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Ytterbium triflate catalyzed electrophilic substitution of indoles: the synthesis of unnatural tryptophan derivatives

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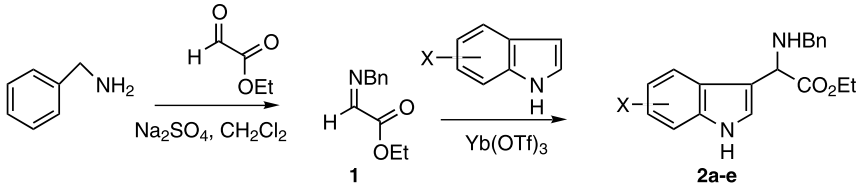
Abstract—Benzylamine was combined with ethyl glyoxylate to form the intermediate imine which in the presence of catalytic amount of $Yb(OTf)_3$ underwent electrophilic substitution on the 3-position of a variety of indoles to produce unnatural tryptophan derivatives. Penicillin-G-acylase mediated *N*-acylation produced optically active tryptophan derivatives.

Indole and indole derivatives have been a topic of research interest for over a century.[1] This, in part, is due to the fact that indole derivatives, such as tryptophan, are abundantly found in a variety of naturally found compounds that exhibit various physiological properties.[2] Tryptamine, serotonin, sumatriptan, and *N*,*N*-dimethylamines are but a few tryptophan derivatives that exhibit neurophysiological effects.[3,4] Ondansteron,[5] another tryptophan derived pharmaceutical, is a potent 5-HT_3 which is used clinically for the treatment of nausea associated with conventional chemotherapy. Clearly, facile synthesis into these types of aminoalkylindole compounds is of great significance.

While there are many available methods for the synthesis of tryptophan derivatives, one of the most efficient is the Mannich carbon–carbon bond reaction.[6] Other methods have employed the use of imines, under acidic conditions, for the synthesis of aminoalkylindoles.[7] Previously, our group demonstrated that lanthanide triflates are effective catalysts in promoting electrophilic aromatic substitution.[8] In order to further investigate the utility of this reaction we explored $Yb(OTf)_3$-catalyzed synthesis of amino-indole-3-yl acetic acids. Herein, we report the successful lanthanide catalyzed alkylation of a variety of indole derivatives as well as and enzymatic approach to obtain optically active products (Scheme 1).

The two-step tryptophan derivative synthesis was carried out in a one-pot procedure. Benzyl amine and ethyl glyoxylate were dissolved in CH_2Cl_2. Na_2SO_4 was utilized instead of 4 Å molecular sieves to absorb the evolution of water during the course of the reaction. Commercially available indole and indole derivatives were added to the in situ generated imine **1** followed by the addition of 5 mol% $Yb(OTf)_3$. The corresponding substituted indoles **2a**–**e** were obtained in yields ranging from 60 to 85% (Table 1).

Enzymatic resolution appeared to be a quick and potentially useful way of obtaining optically active indole derivatives. Extensive work has been done using enzymes in catalyzing several asymmetric transforma-



Scheme 1.

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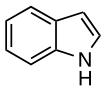
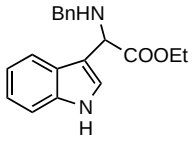
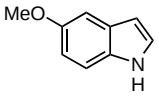
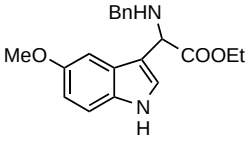
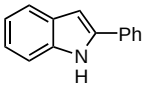
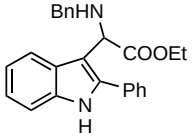
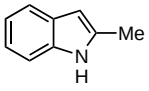
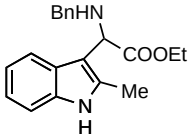
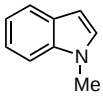
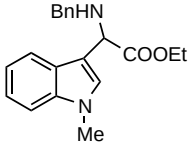
Table 1. $Yb(OTf)_3$-catalyzed substitution

