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A new synthesis of 5-aminolevulinic acid via dye-sensitized oxygenation of N-furfurylphthalimide

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Abstract

Dye-sensitized oxygenation of N-furfurylphthalimide using Rose Bengal, fullerene-C_{60}, and coronene as sensitizers yielded 5-phthalimido-4-oxopentenoic acid. The acid was then hydrogenated with palladium-on-carbon, and was hydrolyzed to finally produce 5-aminolevulinic acid (**1**) at about 50% total yield. The oxygenation process was studied in relation to the mechanistic process and the improvement of yield, using several solvent systems and 2,3-dimethyl-2-butene, and was explained as a singlet oxygen reaction. The synthesis method used for **1** was an improvement on previously reported methods with respect to: the total yield, the commercial availability of the starting materials, and the economical nature of the oxygenation process, even on a large scale.

Keywords: Dye-sensitized oxygenation; Rose bengal; Fullerene; Coronene

1. Introduction

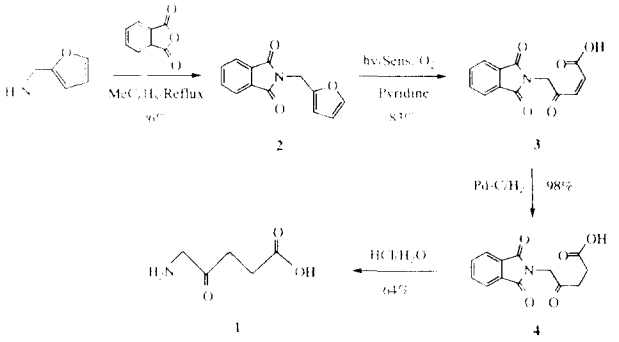
Recently, much attention has been focused on 5-aminolevulinic acid (**1**) because of its potential use as a herbicide [1] and a plant growth regulator [2], and also because it is well-known as a precursor of natural tetrapyrrole compounds such as hems, corrins and chlorophyll [3]. Therefore, several studies relating to methods for the synthesis of **1** have been published [4], describing for instance the use of 2-hydroxypyridine [5], tetrahydrofurfurylamine [6], and furfurylamine [7] as starting materials for a three-stage preparation process on a small scale. However, these studies share the same practical and economic problems concerning the total yield, commercial availability of the starting materials, and the use of expensive metal oxidants in the oxygenation processes. In this paper, we report a new three-stage synthesis method for **1** from N-furfurylphthalimide including dye-sensitized oxygenation, which with respect to the points described above has clear advantages over the methods used by other researchers.

2. Results and discussion

2.1. Dye-sensitized oxygenation of N-furfurylphthalimide (2)

2.1.1. Effect of solvent

Rose Bengal (RB)-sensitized oxygenation of **2** in pyridine, prepared from furfurylamine and phthalic anhydride [6,8], gave 5-phthalimido-4-oxopentenoic acid (**3**) at 83% yield (Scheme 1). Similar oxygenation of **2** in methanol, acetone, and N,N-dimethylformamide produced complicated unknown products, while that in N,N-dimethylaniline, N-methylaniline, and triethylamine did not proceed at all as



Scheme 1.

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shown in Runs 5–7, Table 1. Other mixed solvent systems consisting of methanol/pyridine, acetone/pyridine, acetone/triethylamine, and benzene/pyridine were also investigated (Runs 8–19); as a result, neat pyridine was found to be the most efficient solvent to yield **3** in the photooxygenation process. As shown in Runs 10–15, the addition of a certain amount of pyridine or triethylamine to methanol and acetone is necessary to form **3**, which indicates that a certain amount of base is essential in the process. By contrast, in the case of neat amines (Runs 5–7) and the addition of amines in high concentration to acetone (Run 16), the photooxygenation process was completely quenched. This is probably because, although singlet oxygen ($^1O_2$) was expected to be an active oxidant, these amines would work as quenchers [9].

Although there have been few cases in which pyridine was used as a solvent in dye-sensitized oxygenation [10], it has several advantages over other solvents; for example: the high solubility of RB and **2** in pyridine; the lifetime of $^1O_2$; and the suppression effect on bleaching of RB during irradiation. It has been reported that the lifetime of $^1O_2$ depends on the solvent used: 33 μs in pyridine, 26 μs in acetone, 12.5–24 μs in benzene, and 5–7 μs in methanol [11]. Although there are other solvents, freons for example, in which $^1O_2$ has a much longer lifetime (1000 μs) than in the above solvents, they cannot be employed for this process because of the resultant low solubility of the starting materials. In addition, it was confirmed that by-products such as N-methylphthalimide, phthalic acid, maleic acid, and fumaric acid accelerate the bleaching of RB. Therefore, it is noteworthy that pyridine is the only solvent to have a suppression effect on fading in the present reaction.

