Applications of Heterocyclic Synthesis

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Applications of heterocyclic synthesis

by

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Ames, Iowa

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CHAPTER 1: SYNTHESIS OF 2,3-DISUBSTITUTED INDOLES USING MICROWAVE ASSISTED CONDITIONS

Indoles have many pharmaceutical and medical applications. Indoles are part of many natural products including dragamacidin D (1) and 6-substituted 3-(indol-2-yl) quinolinones (2). Dragamacidin D is a potent inhibitor of serine/threonine protein phosphatases.\(^1\) Recently, 6-substituted 3-(indol-2-yl) quinolinones have been used as inhibitors of Chek 1 that promotes the killing of cancer cells while leaving the healthy cells unharmed.\(^2\)

Combretastatin heteroanalogue 3 is known to have leishmanicidal activity and it has been shown to inhibit tubulin polymerization, leading to its use as a potential anticancer agent.\(^3,4\) A substituted indole with a phenyl ring in the 3-position such as 4 has been shown to have potent antibacterial activity against *Escherichia coli*, and *Staphylococcus aureus* and high antifungal activity against *Candida albicans*, *Aspergillus niger*, and
Aspergillus awamari. Due to their high estrogen receptor binding affinity and environmentally dependent fluorescence, substituted indoles 5a-c can be used as fluorescent probes for breast cancer cells.

Indoles have also been synthesized to prevent and/or treat inflammatory and autoimmune diseases including rheumatoid arthritis, diabetes mellitus, multiple sclerosis, autoimmune nephritis, and allergic inflammation. Indoles have also been studied to treat drug resistant tumors as antitumor agents on their own or for use in co-therapy to enhance the action of known antitumor drugs. Recently, 2-pyrrolidin-2-yl-1H-indoles have also been shown to treat migraines by inhibiting NO synthase.
Recent work in our group has focused on how to produce substituted indoles in a fast and efficient manner. As microwave techniques are becoming a mainstay in synthetic organic chemistry, it was natural to use this technique to produce a variety of substituted indoles. Kraus and Guo developed a methodology for producing 2-substituted indoles from a phosphonium salt and a substituted aldehyde using microwave chemistry. Recently, 2-aminobenzyltriphenylphosphonium bromide was reacted with aromatic or $\alpha$, $\beta$-unsaturated aldehydes under microwave assisted conditions to produce 2-substituted indoles in high yields.

**Scheme 1**

Only three examples of heterocyclic aldehydes were used in the previous work, furfural, pyridine-3-carboxaldehyde, and indole-4-carboxaldehyde. Due to the abundance of indoles substituted in the 2-position with heterocycles, it was decided that as an extension of the previous work, heteroaromatic aldehydes would be used in the microwave reaction. Also, there is a phenyl group in the 3-position of the three compounds with antibacterial and antifungal activity (4a-c) and a phenoxy group in the 3-position of the indoles used for detecting breast cancer cells. For these reasons, the phosphonium salt with a phenyl group was needed. Due to interest in indoles containing heterocycles, a variety of indoles with heterocyclic units in the 2-position
were synthesized using the microwave methodology developed previously in the group. The procedure is shown in Scheme 2.

**Scheme 2**

Based on the success of the microwave reactions, the next goal was to produce a natural product using our procedure. Staurosporinone (6) is an indolo[2,3-a]pyrrolo[3,4-c]carbazole alkaloid with a variety of biological uses. Staurosporinone is known to form aggregates and act as a non-specific kinase inhibitor.14 This indole containing natural product has been shown to have moderate inhibitory activity against D1-CDK4 and inhibits the proliferation of human colon and human lung carcinoma cell lines.15

Staurosporinone has also shown cytotoxic and apoptotic activity against a human chronic myelogenous leukemia cell line.16 In 1998, a group of research scientists at the Lilly Research Laboratories, synthesized staurosporinone in three steps, shown in Scheme 3.17h Dr. Orito’s research laboratory, synthesized staurosporinone in five steps as shown in Scheme 4.17b The first synthesis suffers because the starting materials are not commercially available and the second synthesis requires six overall steps many
with multiple pot reactions. While the synthesis of staurosporinone has been completed by several groups, our approach is more direct and efficient.\textsuperscript{17a-m}

