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# Synthesis of Tryptamine Derivatives via a Direct, One-Pot Reductive Alkylation of Indoles

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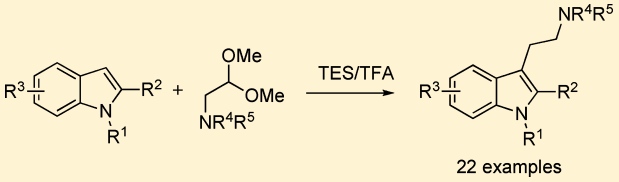
Supporting Information

**ABSTRACT:** An efficient, one-pot reductive alkylation of indoles with *N*-protected aminoethyl acetals in the presence of TES/TFA is reported. It represents the first general method for the direct synthesis of tryptamine derivatives from indoles and nitrogen-functionalized acetals. This convergent and versatile approach employs safe and inexpensive reagents, proceeds under mild conditions, and tolerates several functional groups. The new procedure was efficiently applied to a gram-scale synthesis of both luzindole, a reference MT2-selective melatonin receptor antagonist, and melatonin.




Tryptamines are an important class of biologically active compounds whose structural motif is embedded in numerous natural products, including commercial drugs[1] (Figure 1). In addition, tryptamine is a biosynthetic precursor of many alkaloid natural products, including approximately 3000 monoterpene indole alkaloids,[2] and is frequently used as a chemical building block in the total synthesis of biologically active and pharmaceutically important compounds.[3] Thus, there is currently increased interest in tryptamines, and methods for their synthesis are being studied.[4−8]

A variety of well-documented traditional and modern methods for the synthesis of tryptamines have been described, which can be divided into two broad categories. The first approach involves a multistep sequence for the introduction of the ethylene amine side chain in position 3 of the indole ring. Two of the most important methods in this category utilize an electrophilic aromatic substitution reaction with oxalyl chloride followed by amidation and reduction[4] or nitroethylation of indoles followed by reduction.[5] The second approach constructs the pyrrole ring using an annulation method, such as the Fischer[6] indolization of arylhydrazines with a 4-aminobutanal equivalent or the Larock heteroannulation between *o*-haloanilines and an internal alkyne.[7] Recently, Nicolaou et al. reported a new three-step synthesis of tryptamines starting from N-Boc-protected anilines.[8] However, some drawbacks of the above methodologies, including the necessary isolation or preparation of reactive intermediates and the use of multistep reaction sequences (one of which requires the use of a strong reducing agent), leave room for improvements.

As part of our ongoing efforts to synthesize melatonin receptor agonists and antagonists,[9] we recently reported an efficient and selective one-pot reductive amination of anilines for the rapid assembly of functionalized unsymmetrically substituted ethylenediamine derivatives.[10] A convenient alkylating system for our purpose was *N*-protected aminoacetaldehyde dimethyl acetal and $Et_3SiH$/TFA as a reagent combination. We speculated that these reagents and reaction conditions could also be used for the C-3 reductive alkylation of indoles, in order to obtain tryptamine derivatives of pharmaceutical interest in a single step. Although some examples of C-3 reductive alkylation of indoles are known,[11] there are no reports describing the use of this protocol for the direct synthesis of tryptamine derivatives. Herein, we describe the optimized conditions, scope and applications for the selective C-3 reductive alkylation of indoles with some protected aminoacetaldehydes (glycinaldehydes). We envisaged that achieving C-3 reductive alkylation of indoles with suitable two-carbon nitrogen-containing electrophiles such as N-protected aminoacetaldehyde dimethyl acetals, would open up promising perspectives to the rapid and practical synthesis of tryptamine and its derivatives.

Our investigation began by screening reaction parameters using 2-methylindole **1a**, which is not prone to polymerization, as the model substrate and *N*-acetylaminoacetaldehyde dimethyl acetal **2** with triethylsilane as the reductant, in DCM (Table 1). As expected, no reaction occurred in the absence of any acid additive (Table 1, entry 1). In agreement with previous reports,[11] in the presence of 1.5 equiv of trifluoroacetic acid (TFA), bisindolyl derivative **4** was the major product instead of the desired tryptamine **3a** (Table 1, entry 2). The amount of TFA required in our C-3 reductive alkylation protocol could be critical, as it is necessary to activate different stages of the process. Therefore, we decided to increase the amount of TFA used, and we repeated the reaction using 3 equiv of TFA. As outlined in Table 1 (entry 3), we observed formation of the desired 2-methyl-*N*-acetamidotryptamine in addition to the bisindolyl derivative **4**. Encouraged by this

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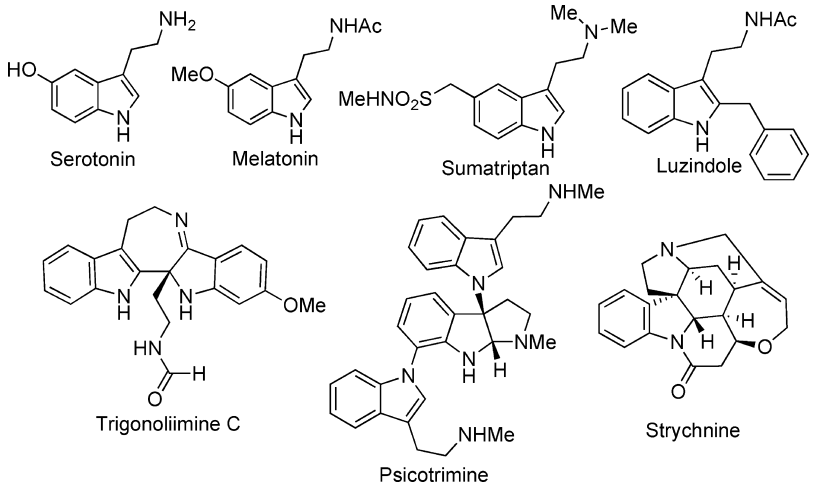
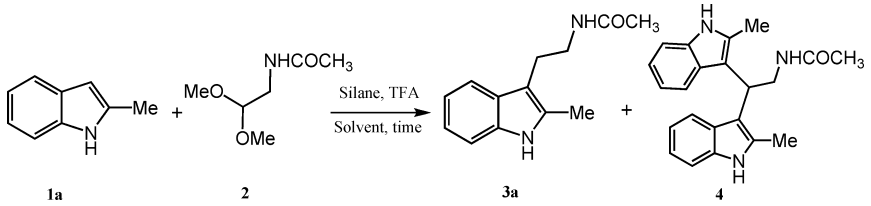



