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Synthesis of a Novel Pyrrole Family as Potential Anti-Cancer Agents

Sang T. Truong
DePauw University, sangtruong_2021@depauw.edu

Jeffrey A. Hansen
DePauw University

SYNTHESIS OF A NOVEL PYRROLE FAMILY AS POTENTIAL ANTI-CANCER AGENTS

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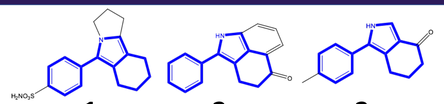
Sang T. Truong and Jeffrey A. Hansen, Department of Chemistry & Biochemistry, DePauw University, IN, USA

ABSTRACT

An one-step selective reaction was developed to synthesize a novel pyrrole family (20 different members) from a keto-epoxide at room temperature in 3h. Kinetic behavior of the reaction and structure of the product were characterized by nuclear magnetic resonance spectroscopy. These pyrroles have a strong potential for pharmaceutical application.

INTRODUCTION



1 **2** **3**

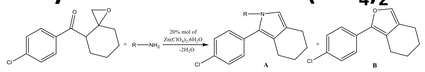
Experimental data show that pyrrole derivatives compound could potentially have interesting bioactivity. For example, **1** is COX-2 inhibitor, **2** is a bromodomain inhibitors, and **3** is a cell protective agents

EXPERIMENTAL DATA

1. The general synthesis procedure

Reaction mixture → Stir in 3-5h → Work-up (HCl 1M) → Flask chromatography cyclohexane → Rota-evaporation

2. The selectivity of reaction with $Zn(ClO_4)_2.6H_2O$



- If RNH_2 is aniline, aniline derivatives (o/m/p Cl/Br/ OCH_3/CH_3-aniline, 3-methyl-2-aminopyridine, 2,5-dimethyl-aniline, 2,4-dimethyl-aniline, ethanol-amine, or phenylhydra-zine, **A** is observed.
- If RNH_2 is 1,3-diamino-propane, **B** is observed.
- If RNH_2 is butylamine, benzylamine, or phenethylamine, both **A** and **B** are observed.

Amine	Product's structure	Yield	Reaction condition
		95%	5h, RT
		93%	5h, RT
		85%	3h,RT
		97%	5h, RT

3. Optimizing the reaction condition

- In attempt to synthesize the pyrrole derivatives from aliphatic amine, we tried various catalysts (CeCl3.7H2O, NaI, SiO_2, CeCl3-NaI-SiO2 composite, HBr-CH3COOH) and reaction condition (microwave, reflux). Although more than 50 trials were ran, we have not succeeded in synthesize selectively any aliphatic pyrrole derivatives yet.

2. Characteristic of some typical products

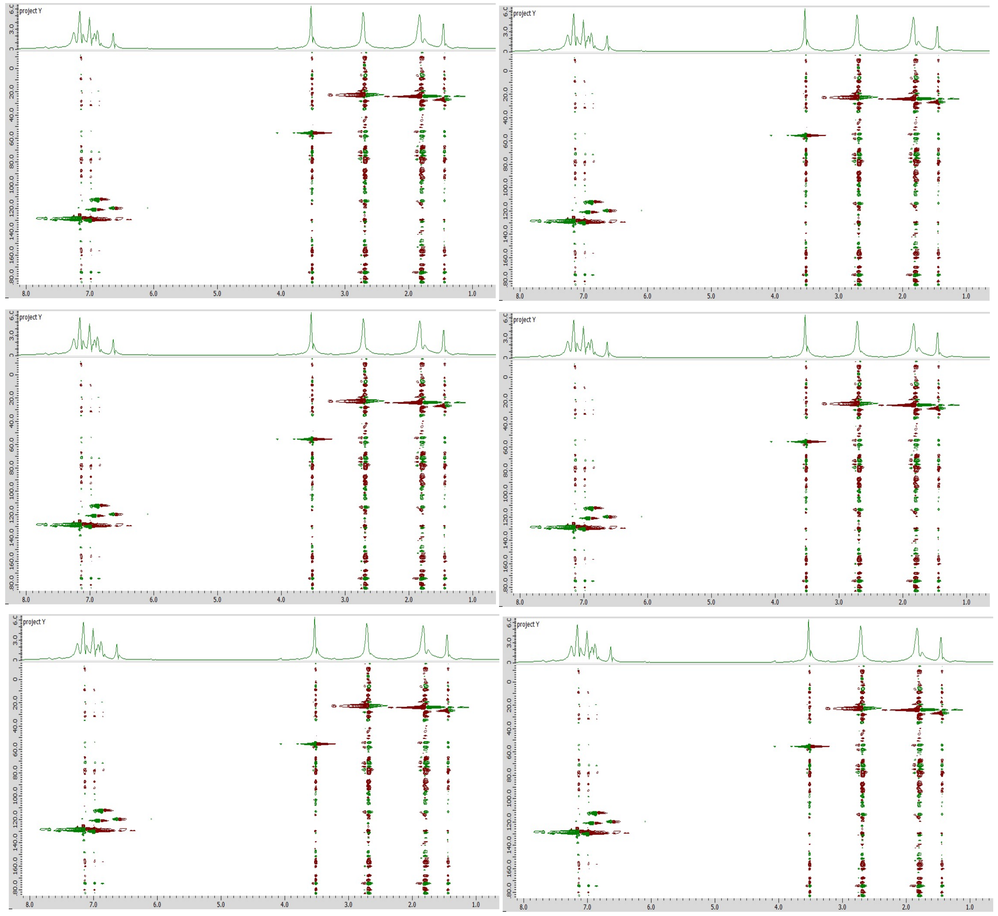


Figure 1. HSQC of pyrrole aniline (1a), HMBC of pyrrole aniline (1b), HSQC of pyrrole anisidine (2a), HMBC of pyrrole anisidine (2b), H-HNR of furan (3), and H-NMR of pyrrole aniline over time.

