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PAPER

Synthesis of amino-substituted indoles using the Bartoli reaction†

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We report herein the concise preparation of a range of functionalised aminoindoles *via* a new application of the Bartoli reaction. Scope and limitations of the methodology have been extensively studied to reveal the importance of protecting groups and substitution patterns. The use of amino substituted nitroanilines for the Bartoli reaction is to our knowledge unprecedented. Our work thus represents a novel entry into substituted aminoindoles which are relevant building blocks for both the fine chemical and pharmaceutical industry.

Introduction

The indole ring system is found in many pharmaceuticals and natural products motifs,[1] and numerous approaches have been published for the formation of this heteroaromatic core.[2]

The Bartoli indole synthesis involves the reaction of a nitroarene with a vinyl Grignard reagent, providing quick access to substituted indoles (Scheme 1).[3]

This reaction is generally known to give moderate yields that are rarely higher than 60% and can be as low as 10–15% in more complex cases. Moreover, these transformations can be very substrate dependent and often no clear reactivity trends can be observed.[3,4] That said, the conciseness of this reaction often outweighs the moderate yields as demonstrated by the recent publications on the expeditious synthesis of azaindoles and on the synthesis of indoles on solid support.[4,5]

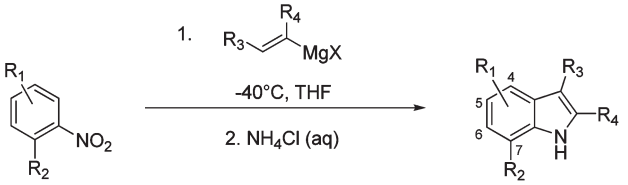
Despite these recent advances in widening the scope of the Bartoli reaction, some indole substitutions have not yet been tackled. In the context of a medicinal chemistry program, we wished to quickly access an aminoindole scaffold with an additional halogen functionality for further synthetic manipulations. We were surprised to find that a concise approach to such aminoindoles had not been published. Current methods involve late stage modification of the indole ring, such as reduction of a nitro group,[6] or metal-catalysed coupling reactions.[7] These approaches can be lengthy, can have uncontrollable regioselectivity,[8] and pose a limit to the number and type of functional groups present on the arene ring.[7]

We hypothesised that the Bartoli reaction of suitably *N*-protected bromo-nitroanilines would give easy access to the desired substituted aminoindoles. The aminoindoles would also be amenable for easy derivatisation at positions N-1 through C-3, for example using alkylations at N-1, and exploiting the natural reactivity of the indole ring to install groups at C-3.[9] To the best of our knowledge, direct synthesis of aminoindoles using this method has not been reported.

Results and discussion

We initially attempted the reaction of Boc-protected 4-bromo-3-nitroaniline **1** under commonly applied conditions using 3 equivalents of vinylmagnesium bromide **2** as required according to the accepted Bartoli reaction mechanism.[10] However, this reaction was not successful and we hypothesised that an additional equivalent of reagent **2** was required to compensate for the deprotonation of the carbamate group. Use of 4 equivalents of vinylmagnesium bromide indeed led to the formation of the desired indole **3** in 28% yield (Table 1, entries 1 and 2).

Next, we investigated the effect of the solvent, as we observed that the reaction was heterogeneous. It has previously been shown that adding a second ethereal solvent to the reaction can improve the yield by increasing the solubility of Grignard reagent **2** at low temperatures.[11] Diethyl ether was chosen due to its low boiling point and relatively low toxicity compared to



Scheme 1 Reaction of vinyl Grignard reagents with nitroarenes in the Bartoli reaction.

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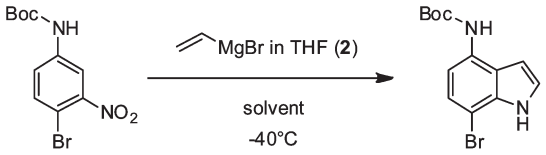
†Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of starting substrates and copies of ^{1}H and ^{13}C NMR spectra available. See DOI: 10.1039/c2ob25256b

Table 1 Optimisation of reaction conditions

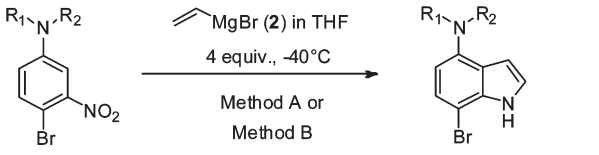


1 3

Entry	Grignard reagent equiv.	Solvent% Et_2O in THF[a]	Conc. (M)	Yield (%)
1	3	0	0.1	0
2	4[b]	0	0.1	28
3	4[b]	25	0.1	41
4	4[b]	57	0.1	64
5	4[b]	57	0.06	48
6	4[b]	75	0.06	56