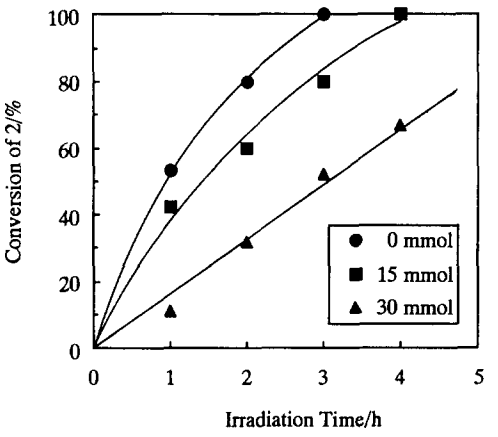


Fig. 1. Effect of TME on RB-sensitized oxygenation of **2** in pyridine: **2**, 15 mmol; RB, 0.03 mmol; pyridine, 150 ml.

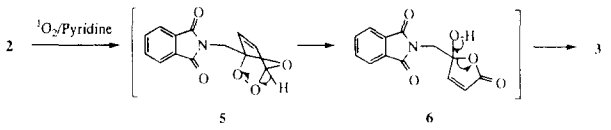
2.1.2. *Effect of 2,3-dimethyl-2-butene (TME)*

Fig. 1 shows the results of RB-sensitized oxygenation of **2** in the presence of TME as a singlet oxygen quencher [11,12]. The quenching study indicates that $^1O_2$ is probably a reactive oxidant. In the presence of 30 mmol TME, as shown in Fig. 1, the oxygenation of 2 (15 mmol) still proceeds efficiently. In fact, the ratio of the reaction-rate constants of $^1O_2$ for 2,3-dimethylfuran and TME (k_F/k_{TME}) has been measured to be about 8.5 [11]. This suggests that furan derivatives are more reactive than TME against $^1O_2$. Oxygenation of furan derivatives by $^1O_2$, in general, gives [2+4] cycloadducts as primary products; however, in the presence of weak base, the adducts probably isomerize into products with carbonyl and hydroxy groups, a process similar to the decomposition of peroxides [13]. Therefore, under the reac-

Table 1
Effect of solvent on Rose Bengal-sensitized oxygenation of **2**

Run	Solvent	Time (h) [a]	Conv. (%)	Yield of **3** (%)
1	Pyridine	3	100	83
2	MeOH	3	100	[b]
3	Me_2CO	3	100	[b]
4	$HCONMe_2$	3	100	[b]
5	N,N-Dimethylaniline	4	0	0
6	N-Methylpiperidine	4	0	0
7	NEt_3	4	0	0
8	MeOH/Pyridine (10 mmol)	3	100	[b]
9	MeOH/Pyridine (20 mmol)	3	100	[b]
10	MeOH/Pyridine (160 mmol)	3	100	45
11	MeOH/Pyridine (500 mmol)	3	100	75
12	Me_2CO/Pyridine (10 mmol)	3	100	31
13	Me_2CO/Pyridine (20 mmol)	3	100	37
14	Me_2CO/Pyridine (160 mmol)	3	100	40
15	Me_2CO/NEt_3 (20 mmol)	4	64	42
16	Me_2CO/NEt_3 (160 mmol)	4	0	0
17	Benzene/Pyridine (10 mmol)	4	0	0
18	Benzene/Pyridine (160 mmol)	4	50	35
19	$MeOH/NaHCO_3$ (10 mmol)	3	100	[b]

[a] Irradiation time.
[b] Complicated unknown products were obtained.



Scheme 2.

tion conditions shown in Scheme 2 it may be possible that the corresponding cycloadduct **5** and alcohol **6** are formed as part of the process of obtaining the acid **3** [14]. This hypothesis is supported by the calculation of the heat of formation (H) for **3** and **6** using the semiempirical molecular orbital method PM3: namely, $\Delta H = H_6 - H_3 = 3.8$ kcal mol^{-1} [15].