Scheme 3

\[ \text{7} + \text{8} \rightarrow \text{9} \]

1. Pd(OAc)$_2$
2. LiAlH$_4$
3. 10\% Pd/C

Scheme 4

\[ \text{10} + \text{11} \rightarrow \text{12} \]

1. CF$_3$COOH
2. DDQ
RESULTS AND DISCUSSION

Our synthesis began by reducing 2-aminobenzophenone with sodium borohydride to produce alcohol 17 in 85% yield. Compound 17 was then treated with triphenylphosphine hydrobromide to produce the phosphonium salt 18 in 80% yield.

Scheme 5
With the phosphonium salt 18 available, the next step was to react it with various heterocyclic aldehydes. The procedure is shown in Scheme 6.

Scheme 6

A variety of heterocyclic aldehydes were used including furans, thiophenes, pyridines, pyrroles, and indoles. Table 1 shows the results for this reaction with different heterocyclic aldehydes. The reaction was successful with base sensitive indoles, acid sensitive pyridines, and with furans with acidic hydrogens. We have found an efficient, fast and useful way to produce indoles containing heterocycles that can be studied for their biological activity. Future work may include the total synthesis of other indole containing compounds or the use of leaving groups other than triphenyl phosphine.

Table 1 Synthesis of Heterocyclic Indoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Melting Point (°C)</th>
<th>Literature m.p.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>O-CHO</td>
<td></td>
<td>47</td>
<td>120-123</td>
<td>(120-123)(^{12})</td>
</tr>
<tr>
<td>----</td>
<td>----------------</td>
<td>------------------------------------------</td>
<td>----</td>
<td>---------</td>
<td>---------------------</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Ph})</td>
<td></td>
<td>67</td>
<td>149-150</td>
<td>(149-150)(^{13a})</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Ph})</td>
<td></td>
<td>85</td>
<td>175-176</td>
<td>(170-175)(^{13b})</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Ph})</td>
<td></td>
<td>61</td>
<td>98-101</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(\text{Ph})</td>
<td></td>
<td>70</td>
<td>133-135</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(\text{Ph})</td>
<td></td>
<td>78</td>
<td>oil</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(\text{Ph})</td>
<td></td>
<td>56</td>
<td>202-204</td>
<td></td>
</tr>
</tbody>
</table>

Yield\(^a\) is an average of two runs.

EXPERIMENTAL SECTION
General.

All $^1$H and $^{13}$C spectra were recorded at 400 MHz unless otherwise noted. All melting points are uncorrected. Unless otherwise noted, reactions were carried out under argon. Microwave reactions were conducted in a capped vial using a CEM Discovery system. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected using short wavelength UV light (254 nm). High-resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All yields reported represent an average of at least two independent runs.

General Procedure:

To a microwave vial containing a stirbar, phosphonium salt 20 (0.5244 g, 1.0 mmol), methanol (5 mL), a heterocyclic aldehyde (1.0 mmol) and glacial acetic acid (23 µL) were added. The vial was sealed and stirred thoroughly before being placed in a microwave reactor set for 300 W at 80 °C for ten minutes. The mixture was cooled to room temperature and the methanol removed in vacuo. Tetrahydrofuran (8 mL) was added along with 1.6 mL of a 1M potassium tert-butoxide solution drop wise. The reaction was stirred at 25 °C for one hour.

A saturated ammonium chloride solution was added to quench the reaction, and it was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The residue
was purified by silica gel column chromatography using a combination of ethyl acetate and hexanes as an eluent.

**2-furyl-3-phenyl indole**

The product was purified by chromatography on silica gel (40:1 hexanes:ethyl acetate). The compound was a red/brown solid (117.9 mg, 45% yield). Mp: 120-123 °C (Lit. mp: 120-123 °C). ¹H NMR (300 MHz, CDCl₃): 8.67 (s, 1H), 7.64-7.62 (d, J = 8 Hz, 3H), 7.55-7.52 (t, J = 4 Hz, 2H), 7.45-7.42 (d, J = 12 Hz, 3H), 7.31-7.29 (d, J = 8 Hz, 1H), 7.20-7.16 (t, J = 8 Hz, 1H), 6.41 (s, 2H).