**Figure 1.** Natural products and pharmaceuticals containing tryptamines.

**Table 1. Optimization of the Reaction Parameters**




| | | | | | yield[b] (%) | |
|---|---|---|---|---|---|---|
| entry[a] | TFA (equiv) | solvent (0.25 M) | silane | time (h) | **3a** | **4** |
| 1 | | DCM | TES | 48 | NR[c] | NR |
| 2 | 1.5 | DCM | TES | 16 | | 91 |
| 3 | 3 | DCM | TES | 16 | 39 | 45 |
| 4 | 5 | DCM | TES | 3 | 90 | |
| 5 | 5 | $CHCl_3$ | TES | 3 | 85 | |
| 6 | 5 | toluene | TES | 3 | 71 | |
| 7 | 5 | THF | TES | 16 | NR | NR |
| 8 | 5 | $Et_2O$ | TES | 16 | NR | NR |
| 9 | 5 | dioxane | TES | 16 | NR | NR |
| 10 | 5 | $CH_3CN$ | TES | 16 | 47 | |
| 11 | 5 | DMF | TES | 16 | 36 | |
| 12 | 5 | TFE | TES | 16 | 35 | |
| 13 | 5 | $H_2O$ | TES | 16 | | 52 |
| 14 | 5 | DCM | PMHS | 16 | | 11 |
| 15 | 5 | DCM | $(EtO)_3SiH$ | 16 | | 32 |
| 16 | 5 | DCM | TMDSO | 16 | *d* | |
| 17 | 5 | DCM | $Ph_2SiH_2$ | 16 | *d* | |

[a]All reactions were performed at room temperature with 1.1 equiv of acetal, 1.0 equiv of **1a**, and 3 equiv of silane in solvent/TFA with no precautions taken to exclude moisture. [b]Isolated yields. [c]NR: no reaction. [d]A complicated crude mixture was observed.

result, we further increased the amount of TFA (5 equiv) to obtain the desired tryptamine derivative **3a** as the only reaction product in excellent isolated yield (90%) (Table 1, entry 4). A similar phenomenon was observed in chloroform and toluene, although the selectivity and yields were lower than in DCM. All our attempts to improve the yields or the selectivity outcome by changing the solvent were unsuccessful (Table 1, entries 7−13). Decreased yields of the desired tryptamine derivative were observed in trifluoroethanol, DMF, and acetonitrile, and no reaction occurred with ethereal solvents such as diethyl ether, THF, and dioxane. Only the bisindolyl adduct **4** was observed in water. It appears that decreasing the nucleophilicity of the medium increases the acidity of the system, thus promoting the reaction. In addition to $Et_3SiH$, other silanes such as $Ph_2SiH_2$, $(EtO)_3SiH$, polymethylhydrosiloxane (PMHS), and tetramethyldisiloxane (TMDS) were also tested as reductants, but none of them gave appreciable results (Table 1, entries 14−17).

Once reliable conditions to synthesize 2-methyl-*N*-acetamidotryptamine were established, we next investigated the scope of this reaction using indoles with different substitution patterns as summarized in Table 2.

A variety of 2-alkyl/aryl-substituted indoles were alkylated smoothly in good yields, regardless of the length or steric hindrance of the C-2 substituent (Table 2, entries 1−6). Interestingly, it was also possible to perform C-3 reductive alkylation of *Nω*-acetyl isotryptamine **1g**[12] to give the


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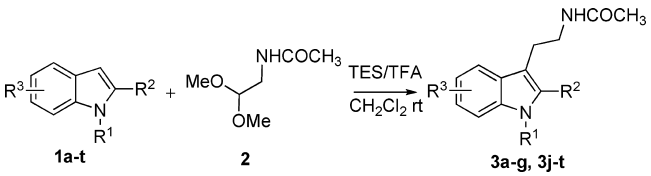
**Table 2. Scope of Indoles 1a−t in the C-3 Reductive Alkylation with 2**




| entry[a] | product | $R^1$ | $R^2$ | $R^3$ | time (h) | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | H | Me | H | 3 | 90 |
| 2 | **3b** | H | But | H | 3 | 70 |
| 3 | **3c** | H | cyclopentyl | H | 6 | 76 |
| 4 | **3d** | H | *t*-But | H | 3 | 66 |
| 5 | **3e** | H | Bn | H | 4 | 74 |
| 6 | **3f** | H | Ph | H | 4 | 97 |
| 7 | **3g** | H | $CH_2CH_2NHAc$ | H | 3 | 60 |
| 8 | **3h** | H | COOH | H | | NR[d] |
| 9 | **3i** | H | COOMe | H | | NR |
| 10 | **3j** | H | Me | 5-Me | 3 | 85 |
| 11 | **3k** | H | Me | 5-Cl | 3 | 87 |
| 12 | **3l** | H | Me | 5-Bpin | 3 | 70 |
| 13 | **3m** | H | Me | 5-OMe | 2 | 63[c] |
| 14 | **3n** | H | Ph | 6-OMe | 2 | 43[c] |
| 15 | **3o** | Me | Me | H | 3 | 77 |
| 16 | **3p** | Me | H | H | 4 | 50 |
| 17 | **3q** | Bn | H | H | 16 | 65 |
| 18 | **3r** | Bn | H | 5-OMe | 2 | 56[c] |
| 19 | **3s** | PMB | H | H | 16 | 45 |
| 20 | **3t** | Allyl | H | H | 16 | 40 |

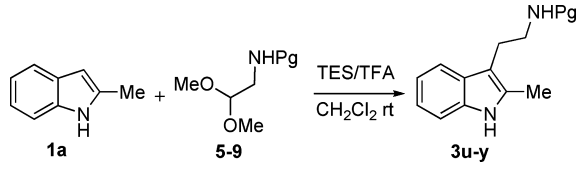
[a]Reaction conditions: **2** (1 mmol), **1a−t** (1.1 mmol), TFA (5 mmol), and TES (3 mmol) in DCM (0.25 M) at rt for 3−60 h. [b]Yield after flash chromatography. [c]DCE at 60 °C. [d]NR: no reaction.