2.1.3. Effect of sensitizers

To suppress the bleaching of dye is quite important in dye-sensitized oxygenation [16]. To improve the oxygenation process of **2** to **3**, fullerene-C_{60} and coronene were employed as sensitizers instead of RB as shown in Table 2 [17]. When the mixed solvent system of toluene/pyridine = 1/3 was used because of the low solubility of fullerene-C_{60} and coronene in neat pyridine, the yield of **3** was similar to that with RB. Furthermore, the bilayer system of toluene/pyridine/water was found to be more efficient and economical than the above mixed solvent. In this system, **2** and the sensitizers are contained in the toluene layer, whereas product **3** is transferred to the water layer. In addition, the toluene layer containing the sensitizers can be reused for the photooxygenation repeatedly without any further treatment. In the case of coronene in particular it should be noted that acid **3** can be produced at more than 75% yield even after the toluene layer has been recycled more than ten times.

*2.2. Preparation of 5-aminolevulinic acid hydrochloride (**1**·HCl)*

Catalytic hydrogenation of **3** with 5%-paradium on carbon (Pd/C) formed 5-phthalimidolevulinic acid (**4**) readily at 98% yield as shown in Table 3, followed by acid catalyzed hydrolysis to give 5-aminolevulinic acid hydrochloride (64%). With regard to the practical use of the synthesis of **1**, it is significant that the reaction mixture after the photooxidation of **2** can be used for the hydrogenation without any additional purification.

Table 2
Photooxygenation of **2** with fullerene-C_{60} and coronene

Run	Sensitizer	Solvent	Conv. (%)	Yield of **3** (%)
1	C_{60}	Pyridine	0	0
2	Coronene	Pyridine	17	5
3	C_{60}	Py/H_2O/Toluene [a]	100	80
4	Coronene	Py/H_2O/Toluene [a]	100	81
5	C_{60}	Py/Toluene [b]	100	70
6	Coronene	Py/Toluene [b]	100	70
7	C_{60}	Toluene	100	[c]
8	Coronene	Toluene	100	[c]
9	C_{60}	NEt_3/Toluene [d]	0	0
10	Coronene	NEt_3/Toluene [d]	0	0

[a] Pyridine/H_2O/toluene = 1/3/3.
[b] Pyridine/toluene = 1/3.
[c] Complicated products were obtained.
[d] NEt_3/toluene = 1/3.

Table 3
Preparation of **4** from **3** by catalytic hydrogenation

Run		Solvent	Catalyst	Time (h) [a]	Yield of **4** (%)
1	**3** [b]	MeOH	5%-Pd/C	5	98
2	**3**/Py salt [c]	MeOH	5%/Pd/C	5	98
3	**3**/Py salt [c]	Pyridine	5%-Pd/C	2	84
4	**3**/Py salt [d]	Pyridine	5%-Pd/C	4	99
5	**3**/Py salt [d]	Pyridine	5%-Pd/Al_2O_3	4	99
6	**3**/Py salt [d]	Pyridine	Raney-Ni	4	54

[a] Reaction time.
[b] **3** isolated.
[c] Salt of **3** with pyridine isolated.
[d] Reaction mixtures obtained by dye-sensitized oxygenation of **2** were used without any further treatment.

3. Experimental details

3.1. General

All melting points (mp) are uncorrected. IR spectra were measured with a JASCO IR-810 spectrometer. NMR spectra were measured with tetramethylsilane as the internal standard at 400 MHz with a JEOL Alpha-400 spectrometer. GC-MS analysis was performed using a Shimadzu QP-5000 GC-MS spectrometer. HPLC analysis was carried out using a TOSOH CCP8020 fitted with a GL-science ODS-2 column (ϕ 4.6 mm × 250 mm) with a constant elution gradient from an aqueous solution of 5 mM tetra-n-butylammonium phosphate to MeOH at a constant flow rate of 1 ml min^{-1}.

3.2. N-Furfurylphthalimide (2)

Furfurylamine (400 ml, 4.5 mol) was dropped into a solution of phthalic anhydride (670 g, 4.5 mol) in toluene (1.4 L) with continuous stirring below 30 °C and heated for 6 h under reflux, removing the water produced. After cooling to room temperature, the light yellow needles precipitated were collected by filtration. The needles were dissolved in chloroform, washed with a saturated aqueous solution of $NaHCO_3$, dried over magnesium sulfate, and concentrated in vacuo. The residue was recrystallized from toluene to give pure **2** (983 g, 96%): m.p. 116–117 °C (120–121 °C [8]); ^1H NMR ($CDCl_3$): δ 4.86 (2H, s), 6.30 (1H, dd, J = 3.2 and 2.0 Hz), 6.37 (1H, d, J = 3.2 Hz), 7.33 (1H, d, J = 2.0 Hz), 7.70–7.73 (2H, m), 7.85–7.88 (2H, m); ^{13}C NMR ($CDCl_3$): δ 34.3, 108.8, 110.5, 123.4, 132.0, 134.0, 142.4, 149.3, 167.6.

