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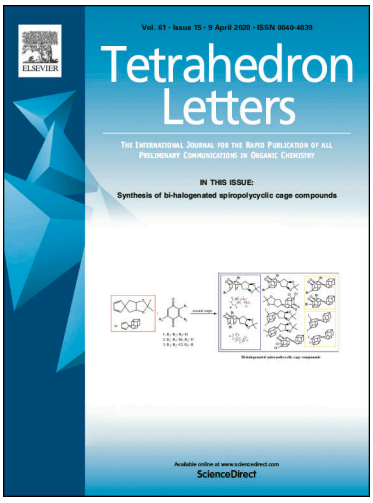

General Synthesis of Unnatural 4-, 5-, 6-, and 7-Bromo-D-Tryptophans by Means of a Regioselective Indole Alkylation

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General Synthesis of Unnatural 4-, 5-, 6-, and 7-Bromo-D-Tryptophans by Means of a Regioselective Indole Alkylation

Francesca Bartoccini, Fabiola Fanini, Michele Retini and Giovanni Piersanti*

Department of Biomolecular Sciences, University of Urbino Carlo Bo, Piazza Rinascimento 6, 61029 Urbino, PU, Italy
E-mail: giovanni.piersanti@uniurb.it

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ABSTRACT

A general two-step approach to enantiopure bromotryptophans from unprotected bromoindoles has been developed. Indole nucleophiles prepared with MeMgCl in the presence of CuCl reacted with cyclic sulfamidates derived from enantiopure D-serine to form 4-, 5-, 6-, or 7-bromo-D-tryptophan and some other halogenated tryptophans in moderate yields but with complete regioselectivity. The bromotryptophan derivatives were deprotected using mild conditions.

Natural nonproteinogenic bromotryptophans and unnatural bromotryptophan derivatives are essential starting materials for the biosynthesis and synthesis of both indole alkaloid natural products and pharmaceutically interesting products including peptide analogues (Figure 1).[1] The bromide functionality in natural products and peptides not only has been demonstrated to improve properties such as metabolic stability and bioavailability compared to the desbromo counterparts,[2] but it could offer a unique, site-selective synthetic handle that can be utilized for a wide range of applications, for instance, bioorthogonal reactions, fluorescence labeling, late-stage modification, and bicyclic tryptophan-stapled peptides.[3] By replacing tryptophan in proteins with bromotryptophan, it has been possible to probe π–cation interactions, which are known to be of high importance in biological systems and are of increasing interest in medicinal chemistry.[4] Recently, it also has been reported that serum 6-bromotryptophan is a consistent and novel risk factor for chronic kidney disease progression.[5]

Thus, important inroads into selective synthetic strategies yielding enantiopure bromotryptophan have been made through chemo- and biocatalysis. Besides the standard use of chiral auxiliaries,[6] chiral pools,[7] and the largely employed L-acylase-mediated kinetic resolution approach,[8] there are three other catalytic asymmetric approaches to bromotryptophan worth mentioning: (a) the synthesis of an appropriate dehydrotryptophan precursor followed by Rh-catalyzed asymmetric hydrogenation;[9] (b) bromination of L-tryptophan by tryptophan halogenases or a fermentative process;[10] and (c) the use of tryptophan synthase to catalyze the formation of a C–C bond between L-serine and a variety of bromoindoles.[11] The synthetic routes to selective and enantiomerically pure bromotryptophans typically require multiple steps, the use of exclusive methodology/reagents with a lack of generality, and a specific procedure for each regioisomer and/or enantiomer. In view of these issues, devising a straightforward procedure for the chemical synthesis of enantiomerically pure unprotected bromotryptophans is highly desirable.