[a] Solvent ratio and concentration listed are those reached after complete addition of all reagent solutions. [b] When using 4 equivalents of **2**, the dissolved substrate was added to the stirring Grignard mixture in a so called "inverse addition" in order to maintain a constant excess of **2** in the reaction (see experimental procedure).[12]

Table 2 Examination of suitable protecting groups



1, 4a - l 3, 5a - l

Entry	Starting material	R_1	R_2	Product	Method A yield (%)	Method B yield (%)
1	**4a**	H	H	**5a**	0	—
2	**1**	Boc	H	**3**	64	41
3	**4b**	Bn	H	**5b**	0	0
4	**4c**	PMB	H	**5c**	0	0
5	**4d**	Cbz	H	**5d**	7	13
6	**4e**	Alloc	H	**5e**	6	10
7	**4f**	Ac	H	**5f**	4	0
8	**4g**	Bz	H	**5g**	0	6
9	**4h**	Ts	H	**5h**	17	16
10	**4i**	Boc	PMB	**5c**[b]	34[a]	47[a]
11	**4j**	Cbz	PMB	**5j**	0[a]	0[a]
12	**4k**	Boc	Et	**5k**[b]	—	30[a]
13	**4l**	Boc	CH_2–C_3H_5	**5l**[b]	—	0[a]

Method A: 57% (v/v) Et_2O in THF. **Method B**: 25% (v/v) Et_2O in THF.[a] 3 equivalents of Grignard used. [b] Boc group removed in reaction conditions.

other ethers. Although it did not completely solve the problem of a heterogeneous mixture, addition of diethyl ether to the reaction mixture proved beneficial and allowed indole **3** to be formed in a 41% yield (entry 3) as the major product. Systematic variation of the THF : Et_2O ratio further improved the yield to 64% by increasing the ratio of ether relative to THF from 25% to 57% (entry 4). A decrease in concentration from 0.1 M to 0.06 M led to a decrease in yield of indole **3** (64 to 48%, Table 1, entries 4 and 5), which was partially countered by increasing the proportion of diethyl ether (Table 1, entries 5 and 6).

Entries 3 and 4 were chosen as the optimal conditions in order to keep solvent levels down at larger scales (Table 1, entry 4, method A; entry 3 method B) and were both used throughout this study. In all cases in this paper where the reaction was unsuccessful, significant amounts of starting material were recovered.

Next, a selection of commonly used protecting groups were introduced onto 4-bromo-3-nitroaniline and the resulting nitro compounds **4a–j** were subjected to methods A and B to determine the role of the *N*-protecting group (Table 2).[13] In all cases except unprotected **4a**, Bn protected **4b** and PMB protected **4c** (entries 1, 3 and 4), the expected product was formed to some extent and isolated along with substantial amounts of starting material. Boc derivative **1** gave by far the best yield (entry 2). Cbz derivative **4d**, allyl carbamate **4e** (entries 5 and 6) and tosyl amide **4h** (entry 9) were found to be lower yielding, with only carboxyamides **4f** and **4g** (entries 7 and 8) producing very small amounts of indole product. Method B gave comparable yields to method A except in the case of Boc derivative **1** where the yield was somewhat lower.

We hypothesised that the reaction could be more successful by using a second protecting group to prevent deprotonation of the carbamate nitrogen. Interestingly, using the doubly protected starting material **4i**, featuring both Boc and PMB groups on the nitrogen atom, led to a product containing only the PMB group (**5c**) with yields comparable to indole **3** (entry 10) using 3 equivalents of Grignard **2**. In order to test whether this double protection method could be applied using PMB with other carbamoyl protecting groups, we prepared starting material **4j**, where the Boc group is replaced by a Cbz group. Interestingly and in sharp contrast, treatment of **4j** with either method A or B did not yield any product and only starting material was recovered (entry 11).

In addition to these double protection experiments, we wanted to test whether it was possible to install alkyl groups on the nitrogen atom. As stated previously, starting materials were prepared by alkylation of 4-bromo-3-nitroaniline and subsequent Boc protection. Both ethyl and cyclopropylmethyl groups were explored (entries 12 and 13),[14] though only the former took part in the Bartoli reaction and showed the formation of a significant amount of indole (**5k**). Again, as seen in previous examples, a significant amount of starting material was recovered when cyclopropylmethyl derivative **4l** was used. Cyclopropyl groups contain π character in their carbon–carbon bonds and the difference in electronic properties compared to ethyl may at least in part explain the lack of reactivity.[15]

Two conclusions can be drawn from testing different protecting groups. Firstly, the Boc group proved to give the best results. Secondly, it can be employed either alone or in conjunction with a PMB group. Some simple alkyl groups can also be installed using this method.