interesting (bis-ethylamino)indole derivative **3g** as a single product in good yield (60%) (Table 2, entry 7); the same compound **3g** could be theoretically obtained by reacting Nω-acetyltryptamine under the same reaction conditions, but these attempts gave only polymerization side products. On the contrary, no reactivity was observed with indoles bearing an electron-withdrawing group in the C-2 position, such as 2-indolecarboxylic acid or its ester (Table 2, entries 8 and 9), even if higher reaction temperatures and prolonged reaction times were used. A possible reason is that the presence of an electron-withdrawing group might render the indoles highly electron-deficient, preventing the electrophilic alkylation. A similar lack of reactivity was observed with *N*1-acetyl- and *N*1-sulfonylindoles (data not shown). Our synthetic protocol worked well for indoles with both moderately electron-donating (i.e., methyl, entry 10) and electron-withdrawing (i.e., chloro, entry 11) 5-substituents giving the corresponding tryptamines in high yields. However, when 5-methoxy-2-methylindole reacted with acetal **2**, only 19% yield was obtained. However, increasing the reaction temperature to 60 °C led to a consistent improvement in the yield of the desired tryptamine (Table 2, entry 13). Remarkably, the proposed C-3 reductive alkylation also tolerates the presence of a boronate ester in the indole ring, offering unique, site-specific handles that can be utilized in cross-coupling methodology for further functionalization of tryptamines (Table 2, entry 12). Encouraged by these results, we applied the reaction conditions to 2-unsubstituted indole substrate. Gratifingly, the above indole C-3 reductive alkylation strategy could also be extended to *N*-alkylated indoles **1o−t**,[13] independent of the presence of a C-2 indole substituent to give the corresponding desired tryptamines **3o−t**, although in slightly lower yields (45−77% yield) and requiring longer reaction times (Table 2, entries 16−20).

Unfortunately, the indole does not afford the desired Nω-acetyltryptamine. The shortcomings associated with completely unsubstituted indoles in the reductive alkylation reaction are likely a manifestation of increased reactivity of the product toward further reaction with electrophiles present in the reaction mixture, giving a complicated mixture of dimer and oligomer products.[14]

To further expand the potential of this new one-pot single-step synthesis of tryptamine derivatives, we also investigated an orthogonal set of easily removable N-protected aminoalkyl acetals.[15] The reaction proceeded well in all cases (Table 3, entries 1−4), although more slowly. Interestingly, the *N*-trifluoroacetyl protecting group proved to be well tolerated to the reaction conditions and easily removed by simple basic hydrolysis, directly on the crude reaction mixture, to give tryptamine **3y** in very high yield;[16] the same compound was not obtained by using the simple amino acetal **9**.

**Table 3. Scope of Acetals 5−9 in the Reductive Alkylation of 1a**

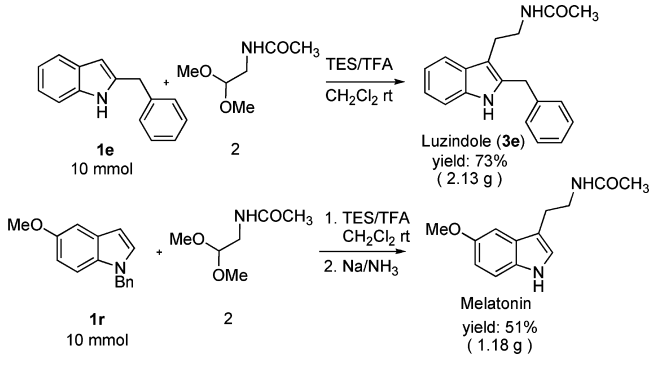



| entry[a] | protecting group (Pg) | time (h) | yield[b] (%) | product |
|---|---|---|---|---|
| 1 | Cbz (**5**) | 16 | 60 | **3u** |
| 2 | Ftal (**6**) | 16 | 78 | **3v** |
| 3 | Ts (**7**) | 16 | 50 | **3w** |
| 4 | $COCF_3$ (**8**) | 16 | 89 | **3x** |
| 5 | H (**9**) | 16 | NR[c] | **3y**[d] |

[a]Reaction conditions: **5−9** (1 mmol), **1a** (1.1 mmol), TFA (5 mmol), and TES (3 mmol) in DCM (0.25 M) at rt for 3−16 h. [b]Yield after flash chromatography. [c]NR: no reaction. [d]From **3x** using base.

A wide range of synthetic applications of this procedure can be envisaged. For instance, the method was extended to the practical gram-scale synthesis of luzindole (Scheme 1), a widely used and expensive $MT_2$ melatonin receptor antagonist.

**Scheme 1. Multigram-Scale Reductive Alkylation for the Synthesis of Luzindole and Melatonin**





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Although it constitutes a standard reference compound for pharmacologists in the melatonin field, the reported multistep preparation sequences are laborious and give poor overall yields.[17] The single step gram-scale preparation reaction is conveniently carried out at room temperature under an air atmosphere with the inexpensive and easily handled starting material 2-benzylindole in good yield. In order to show the viability of this method, we also prepared 2-unsubstituted tryptamine derivatives in gram scale. The treatment of readily available *N*-benzyl-5-methoxyindole with acetal **2**, followed by reductive removal of the *N*1-benzyl group by $Na/NH_3$, afforded, in acceptable yields, *N*-acetyl-5-methoxytryptamine (melatonin), a neurohormone mainly secreted by the pineal gland and known to play a key role in regulating the body's circadian rhythms, including the sleep−wake cycle and mood.[18] This chemistry can in principle be easily adapted to provide access to various analogues of 5-alkoxy- and/or 5-hydroxytryptamine, which may not be readily available otherwise.

In summary, a new, direct, one-pot method for the synthesis of tryptamine derivatives has been developed, via C-3 reductive alkylation of indoles and readily available protected glycinaldehyde acetals. Protected glycinaldehyde acetals have shown to be useful two-carbon nitrogen containing electrophiles and could be utilized to obtain products incorporating the amino ethane fragment. The present approach constitutes one of the most efficient, practical, and straightforward methods for a variety of substituted tryptamines. This powerfully simplified reaction has enabled the gram-scale synthesis of two important and biologically active tryptamine derivatives: the neurohormone melatonin and the reference melatonin receptor antagonist luzindole. Given the simplicity, efficiency, and functional group tolerance, this general method is expected to find wide applications in chemical synthesis in general and in the construction of tryptamine-based complex molecules.