3.3. RB-sensitized oxygenation of 2 in pyridine

A solution of **2** (1.5 mmol) in pyridine (15 ml) was irradiated in the presence of RB (3 mg) with a tungsten-halogen lamp (Toshiba JD-110V 100W). Dry oxygen was bubbled through the solution during the irradiation. The reaction was followed by HPLC analysis. When **2** was completely consumed, the pyridine was removed with a rotary evaporator at room temperature. The residue was treated in the usual manner to give **3** as pyridine salt at 83% yield. Pure **3** was obtained by ion-exchange with Amberlyst 15E resin or recrystallization from hot water: m.p. 163–164 °C (163 °C [18]); IR (Nujol): ν_{max} cm^{-1} 1780, 1730, 1690, 1630; ^1H NMR ($CDCl_3$): δ 4.80 (2H, s), 6.84 (1H, d, J = 16 Hz), 7.13 (1H, d, J = 16 Hz), 7.79–7.82 (2H, m), 7.87–7.90 (2H, m); ^{13}C NMR ($CDCl_3$): δ 45.7, 123.5, 131.9, 134.0, 134.3, 135.6, 166.5, 167.4, 191.4.

3.4. Photooxygenation of 2 with coronene

The imide **2** (2.3 g, 10 mmol) and coronene (50 mg, 0.17 mmol) were added to a biphasic solution of toluene (75 ml), water (75 ml), and pyridine (25 ml). The solution was irradiated under conditions similar to those mentioned above. After 3 h, the toluene layer was separated and extracted with water. The water layer was washed with toluene and concentrated in vacuo. The residue was washed with dichloromethane to give pyridine salt of **3**. The toluene layer was concentrated to 75 ml and reused for the next run (see Table 2).

3.5. 5-Phthalimidolevulinic acid (4)

Pyridine salt of **3** (450 mg, 1.3 mmol) and 5%-Pd/C (28 mg, 0.013 mmol for Pd) were added to methanol or pyridine and hydrogenation was carried out under the conditions shown in Table 3. After the reaction was finished, the catalyst was removed and the filtrate was concentrated. The residue obtained was recrystallized from 0.5 N HCl to give pure **4**: m.p. 160–161 °C (160–162 °C [6]); IR (Nujol): ν_{max} cm^{-1} 1770, 1720, 1705; ^1H NMR ($CDCl_3$): δ 2.59 (2H, t, J = 6.8 Hz), 2.84 (2H, t, J = 6.8 Hz), 4.58 (2H, s), 7.77–7.81 (2H, m), 7.85–7.89 (2H, m); ^{13}C NMR ($CDCl_3$): δ 27.6, 34.4, 46.5, 123.3, 131.8, 134.2, 167.3, 173.7, 201.3.

3.6. 5-Aminolevulinic acid hydrochloride (1 · HCl)

Acid **4** (20 g, 77 mmol) was added to 800 ml of 6 M HCl and heated while being stirred under reflux for 8 h. After cooling, the solution was kept at 0 °C overnight to yield a precipitated solid. The solid was removed and the filtrate was concentrated. The residue was recrystallized from 95% EtOH to give pure **1** as hydrochloride salt (8.2 g, 64%): m.p. 148–150 °C (145–148 °C [6]); IR (Nujol): ν_{max} cm^{-1} 3100, 1725, 1580, 1560; ^1H NMR (D_2O): δ 2.70 (2H, t, J = 6.3 Hz), 2.80 (2H, t, J = 6.3 Hz), 4.10 (2H, s).

4. Conclusion

Synthesis of **1** was achieved via the oxygenation of **2** by $^1O_2$ in pyridine quite efficiently and economically. The overall yield for **1** was about 50% in three stages from **2**. It was found that both fullerene-C_{60} and coronene are useful as sensitizers, because of their high stability in the bilayer solvent system consisting of toluene/pyridine/water. Furthermore, the toluene layer containing the sensitizers can be reused at least ten times in the case of coronene. This method is clearly free from expensive and highly toxic metal oxidants and would have a potential application in the synthesis of **1** on an industrial scale.

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