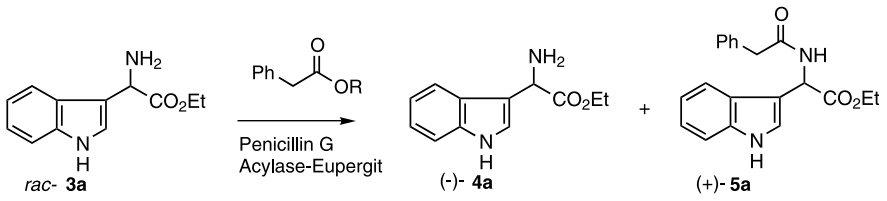
Entry	Indole derivative	Product	Yield%
1		 **2a**	82
2		 **2b**	70
3		 **2c**	68
4		 **2d**	85
5		 **2e**	58

tions.[9] One particular area of research interest has been the synthesis of β-amino acids. Numerous studies have been carried out using penicillin G acylase (PGA) (E.C. 3.5.1.11) as a resolving agent.[10] It is known that PGA has a high affinity to phenyl acetic acid derivatives. The enzyme exhibits moderate to excellent stereochemical discrimination of α-aminoalkylphosphonic acids, α-, β-, and γ-amino acids, sugars, amines, peptides, and ester of phenylacetic acid.[11] Most examples using PGA demonstrate the ability of the enzyme to selectively hydrolyze the phenyl acetyl moiety. However, Zmijewski and co-workers were one of the first to pioneer the use of PGA in selective acylation.[12] Since then there has been other literature precedence in which, depending on the conditions, the enzyme can selectively acylate.[10a,c,13]

In order to evaluate the possibility of using PGA in obtaining optically active derivatives a model study was carried out using product **2a**. However, compound **2a** required conversion to the free amine **3a** prior to the enzymatic resolution. This was accomplished by simple catalytic hydrogenation to remove the benzyl moiety.

We proceeded in using immobilized PGA on Eupergit® C[14] in catalyzing the acylation of the free amine (Scheme 2). Phenyl acetic acid and methylphenyl acetate were chosen as substrates for the *N*-acylation. Several reaction conditions were examined (Table 2) and we found that the most effective solvent system was Tol:H_2O in a 98:2 ratio. This coincides with pervious studies in which the rate of saponification of methyl phenylacetate by PGA, a competing reaction that reduces the rate of *N*-acylation, is significantly retarded when a non-polar solvent such as toluene is used instead of ethyl acetate. The reaction was monitored using TLC until approximately 50% conversion was achieved. In prolonged conditions and higher concentrations, the enzyme has been known to eventually acylate both isomers. Product **5a** was isolated and purified by column chromatography to give a crystalline product. Compound **5a** was then evaluated for optical activity using polarimetry. The standard optical rotation of the compound was found to be $[\alpha]_D^{25} = +92.9°$. Substrate **4a** was also isolated and evaluated for optical rotation as well. The standard optical rotation of compound **4a** was observed to be $[\alpha]_D^{25} = -88.0°$. Enantiomer excess of both product **5a** and substrate **4a** was determined by ^1H NMR using (+)-$Eu(hfc)_3$[15] or synthesizing a Mosher derivative.[16] From the initial results it appears that methyl phenylacetate is the most suitable substrate for the resolution of the racemate **3a** leading to substrate (−)-**4a** and product (+)-**5a** in both fair yields and high enantiomeric excess (entry 4). Phenyl acetic acid also demonstrated to be a useful substrate for the enzyme-catalyzed reaction (entry 1); however, the yield and enantiopurity was somewhat diminished for substrate **4a**.

A typical procedure for the electrophilic addition is as follows: A suspension of 1.0 g of benzyl amine, 1 equiv. of ethyl glyoxylate (50% in tol) and 5.0 g of anhydrous Na_2SO_4 was stirred in 20 mL of CH_2Cl_2. After approx-



Scheme 2.

