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Research Article

STUDYING MODIFICATION OF STICTIC ACID UNDER $AlCl_3$ CATALYST IN DIMETHYLFORMAMIDE SOLVENT

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ABSTRACT

Stictic acid, a depsidone in many lichen species, is a potentially bioactive compound. Derivatives of stictic acid were synthesised by halogenation or esterification. However, the effects of these conditions on the decomposition of stictic acid have yet to be studied. Hence, the modification of stictic acid was investigated using an $AlCl_3$ catalyst and dimethylformamide solvent. The results showed that approximately 20% of the stictic acid yield was transformed into other compounds in these media. The decomposition of stictic acid is due to lactone ring-opening by the $AlCl_3$ catalyst or the dimethylamine produced by the reaction of $AlCl_3$ and dimethylformamide.

Keywords: $AlCl_3$; decomposition; dimethylformamide; lichen; stictic acid

1. Introduction

Lichens are an important source of bioactive compounds. Studies on the biological activity of these compounds showed that depsidones isolated from lichen have antioxidant, antibacterial, anti-inflammatory, antiviral and anti-cancer activity (Ranković et al., 2012; Manojlović et al., 2012; Bhattarai et al., 2013; Khadhri et al., 2022; Wang et al., 2022). The most typical depsidone of these compounds is stictic acid found in many lichen species such as *Usnea aciculifera, Parmotrema sp. (Parmotrema eliasaroanum…), Evernia prunastri, Pseudevernia (Pseudevernia furacea…), Relicina (Relicina sydneyensis…), Xanthoparmelia lusitam* (Rankovíc, 2015). Stictic is a depsidone that consists of two phenolic components linked together by an ether bond and an ester bond (Fig. 1) (Ismed et al., 2017).

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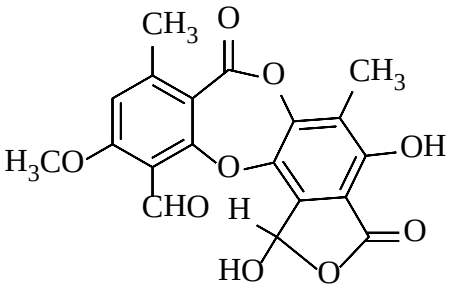


Figure 1. *Structure of stictic acid*

The stictic acid products can be modified by halogenation or esterification (Pham et al., 2021; Huynh et al., 2018). The ester and ether bonds in the structure of stictic acid can be affected during these transformations. However, very few studies have been conducted on stictic acid derivative synthesis, and there has yet to be an investigation of the decomposition of stictic acid in these reaction media. In this study, we investigated the effect of $AlCl_3$ and dimethylformamide (DMF) as a solvent in the structural modification of stictic acid at high temperatures.

2. Experimental

2.1. General experimental procedure

NMR spectra were recorded on a Bruker Avance spectrometer (500 MHz for ^{1}H-NMR and 125 MHz for ^{13}C-NMR) in DMSO-d_6 and $CDCl_3$. Thin-layer chromatography was carried out on silica gel 60 (Merck, 40-63 μm), and spots were visualised by spraying with a 10% H_2SO_4 solution, followed by heating. HRESIMS data were recorded on an LC-Agilent 1100 LC-MSD trap using a MicrOTOF-Q mass spectrometer.

2.2. Stictic acid modification procedure

$AlCl_3$ (22 mg, 0.165 mmol) was added to a solution of stictic acid (**1**, 100.0 mg, 0.26 mmol) in acetic acid: DMF solvent (2.0 mL, 1:1, v/v). The mixture was stirred at 110 ^{o}C for 5 h. The reaction was periodically monitored using TLC. The resulting solution was neutralised with saturated sodium hydrogen carbonate, then extracted with ethyl acetate-water (1:1, v/v) to gain an organic layer. This layer was subsequently washed with brine three times, then dried and applied to silica gel CC, eluted with hexane-chloroform-ethyl acetate-acetone-acetic acid-water (50:125:250:250:1.5:1, v/v/v/v/v/v) to obtain **1a, 1b, 1c.**