**2-(2-pyridinyl)-3-phenyl indole**

The product was purified by chromatography on silica gel (30:1 hexanes:ethyl acetate). The compound was a light yellow solid (183.8 mg, 67% yield). Mp: 149-150 °C (Lit. mp: 149-150 °C). ¹H NMR (300 MHz, CDCl₃): 9.66 (s, 1H), 8.61-8.60 (d, J = 4 Hz, 1H), 7.56-7.30 (m, 10H), 7.13-7.09 (m, 2H).

**2-(3-pyridinyl)-3-phenyl indole**

The product was purified by chromatography on silica gel (3:2 hexanes: ethyl acetate). The product was obtained as a white solid (164.9 mg, 85% yield). Mp: 175-176 °C (Lit. mp: 170-175 °C). ¹H NMR (400 MHz, Acetone-d₆): 10.90 (s, 1H), 9.12-9.13 (m, 1H), 8.51-8.53 (dd, J=4.8, 1.6 Hz, 1H), 8.18-8.21 (dt, J=8, 2 Hz, 1H), 7.60-7.62 (d, J=8 Hz, 1H), 7.42-7.45 (m, 2H), 7.13-7.17 (td, J=8, 0.8 Hz 1H), 7.04-7.08 (td, J=8, 0.8 Hz, 1H),
7.02-7.03 (d, J=1.6 Hz, 1H). $^{13}$C NMR (400 MHz, Acetone-d$_6$): 149.2, 147.4, 138.7, 135.8, 132.8, 130.1, 129.5, 124.7, 123.3, 121.4, 120.8, 112.2, 101.2. HRMS electrospray (m/z): calculated, for C$_{13}$H$_{10}$N$_2$, 194.0844; found, 194.0846.

### 2-(2-methylfuryl)-3-phenyl indole

The product was purified by chromatography on silica gel (30:1 hexanes: ethyl acetate). The compound was a brown solid (179.2 mg, 61% yield). Mp: 98-101 °C. $^1$H NMR (400 MHz, CDCl$_3$): 8.61 (s, 1 H), 7.59-7.54 (m, 3H) 7.49-7.46 (t, J = 4 Hz, 2H), 7.43-7.35 (m, 2H), 7.24-7.21 (t, J = 8 Hz, 1H), 7.13-7.09 (t, J = 8 Hz, 1H), 6.24 (s, 1H), 5.96 (s, 1H), 2.37 (s, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$): 151.4, 145.5, 135.5, 131.0, 130.4, 128.7, 127.0, 125.7, 122.7, 120.4, 119.4, 113.6, 110.9, 108.1, 108.0, 13.8. HRMS electrospray (m/z) Calculated for C$_{19}$H$_{15}$NO, 273.1154; found, 273.1161.

### 2-(1-methyl-pyrrolyl)-3-phenyl indole

The product was purified by chromatography on silica gel (40:1 hexanes:ethyl acetate). The compound was a green solid (190.4 mg, 70% yield). Mp: 133-135 °C. $^1$H NMR (400 MHz, CDCl$_3$): 8.14 (s, 1H), 7.88-7.86 (d, J = 8 Hz, 1H), 7.43-7.35 (m, 5H), 7.30-7.19 (m, 3H), 6.66 (s, 1H), 6.41 (s, 1H), 6.28-6.26 (t, J = 8 Hz, 1H), 3.05 (s, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$): 135.8, 135.7, 128.9, 128.7, 127.5, 127.0, 126.0, 125.6, 123.8, 122.7, 120.5, 119.6, 115.8, 111.0, 110.5, 108.3, 34.4. HRMS electrospray (m/z) Calculated for C$_{19}$H$_{16}$N$_2$: 272.1313; found: 272.1318.
2-(3-methyl thiophenyl)-3-phenyl indole