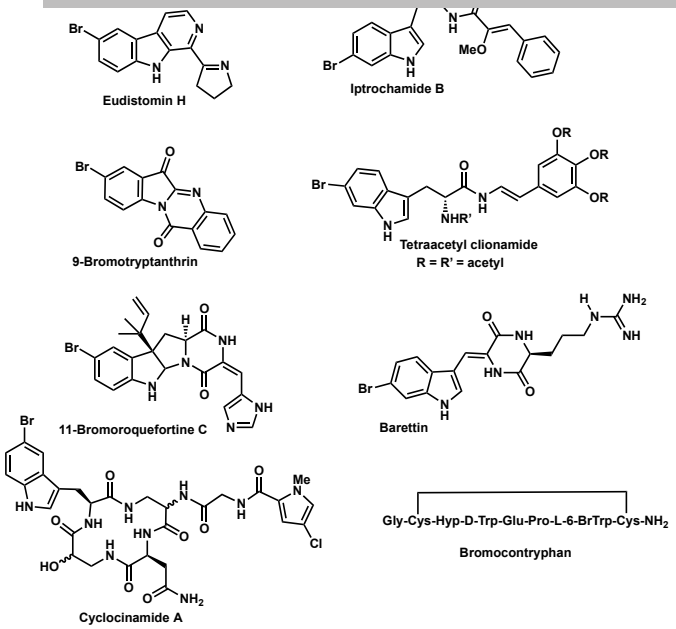
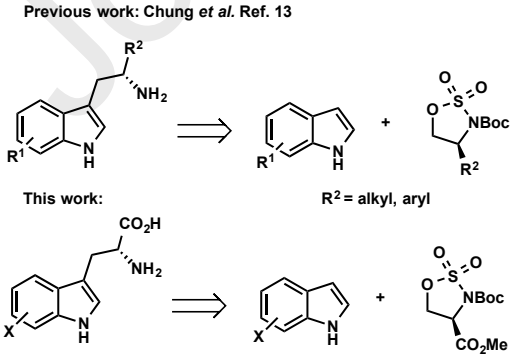


Figure 1. Representative natural products containing bromotryptophan or derived from bromotryptophan.

As part of our research program aimed at establishing new methods for the enantioselective synthesis of indole alkaloid natural products and their associated analogues,[12] we are interested in developing convergent and efficient syntheses of enantiopure bromotryptophans from simple unprotected indole starting materials and a suitable electrophile. Inspired by the work of Chung and collaborators[13] on the synthesis of chiral tryptamines using cyclic sulfamidates derived from chiral amino alcohols, we sought to develop a more streamlined process for the direct conversion of all commercially available regioisomer bromoindoles to the corresponding enantiopure bromotryptophans (Scheme 1). By taking advantage of the more nucleophilic/basic C3 position of these C3-unsubstituted indoles (i.e., **3a**) and the relatively good electrophilicity of the chiral serine-derived cyclic sulfamidate electrophile (i.e., **2**), we were able to fashion a regioselective two-step synthesis of enantiopure 4-, 5-, 6-, and 7-bromotryptophans (Scheme 1). The premise behind this alkylation/deprotection sequence was our recognition of cyclic sulfamidates derived from serine (i.e., **2**) as a rapidly accessible two-carbon amino acid-containing electrophile and its high propensity to readily undergo a regioselective ring-opening reaction with an adequate nucleophile.[14]

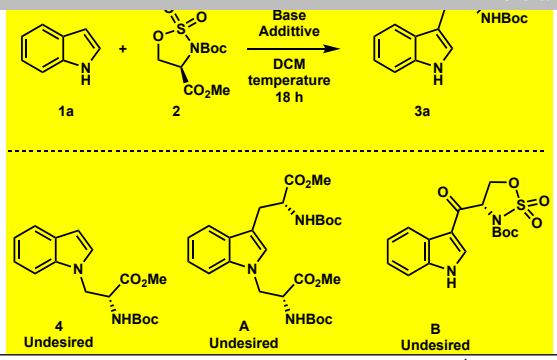


Scheme 1. Regioselective indole alkylation with a cyclic sulfamidate

clic *N*-Boc-sulfamidate (**2**) obtained from *N*-Boc-D-serine methyl ester[15] as the reaction partner for our optimization studies. We decided to explore the preparation of the D-enantiomer of bromotryptophan due to the increasing use of this enantiomer in the production of pharmaceuticals and unnatural peptide-based drugs[16] and limited methods (mainly enzymatic kinetic resolution) for their production. Obviously, the same chemistry can be applied to the natural L-serine cyclic *N*-Boc-sulfamidate version.

