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Synthesis of Substituted-(*l*)-Tryptophanols from an Enantiomerically Pure Aziridine-2-methanol

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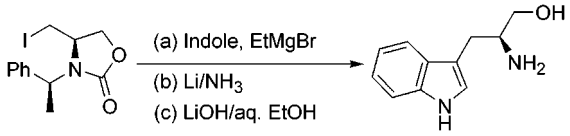
ABSTRACT



Enantiomerically pure (*l*)-tryptophanol (5) was synthesized from 4(*R*)-iodomethyl-2-oxazolidinone (2) and indolylmagnesium bromide in three steps (52% overall yield). Using this procedure, we also prepared various tryptophanols with substituent(s) on the indole ring. Furthermore, optically active 4(*R*)-iodomethyl-2-oxazolidinone was readily prepared from an enantiomerically pure aziridine-2(*S*)-methanol in high yield.

(*l*)-Tryptophan has received much attention because it activates the *trp* RNA-binding attention protein (TRAP)[1] of *Bacillius subtilis*[2] and also is an essential amino acid. Furthermore, the 5-methyltryptophan inhibits the growth of *Bacterium coli*[3] and enantiomerically pure tryptophan can be used as a chiral building block in the asymmetric synthesis of biologically active compounds.[4] These results have prompted many organic chemists to develop efficient enantioselective synthetic methods.[5] The synthesis of enantiomerically pure tryptophan has been accomplished by resolution,[6] Shöllkopf chiral auxiliary,[7] iminoglycinate auxiliary,[8] and asymmetric reduction.[9] The need for various indole substituted α-amino acids prompted us to investigate a more general and efficient preparative method for enantiomerically pure tryptophanols. We report herein an efficient synthesis of tryptophanol and its analogues by coupling enantiomerically pure 4(*R*)-iodomethyl-2-oxazolidinone (**2**), which was prepared from a chiral aziridine in one step, with indolylmagnesium bromide.[10]

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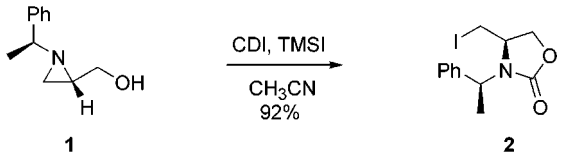
We recently reported the preparation of chiral aziridine-2-methanol (**1**) from readily available starting materials in two steps.[11] The enantiopure 4(*R*)-iodomethyl-2-oxazolidinone (**2**) and its analogues are useful chiral building blocks for asymmetric organic synthesis.[12] The iodomethyl group in the oxazolidinone can be converted to various functional groups such as alkyl,[13] alkene,[14] methoxy,[15] acetoxy,[16] lactam,[17] and silyl[18] groups. 4(*R*)-Iodomethyl-2-oxazolidinone (**2**) was prepared from the aziridine-2(*S*)-methanol (**1**) through regiospecific C(3)-*N* bond cleavage by iodotrimethylsilane and then intramolecular cyclization with carbonyldiimidazole (Scheme 1). Ring opening and intramolecular

Scheme 1



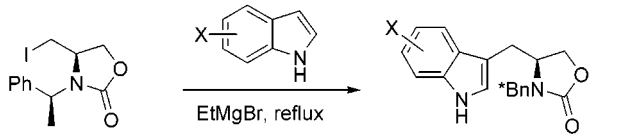
1 **2**

cyclization proceed in one pot to provide a high yield of the oxazolidinone (**2**). Although 4(*S*)- and 4(*R*)-iodomethyl-2-oxazolidinone systems can be prepared from (*l*)- and (*d*)-serines, those conversions require a multistep process. However, using aziridine-2(*S*)-methanol (**1**) we can prepare the target oxazolidinone system in one step with high chemical yield.

Indolylmagnesium bromide is known to react with alkylating reagents to give C(3)-alkylated indoles.[19] We found that the reaction of 2 equiv of indolylmagnesium bromide with 4(*R*)-iodomethyl-2-oxazolidinone (**2**) in refluxing toluene afforded protected tryptophanol (**3**) in a reproducible yield of 62% based on **2**. When 1 equiv of Grignard reagent was used, the protected tryptophanol (**3**) was formed in 17% yield. Unfortunately, protected tryptophanol (**3**) was not detected when the reaction was heated to reflux in THF or DMF. Some clear trends are evident from the results described in Table 1. The result indicates that the alkylating process is more effective in refluxing toluene (62%) than benzene (48%), chlorobenzene (36%), and xylene (37%) (entries b−e).