The product was purified by chromatography on silica gel (40:1 hexanes:ethyl acetate). The compound was a yellow/orange oil (220.5 mg, 78% yield). $^1$H NMR (400 MHz, CDCl$_3$): 8.18 (s, 1H), 7.95-7.96 (d, $J = 4$ Hz, 1H), 7.58-7.31 (m, 9H), 7.01-6.90 (dd, $J = 4$ Hz, 20 Hz, 1H), 1.95 (s, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$): 136.8, 136.1, 135.3, 130.7, 129.4, 128.6, 127.6, 126.9, 126.1, 125.6, 122.9, 120.9, 120.6, 119.7, 117.2, 111.1, 14.7. HRMS electrospray (m/z) Calculated for C$_{19}$H$_{15}$NS, 289.0925; found, 289.0929.

3-phenyl-1H,1'H-2,3'-biindole

The product was purified by chromatography on silica gel (40:1 hexanes:ethyl acetate). The compound was a yellow solid (172.6 mg, 56% yield). Mp 202-204 ºC. $^1$H NMR (400 MHz, DMSO-d$_6$): 11.34 (s, 1H), 11.25 (s, 1H), 7.60-7.58 (d, $J = 8$ Hz, 1H), 7.49-7.43 (m, 3H), 7.40-7.38 (d, $J = 8$ Hz, 2H), 7.29-7.26 (t, $J = 8$ Hz, 2H), 7.18-7.03 (m, 5H), 6.85-6.81 (t, $J = 16$ Hz, 1H). $^{13}$C NMR (400 MHz, DMSO-d$_6$): 136.7, 136.6, 130.9, 129.6, 128.9, 128.3, 125.9, 125.7, 125.5, 125.5, 122.1, 121.6, 120.4, 120.0, 119.8, 118.4, 112.6, 112.2, 111.7, 108.2. HRMS electrospray (m/z) Calculated for C$_{22}$H$_{16}$N$_2$, 308.1313; found, 308.1319.

3-H-1H,2'H, 2,2'-biindole
The product was purified using chromatography on silica gel (7:1 hexanes: ethyl acetate). The compound is a red-brown solid (92.8 mg, 40% yield). $^1$H NMR (400 MHz, DMSO-d$_6$): 11.55 (s, 2H), 7.60 (d, $J=8.5$ Hz, 2H), 7.40 (d, $J=8.5$ Hz, 2H), 7.10 (t, $J=8.1$ Hz, 2H), 7.00 (t, $J=8.1$ Hz, 2H), 6.92 (s, 2H). The thermometers on our Mel-Temp device only go to 250 °C, so the melting point is not reported. (Lit. mp: 310-312 °C)$^{18}$.

REFERENCES


CHAPTER 2: SYNTHESIS OF BIOBASED LINKER 2,2'-DITHIODISUCCINIC ANHYDRIDE AND ITS USE IN MODIFYING CORNSTARCH

Biobased linkers are an important part of an environmentally benign building and manufacturing process. Lignin when reacted with cross linking agents like epichlorohydrin, 1,2,3,4-diepoxy-butane, or ethene glycol-bis-epoxypropyl ether can produce high molecular weight lignin gel beads for fractionation and recovery of compounds by gel permeation. ¹