As illustrated in Table 1, similar to the results obtained by Chung,[13] we observed a low yield and regioselectivity when only the Grignard reagent was used as the base (Table 1, entry 1). Next, we determined that it was absolutely necessary to use a stoichiometric amount of copper salt in order to have nucleophilicity through the C(3) position of the indolyl core, to avoid the formation of N1-alkylated **4**, as well as to obtain reproducibility and scalability of this transformation (Table 1, entries 2 and 3). The best combination was 1.3 equiv of MeMgCl and 1.3 equiv of CuCl at -20 °C with a slight excess of indole (1.5 mmol). Different Grignard reagents with copper salt gave a lower yield and/or regioselectivity (Table 1, entries 6 and 7). We reasoned that the presence of the ester group in cyclic sulfamidate **2** in comparison with the cyclic sulfamidate reported by Chung (Scheme 1) would increase the lability of the C-O bond involved in the reaction. At -40 °C, a significantly decreased yield was observed, which was probably due to the reduced reactivity of the cuprate (Table 1, entry 5). Based on these preliminary optimization reactions, we found that (1) the ring-opening reactions proceeded with complete conversion of **2**, and competitive β-elimination reactions (dehydroalanine byproduct) were never observed; (2) a prolonged reaction at -20 °C was necessary to achieve high substrate conversions at reasonable rates and acceptable yields; (3) the presence of the *N*-Boc group at the sulfamidate was critical for the ring-opening reaction to proceed; and (4) anhydrous solvent (dichloromethane) and triturated Grignard reagent needed to be utilized to achieve a good yield. However, minimal formation of the C3,N1-dialkylated byproduct (**A**) along with traces of a ketone byproduct (**B**) arising from attack of the C-3 position onto the methyl ester side chain of sulfamidate, also reported by others[14l] were observed in the crude reaction mixture (according to LC-MS analysis); these findings can partially justify the suboptimal yields. Moreover, the ^{1}H NMR of the crude reaction mixture, after work-up procedure, showed the absence of any detectable sulfamidate **2** or derived from, and excellent conversion of indole into the alkylated product. The excess of indole **1a** employed was totally recovered. Although not completed clarified yet, it appears that, the yield of the isolated **3a** was restrained as a result of its partial sensitivity to the slightly acidic treatment required for the hydrolysis of the sulfamate group during the purification step and/or minimal retaining of the sulfamate group, which release a water-soluble side product. Indeed, the weight of crude mixture to be purified was marginally lower than theoretical weight.

Table 1. Optimization of reaction conditions[a]

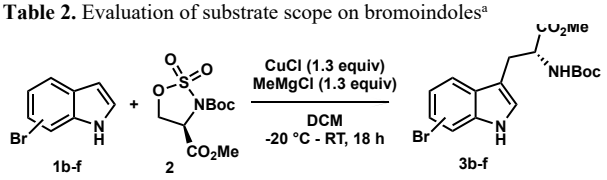


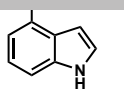
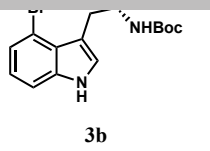
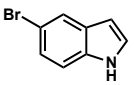
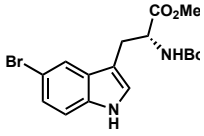
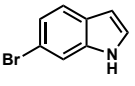
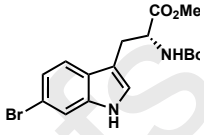
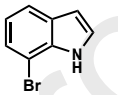
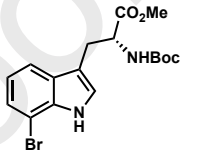
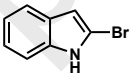
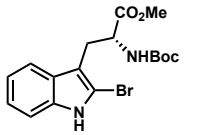
Entry	Base	Additive	Temp.	C3/N1[b]	Yield **3a**[c]
1	MeMgCl	-	-20 °C	20/80	9%[d]
2[e]	MeMgCl	CuCl	-20 °C	21/79	5%[f]
3	MeMgCl	CuCl	-20 °C	100/0	59%
4[g]	MeMgCl	CuCl	-20 °C	100/0	34%
5	MeMgCl	CuCl	0 °C	100/0	27%
6	MeMgCl	CuCl	-40 °C	100/0	38%
7	MeMgBr	CuCl	-20 °C	75/25	8%
8	PhMgCl	CuCl	-20 °C	100/0	29%
9[h]	MeMgCl	CuCl	-20 °C	–	NR

[a]Base (1.3 equiv) was added to a mixture of **1a** (1.5 equiv) and additive (1.3 equiv) in DCM (0.3 M), followed by **2** (1 equiv) in DCM (0.85 M). The cuprate was prepared at 0 °C, and a solution of **2** was added at 0 °C or -20 °C. [b]Ratio of C3/N1 alkylation was determined by HPLC analysis. [c] Isolated yield. [d] Undesired compound **4** was also obtained in 33% yield and traces of undesired compounds **A** and **B** were observed by HPLC analysis. [e]A catalytic amount of CuCl (0.2 equiv) was used. [f]Traces of undesired compounds A and B were observed by HPLC analysis. [g]The cuprate was prepared at 0 °C for half an hour instead of one hour. [h]NH sulfamidate was used instead of **2**.