Table 2. Enzymatic resolution

Entry	R	Conditions	5a		4a	
			% Yield[a]	% ee[b]	% Yield	% ee[c]
1	H	Tol:H_2O (98:2) 12 h, rt	43	98 (+)	40	69 (−)
2	H	H_2O:EtOH (50:50) 72 h, rt	0	–	>95	–
3	H	EtOAc:H_2O (90:10) 36 h, rt	10	95 (+)	70	38 (−)
4	Me	Tol:H_2O (98:2) 36 h, rt	42	98 (+)	39	83 (−)

[a] Isolated product after column chromatography.
[b] Determined by ^{1}H NMR using (+)-Eu(hfc)$_3$ as a chiral shift reagent.
[c] Determined by ^{1}H NMR by Mosher techniques.[16]

imately 1 h, or until the disappearance of ethyl glyoxylate as monitored by TLC (1:1 EtOAc:hex), 1.1 equiv. of indole was introduced followed by 5 mol% Yb(OTf)$_3$. Once the reaction was complete, approximately 18 h, the mixture was filtered and poured over ice cold saturated $NaHCO_3$ solution. The organic layer was diluted with methylene chloride and washed (2×10 mL) with water, then brine (2×10 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography using ethyl acetate and hexane for elution (1:3 EtOAc:hex).[17]

A typical procedure for the use of the enzyme and isolation of the product is as follows: 50 mg of compound **3a** was dissolved in 3 mL of a Tol:H_2O (98:2) solution. Then, 50 mg of immobilized PGA (106 U/g) was introduced. The suspension was stirred until approximately 50% conversion was observed, as monitored by TLC (2:1 hex:EtOAc). The solution was then diluted with toluene (2 mL) and filtered. The filtrate was then extracted with 1N HCl solutions (3×5 mL). The aqueous layer contained the hydrochloric salt of substrate **4a**. The organic layer was then neutralized using satd $NaHCO_3$ (2×5 mL). Next, the organic layer was washed with brine (1×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue purified by column (2:1 hex:EtOAc) and acylated product **5a** was isolated. The aqueous layer containing substrate **4a** was made basic (pH 8) using 1N NaOH and extracted with $CHCl_3$ (3×5 mL). The organic layer was then washed with satd $NaHCO_3$ (2×5 mL), brine (2×5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The compound was then evaluated without further purification. ^{1}H NMR results indicated a relatively pure product.[18]

In conclusion, we have successfully synthesized a series of indole derivatives using catalytic amounts of Yb(OTf)$_3$ to promote the electrophilic addition. In addition, we have demonstrated the use of PGA for resolving the resulting aminoalkylindole compound into optically active compounds. This work presents a simple and efficient means of obtaining a variety of unnatural tryptophan derivatives.