## EXPERIMENTAL SECTION

**General Information.** All reactions were run in round-bottom flasks. Column chromatography purifications were performed in flash conditions using 230−400 mesh silica gel. Analytical thin-layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 $F_{254}$) that were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM). $^1$H NMR and $^{13}$C NMR spectra were recorded at 200/50 MHz on spectrometer using $CDCl_3$ or DMSO-$d_6$ as solvent. Chemical shifts (scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (*J* values) are given in hertz (Hz). ESI-MS spectra were taken on an LC−MS instrument. Only molecular ions (M + 1) are given for the ESI-MS analysis. Absorbances are reported in $cm^{-1}$ for the IR analysis. Melting points were determined on a capillary melting point apparatus and are uncorrected. Elemental analyses were within ±0.4 of the theoretical values (C, H, N).

**General Procedure for the Reductive Alkylation of Indoles.** A solution of suitable indole (1 mmol) and acetal (1.1 mmol) in DCM (2 mL) was added to a solution of trifluoroacetic acid (TFA, 5 mmol) and triethylsilane (TES, 3 mmol) in DCM (2 mL), and the resulting mixture was stirred at room temperature for 3−16 h. The reaction was cooled at 0 °C and carefully neutralized with saturated solution of $NaHCO_3$ and diluted with DCM. The two phases were separated, and the aqueous layer was extracted three times with DCM (20 mL). The combined organic phase was washed with brine, dried over $Na_2SO_4$, filtered, and evaporated on rotary evaporator. The residue was purified by flash chromatography on silica gel affording desired compounds.

*N-[2-(2-Methyl-1H-indol-3-yl)ethyl]acetamide* (***3a***). Purification by silica gel column chromatography (EtOAc) gave the product in 90% yield (194 mg): yellow solid; mp 83−85 °C (EtOAc); MS (ESI) 217 $[M + H]^+$; IR (film, $cm^{-1}$) 1620; $^1$H NMR ($CDCl_3$) $\delta$ 1.89 (s, 3H), 2.36 (s, 3H), 2.91 (t, $J$ = 6.5 Hz, 2H), 3.49 (dt, $J_1 \approx J_2$ = 6.5 Hz, 2H), 5.75 (bs, 1H), 7.05−7.17 (m, 2H), 7.25−7.29 (m, 1H), 7.47−7.51 (m, 1H), 8.44 (bs, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 11.5, 23.3, 24.1, 40.1, 108.3, 110.4, 117.7, 119.3, 121.1, 128.6, 132.1, 135.3, 170.3. Anal. Calcd for $C_{13}H_{16}N_2O$ (216): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.10; H, 7.18; N, 12.94. Data was consistent with that reported in the literature.[18a]

*N-[2-(2-Butyl-1H-indol-3-yl)ethyl]acetamide* (***3b***). Purification by silica gel column chromatography (cyclohexane/EtOAc 1:1) gave the product in 70% yield (181 mg): yellowish oil; ESI MS (*m*/*z*) 259 $[M + H]^+$; IR ($cm^{-1}$, film) 1620; $^1$H NMR ($CDCl_3$) $\delta$ 0.96 (t, $J$ = 7 Hz, 3H), 1.35−1.50 (m, 2H), 1.58−1.73 (m, 2H), 1.91 (s, 3H), 2.75 (t, $J$ = 7 Hz, 2H), 2.93 (t, $J$ = 6.5 Hz, 2H), 3.54 (dt, $J_1 \approx J_2$ = 6.5 Hz, 2H), 5.53 (bs, 1H), 7.07−7.19 (m, 2H), 7.27−7.34 (m, 1H), 7.51−7.55 (m, 1H), 7.98 (bs, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.9, 22.6, 23.3, 24.1, 25.8, 32.2, 40.2, 107.9, 110.6, 117.9, 119.2, 121.1, 128.5, 135.4, 136.9, 170.3. Anal. Calcd for $C_{16}H_{22}N_2O$ (258): C, 74.38; H, 8.58; N, 10.84. Found: C, 74.29; H, 8.45; N, 10.69. Data was consistent with that reported in the literature.[18a]

*N-(2-(2-Cyclopentyl-1H-indol-3-yl)ethyl)acetamide* (***3c***). Purification by silica gel column chromatography (cyclohexane/EtOAc 1:1) gave the product in 76% yield (205 mg): off-white solid; mp 147−149 °C ($Et_2O$); ESI MS (*m*/*z*) 271 $[M + H]^+$; IR ($cm^{-1}$, film) 1654; $^1$H NMR ($CDCl_3$) $\delta$ 1.60−2.09 (m, 11H), 2.96 (t, $J$ = 6.5 Hz, 2H), 3.22−3.39 (m, 1H), 3.54 (dt, $J_1 \approx J_2$ = 6.5 Hz, 2H), 5.62 (bs, 1H), 7.06−7.19 (m, 2H), 7.27−7.35 (m, 1H), 7.50−7.54 (m, 1H), 8.19 (bs, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 23.4, 24.2, 25.8, 33.6, 36.7, 40.2, 107.8, 110.6, 117.9, 119.3, 121.2, 128.5, 135.4, 139.8, 170.0. Anal. Calcd for $C_{17}H_{22}N_2O$ (270): C, 75.52; H, 8.20; N, 10.36. Found: C, 75.56; H, 8.39; N, 10.64.

*N-(2-(2-tert-Butyl-1H-indol-3-yl)ethyl)acetamide* (***3d***). Purification by silica gel column chromatography (cyclohexane/EtOAc 1:1) gave the product in 66% yield (170 mg): amorphous off-white solid; ESI MS (*m*/*z*) 259 $[M + H]^+$; IR ($cm^{-1}$, film) 1647; $^1$H NMR ($CDCl_3$) $\delta$ 1.50 (s, 9H), 1.95 (s, 3H), 3.14 (t, $J$ = 7 Hz, 2H), 3.59 (dt, $J_1 \approx J_2$ = 7 Hz, 2H), 5.84 (bs, 1H), 7.06−7.20 (m, 2H), 7.32−7.36 (m, 1H), 7.55−7.60 (m, 1H), 8.26 (bs, 1H); $^{13}$C NMR ($CDCl_3$) 23.4, 25.4, 30.7, 33.0, 40.5, 106.7, 110.5, 118.0, 119.3, 121.2, 129.7, 134.1, 143.0, 170.2. Anal. Calcd for $C_{16}H_{22}N_2O$ (258): C, 74.38; H, 8.58; N, 10.84. Found: C, 74.45; H, 8.63; N, 11.12.