They have been used in biodegradable and recyclable resins for use in printed circuit boards. These resins are mainly a cellulose fiber that can be degraded when placed for forty days at thirty degrees in Alcaligenes faecalis culture. ² Printed wiring boards are used in a variety of electronics like computers and appliances. Printed wiring boards were made by applying thin layers of thermosetting epoxy resins applied to woven fabric or carbon and glass fibers and lead solders are used to adhere the layers together. All of these materials lead printed wiring boards to be considered as solid waste to be disposed of in a landfill. ³ Biodegradable printed wiring boards are needed to decrease landfill volume. These biobased materials must of course meet or exceed current mechanical and electrical standards for epoxy based laminates. ³ Cross-linked polymers for this purpose can be chosen from lignin, crop oils, wood resins, tannins, polysaccharide resins or a combination thereof. The best option is biobased ethers and lignin based on tests of electrical conduction and other requirements.
Amylopectin and amylose are the major molecular components of starch. The proportions of the two compounds differ depending on the source of the starch. While both components are present in various types of starch, it was unclear as to their distribution in the starch granules in the early 1990’s. When starch undergoes a thermal transition from a double to a single helical conformation under aqueous alcohol conditions, normal cornstarch granules retain their shape but waxy cornstarch granules change shape. It has been suggested that the amylopectin and amylose are interacting in the normal cornstarch granules to retain their shape. The structure of the starch granules was unclear, at the time. Blanchard has suggested that amylose is in bundles in amorphous regions in wheat starch but is partly co-crystallized with amylopectin in potato starch. Jane and coworkers have shown that through the use of cross-linking with epichlorohydrin that the viscosity of corn and potato starches increased with increased cross-linking. It was also shown by gel-permeation column chromatography that amylose was interspersed with the amylopectin and was not in bundles in the starch granules as Blanchard suggested. Following up on this work, Jane and coworkers cross-linked normal maize starch granules using phosphorous oxychloride to form phosphodiester cross-linked granules as well as phosphomonoester derivatives. Using phosphorous-31 nuclear magnetic resonance, it was confirmed that amylose does not clump together in bundles but is rather distributed with amylopectin inside normal maize granules. Biobased linkers are now being used to change the viscosity patterns of starch granules and to perform more structure elucidation as to the organization of starch molecules.
Due to interest in the biobased linkers for use in structure elucidation, our group undertook the task of preparing a variety of biobased linkers. The first set of biobased linkers was lactones or bisanhydrides 1-3. The compounds proved to be difficult to form due to problems with oxidizing the aldehydes to acids. Another group of compounds that were attempted contained one or two sulfide linkages, 4-6. Compound 3 was especially promising as it could be made in one step from readily available citric acid. The attempted synthesis of compound 3 is shown in Scheme 7.
Instead of the expected spiro compound 3, the alcohol acylated and the elimination product was formed instead, compound 9. This was unfortunate because citric acid is readily available and would have lead directly to the linker. Similar problems arose during attempts to synthesize compound 1. In the case of compound 2, several starting materials were tried but the oxidation of the aldehydes from ozonolysis was unsuccessful. The bases used in the reactions to produce compounds 4-6 were unable to produce the coupling products. Due to the problems with the previous compounds, a bisanhydride with a disulfide linkage was synthesized instead. Following the literature precedent of Kurihara and coworkers, two equivalents of mercaptosuccinic acid were reacted with eight molar
sodium hydroxide and thirty percent hydrogen peroxide to produce the disulfide linkage. The tetra acid 9 was then dehydrated to form the bisanhydride 10, as seen in Scheme 8.

**Scheme 8**

Dr. Jane’s group at Iowa State University was supplied with five grams of 2,2'-dithiodisuccinic anhydride to study the effects of cross-linking on cornstarch. Dr. Huang in Dr. Jane’s group produced a bisanhydride modified normal corn starch using the procedure in the experimental section. As mentioned above, when there is a thermally induced transition between the double and single helical conformation in starch, there is a change in the viscosity of the sample. If there is a difference between the bisanhydride modified cornstarch and normal cornstarch in this conformational change and the resulting viscosity, cross-linking of the starch has occurred. As you can
see from Figure 1, there is indeed a difference in the viscosity between the bisanhydride-modified cornstarch and normal cornstarch, so cross-linking did occur.

**Figure 1 Pasting Properties of normal cornstarch and bisanhydride modified starch**

The results of the viscosity test including a test for pasting temperature are shown in Table 1.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Peak 1 (CP)</th>
<th>Trough 1 (CP)</th>
<th>Breakdown (CP)</th>
<th>Final Visc (CP)</th>
<th>Setback (CP)</th>
<th>Pasting Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisanhydride modified starch</td>
<td>2000.4</td>
<td>1230</td>
<td>770.4</td>
<td>2767.2</td>
<td>1537.2</td>
<td>73.15</td>
</tr>
<tr>
<td>Corn starch</td>
<td>1712.4</td>
<td>1153.2</td>
<td>559.2</td>
<td>2133.6</td>
<td>980.4</td>
<td>81.15</td>
</tr>
</tbody>
</table>

Starch concentration was 8%, dry basis, and the viscosity was measured in centipoids (CP)
While low levels of cross-linking between the bisanhydride and the cornstarch did lead to a decrease in the pasting temperature, several difficulties are present in the process.

