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Regioselective acylation at the 5- or 6-position of L-tryptophan derivatives

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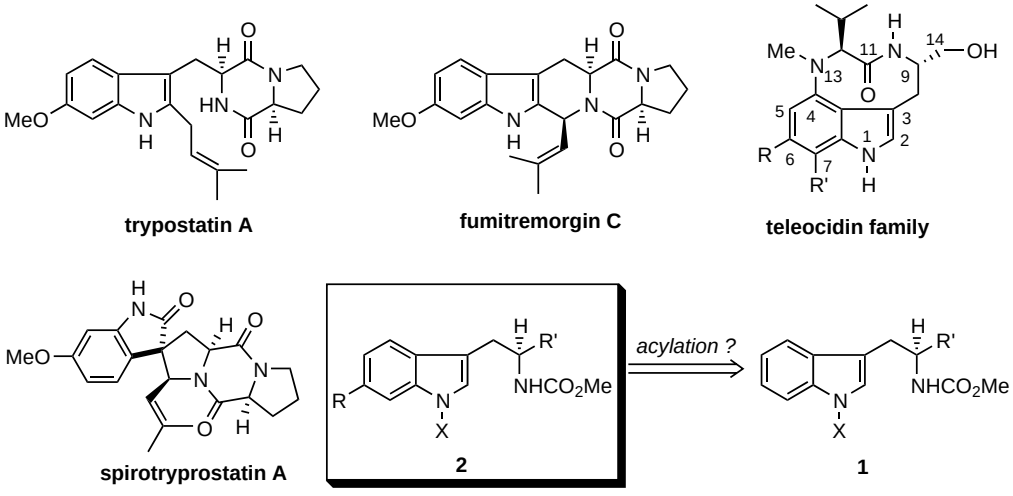
Abstract—The reaction of 1-acyl tryptophan derivatives with chloroacetyl chloride or the reaction of 1-tosyl tryptophan derivatives with acetyl chloride provides the corresponding 6-acylation products, while acylation of the 3-oxo tryptophan derivative gives a 5-substituted product.

6-Substituted L-tryptophan moieties exist in many biologically important molecules such as the cell cycle modulator, trypostatin A[1] and fumitremorgin C,[2] a reversal agent for multi-drug resistance (MDR). In addition, 6-substituted tryptophan derivatives have served as a starting material for synthesizing spirotryprostatin A,[3] and are obviously useful intermediates for synthesizing the teleocidin family of compounds[4] which show potent protein kinase C (PKC) activation activity (Scheme 1).

In connection with our research on the design and synthesis of novel and isoform-selective PKC modulators,[5] we needed a powerful method to synthesize 6-substituted L-tryptophan derivatives of type **2**. A literature survey for the preparation of these compounds indicated that few methods were suitable. Considering that Friedel–Crafts acylation was a useful approach to introduce substituents into the aromatic ring, and that there was not a report concerning this reaction with L-tryptophan derivatives as substrates, we



Scheme 1.

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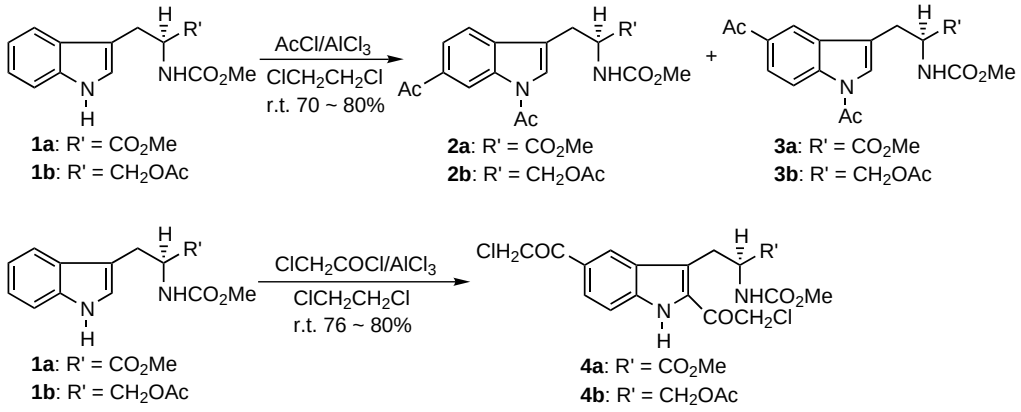
decided to explore the Friedel–Crafts acylation of several L-tryptophan derivatives.