*N-[2-(2-Benzyl-1H-indol-3-yl)ethyl]acetamide* (***3e***). The reaction was run on 10 mmol (2.07 g) scale. Purification by silica gel column chromatography (cyclohexane/EtOAc 1:1) gave the product in 74% yield (2.16 g): white solid; mp 103−104 °C (EtOAc); ESI MS (*m*/*z*) 293 $[M + H]^+$; IR ($cm^{-1}$, film) 1630; $^1$H NMR ($CDCl_3$) $\delta$ 1.80 (s, 3H), 3.01 (t, $J$ = 6.5 Hz, 2H), 3.54 (dt, $J_1 \approx J_2$ = 6.5 Hz, 2H), 4.13 (s, 2H), 5.48 (bs, 1H), 7.08−7.38 (m, 8 H), 7.55−7.59 (m, 1H), 7.84 (bs, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 23.2, 24.2, 32.2, 40.1, 109.4, 110.7, 118.2, 119.5, 121.6, 126.8. 128.4, 128.5, 128.9, 134.3, 135.7, 138.7, 170.1. Anal. Calcd for $C_{19}H_{20}N_2O$ (292): C, 78.05; H, 6.89; N, 9.58. Found: C, 78.14; H, 6.75; N, 9.64. Data was consistent with that reported in the literature.[17b]

*N-[2-(2-Phenyl-1H-indol-3-yl)ethyl]acetamide* (***3f***). Purification by silica gel column chromatography (cyclohexane/EtOAc 1:1) gave the product in 97% yield (270 mg): yellow solid; mp 114−116 °C (hexane); ESI MS (*m*/*z*) 279 $[M + H]^+$; IR ($cm^{-1}$, film) 1620; $^1$H NMR ($CDCl_3$) $\delta$ 1.77 (s, 3H), 3.14 (t, $J$ = 7 Hz, 2H), 3.56 (dt, $J_1 \approx J_2$ = 7 Hz, 2H), 5.52 (bs, 1H), 7.13−7.27 (m, 2 H), 7.35−7.68 (m, 7H), 8.37 (bs, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 23.1, 24.4, 40.2, 109.7, 111.1, 118.9, 119.8, 122.4, 127.9, 128.0, 129.0, 133.0, 135.4, 136.0, 170.2. Anal. Calcd for $C_{18}H_{18}N_2O$ (278): C, 77.67; H, 6.52; N, 10.06. Found: C, 77.65; H, 6.45; N, 10.21. Data was consistent with that reported in the literature.[18a]

*N,N′-[2,2′-(1H-Indole-2,3-diyl)bis(ethane-2,1-diyl)]diacetamide* (***3g***). Purification by silica gel column chromatography (EtOAc/MeOH 9:1) gave the product in 60% yield (172 mg): amorphous off-white solid; ESI MS (*m*/*z*) 288 $[M + H]^+$; IR ($cm^{-1}$, film) 1640; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.79 (s, 3H), 1.81 (s, 3H), 2.73−2.86 (m, 4H), 3.17−3.40 (m, 4H), 6.90−7.04 (m, 2H), 7.24−7.28 (m, 1H), 7.45−7.48 (m, 1H), 7.90−7.95 (m, 2H), 10.76 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 23.0, 23.1, 24.7, 26.5, 108.9, 111.1, 118.1, 118.6, 120.7, 128.6,


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134.3, 136.0, 169.5, 169.7. Anal. Calcd for $C_{16}H_{21}N_3O_2$ (287): C, 66.88; H, 7.37; N, 14.62. Found: C, 66.91; H, 7.56; N,14.91.

*N-[2-(2,5-Dimethyl-1H-indol-3-yl)ethyl]acetamide* (**3j**). Purification by silica gel column chromatography (EtOAc) gave the product in 85% yield (196 mg): red viscous oil; ESI MS ($m/z$) 231 $[M + H]^+$; IR ($cm^{-1}$, film) 1650, 2920, 3280; $^1H$ NMR ($CDCl_3$) $\delta$ 1.91 (s, 3H), 2.37 (s, 3H), 2.46 (s, 3H), 2.89 (t, $J$ = 6.5 Hz, 2H), 3.50 (dt, $J_1 \approx J_2$ = 6.5 Hz, 2H), 5.58 (bs, 1H), 6.97 (d, $J$ = 8 Hz, 1H), 7.18 (d, $J$ = 8 Hz, 1H), 7.28−7.29 (m, 1H), 7.97 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.6, 21.5, 23.3, 24.1, 40.1, 107.9, 110.1, 117.6, 122.6, 128.5, 128.8, 132.2, 133.6, 170.2. Anal. Calcd for $C_{14}H_{18}N_2O$ (230): C, 73.01; H, 7.88; N, 12.16. Found: C, 73.03; H, 7.81; N, 12.22 .

*N-(2-(5-Chloro-2-methyl-1H-indol-3-yl)ethyl)acetamide* (**3k**). Purification by silica gel column chromatography (EtOAc) gave the product in 87% yield (218 mg): pink solid; mp 121−125 °C ($Et_2O$); ESI MS ($m/z$) 251 $[M + H]^+$; IR ($cm^{-1}$, film) 1630; $^1H$ NMR ($CDCl_3$) $\delta$ 1.92 (s, 3H), 2.34 (s, 3H), 2.85 (t, $J$ = 7 Hz, 2H), 3.44 (dt, $J_1 \approx J_2$ = 7 Hz, 2H), 5.82 (bs, 1H), 7.01−7.18 (m, 1H), 7.43 (1H), 8.66 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.1, 24.4, 40.2, 109.7, 111.1, 118.9, 119.8, 122.4, 127.9, 128.0, 129.0, 133.0, 135.4, 136.0, 170.2. Anal. Calcd for $C_{13}H_{15}ClN_2O$ (250): C, 62.28; H, 6.03; N, 11.17. Found: C, 62.35; H, 6.28; N, 11.51.