Acknowledgements

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17. **2a** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.73 (d, $J=8.5$ Hz, 1H), 7.37–7.31 (m, 5H), 7.29–7.25 (m, 1H), 7.21–7.18 (m, 1H), 4.72 (s, 1H), 4.27–4.21 (m, 1H), 4.17–4.10 (m, 1H), 3.84 (q, $J=21.5$ Hz, 2H), 2.40 (broad s, 1H), 1.22 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 139.8, 136.6, 128.7, 128.6, 127.3, 126.3, 123.2, 122.5, 120.1, 119.7, 113.3, 111.5, 61.3, 57.7, 51.8, 14.4; MS $(M+H)^+$ m/z 309.12. **2b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.38–7.25 (m, 5H), 7.19–7.07 (m, 3H), 6.84 (dd, $J=8.8$, 2.4 Hz, 1H), 4.67 (s, 1H), 4.28–4.21 (m, 1H), 4.18–4.11 (m, 1H), 3.89–3.79 (m, 5H), 2.24 (broad s, 1H), 1.22 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 154.3, 139.9, 131.6, 128.7, 128.69, 127.4, 126.7, 123.8, 113.0, 112.9, 112.3, 101.0, 61.3, 57.5, 56.0, 51.8, 14.5; MS $(M)^+$ m/z 338.17. **2c** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.52 (d, $J=7.5$ Hz, 1H), 7.61–7.59 (m, 2H), 7.42–7.31 (m, 3H), 7.30–7.14 (m, 8H), 4.88 (s, 1H), 4.27–4.21 (m, 1H), 4.18–4.09 (m, 1H), 3.68 (q, $J=25.5$ Hz, 2H), 2.59 (broad s, 1H), 1.21 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 139.9, 137.8, 136.3, 132.6, 129.1, 129.0, 128.7, 128.5, 127.2, 127.1, 122.6, 120.5, 120.4, 11.4, 109.3, 61.4, 57.1, 51.3, 14.4; MS $(M)^+$ m/z 384.18. **2d** ^{1}H MNR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.75 (d, $J=8.8$ Hz, 1H), 7.34–7.25 (m, 5H), 7.20–7.11 (m, 4H), 4.70 (s, 1H), 4.25–4.17 (m, 1H), 4.13–4.05 (m, 1H), 3.81 (q, $J=22.0$ Hz, 2H), 2.55 (broad s, 1H), 2.25 (s, 3H), 1.18 (t, $J=7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 140.0, 135.5, 134.0, 128.7, 127.3, 121.4, 121.4, 119.9, 119.0, 110.8, 108.0, 61.3, 56.9, 51.3, 14.4, 12.0; MS $(M+H)^+$ m/z 323.08. **2e** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, $J=7.5$ Hz, 1H), 7.46–7.15 (m, 9H), 4.81 (s, 1H), 4.35–4.29 (m, 1H), 4.24–4.18 (m, 1H), 3.94 (q, $J=24.0$ Hz, 2H), 3.76 (s, 3H), 2.52 (broad s, 1H), 1.31 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 140.2, 137.5, 128.7, 128.69, 127.8, 127.4, 126.9, 122.2, 119.9, 119.7, 111.9, 109.7, 61.3, 57.8, 51.9, 33.0, 14.5; MS $(M)^+$ m/z 322.17. **2a** was dissolved in dry methanol followed by the addition of a catalytic amount of $Pd(OH)_2$–C. The reaction vessel was then charged with 30 PSI of hydrogen gas and agitated for 12 h followed by standard work-up procedures to afford compound **3a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.73 (d, $J=8.4$ Hz, 1H), 7.31 (d, $J=8.0$ Hz, 1H), 7.25–7.10 (m, 3H), 4.91 (s, 1H), 4.26–4.18 (m, 1H), 4.15–4.07 (m, 1H), 2.12 (broad s, 2H), 1.20 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 136.7, 125.6, 122.6, 122.5, 120.0, 119.4, 115.3, 111.6, 61.5, 52.1, 14.4; MS $(M)^+$ m/z 218.10.
18. **4a** $[\alpha]_D^{25}=-88.0°$ (c 0.434 g/100 mL, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.74 (d, $J=8.0$ Hz, 1H), 7.34 (d, $J=8.5$ Hz, 1H), 7.21 (t, $J=8.5$ Hz, 1H), 7.16–7.12 (m, 2H), 4.91 (s, 1H), 4.26–4.19 (m, 1H), 4.15–4.09 (m, 1H), 2.03 (broad s, 2H), 1.21 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 136.6, 125.6, 122.7, 122.5, 120.1, 119.4, 115.2, 111.7, 61.6, 52.1, 14.3; MS $(M)^+$ m/z 218.11. **5a** $[\alpha]_D^{25}=+92.9°$ (c 0.165 g/100 mL, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.53 (d, $J=8.0$ Hz, 1H), 7.32–7.24 (m, 6H), 7.21 (t, $J=8.5$ Hz, 1H), 7.17–7.04 (m, 2H), 6.46 (d, $J=6.5$ Hz, 1H), 5.80 (d, $J=7.0$ Hz, 1H) 4.22–4.16 (m, 1H), 4.12–4.06 (m, 1H), 3.59 (q, $J=20.5$ Hz, 2H), 1.16 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 170.9, 136.5, 134.7, 129.6, 129.1, 127.5, 125.4, 123.9, 122.7, 120.3, 119.1, 111.8, 110.7, 61.9, 50.5, 43.6, 14.2; MS $(M)^+$ m/z 336.14.