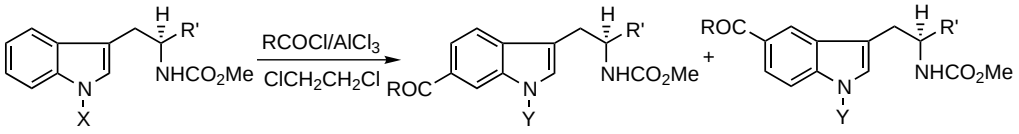
Initially, we tested the direct acylation of compounds **1a** and **1b** derived from L-tryptophan through simple operations. When acetyl chloride was used as an acylation reagent, both **1a** and **1b** gave 1,6- and 1,5-diacylation products in the ratio of about 1:1. However, under the same conditions, only a 2,5-diacylation product was isolated when chloroacetyl chloride was reacted with either **1a** or **1b** (Scheme 2). These observations indicated that the regioselectivity of the acylation was highly dependent on the nature of the acylating agent. A similar phenomenon was noticed when Nakatsuka and co-workers investigated the acylation reaction of 1-substituted indoles.[6]

The initial results outlined in Scheme 2 implied that the 1- and 2-positions of L-tryptophan were also active sites for acylation. In order to avoid acylation at these two positions, we decided to protect the 1-position as an amide or sulfonamide. This protection would not only block acylation at the 1-position, but would also deactivate the 2-position via both electronic[7] and steric effects. Accordingly, the compounds **1c**–**1f** were prepared by treatment of **1a** or **1b** with AcCl/TEA/DMAP or TsCl/NaH in methylene chloride. The yields for these conversions were 90 ~ 100%. As summarized in Table 1, in the case of **1c** as a substrate, acylation using acetyl chloride did not occur at room temperature, or even at higher temperature. However, when the more active chloroacetyl chloride was employed, the reaction occurred at room temperature to afford the 6-acylation



Scheme 2.

Table 1. Acylation of 1-substituted L-tryptophan derivatives[a]



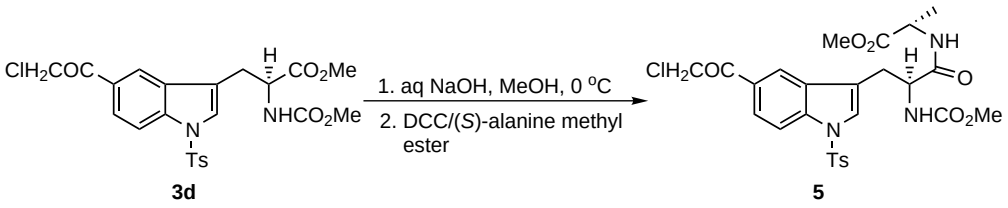
1c: X = Ac, R' = CO_2Me
1d: X = Ac, R' = CH_2OAc
1e: X = Ts, R' = CO_2Me
1f: X = Ts, R' = CH_2OAc

2c: Y = Ac, R' = CO_2Me, R = CH_2Cl
2d: Y = Ac, R' = CH_2OAc, R = CH_2Cl
2e: Y = Ts, R' = CO_2Me, R = Me
2f: Y = Ts, R' = CH_2OAc, R = Me
2g: Y = Ts, R' = CH_2OAc, R = CH_2Cl
2h: Y = Ts, R' = CO_2Me, R = CH_2Cl