The key feature distinguishing the Boc protecting group from the other carbamoyl group is the steric bulk exerted by the tertiary butyl residue. In order to find out whether steric factors are responsible for the yields achieved with **1**, we performed a series of experiments (Table 3). Firstly we replaced the Boc protecting group with the pivaloyl amide protecting group (**6a**) which

shows similar steric properties. Secondly, the tertiary butyl group was truncated to the isopropyl (**6b**) and ethyl groups (**6c**) in order to establish whether changing the steric properties would affect the yields of the reaction.

Reaction of starting materials **6a–c** gave modest yields of around 20% in every case and thus significantly below the 61 and 41% yields achieved with **1**. These results show that the *tert*-butyl group as well as the carbamoyl moiety are critical for good yields, suggesting that the Boc group exerts electronic and steric effects that are crucial for the success of the reaction.

After establishing Boc as the most efficient protecting group for the reaction to proceed, different Grignard reagents and substrates were examined to assess the scope of the reaction (Table 4). Nitroarene **1** (entries 1 to 4) was reacted with four different commercially available alkenyl Grignard reagents. As reported for other Bartoli reactions, we found that the yield strongly depended on the nature of the Grignard reagent. For example, when 1-methyl-1-propenylmagnesium bromide was employed in the reaction with nitroaniline **1**, only starting material was recovered (entry 4). Also, substitution of Br with Me at C-7 of **1** (**8a**, entry 5) resulted in an unsuccessful reaction.

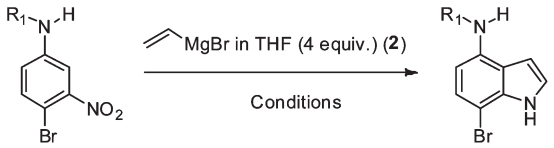
We next tested protected 3-bromo-4-nitroaniline **8b** (entries 6 to 9). In this case higher substituted Grignard reagents generally led to an increase in yields. Also, as seen with the 4-NHBoc substrate **8a**, substituting the Br at C-7 for a Me group did not give any product (**8c**, entry 10).

Surprisingly, moving the amino group further round the arene ring (entries 11–14) did not yield indole product for any of the Grignard reagents. Interestingly, however, substituting the C-7 Br for a Me group in **8k** led to some product being formed with both methods (entry 15).

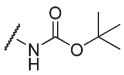
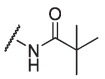
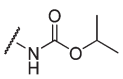
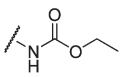
Again, in the cases where no product was formed, significant amounts of starting material were recovered. As shown in Table 4, substrate **1** produced the highest yields of indole product, with substrate **8g** (6-NHBoc derivative) being completely unreactive. The reason for this variance in reactivities is unclear.

It has previously been established that the first step in the mechanism is a reduction of the nitro group to the corresponding nitroso compound (Fig. 1) through a single electron transfer

Table 3 Investigation of Boc group importance

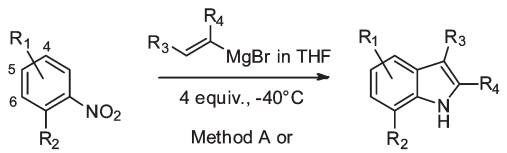


1, 6a - c **3, 7a - c**

Entry	Starting material	R_1	Product	Method A yield (%)	Method B yield (%)
1	**1**		**3**	64	41
2	**6a**		**7a**	17	16
3	**6b**		**7b**	22	13
4	**6c**		**7c**	26	16

Method A: 57% (v/v) Et_2O in THF. **Method B**: 25% (v/v) Et_2O in THF.

Table 4 Reactions to determine substrate scope



1, 8a - 8k **3, 3a - 3c, 9a - 9k**

Entry	Starting material	R_1	R_2	R_3, R_4	Product	Method A yield (%)	Method B yield (%)
1	**1**	4-NHBoc	Br	H, H	**3**	64	41
2	**1**	4-NHBoc	Br	H, Me	**3a**	44	43
3	**1**	4-NHBoc	Br	Me, H	**3b**	0	22
4	**1**	4-NHBoc	Br	Me, Me	**3c**	0	0
5	**8a**	4-NHBoc	Me	H, H	**9a**	0	0
6	**8b**	5-NHBoc	Br	H, H	**9b**	0	0
7	**8b**	5-NHBoc	Br	H, Me	**9c**[a]	13	19
8	**8b**	5-NHBoc	Br	Me, H	**9d**	0	33
9	**8b**	5-NHBoc	Br	Me, Me	**9e**	15	22
10	**8c**	5-NHBoc	Me	H, H	**9f**	0	0
11	**8g**	6-NHBoc	Br	H, H	**9g**	0	0
12	**8g**	6-NHBoc	Br	H, Me	**9h**	0	0
13	**8g**	6-NHBoc	Br	Me, H	**9i**	0	0
14	**8g**	6-NHBoc	Br	Me, Me	**9j**	0	0
15	**8k**	6-NHBoc	Me	H, H	**9k**	22	27

[a] Product quickly decomposes upon storage. **Method A**: 57% (v/v) Et_2O in THF. **Method B**: 25% (v/v) Et_2O in THF.