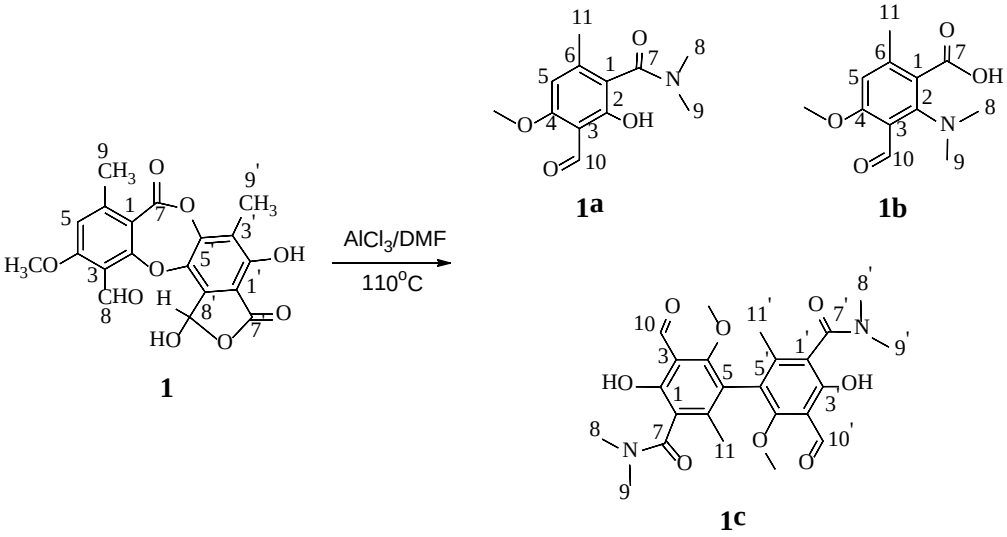
1a White amorphous powder; ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1. HRESIMS found *m/z* 238.1052 (calcd. for $[C_{12}H_{15}NO_4+H]^+$, *m/z* 238.1001) .

1b White amorphous powder; ^{1}H NMR (DMSO-d_6, 500 MHz): see Table 1.

1c Yellow amorphous powder; ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1.

3. Results and discussion

Stictic acid **1** was modified using an $AlCl_3$ catalyst in DMF solvent. The results showed that three compounds (**1a**, **1b** and **1c**) were isolated after 5h of reaction (Scheme 1).



Scheme 1. *Modification of stictic acid with $AlCl_3$ and DMF*

The ^{1}H NMR spectrum of **1** exhibited the presence of two methyl groups [δ_H 2.51 (3H, s, H-9) and 2.20 (3H, s, H-9')], one methoxy group at δ_H 3.92 (3H, s, 4-OCH_3), one aldehyde proton at δ_H 10.44 (1H, s, H-8), two hydroxy groups [δ_H 8.21 (1H, br, 8'-OH) and 10.19 (1H, s, 2'-OH)], and one aromatic proton at δ_H 7.10 (1H, s, H-5).

The ^{1}H NMR spectrum of **1a** resembled those of **1**: an aromatic proton (δ_H 6.28, 1H, s), an aldehyde proton (δ_H 10.27, 1H, s), and a methoxy group (δ_H 3.92, 3H, s) indicated the presence of ring A of **1a**. However, the absence of one methyl group at 8'-CH_3 (δ_H 2.20, 3H, s) and a hydroxy group at C-2' (δ_H 10.19, 1H, s) indicated that ring B was absent in the structure of **1a**. In addition, the ^{13}C NMR spectrum of **1a** also showed a lack of signals on ring B, two new methyl groups [(δ_H 2.51 (3H, s) and 2.50 (3H, s)] and a hydroxy group (δ_H 12.24, 1H, s) were observed. HMBC correlation of **1a** showed that the two methyl groups correlated with C-7 (δ_C 167.6), and the correlation between the two methyl groups indicated that it was an amide group at C-1. The correlation of the hydroxy group (δ_H 12.24, 1H, s) with C-1 defined the appearance of a hydroxy group at C-2 0(Fig. 2).

Table 1. *NMR data of stictic acid and its transformation derivatives*

No	1		1a		1b	1c	
	δ_H (multi, *J* in Hz) (DMSO-d_6, 500 MHz)	**δ_C (DMSO-d_6, 125 MHz)**	**δ_H (multi, *J* in Hz) ($CDCl_3$, 500MHz)**	**δ_C ($CDCl_3$, 125MHz)**	**δ_H (multi, *J* in Hz) (DMSO-d_6, 500MHz)**	**δ_H (multi, *J* in Hz) ($CDCl_3$, 500MHz)**	**δ_C ($CDCl_3$, 125MHz)**
1	-	113.0	-	118.6	-	-	123.4
2	-	161.9	-	159.7	-	-	156.7
3	-	114.7	-	108.8	-	-	113.6
4	-	162.9	-	162.2	-	-	159.0
5	7.10 (1H, s)	112.6	6.28 (1H, s)	103.3	7.13(1H, s)	-	118.8