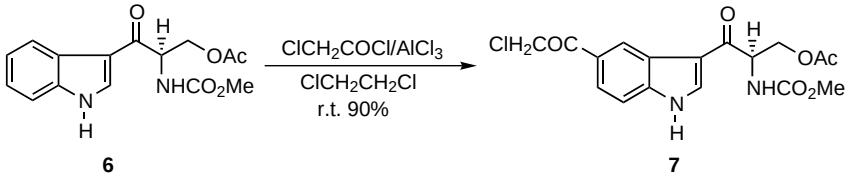
3c: Y = Ts, R' = CO_2Me, R = Me
3d: Y = Ts, R' = CO_2Me, R = CH_2Cl
3e: Y = Ts, R' = CH_2OAc, R = CH_2Cl

Entry	Substrate	R	Temp. (°C)	Time (h)	Products (yield (%))[b]	
1	**1c**	Me	25	48	–	
2	**1c**	$ClCH_2$	25	36	**2c** (80)	
3	**1d**	Me	25	18	**2b** (10)[c]	**3b** (20)[c]
4	**1d**	$ClCH_2$	25	24	**2d** (31)	
5	**1e**	Me	0	2	**2e** (64)[c]	**3c** (21)[c]
6	**1e**	Me	25	12	**2a** (80)	
7	**1f**	Me	0	1	**2f** (91)	
8	**1f**	Me	25	12	**2b** (90)	
9	**1e**	$ClCH_2$	15	5	**2h** (45)	**3d** (45)
10	**1f**	$ClCH_2$	0	4	**2g** (42)	**3e** (43)

[a] Reaction conditions: **1** (1 mmol), RCOCl (4.7 mmol), $AlCl_3$ (4.5 mmol) in 10 mL of $ClCH_2CH_2Cl$.
[b] Isolated yield.
[c] The ratio for **2** and **3** was determined by ^1H NMR.



Scheme 3.



Scheme 4.

product, **2c**, exclusively. Surprisingly, reaction of another 1-acyl substrate **1d** with acetyl chloride worked but provided both 6- and 5-acylation products (entry 3), while a lower yield was observed in the case of chloroacetyl chloride as acylation agent (entry 4). The two substrates bearing a 1-tosyl group gave more dramatic results. Reaction of **1e** with acetyl chloride provided 6- and 5-substituted products **2e** and **3c** in a ratio of 3:1 at 0°C (entry 5). Increasing the reaction temperature afforded **2a** (entry 6), where the tosyl group was cleaved. A similar result was observed in the reaction of **1f** with acetyl chloride (entry 8), although it gave a single 6-acylation product at 0°C (entry 7). Furthermore, either **1e** or **1f** produced a mixture of 6- and 5-substituted products when chloroacetyl chloride was used as the acylation agent (entries 9 and 10). Taking these results together, we concluded that 6-acylation products could be regioselectively obtained via either reaction of 1-acyl tryptophan derivatives with chloroacetyl chloride or reaction of 1-tosyl tryptophan derivatives with acetyl chloride.

In order to check if any racemization occurred during the present reaction, the acylation product **3d** was hydrolyzed and then condensed with (*S*)-alanine methyl ester to afford **5**. Both HPLC analysis and a ^{1}H NMR study indicated that the purity of **5** was over 98%, which implied that no racemization occurred in the acylation reaction (Scheme 3).

Although it was reported that nitration of 3-oxoindoles gave 4- and 6-substituted indoles,[8] we found that acylation of **6** provided the 5-acylation product **7** as a single product (Scheme 4).

In conclusion, we have studied the acylation of several L-tryptophan derivatives and found suitable conditions for regioselective acylation at either the 6- or 5-positions. Our observations also illustrated that the regioselectivity of the acylation of L-tryptophan derivatives were highly dependent on the nature of the substrates and acylation agents.

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