(SET) mechanism.[10] Retrieval of starting material suggests that this first step does not take place as none of the nitroso intermediates **10** were isolated or observed in all the reactions performed. The reason for this stalling in the first step is not clear, but could be related to the inability of the nitro group to be reduced by the Grignard reagent. 5-NHBoc nitrobenzenes have a *para* relationship between the nitro and carbamate groups which would put more electron density on the nitro group when the carbamate is deprotonated. This may render it less reactive to the reducing processes. However, this does not explain entries 11–14 (Table 4) where the relationship is *meta* and yet no reaction occurs.

In order to confirm that the first step of the mechanism is likely to pose an obstacle to the reaction progression, we decided to synthesise a nitroso compound through an alternative method and react it under our set of conditions. In this case, only 3 equivalents of Grignard reagent would be necessary as the initial reduction of the nitro group is no longer needed.

We decided to produce the nitroso version of **8a** as this substrate did not produce any indole product under our conditions (Table 4, entry 5), and it did not contain a Br atom which could be lost in the reduction step of the synthesis (Scheme 2).[16] We found that indole product **9a** was formed, although in a low yield of 9%.

This result suggests that the first step of the mechanism (SET) could well be preventing the reaction from proceeding, as some product was formed when this step was circumvented.

Conclusions

We have discovered and developed a new application of the Bartoli reaction for the synthesis of substituted aminoindoles with yields comparable to those of other substitution patterns previously reported in the literature. Different *N*-protecting groups for bromo-nitroanilines were investigated, leading to the conclusion that the Boc group is the most effective; a combination of protecting groups can also be employed to produce PMB-protected aminoindoles in useful yields.

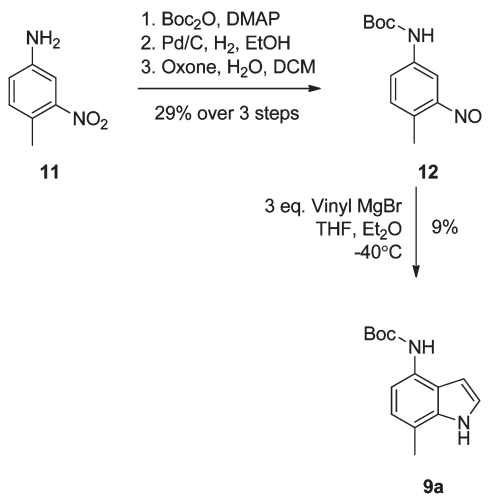
The results presented here reveal no clear trend for the reactivity of amino-nitrobenzenes with vinyl Grignard reagents, which is consistent with previous literature studies.[3,4] However, the general lack of reactivity trends highlights the importance of systematic explorations like this one to identify substrates that can successfully be prepared and utilised as starting materials.

Further studies on the employment of such highly functionalised building blocks in medicinal chemistry will be reported in due course.

Experimental section

General information

Starting materials, reagents and solvents for reactions were reagent grade and used as purchased. Chromatography solvents were HPLC grade and were used without further purification. Thin layer chromatography (TLC) analysis was performed using silica gel 60 F-254 thin layer plates. Flash column chromatography was carried out using columns pre-packed with 40–63 μm silica. LC yield determination, LCMS and HRMS analyses were performed on a HPLC system with diode array



Scheme 2 Synthesis and reaction of a nitroso derivative in the Bartoli reaction.

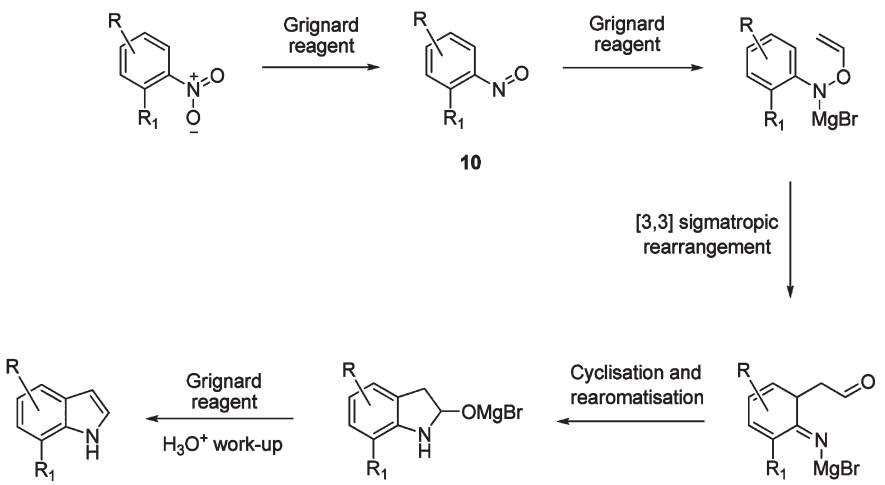


Fig. 1 Proposed mechanism of the Bartoli reaction.