With optimized conditions in hand, we investigated the desired bromoindoles. The reaction of differently substituted bromoindoles **1b-e** with *N*-Boc-D-sulfamidate **2** provided the desired products **3b–e** in modest yields but with complete chemo, regio-, and enantioselectivities (Table 2). However, in the reaction with the bromoindole bearing a bromide group at the C-2 position, the desired product **3f** was observed, but its purification proved to be very difficult, probably due to its higher lability.[17] Although the L-forms have already been reported and used for the total synthesis of a structurally and biologically fascinating class of alkaloid natural products, the syntheses of compounds (*R*)-**3b** and (*R*)-**3e** have not yet been described. The optical purity of these compounds was confirmed by comparing the specific rotation values reported in the literature for the enantiomers. (For example, (*R*)-**3e** showed $[\alpha]_D^{20}$ = -42 (c = 1.01, $CHCl_3$) versus the *S*-form: Lit.[8c] $[\alpha]_D^{20}$ = +37 (c = 1.0, $CHCl_3$)). Reactions were typically carried out using 200 – 300 mg of haloindole (1 mmol) but could be readily scaled up to enable conversions of around 3 g of bromoindole (see SI).

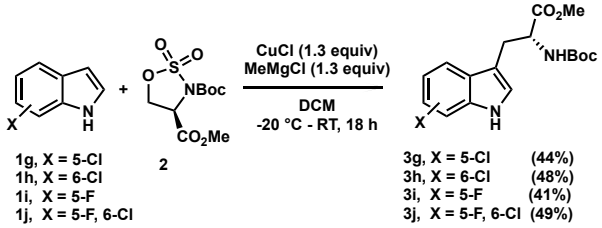
Table 2. Evaluation of substrate scope on bromoindoles[a]



Entry	Substrate	Product	Yield[b]
1			55 52[c]
	1b	**3b**	
2			57
	1c	**3c**	
3			48
	1d	**3d**	
4			46
	1e	**3e**	
5			-
	1f	**3f**	

[a]MeMgCl (1.3 equiv) was added to a mixture of **1b–f** (1.5 equiv) and CuCl (1.3 equiv) in DCM (0.3 M), followed by **2** (1 equiv) in DCM (0.85 M). The cuprate was prepared at 0 °C, and a solution of **2** was added at -20 °C. [b]Isolated yield.

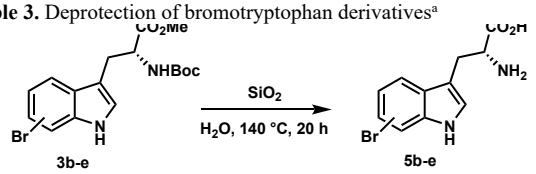
Fluorine- and chlorine-containing tryptophans are becoming increasingly prominent in new drugs.[18] The reaction described herein is compatible with both chlorine and fluorine on the indole substituents, and compounds **3g–j** were obtained in modest yields but comparable with those of the bromide-substituted indoles (Scheme 2). Of note, 6-chloro-5-fluoro-D-tryptophan derivative **3j** is the key intermediate for the synthesis of KAE609 (cipargamin), which was discovered recently by Novartis as a novel and potent antimalarial agent and is now in phase 2 clinical trials with promising prospects. The synthesis previously reported consisted of five steps (including enzymatic kinetic resolution with L-aminoacylase) and an overall yield of 5.5% starting from the same 6-chloro-5-fluoroindole **(1j)**.[19] The electron-withdrawing substituents on the indole facilitate the reaction. For example, when an electron-donating group, such as methoxy, was introduced to the 5-position of indole, the reaction was much less regioselective, and the coupling product was obtained in a lower yield with some unidentified polar byproducts (data not shown).