6	-	151.1	-	147.4	-	-	145.0
7	-	166.5	-	167.6	-	-	166.4
8	10.44 (1H, s)	186.4	3.16 (3H, s)	34.7	2.51 (3H, s)	3.09 (3H, s)	34.6
9	2.51 (3H, s)	21.4	2.92 (3H, s)	37.8	2.50 (3H, s)	2.83 (3H, s)	37.7
10	-	-	10.27 (1H, s)	193.7	10.28 (1H, s) 10.26 (1H,s)	10.14 (1H, s)	193.9
11	-	-	2.31 (3H, s)	20.8	2.28 (3H, s)	2.27 (3H, s)	18.4
1'	-	109.0	-	-	-	-	123.4
2'	10.19 (1H, s)	152.0	-	-	-	-	156.7
3'	-	121.1	-	-	-	-	113.6
4'	-	148.1	-	-	-	-	159.0
5'	-	135.8	-	-	-	-	118.8
6'	-	137.6	-	-	-	-	145.0
7'	-	160.0	-	-	-	-	166.4
8'	6.61 (1H, d) 8.21 (1H, d)	9.4	-	-	-	3.09 (3H, s)	34.6
9'	2.20 (3H, s)	95.2	-	-	-	2.83 (3H, s)	37.7
10'	-	-	-	-	-	10.14 (1H, s)	193.9
11'	-	-	-	-	-	2.27 (3H, s)	18.4
2-OH	-	-	12.24 (1H, s)	-	-	11.70 (1H, s)	-
4-OCH_3	3.92 (3H, s)	56.6	3.92 (3H, s)	56.0	3.93 (3H, s)	3.92 (3H, s)	63.1
2'-OH	-	-	-	-		11.70 (1H, s)	-
4'-OCH_3	-	-	-	-		3.92 (3H, s)	63.1

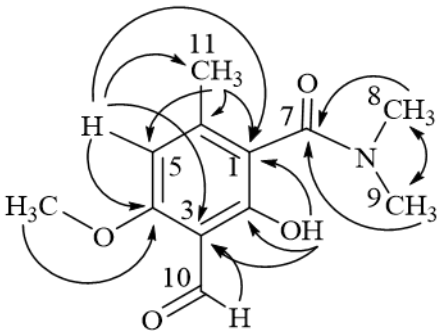


Figure 2. *HMBC correlation of* ***1a***

The ^{1}H NMR spectrum of **1b** showed signals identical to those of **1a**. However, the two methyl groups [δ_H 2.51(3H, s) and 2.50 (3H, s)] of **1b** shifted to a higher frequency field than the two methyl groups of **1a** [δ_H 3.16 (3H, s) and 2.92 (3H, s)]. The lack of a hydroxy group at C-2 of **1b** indicated the presence of an amine group in the structure of **1b** at C-2.

The ^{1}H and ^{13}C NMR spectra of **1c** resemble those of **1a**, except for the absence of a proton at C-5. The HMBC spectrum of **1c** also showed a correlation between the amide and hydroxy groups at C-2, similar to the structure of **1a** (Fig. 3). The absence of a proton at C-5 is the key to deduce that the structure of compound **1a** is linked at C-5.

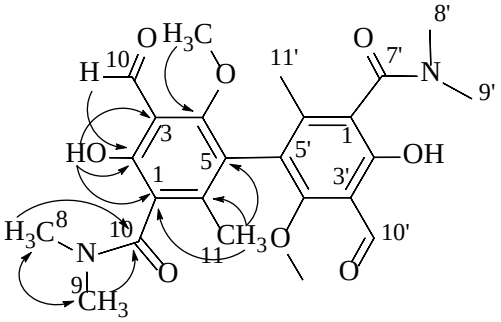


Figure 3. *HMBC correlation of* ***1c***

Based on the products' formation, the proposed reaction mechanism is suggested to involve two steps. The first step is the hydrolysis of DMF using an $AlCl_3$ catalyst when heated (Fig. 4). This resulted in the formation of dimethylamine and formic acid, reagents for other transformations. Step two involves the formation of two products, **1a** and **1b**. Dimethylamine produced from the hydrolysis of DMF attacked the ester group of stictic acid, leading to the lactone ring opening. Then, water reacted at C-2 of ring A and ring B was removed to synthesise **1a** (Fig. 5). The mechanism of **1b** preparation followed the reversible order of **1a** synthesis (Fig. 6). Water ring-opening of the lactone ring, followed by the reaction of dimethylamine at C-2 of ring A, leads to the disconnection of ring B to produce **1b**. **1c** was synthesised by the dimerisation of **1a** using an $AlCl_3$ catalyst (Sartori et al., 1995) (Fig. 7).