detector operating at 254 nm, fitted with a reverse-phase 50 × 4.6 mm column at a temperature of 22 °C, connected to a Quadrupole Time of Flight (QToF) or Time of Flight (ToF) mass spectrometer (simultaneous ESI and APCI or ESI respectively). The following solvent system, at a flow rate of 2 mL min^{-1}, was used: solvent A: methanol; solvent B: 0.1% formic acid in water. Gradient elution was as follows: 1 : 9 (A : B) to 9 : 1 (A : B) over 2.5 min, 9 : 1 (A : B) for 1 min, then reversion back to 1 : 9 (A : B) over 0.3 min, 1 : 9 (A : B) for 0.2 min IR analyses were carried out on NaCl plates. NMR data are given as follows: chemical shift (δ) in ppm, referenced to residual $CHCl_3$ at 7.26 ppm, integration, multiplicity, coupling constants (J) given in Hz.

General procedure for synthesis of indoles

Method A. Vinylmagnesium bromide ([1 M] in THF, 4 equiv.) and Et_2O (2.5 ml $mmol^{-1}$) were mixed in an oven dried flask and cooled to −40 °C under N_2 with stirring. Aniline was dissolved in THF (2.5 ml $mmol^{-1}$) and added dropwise to the Grignard mixture. The solution was stirred at −40 °C for 4 h, then quenched with sat. aq. NH_4Cl. The aqueous layer was separated and extracted using EtOAc, the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by silica column chromatography (0–15% EtOAc in cyclohexane) to yield the title compound.

Method B. Vinylmagnesium bromide (1 M in THF, 4 equiv.) and Et_2O (2.5 ml $mmol^{-1}$) were mixed in an oven dried flask and cooled to −40 °C under N_2 with stirring. Aniline was dissolved in additional Et_2O (2.5 ml $mmol^{-1}$) and added dropwise to the Grignard mixture. The solution was stirred at −40 °C for 4 h, then quenched with sat. NH_4Cl. The aqueous layer was separated and extracted using EtOAc, the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by silica column chromatography (0–15% EtOAc in cyclohexane) to yield the title compound.

***tert*-Butyl 7-bromo-1*H*-indol-4-ylcarbamate (3).** Pale yellow oil, 4.87 g (67%); R_f = 0.47 (20% cyclohexane in DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 1.57 (9H, s), 6.58 (1H, dd, J = 1.0, 2.5), 6.65 (1H, br s), 7.24 (1H, t, J = 2.5), 7.31 (1H, d, J = 8.5), 7.55 (1H, br d, J = 8.5), 8.39 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.4, 80.7, 98.6, 99.9, 110.8, 120.3, 123.9, 124.9, 130.2, 134.9, 152.8; IR (film) 3210, 2955, 1756; HRMS (ESI) m/z calcd for $C_{13}H_{15}BrN_2O_2Na$ $[M + Na]^+$ 333.0215, found $[M + Na]^+$ 333.0210; HPLC purity >95%.

7-Bromo-*N*-(4-methoxybenzyl)-1*H*-indol-4-amine (5c). Pale yellow oil/glass, 54 mg (47%); R_f = 0.52 (30% EtOAc in cyclohexane); ^1H NMR (500 MHz, $CDCl_3$) δ 3.78 (3H, s), 4.82 (2H, s), 6.41 (1H, dd, J = 3, 2), 6.67 (1H, br s), 6.80 (2H, d, J = 8.5), 7.12–7.14 (2H, m), 7.17–7.19 (1H, m), 7.22 (1H, d, J = 8), 8.36 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.1, 55.2, 102.2, 102.7, 113.6, 120.1, 124.2, 124.6, 126.6, 129.5, 130.9, 134.5, 135.4, 158.8; IR (solid) 3248, 1659, 1244, 1038; HRMS (ESI) m/z calcd for $C_{16}H_{16}BrN_2O$ $[M + H]^+$ 331.0441, found $[M + H]^+$ 331.0444; HPLC purity >95%.