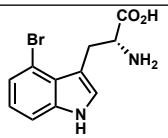
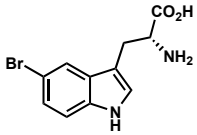
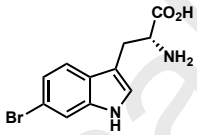
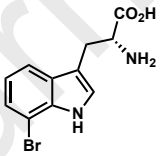


Scheme 2. Evaluation of substrate scope on chloro- and fluoroindoles

To complete the preparations of bromotryptophans **5b–e**, only the removal of the Boc and methyl groups remained. Numerous methods are available for removal of the Boc group with preservation of the methyl ester functionality and vice versa. However, there are very few simple and efficient methods for the one-pot double-deprotection reaction with a single reagent resulting in the formation of an optically pure free amino acid in quantitative yield. Treatment with a large excess of HBr or BBr_3 at 23 °C resulted in cleavage of both the Boc group and the methyl ester as well as multiple other side products. On the other hand, 4% aq. KOH in dioxane proved to be a mild and highly effective method for the selective hydrolysis of the methyl ester followed by Boc cleavage by heating with 50% AcOH at 80 °C for 3 h to give *S*-**5b** in 87% overall yield from *S*-**3b**.

Table 3. Deprotection of bromotryptophan derivatives[a]



Entry	Substrate	Product	Yield[b]
1	**3b**	 **5b**	92%
2	**3c**	 **5c**	95%
3	**3d**	 **5d**	94%
4	**3e**	 **5e**	96%

[a] **3b–e** (0.1 mmol), SiO_2 (200 mg, 60 Å), H_2O (3 mL), 140 °C, 20 h.

However, partial racemization was unavoidable and high optical purity of the D-amino acid could not be attained (92% ee).[9] Nevertheless, treatment of compound **3b** with SiO_2 in H_2O[20] at 140 °C for 20 h removed the Boc group and hydrolyzed the methyl ester to provide the target compound **5b** in almost quantitative yield (Table 3, entry 1) without any racemization. The same reaction conditions were applied to enantiopure Trp **3c–e**, providing the same reproducibility and results.

To summarize, 4-, 5-, 6-, and 7-bromo-D-tryptophans and their *N*-Boc methyl ester derivatives were conveniently synthesized enantioselectively in two steps and one step, respectively, by chemo- and regioselective indole alkylation using unprotected D-serine. A few examples of other halotryptophans were also obtained. These examples demonstrate that serine-derived cyclic sulfamidates are versatile chiral building blocks with complementary reactivity to the related beta-alanine cation equivalents, but are not regioselective, such as aziridine carboxylate.[21] Moreover, the very common β-elimination side reaction on the serine sulfamidate, occurring even under slightly basic conditions, was completely prevented. Considering the crucial importance of unnatural functionalized tryptophans and the simplicity of the reaction conditions, we believe that this method will find broader applications in the asymmetric synthesis of related indole alkaloids as well as unnatural peptide-based drugs and chemical probes. Such efforts are ongoing in our laboratory and will be reported in due course.

Declaration of Competing Interest

The authors declare no competing financial interest.

Supplementary Material

Experimental procedures, compound characterizations, and copies of ^1H NMR and ^{13}C NMR spectra can be found in Supplementary Information.

References and notes

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Graphical Abstract

Highlights

General Synthesis of Unnatural 4-, 5-, 6-, and 7-Bromo-D-Tryptophans by Means of a Regioselective Indole Alkylation

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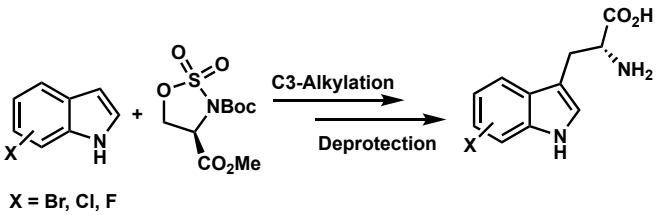
Francesca Bartoccini, Fabiola Fanini, Michele Retini and Giovanni Piersanti*



X = Br, Cl, F

G
bromotryptophans.

Regioselective C3-alkylation of (NH)-indoles.

Serine-derived cyclic sulfamidate as a suitable source for the amino acid fragment.

One-pot double-deprotection reaction with a single reagent.