H).

Reference

1. Hasaninejad, A., Zare, A., Sharghi, H., Shekouhy, M., Khalifeh, R., Beni, A., & Zare, A. (2007). A solvent-free protocol for facile condensation of indole with carbonyl compounds using silica chloride as a new, highly efficient, and mild catalyst. *Canadian Journal Of Chemistry*, *85*(6), 416-420. doi:10.1139/V07-051
2. Tiwari, A., & Jain, M. (2009). Green Protocol for the Synthesis of Bisindolylmethanes and Evaluation of Their Antimicrobial Activities. *Phosphorus, Sulfur & Silicon & The Related Elements*, *184*(11), 2835-2845. doi:10.1080/10426500802590178