Benzyl 7-bromo-1*H*-indol-4-ylcarbamate (5d). Off-white crystalline residue, 19 mg (13%); R_f = 0.58 (30% EtOAc in cyclohexane); ^1H NMR (500 MHz, $CDCl_3$) δ 5.27 (2H, s), 6.56 (1H, dd, J = 3, 2), 6.86 (1H, br s), 7.22–7.24 (1H, m), 7.33 (1H, d, J = 8), 7.37 (1H, ddd, J = 7, 3.5, 1.5), 7.37–7.41 (2H, m), 7.43–7.46 (2H, m), 7.57 (1H, br s), 8.43 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 67.3, 99.3, 99.8, 111.2, 124.2, 124.9, 128.4, 128.6–128.7, 129.6, 134.9, 136.0, 153.4; IR (film) 3272, 1676, 1225; HRMS (ESI) m/z calcd for $C_{16}H_{14}BrN_2O_2$ $[M + H]^+$ 345.0233, found $[M + H]^+$ 345.0235; HPLC purity >90%.

Allyl 7-bromo-1*H*-indol-4-ylcarbamate (5e). Clear oil, 15 mg (10%); R_f = 0.52 (30% EtOAc in cyclohexane); ^1H NMR (500 MHz, $CDCl_3$) δ 4.73 (2H, d, J = 6), 5.31 (1H, d, J = 10, 1), 5.41 (1H, d, J = 17, 1), 6.02 (1H, ddd, J = 17, 10, 6), 6.58 (1H, dd, J = 3, 2), 6.82 (1H, br s), 7.23–7.26 (1H, m), 7.33 (1H, d, J = 8), 7.56 (1H, br s), 8.43 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 66.1, 99.2, 99.8, 111.1, 118.5, 120.6, 124.2, 124.9, 129.5, 132.4, 134.9, 153.2; IR (film) 3291, 1729, 1617, 1248, 995, 918; HRMS (ESI) m/z calcd for $C_{12}H_{12}BrN_2O_2$ $[M + H]^+$ 295.0077, found $[M + H]^+$ 295.0073; HPLC purity >95%.

***N*-(7-Bromo-1*H*-indol-4-yl)acetamide (5f).** Clear oil, 6 mg (4%); R_f = 0.31 (30% EtOAc in cyclohexane); ^1H NMR (500 MHz, $CDCl_3$) δ 2.27 (3H, s), 6.56 (1H, br s), 7.26 (1H, s (under $CDCl_3$ peak)), 7.31 (1H, d, J = 8), 7.34 (1H, br s), 7.68 (1H, d, J = 8), 8.45 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.7, 99.9, 100.1, 113.1, 121.3, 124.3, 124.8, 129.4, 134.9, 168.4; IR (film) 3419, 3264, 1654, 1530; HRMS (ESI) m/z calcd for $C_{10}H_{10}BrN_2O$ $[M + H]^+$ 252.9971, found $[M + H]^+$ 252.9979; HPLC purity >95%.

***N*-(7-Bromo-1*H*-indol-4-yl)benzamide (5g).** Off-white residue, 9 mg (6%); R_f = 0.32 (30% EtOAc in cyclohexane); ^1H NMR (500 MHz, $CDCl_3$) δ 6.64 (1H, dd, J = 3, 2), 7.28–7.30 (1H, m), 7.38 (1H, d, J = 7.5), 7.54 (2H, ddd, J = 9, 6.5, 3.5), 7.58–7.60 (1H, m), 7.84 (1H, d, J = 7.5), 7.95 (2H, dd, J = 5, 3.5), 8.03 (1H, br s), 8.49 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 100.0, 100.4, 113.2, 120.8, 121.3, 124.4, 124.9, 127.1, 128.9, 129.6, 131.9, 135.1, 165.5; IR (film) 3288, 1731; HRMS (ESI) m/z calcd for $C_{15}H_{12}BrN_2O$ $[M + H]^+$ 315.0128, found $[M + H]^+$ 315.0143; HPLC purity >95%.

***N*-(7-Bromo-1*H*-indol-4-yl)-4-methylbenzenesulfonamide (5h).** Clear oil, 25 mg (17%); R_f = 0.48 (30% EtOAc in cyclohexane); ^1H NMR (500 MHz, Acetone-d_6) δ 2.32 (3H, s), 6.80 (1H, d, J = 3), 7.04 (1H, d, J = 8), 7.23 (1H, d, J = 8), 7.26 (2H, d, J = 8), 7.32 (1H, d, J = 3), 7.69 (2H, d, J = 8), 8.87 (1H, br s), 10.45 (1H, br s); ^{13}C NMR (126 MHz, Acetone-d_6) δ 20.4, 100.5, 100.7, 113.5, 123.6, 124.0, 125.3, 125.5, 127.1, 129.4, 135.3, 137.6, 143.4; IR (film) 3389, 3261, 1156; HRMS (ESI) m/z calcd for $C_{15}H_{14}BrN_2O_2S$ $[M + H]^+$ 364.9954, found $[M + H]^+$ 364.9967; HPLC purity >95%.