*N-(2-(2-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)ethyl)acetamide* (**3l**). Purification by silica gel column chromatography (EtOAc) gave the product in 70% yield (239 mg): amorphous off-white solid; ESI MS ($m/z$) 343 $[M + H]^+$; IR ($cm^{-1}$, film) 1658; $^1H$ NMR ($CDCl_3$) $\delta$ 1.37 (s, 12H), 1.91 (s, 3H), 2.37 (s, 3H), 2.91 (t, $J$ = 6.5 Hz, 2H), 3.47 (dt, $J_1 \approx J_2$ = 6.5 Hz, 2H), 5.55 (bs, 1H), 7.25−7.29 (m, 1H), 7.59 (d, $J$ = 8 Hz, 1H), 8.00 (s, 1H), 8.21 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.5, 23.3, 24.0, 24.9, 40.3, 83.5, 109.0, 109.9, 125.4, 127.5, 128.3, 132.2, 137.5, 170.2 (carbon adjacent to boron was not observed). Anal. Calcd for $C_{19}H_{27}BN_2O_3$ (342): C, 66.68; H, 7.95; N, 8.19. Found: C, 66.65; H, 7.98; N, 8.31.

*N-[2-(5-Methoxy-2-methyl-1H-indol-3-yl)ethyl]acetamide* (**3m**). Purification by silica gel column chromatography (cyclohexane/EtOAc 3:7) gave the product in 63% yield (155 mg): brownish oil; ESI MS ($m/z$) 247 $[M + H]^+$; IR ($cm^{-1}$, film)1630; $^1H$ NMR ($CDCl_3$) $\delta$ 1.91 (s, 3H), 2.36 (s, 3H), 2.88 (t, 2H, $J$ = 6.5 Hz), 3.49 (dt, 2H, $J_1 \approx J_2$ = 6.5 Hz), 3.85 (s, 3H), 5.58 (bs, 1H), 6.76−6.81 (m, 1H), 6.95−6.97 (m, 1H), 7.15−7.19 (m, 1 H), 7.94 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.6, 23.3, 24.1, 40.0, 56.0, 100.1, 108.2, 110.7, 111.1, 129.0, 130.4, 133.0, 154.0, 170.2. Anal. Calcd for $C_{14}H_{18}N_2O_2$ (246): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.25; H, 7.45; N, 11.22. Data was consistent with that reported in the literature.[6d]

*N-[2-(6-Methoxy-2-phenyl-1H-indol-3-yl)ethyl]acetamide* (**3n**). Purification by silica gel column chromatography (cyclohexane/EtOAc 4:6) gave the product in 43% yield (78 mg): brownish oil; ESI MS ($m/z$) 309 $[M + H]^+$; IR ($cm^{-1}$, film) 1625; $^1H$ NMR ($CDCl_3$) $\delta$ 1.76 (s, 3H), 3.09 (t, 2H, $J$ = 7.0 Hz), 3.53 (dt, 2H, $J_1 \approx J_2$ = 7.0 Hz), 3.86 (s, 3H), 5.58 (bs, 1H), 6.79−6.90 (m, 2H), 7.28−7.56 (m, 6H), 8.43 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.2, 24.5, 40.2, 55.7, 94.6, 109.7, 119.6, 123.5, 127.5, 127.7, 129.0,133.1, 134.1,136.8, 156.8, 170.2. Anal. Calcd for $C_{19}H_{20}N_2O_2$ (308): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.11; H, 6.39; N, 9.36.

*N-[2-(1,2-Dimethyl-1H-indol-3-yl)ethyl]acetamide* (**3o**). Purification by silica gel column chromatography (cyclohexane/EtOAc 3:7) gave the product in 77% yield (177 mg): pink solid; mp 101−104 °C ($Et_2O$); ESI MS ($m/z$) 231 $[M + H]^+$; IR ($cm^{-1}$, film) 1650; $^1H$ NMR ($CDCl_3$) $\delta$ 1.91 (s, 3H), 2.39 (s, 3H), 2.96 (t, 2H, $J$ = 6.5 Hz), 3.49 (dt, 2H, $J_1 \approx J_2$ = 6.5 Hz), 3.68 (s, 3H), 5.65 (bs, 1H), 7.07−7.31 (m, 3H), 7.51−7.55 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 10.2, 23.4, 24.4, 29.6, 40.3, 107.7, 108.7, 117.7, 119.0, 120.8, 127.7, 133.8, 136.6, 170.0. Anal. Calcd for $C_{14}H_{18}N_2O$ (230): C, 73.01; H, 7.88; N, 12.16. Found: C, 73.11; H, 7.92; N, 12.01. Data was consistent with that reported in the literature.[6d]

*N-[2-(1-Methyl-1H-indol-3-yl)ethyl]acetamide* (**3p**). Purification by silica gel column chromatography (EtOAc) gave the product in 50% yield (108 mg): yellowish oil; ESI MS ($m/z$) 217 $[M + H]^+$; IR ($cm^{-1}$, film) 1630; $^1H$ NMR ($CDCl_3$) $\delta$ 1.94 (s, 3H), 2.97 (t, $J$ = 7 Hz, 2 H), 3.59 (dt, $J_1 \approx J_2$ = 7 Hz, 2H), 3.78 (s, 3H), 5.64 (bs, 1H), 6.90 (s, 1H), 7.10−7.35 (m, 3H), 7.59−7.63 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.6, 23.3, 24.1, 40.1, 108.4, 110.4, 117.7, 119.3, 121.1, 128.6, 132.1, 135.3, 170.2. Anal. Calcd for $C_{13}H_{16}N_2O$ (216): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.08; H, 7.55; N, 12.81. Data was consistent with that reported in the literature.[13]

*N-[2-(1-Benzyl-1H-indol-3-yl)ethyl]acetamide* (**3q**). Purification by silica gel column chromatography (EtOAc) gave the product in 65% yield (190 mg): yellowish oil; ESI MS ($m/z$) 293 $[M + H]^+$; IR ($cm^{-1}$, film) 1630; $^1H$ NMR ($CDCl_3$) $\delta$ 1.92 (s, 3H), 2.99 (t, $J$ = 7 Hz, 2H), 3.59 (dt, $J_1 \approx J_2$ = 7 Hz, 2H), 5.30 (s, 2H), 5.62 (bs, 1H), 6.98 (s, 1H), 7.11−7.33 (m, 8H), 7.62−7.66 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.3, 25.3, 40.0, 49.9, 109.8, 112.3, 119.0, 119.3, 122.0, 126.1, 126.9, 127.7, 128.1, 128.8, 136.8, 137.6, 170.1. Anal. Calcd for $C_{19}H_{20}N_2O$ (292): C, 78.05; H, 6.89; N, 9.58. Found: C, 78.14; H, 6.95; N, 9.39. Data was consistent with that reported in the literature.[13]