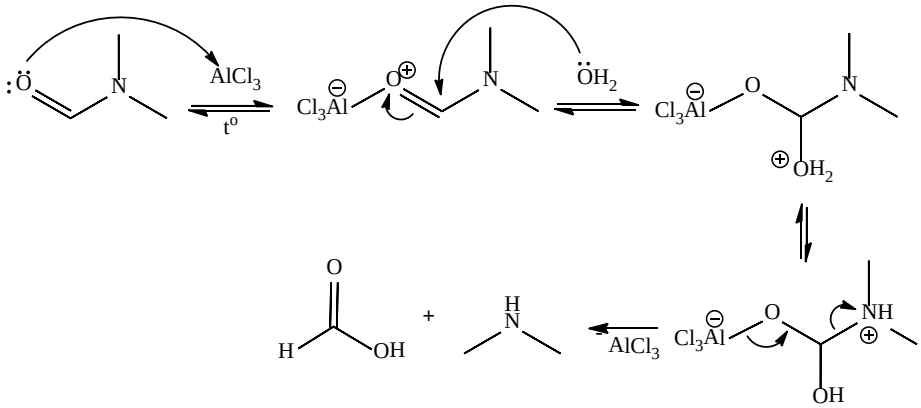


Figure 4. *Hydrolysis of DMF under $AlCl_3$ catalyst*

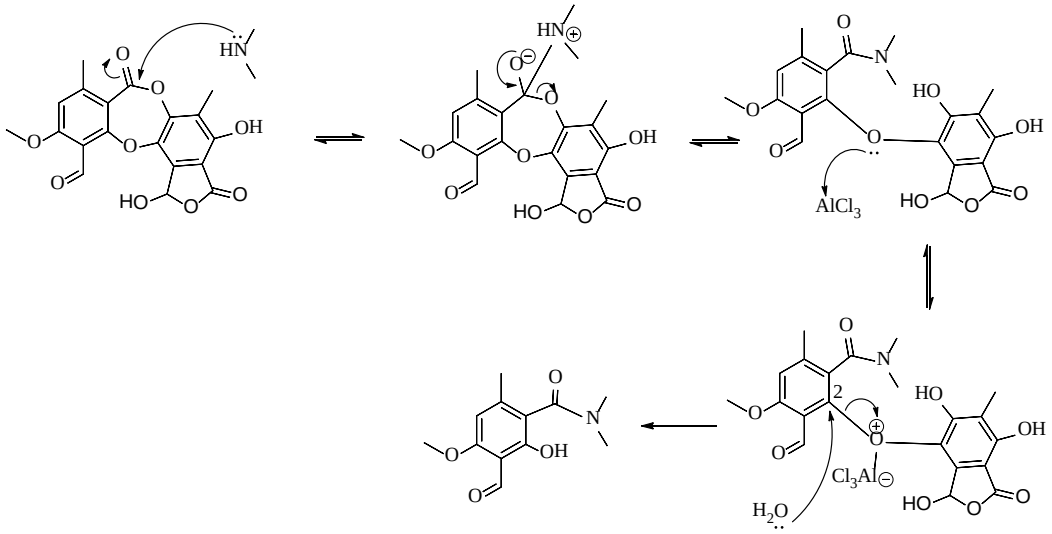


Figure 5. *Transformation of stictic acid to* ***1a***

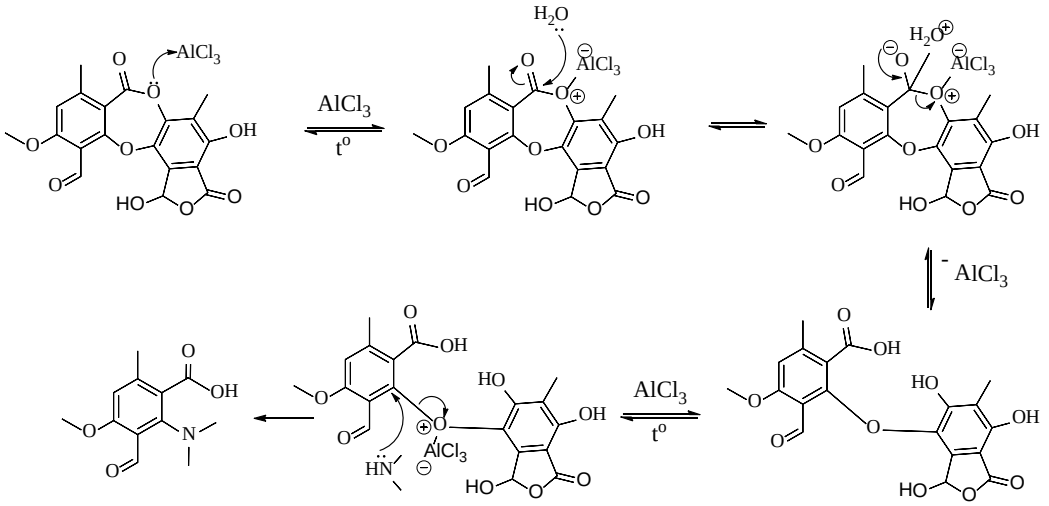


Figure 6. *Transformation of stictic acid to* ***1b***

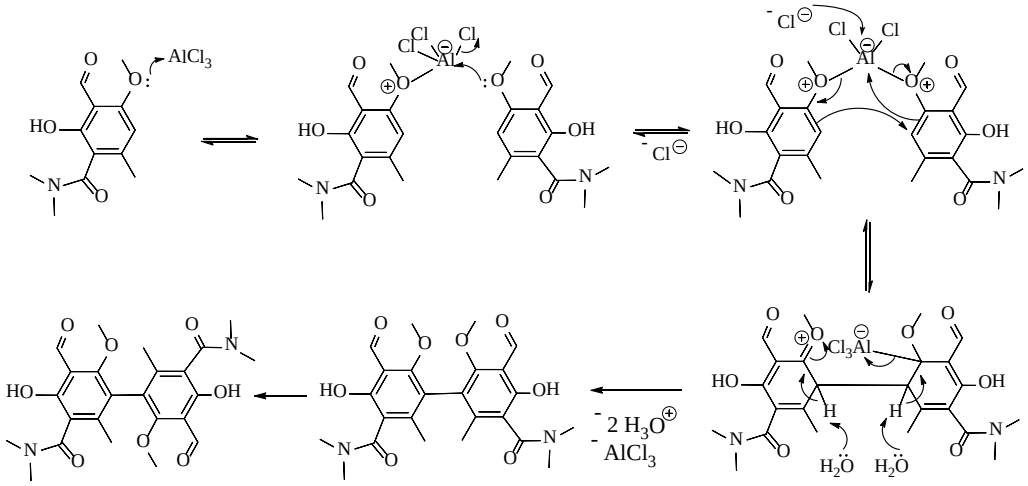


Figure 7. *Dimerisation of* ***1a***

4. Conclusion

This investigation showed that the percentage of transformed stictic acid was small. Under the $AlCl_3$ catalyst, stictic acid was modified into three compounds. Products **1a** and **1b** were produced by ring opening of lactone ring A of stictic acid. The product **1c** was created by dimerising of **1a** using an $AlCl_3$ catalyst.

- ***Conflict of Interest:*** *Authors have no conflict of interest to declare.*
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NGHIÊN CỨU SỰ BIẾN ĐỔI CỦA STICTIC ACID VỚI XÚC TÁC $AlCl_3$ TRONG DUNG MÔI DIMETHYLFORMAMIDE

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TÓM TẮT

*Stictic acid, depsidone được tìm thấy trong nhiều loài địa y, là hợp chất có nhiều hoạt tính sinh học quan trọng. Các dẫn xuất của stictic acid được tổng hợp dựa trên phản ứng halogen hóa hoặc phản ứng ester hóa. Tuy nhiên, ảnh hưởng của điều kiện thực hiện phản ứng đến sự phân hủy của stictic acid chưa được nghiên cứu. Do đó, sự biến đổi của stictic acid khi sử dụng xúc tác $AlCl_3$ và dung môi dimethylformamide được nghiên cứu thực hiện. Kết quả nghiên cứu cho thấy khoảng 20% lượng stictic acid đã bị biến đổi thành những hợp chất khác trong điều kiện này. Sự phân hủy của stictic acid dưới sự ảnh hưởng của $AlCl_3$ do quá trình mở vòng lactone tạo thành sản phẩm **1a**, **1b** và quá trình dime hóa sản phẩm **1a** tạo thành sản phẩm **1c**.*

Từ khóa: $AlCl_3$; phân hủy; dimethylformamide; địa y; Stictic acid