7-Bromo-*N*-ethyl-1*H*-indol-4-amine (5k). Off-white oil, 21 mg (30%); R_f = 0.38 (20% EtOAc in cyclohexane); ^1H NMR (500 MHz, $CDCl_3$) δ 1.12 (3H, t, J = 7), 3.74 (2H, q, J = 7), 6.50 (1H, t, J = 3), 6.82 (1H, br s), 7.23 (1H, t, J = 3), 7.29 (1H, d, J = 8), 8.40 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 44.9, 102.3, 120.1, 124.4, 124.9, 127.1, 134.4, 135.5, 154.8; IR (film) 2976, 1699, 1536, 1366, 1146; HRMS (ESI) m/z calcd for

$C_{10}H_{12}BrN_2$ [M + H]$^+$ 241.0158, found [M + H]$^+$ 241.0155; HPLC purity >98%.

***N*-(7-Bromo-1*H*-indol-4-yl)pivalamide (7a).** Off-white crystalline solid, 25 mg (17%); m.p = 190 °C (decomp); R_f = 0.26 (20% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (9H, s), 6.54 (1H, dd, J = 3, 2), 7.26–7.29 (1H, m), 7.34 (1H, d, J = 8), 7.62 (1H, br s), 7.77 (1H, d, J = 8), 8.47 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.8, 39.9, 99.5, 99.8, 112.8, 121.0, 124.3, 124.9, 129.7, 134.9, 176.5; IR (solid) 3270, 2969, 1633, 1501; HRMS (ESI) m/z calcd for $C_{13}H_{15}BrN_2ONa$ [M + Na]$^+$ 317.0260, found [M + Na]$^+$ 317.0256; HPLC purity >95%.

Isopropyl 7-bromo-1*H*-indol-4-ylcarbamate (7b). Clear oil, 33 mg (22%); R_f = 0.29 (20% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (6H, s), 5.07 (1H, h, J = 6), 6.56 (1H, dd, J = 3, 2), 6.74 (1H, br s), 7.23 (1H, dd, J = 3, 2.5), 7.30 (1H, d, J = 8), 7.56 (1H, br s), 8.44 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.3, 69.1, 99.0, 99.9, 110.9, 120.5, 124.2, 125.0, 130.0, 135.0, 153.4; IR (film) 3388, 2978, 1699, 1502; HRMS (ESI) m/z calcd for $C_{12}H_{14}BrN_2O_2$ [M + H]$^+$ 297.0233, found [M + H]$^+$ 297.0225; HPLC purity >95%.

Ethyl 7-bromo-1*H*-indol-4-ylcarbamate (7c). Pale tan resin, 38 mg (26%); R_f = 0.25 (20% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7), 4.29 (2H, q, J = 7), 6.57 (1H, dd, J = 3, 2.5), 6.81 (1H, br s), 7.24 (1H, dd, J = 3, 2.5), 7.32 (1H, d, J = 8), 7.56 (1H, br s), 8.47 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.6, 61.5, 99.0, 99.8, 111.0, 120.5, 124.2, 124.9, 129.7, 134.9, 153.7; IR (film) 3309, 1670, 1525; HRMS (ESI) m/z calcd for $C_{11}H_{11}BrN_2O_2Na$ [M + Na]$^+$ 304.9896, found [M + Na]$^+$ 304.9888; HPLC purity >95%.

***tert*-Butyl 7-bromo-2-methyl-1*H*-indol-4-ylcarbamate (3a).** Yellow/brown oil, 68 mg (44%); R_f = 0.55 (30% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (9H, s), 2.47 (3H, s), 6.25 (1H, dd, J = 2, 1), 6.57 (1H, br s), 7.21 (1H, d, J = 8), 7.46 (1H, d, J = 8), 8.09 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 28.4, 80.6, 97.8, 98.0, 111.0, 121.4, 123.7, 129.2, 134.9, 135.1, 152.8; IR (film) 3323, 1708, 1509, 1150; HRMS (ESI) m/z calcd for $C_{14}H_{17}BrN_2O_2Na$ [M + Na]$^+$ 347.0366, found [M + Na]$^+$ 347.0361; HPLC purity >95%.