The phenylethyl protecting group on the nitrogen was removed under Birch conditions[20] in the presence of lithium

Table 1. Grignard Reaction of the Corresponding Substituted Indole



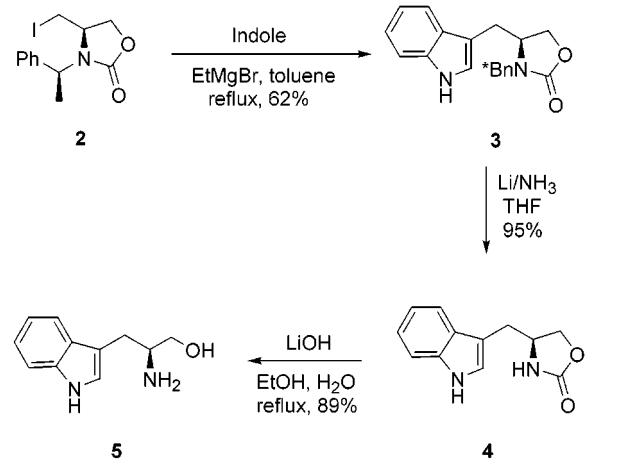
2 **3**

entry	X	solvent	time (h)	yield (%)[a]
a	H	THF	8	
b	H	benzene	12	48
c	H	toluene	4	62
d	H	chlorobenzene	2	36
e	H	xylene	2	37
f	2-methyl	toluene	2	58
g	5-methyl	toluene	4	67
h	6-methyl	toluene	4	59
i	7-methyl	toluene	2	51
j	5-methoxy	toluene	4	59
k	5-fluoro	toluene	6	38
l	5-chloro	toluene	6	40
m	5-bromo	toluene	6	41
n	2,5-dimethyl	toluene	4	64
o	5,6-dimethoxy	toluene	4	36
p	2-methyl-5-methoxy	toluene	3	70

[a] Isolated yield.

and liquid ammonia to provide the 4(*S*)-indolylmethyl-2-oxazolidinone (**4**)[21] almost quantitatively. The 4(*S*)-indolylmethyl-2-oxazolidinone (**4**) was hydrolyzed[22] in the presence of LiOH to give the corresponding (*l*)-tryptophanol (**5**) in 89% yield (Scheme 2). We compared all the analysis data

Scheme 2



2 **3** **5** **4**

including ^{1}H and ^{13}C NMR, optical rotation, and high-resolution mass data of the obtained (*l*)-tryptophanol (**5**) with those of the authentic sample to find good agreement between two samples. When there is a halogen substituent in the indole ring, Birch reduction is not applicable. Since the

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phenylethyl nitrogen protecting group can be removed by anisole and methansulfonic acid,[23] we tried to remove the benzyl group from halogen-substituted compounds **3l** and **3m**. However, we observed the decomposition of the indole ring under the reaction condition. Therefore, with halogen-substituted indole we removed the benzyl group from **2** with anisole and methansulfonic acid before the coupling reaction. The coupling between the Grignard reagent from 5-bromoindole and 4(*R*)-iodomethyloxazolidin-2-one in refluxing toluene provided 33% of the product, and we are currently investigating a better coupling condition for halogen-substituted indoles.[24]

Using this procedure, we also prepared various tryptophanol analogues with substituted indoles under the same reaction condition in refluxing toluene, and the results are summarized in Table 1. The yield of the protected tryptophanols seems to decrease with indoles containing electronegative substituent (entries k−m). The highest yield in the coupling reaction was obtained with 2-methyl-5-methoxyindole to give a 70% yield (entry p).

To summarize the above results, we developed an efficient method for the preparation of enantiomerically pure (*l*)-tryptophanol and its analogues using iodomethyloxazolidinone and indolylmagnesium bromide. Using the same methodology the (*d*)-tryptophanol analogues are also available starting from the aziridine-2(*R*)-methanol.

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Supporting Information Available: Full experimental procedures for the synthesis and characterization data for the listed compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) **Preparation of 4(*R*)-iodomethyloxazolidin-2-one from 2.** To a solution of 4(*R*)-(iodomethyl)-3-[(1*S*)-phenylethyl]oxazolidin-2-one (304 mg, 0.91 mmol) in 4.5 mL of toluene were added anisole (250 μL, 2.29 mmol) and methansulfonic acid (298 μL, 4.59 mmol). The reaction mixture was warmed for 1 h at 50 °C and then cooled to room temperature. The mixture was quenched with 1.0 mL of saturated $NaHCO_3$ and the aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/*n*-hexane = 1/1) provided 195 mg (95%) of the debenzylation product as white crystals. R_f = 0.3 (EtOAc/Hex = 1/1). mp 71−72 °C. $[\alpha]^{25}_D$ +32.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.63 (s, 1H), 4.51 (dt, J = 3.3, 8.3 Hz, 1H), 4.17−4.04 (m, 2H), 3.30−3.19 (m, 2H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.4, 70.3, 52.8, 8.7. HRMS(EI) calcd for $C_4H_6NO_2I$: 226.9443, found 226.9448. **Preparation of 4(*S*)-(5-bromo-1*H*-indol-3-ylmethyl)-oxazolidin-2-one.** To a solution of 4(*R*)-(iodomethyl)oxazolidin-2-one (0.30 mmol) and indole (0.61 mmol) in 1.5 mL of toluene was added EtMgBr (1.0 M solution in THF, 0.6 mmol). The reaction mixture was refluxed for 6 h and cooled to room temperature. The mixture was quenched with 0.5 mL of 1 N HCl. The aqueous layer was extracted with EtOAc (5 mL × 3), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/*n*-hexane) provided 33% of the coupling product as crystals. R_f = 0.2 (EtOAc/Hex = 3/1). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.27(s, 1H), 7.73 (d, J = 11.4 Hz, 1H), 7.36−7.20 (m, 2H), 6.63 (d, J = 8.4 Hz, 1H), 5.68 (s, 1H), 4.20 (m, 1H), 3.84 (m, 1H), 2.95−2.86 (m, 2H).