3. Kinetic behavior of the reaction

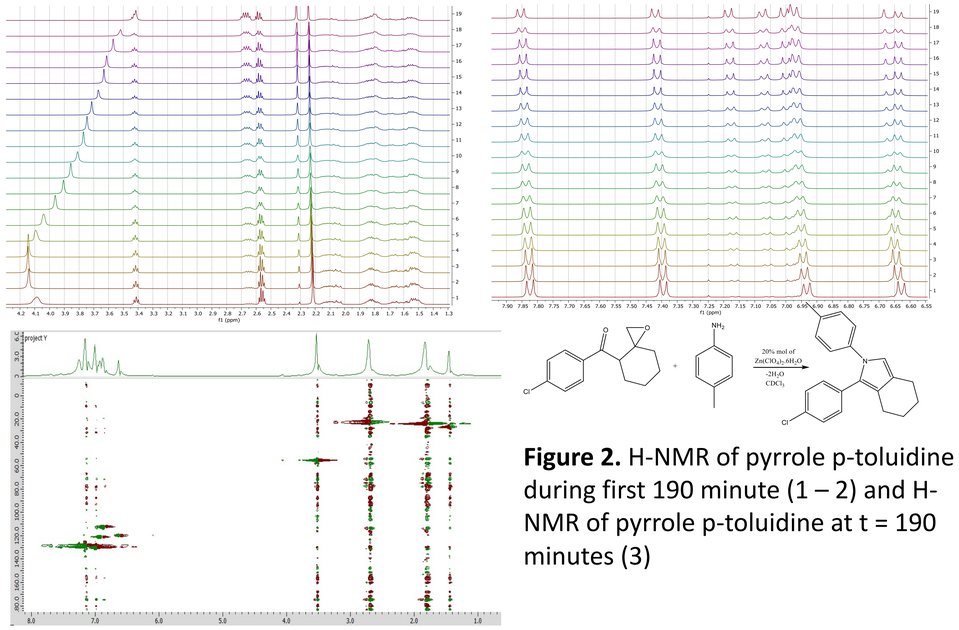


Figure 2. H-NMR of pyrrole p-toluidine during first 190 minute (1 – 2) and H-NMR of pyrrole p-toluidine at t = 190 minutes (3)

COMPUTATIONAL RESULT

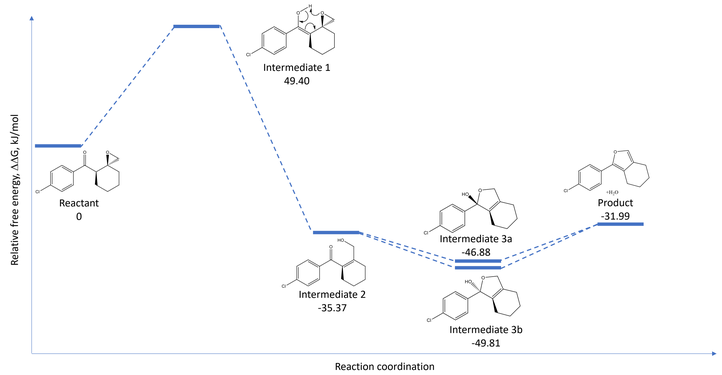


Figure 3. Furan reaction coordination generated by Spartan (Density Functional with B3LYP method and 6-61G* basis set. Job type: geometry optimization) .

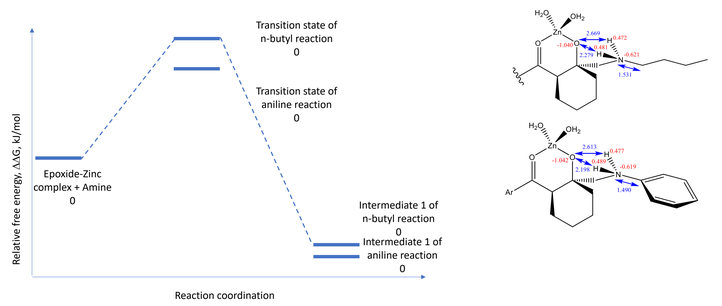


Figure 4. The first step of pyrrole formation reaction, where an amine opens the epoxide ring by SN2 mechanism. Energy of each species was calculated by Spartan with Density Functional Theory using B3LYP method and LACVP basis set (pseudo-potential core). Due to significantly higher activation energy, the epoxide opening reaction of aliphatic amines are slower than that of aromatic amine.

CONCLUSION

- An one-step reaction was optimized to selectively synthesize pyrrole and furan from keto-epoxide. The structure of products were well-characterized by H-NMR, C-NMR, HSQC, gHMBC.
- Reaction mechanism was initially studied by kinetic data and modeling through Spartan.

REFERENCE

Asit K. Chakraborti *et al*, J. Org. Chem. 2007, 72, 3713

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