***tert*-Butyl 7-bromo-3-methyl-1*H*-indol-4-ylcarbamate (3b).** Pale yellow solid, 29 mg (22%); R_f = 0.43 (30% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (9H, s), 2.54 (3H, s), 6.94 (1H, br s), 6.97 (1H, d, J = 1), 7.27 (1H, d, J = 8), 7.44 (1H, d, J = 8), 8.08 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.9, 27.9, 79.9, 99.2, 110.8, 112.7, 121.9, 124.2, 130.8, 135.5, 138.3, 152.8; IR (film) 3355, 1674, 1507; HRMS (ESI) m/z calcd for $C_{14}H_{18}BrN_2O_2$ [M + H]$^+$ 325.0546, found [M + H]$^+$ 325.0538; HPLC purity >90%.

***tert*-Butyl 7-methyl-1*H*-indol-4-ylcarbamate (9a).** Brown oil, 9 mg (9%); R_f = 0.23 (20% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (9H, s), 2.47 (3H, s), 6.52 (1H, dd, J = 3, 2), 6.63 (1H, br s), 6.97 (1H, d, J = 8.5), 7.20 (1H, dd, J = 3, 2), 7.49 (1H, br s), 8.18 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.3, 28.4, 80.3, 99.2, 110.0, 115.7, 119.2, 123.0, 123.2, 128.5, 135.9, 153.2; IR (film) 3317, 2943, 1449, 1022; HRMS (ESI) m/z calcd for $C_{14}H_{18}N_2O_2Na$ [M + Na]$^+$ 269.1260, found [M + Na]$^+$ 269.1262; HPLC purity >98%.

***tert*-Butyl 7-bromo-2-methyl-1*H*-indol-5-ylcarbamate (9c).** Brown oil, 29 mg (19%), decomposes upon storage; R_f = 0.19 (20% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (3H, d, J = 9), 6.27 (1H, br s), 6.72 (1H, d, J = 9), 7.04 (1H, d, J = 8), 7.55 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.4, 28.4, 80.4, 109.3, 111.7, 115.8, 120.1, 123.7, 130.2, 140.2, 148.3, 153.1; IR (film) 3321, 2977, 1693, 1506, 1152; HRMS (ESI) m/z calcd for $C_{14}H_{17}BrN_2O_2Na$ [M + Na]$^+$ 347.0366, found [M + Na]$^+$ 347.0366; HPLC purity >80%.

***tert*-Butyl 7-bromo-3-methyl-1*H*-indol-5-ylcarbamate (9d).** Yellow/orange wax, 43 mg (33%); R_f = 0.56 (30% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (9H, s), 2.30 (3H, d, J = 1), 6.49 (1H, s), 7.02 (1H, d, J = 1), 7.39 (1H, s), 7.54 (1H, s), 7.99 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.3, 27.9, 103.7, 108.4, 112.5, 115.3, 117.2, 122.6, 123.2, 129.7, 131.6, 152.9; IR (film) 3328, 2977, 2918, 1669, 1580; HRMS (ESI) m/z calcd for $C_{14}H_{17}BrN_2O_2Na$ [M + Na]$^+$ 347.0367, found [M + Na]$^+$ 347.0385; HPLC purity <80% (decomposed upon storage).

***tert*-Butyl 7-bromo-2,3-dimethyl-1*H*-indol-5-ylcarbamate (9e).** Brown oil, 35 mg (22%); R_f = 0.41 (30% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (9H, s), 2.19 (3H, s), 2.39 (3H, s), 6.44 (1H, br s), 7.30 (1H, s), 7.42 (1H, s), 7.77 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 8.2, 11.1, 27.9, 79.7, 102.7, 107.7, 108.0, 115.9, 129.9, 130.4, 130.7, 132.1, 152.8; IR (film) 3324, 2977, 2921, 1699; HRMS (ESI) m/z calcd for $C_{15}H_{20}BrN_2O_2$ [M + H]$^+$ 339.0703, found [M + H]$^+$ 339.0708; HPLC purity >95%.

***tert*-Butyl 7-methyl-1*H*-indol-6-ylcarbamate (9k).** Pale yellow oil, 39 mg (27%); R_f = 0.25 (20% EtOAc in cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (9H, s), 2.30 (3H, s), 6.30 (1H, br s), 6.49 (1H, dd, J = 3, 2), 7.05–7.07 (1H, m), 7.21 (1H, br s), 7.44 (1H, d, J = 8), 8.31 (1H, br s,); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.8, 28.4, 80.0, 102.8, 114.5, 117.9, 118.1, 124.5, 125.4, 129.5, 135.8, 154.4; IR (film) 3313, 2976, 1688, 1243, 1155; HRMS (ESI) m/z calcd for $C_{14}H_{18}N_2O_2Na$ [M + Na]$^+$ 269.1260, found [M + Na]$^+$ 269.1253; HPLC purity >90%.

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