*N-[2-(1-Benzyl-5-methoxy-1H-indol-3-yl)ethyl]acetamide* (**3r**). The reaction was run on 10 mmol (2.37 g) scale. Purification by silica gel column chromatography (EtOAc) gave the product in 56% yield (1.81 g): off-white solid; mp 115 °C (EtOAc/hexane); ESI MS ($m/z$) 323 $[M + H]^+$; IR ($cm^{-1}$, film) 1641; $^1H$ NMR ($CDCl_3$) $\delta$ 1.93 (s, 3H), 2.92 (t, $J$ = 7 Hz, 2H), 3.59 (dt, $J_1 \approx J_2$ = 7 Hz, 2H), 3.87 (s, 3H), 5.24 (s, 2H), 5.73 (bs, 1H), 6.85−6.95 (m, 2H), 7.08−7.20 (m, 4H), 7.29−7.32 (m, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.4, 25.3, 40.0, 49.4, 55.3, 109.8, 112.1, 114.1, 119.0, 119.2, 121.9, 126.0, 128.1, 128.3, 129.5, 136.7, 159.1, 170.1. Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.41; H, 6.99; N, 8.59.

*N-[2-(1-(4-Methoxybenzyl)-1H-indol-3-yl)ethyl]acetamide* (**3s**). Purification by silica gel column chromatography (EtOAc) gave the product in 45% yield (145 mg): amorphous off-white solid; ESI MS ($m/z$) 323 $[M + H]^+$; IR ($cm^{-1}$, film) 1626; $^1H$ NMR ($CDCl_3$) $\delta$ 1.92 (s, 3H), 2.98 (t, $J$ = 6 Hz, 2H), 3.59 (dt, $J_1 \approx J_2$ = 6 Hz, 2H), 3.79 (s, 3H), 5.22 (s, 2H), 5.58 (bs, 1H), 6.82−6.87 (m, 2H), 6.95 (s, 1H), 7.07−7.35 (m, 5H), 7.60−7.64 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.4, 25.3, 40.0, 49.4, 55.3, 109.8, 112.1, 114.1, 119.0, 119.2, 121.9, 126.0, 128.1, 128.3, 129.5, 136.7, 159.1, 170.1. Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.43; H, 7.11; N, 8.81.

*N-[2-(1-Allyl-1H-indol-3-yl)ethyl]acetamide* (**3t**). Purification by silica gel column chromatography (EtOAc) gave the product in 40% yield (97 mg): amorphous off-white solid; ESI MS ($m/z$) 243 $[M + H]^+$; IR ($cm^{-1}$, film) 1650; $^1H$ NMR ($CDCl_3$) $\delta$ 1.94 (s, 3H), 2.98 (t, $J$ = 6 Hz, 2H), 3.60 (dt, $J_1 \approx J_2$ = 6 Hz, 2H), 4.69−4.72 (m, 2H), 5.06−5.25 (m, 2H), 5.77 (bs, 1H), 5.90−6.09 (m, 1H), 6.96 (s, 1H), 7.10−7.35 (m, 3H), 7.60−7.64 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.4, 25.2, 40.0, 48.7, 109.7, 112.0, 117.3, 118.9, 119.1, 121.8, 125.7, 128.0, 133.5, 136.6, 170.1. Anal. Calcd for $C_{15}H_{18}N_2O$ (242): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.26; H, 7.24; N, 11.42.

*Benzyl 2-(2-Methyl-1H-indol-3-yl)ethylcarbamate* (**3u**). Purification by silica gel column chromatography (cyclohexane/EtOAc 8:2) gave the product in 60% yield (185 mg): yellowish oil; ESI MS ($m/z$) 309 $[M + H]^+$; IR ($cm^{-1}$, film) 1700, 2930, 3320; $^1H$ NMR ($CDCl_3$) $\delta$ 2.34 (s, 3H), 2.95 (t, $J$ = 7 Hz, 2H), 3.48 (dt, $J_1 \approx J_2$ = 7 Hz, 2H), 4.91 (bs, 1H), 5.15 (s, 2H), 7.08−7.55 (m, 9H), 8.03 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.5, 24.6, 41.5, 66.6, 108.2, 110.4, 117.8, 119.3, 121.1, 124.2, 128.1, 128.5, 130.5, 132.1, 135.3, 136.7, 156.5. Anal. Calcd for $C_{19}H_{20}N_2O_2$ (308): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.08; H, 6.52; N, 9.11.

*2-[2-(2-Methyl-1H-indol-3-yl)ethyl]isoindolyn-1,3-dione* (**3v**). Purification by silica gel column chromatography (cyclohexane/EtOAc 8:2) gave the product in 78% yield (238 mg): pale yellow solid; mp 171−174 °C (hexane); ESI MS ($m/z$) 305 $[M + H]^+$; IR ($cm^{-1}$, film) 1680; $^1H$ NMR ($CDCl_3$) $\delta$ 2.43 (s, 3H), 3.04−3.12 (m, 2H), 3.87−3.95 (m, 2H), 7.05−7.15 (m, 2H), 7.24−7.27 (m, 1H), 7.64−7.87 (m, 6H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.5, 23.5, 38.3, 107.8, 110.3, 117.9, 119.4, 121.1, 123.1, 128.6, 132.0, 132.2, 133.9, 135.2, 168.4. Anal. Calcd for $C_{19}H_{16}N_2O_2$ (304): C, 74.98; H, 5.30; N, 9.20. Found: C, 75.03; H, 5.53; N, 8.93.