The bisanhydride compound has a dark color, pungent odor and sticky texture. It was poorly soluble in water and it was difficult to react with the cornstarch in a slurry. Also, the modified cornstarch while having a light yellow color also has a pungent odor, which poses an obstacle for its use in food and nonfood applications. Despite these difficulties, the fact that cross-linking occurred between the 2,2'-dithiodisuccinic anhydride and the normal corn starch, may one day lead to other commercially relevant cross-linked starches using this bisanhydride or other biobased linkers. Future work may include replacing the sulfur groups with oxygens or methylene groups to reduce the odor issue.

EXPERIMENTAL SECTION

General.

All $^1$H and $^{13}$C spectra were recorded at 400 MHz unless otherwise noted. All melting points are uncorrected. Unless otherwise noted, reactions were carried out under argon. Microwave reactions were conducted in a capped vial using a CEM Discovery system. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected using short wavelength UV light (254 nm). High-resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All
reagents were used directly as obtained commercially unless otherwise noted. All yields reported represent an average of at least two independent runs.

Procedure

**Synthesis of 2,2’-dithiodisuccinic acid**

Eight molar sodium hydroxide (392 mmol) was placed in a flask and 180 mmol of mercaptosuccinic acid was added slowly at 0 °C. Thirty percent hydrogen peroxide was added at 0 °C and the solution was warmed to room temperature and stirred for two hours. After checking for the completion of the reaction using thin-layer chromatography, the solution was acidified to a pH of 1 with 20 % sulfuric acid. The solution was extracted three times with ether and the organic layer was washed two times with brine. The solution was checked for peroxides with starch iodine paper before being dried over magnesium sulfate and concentrated in vacuo.

**Synthesis of 2,2’-dithiodisuccinic anhydride**

Eighteen equivalents of acetic acid (54.12 mmol, 5.12 mL) were added to the tetra acid disulfide (3 mmol, 0.8970g) made previously. The mixture was stirred at 60 °C for three hours. Upon cooling to room temperature, the stirbar was removed and the solution was placed in a Kugelrohr set at 120-150 °C until a black solid was left in the reaction flask. The solution was triturated with ether until the ether layer was clear. The product was obtained by concentration in vacuo.
**2,2'-dithiodisuccinic acid**

Product is a white solid (22.714 g, 84% yield). ${}^1$H NMR (300 MHz, DMSO-d$_6$):

3.82-3.73 (m, 2H), 2.88-2.68 (m, 4H).

**2,2'-dithiodisuccinic anhydride**

Product is a red/brown oil (549.4 mg, 58% yield). ${}^1$H NMR (300 MHz,CDCl$_3$):

4.28-4.15 (m, 2H), 3.78-3.70 (dd, $J = 9$ Hz, 15 Hz, 1H). HRMS electrospray (m/z) Calculated for C$_8$H$_6$O$_6$S$_2$, 261.9606; found, 261.9609.

**Preparation of bisanhydride modified normal cornstarch**

Normal cornstarch (30g, dry starch base) was suspended with distilled water (54 mL), and the pH of the suspension was adjusted to 8.5 with 3% (w/v) NaOH. The temperature of the suspension was maintained at 37º using a water bath. Bisanhydride (0.377 g) was added slowly and the reaction was carried out for 1 hour while maintained the pH. After the reaction was completed, the suspension was neutralized with HCl (0.5 N). The resultant starch suspension was vacuum-filtered through filter paper and washed three times with distilled water and once with absolutely ethanol to remove the residual reagents. The recovered starch was then dried in an oven at 37º for 3 hours. The pasting properties of the normal cornstarch and the bisanhydride-modified starch were analyzed using a Rapid ViscoAnalyzer.
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