*4-Methyl-N-[2-(2-methyl-1H-indol-3-yl)ethyl]-benzenesulfonamide* (**3w**). Purification by silica gel column chromatography (cyclohexane/EtOAc 7:3) gave the product in 50% yield (164 mg): brownish solid; mp 135−137 °C (hexane); ESI MS


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($m/z$) 329 $[M + H]^+$; IR ($cm^{-1}$, film) 1654; $^1H$ NMR ($CDCl_3$) $\delta$ 2.34 (s, 3H), 2.41 (s, 3H), 2.90 (t, $J$ = 6 Hz, 2H), 3.22 (dt, $J_1 \approx J_2$ = 6 Hz, 2H), 4.46 (t, $J$ = 6 Hz, 1H), 6.99−7.33 (m, 6H), 7.61−7.65 (m, 2H), 7.92 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.8, 21.6, 24.7, 43.3, 107.1, 110.5, 117.7, 119.5, 121.4, 127.1, 128.2, 129.7, 132.6, 135.4, 136.9, 143.4. Anal. Calcd for $C_{18}H_{20}N_2O_2S$ (328): C, 65.83; H, 6.14; N, 8.53. Found: C, 65.75; H, 6.09; N, 8.46. Data was consistent with that reported in the literature.[6d]

*2,2,2-Trifluoro-N-[2-(2-methyl-1H-indol-3-yl)ethyl]acetamide (**3x**).* Purification by silica gel column chromatography (cyclohexane/EtOAc 7:3) gave the product in 89% yield (240 mg): brownish solid; mp 98−102 °C (hexane); ESI MS ($m/z$) 271 $[M + H]^+$; IR ($cm^{-1}$, film) 1630; $^1H$ NMR ($CDCl_3$) $\delta$ 2.39 (s, 3H), 3.01 (t, $J$ = 6.5 Hz, 2H), 3.63 (dt, $J_1 \approx J_2$ = 6.5 Hz, 2H), 6.50 (bs, 1H), 7.10−7.34 (m, 3H), 7.49−7.53 (m, 1H), 8.01 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.3, 23.5, 40.3, 107.1, 110.6, 115.9 ($J$ = 285 Hz), 117.5, 119.6, 121.4, 128.2, 132.4, 135.4, 157.3 ($J$ = 35 Hz). Anal. Calcd for $C_{13}H_{13}F_3N_2O$ (270): C, 57.78; H, 4.85; N, 10.37. Found: C, 57.65; H, 4.79; N, 10.26. Data was consistent with that reported in the literature.[6d]

*2-(2-Methyl-1H-indol-3-yl)ethanamine (**3y**).* A solution of **3x** (1 mmol) and potassium carbonate (5 mmol) in MeOH (20 mL)/$H_2O$ (1.5 mL) was heated to reflux for 2 h. After removal of volatiles under reduced pressure, to the residue was added water and the mixture extracted three times with dichloromethane. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (dichloromethane/methanol 95:5): yield 75% (131 mg); mp 95 °C; ESI MS ($m/z$) 175 $[M + H]^+$, 158 $[M + H - NH_3]^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.83 (bs, 2H), 2.38 (s, 3H), 2.83−3.02 (m, 4H), 7.06−7.17 (m, 2H), 7.25−7.29 (m, 1H), 7.50−7.54 (m, 1H), 8.14 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.7, 28.1, 42.5, 108.8, 110.3, 117.9, 119.1, 120.9, 128.7, 132.0, 135.4. Anal. Calcd for $C_{11}H_{14}N_2$ (174): C, 75.82; H, 8.10; N, 16.08. Found: C, 75.79; H, 8.17; N, 16.18. Data was consistent with that reported in the literature.[16]

*N-[2,2-bis(2-Methyl-1H-3-yl)ethyl]acetamide (**4**).* Compound **4** was isolated as the major product when 1.5 equiv of TFA was used. Purification by silica gel column chromatography (cyclohexane/EtOAc 3:7) gave the product in 91% yield (314 mg): yellowish solid; mp 168−170 °C (EtOAc); ESI MS ($m/z$) 215 $[M + H - C_9H_8NH]^+$; IR ($cm^{-1}$, film) 3297, 3209, 1618; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.74 (s, 3H), 2.32 (s, 6H), 3.93 (dd, $J_1 \approx J_2$ = 7 Hz, 2H), 4.60 (t, $J$ = 7 Hz, 1H), 6.76−6.94 (m, 4H), 7.19 (d, $J$ = 7.5 Hz, 2H), 7.36 (d, $J$ = 7.5 Hz, 2H), 7.73 (m, 1H), 10.64 (bs, 2H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 12.7, 23.0, 34.5, 43.6, 111.2,112.4, 118.8, 119.2, 120.3,128.7, 132.4, 136.0, 170.1. Anal. Calcd for $C_{22}H_{23}N_3O$ (345): C, 76.49; H, 6.71; N, 12.16. Found: C, 76.59; H, 6.77; N, 12.18.

**Melatonin.** In THF (40 mL) was condensed $NH_3$ (105 mL) at −78 °C followed by addition of Na (970 mg, 42 mmol). A solution of **3r** (2.25 g, 7 mmol) in THF (40 mL) was then added dropwise, and the mixture was stirred at −33 °C for 1 h. Solid $NH_4Cl$ was added, the bath removed, and the ammonia allowed to evaporate. The solvent was evaporated under reduced pressure, water (80 mL) was added, and the aqueous layer was extracted three times with EtOAc (60 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc) to give melatonin as a white solid: yield 92% (1.18 g); mp 117−120 °C; ESI MS ($m/z$): 233 $[M + H]^+$; IR ($cm^{-1}$, film) 1627; $^1H$ NMR ($CDCl_3$) $\delta$ 1.93 (s, 3H), 2.94 (t, $J$ = 7 Hz, 2H), 3.59 (dd, $J_1 \approx J_2$ = 7 Hz, 2H), 3.86 (s, 3H), 5.69 (bs, 1H), 6.87 (d, $J$ = 8.5 Hz, 1H), 7.02 (d, $J$ = 5.0 Hz, 2H), 7.27 (d, $J$ = 8.5 Hz 1H), 8.32 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.4, 25.3, 39.8, 55.9, 100.4, 112.1, 112.4, 112.6, 122.7, 127.7, 131.6, 154.1, 170.2. Anal. Calcd for $C_{13}H_{16}N_2O_2$ (232): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.15; H, 6.83; N, 12.26. Data was consistent with that reported in the literature.[18c]

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental details of the reactions and copies of $^1H$ NMR and $^{13}C$ NMR spectra for all substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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