Synthesis of Tryptamines from Radical Cyclization of 2-Iodoaryl Allenyl Amines and Coupling with 2-Azallyls

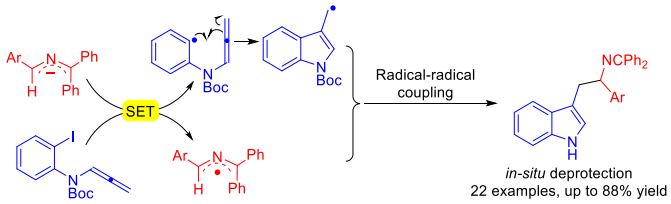
Bo Wang,[a,b] Minyan Li,[a] Gui Gao,[a,c] Alvaro Sanz-Vidal,[a,d] Bing Zheng,[c,*] Patrick J. Walsh[a,*]

[a] Roy and Diana Vagelos Laboratories Department of Chemistry, University of Pennsylvania 231 South 34th Street, Philadelphia, PA (USA). *e-mail: pwalsh@sas.upenn.edu.

[b] Department of Chemistry, Tsinghua University, 100084 Beijing, China.

[c] Department of Chemistry, China Agricultural University, Beijing 100193, P. R. China. *e-mail: 2014026@cau.edu.cn

[d] Departamento de Química Orgánica, Universidad de Valencia, 46100 Burjassot, Spain.



ABSTRACT: An efficient synthesis of tryptamines is developed. Indole structures were constructed using 2-iodoaryl allenyl amines as electron acceptors and radical cyclization precursors. Radical-radical coupling of indolyl methyl radicals and azaallyl radicals led to the tryptamine derivatives. The utility and versatility of this method are showcased by the synthesis of 22 examples of tryptamines in up to 88% yield. In each case, indole formation is accompanied by in situ removal of the Boc protecting group.

Introduction

Tryptamines are an important class of psychoactive substances and are naturally occurring chemical skeletons.[1-3] They have gained great attention in the pharmaceutical industry due to their existence in natural products and commercial medications, such as serotonin, melatonin, sumatriptan and luzindole (Figure 1).[4-6] In addition, they also function as key building blocks in synthetic organic chemistry and as ligand precursors.[7-17] There are two main strategies for the synthesis of tryptamines: (1) functionalization of the C3 carbon of indoles[18-21] and (2) construction of indoles through annulation reactions, which usually employ transition metal catalysts,[22-29] among others.[30, 31]

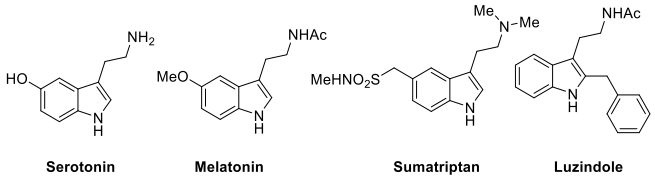


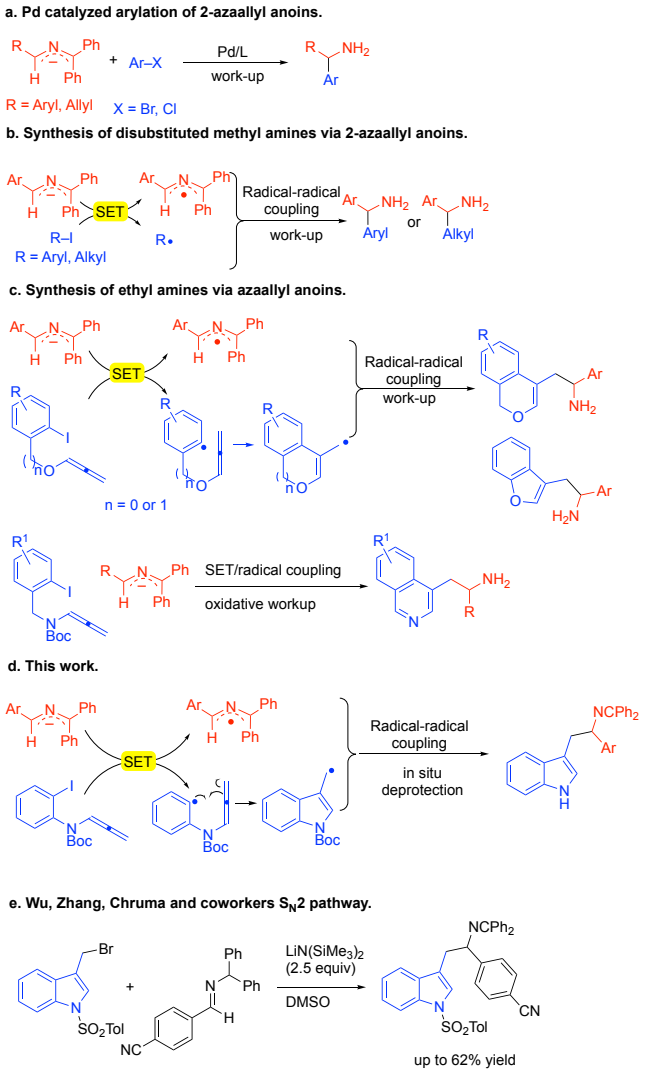
Figure 1. Natural products and pharmaceuticals containing tryptamines.

2-Azaallyl anions have been widely utilized in amine syntheses.[32] Since 2014, members of our team has accessed a wide variety of diarylmethylamines and aryl-allyl-methyl amines through Pd catalyzed functionalization 2-azaallyl anions (Scheme 1a).[33-35] In 2017, Kozlowski, Walsh and coworkers discovered that 2-azaallyl anions could behave as "super electron donors" (SEDs)[36] and developed a series of SED-based radical coupling strategies for the transition metal-free synthesis of alkyl and aryl-methylamines (Scheme 1b).[37] Chruma, Walsh and co-workers found that the highly colored 2-azaallyl anions could reduce less reactive aryl bromides and chlorides upon irradiation.[33] Panetti, Schelter, Walsh and co-workers reported the solid-state structures and electrochemistry of the 2-azaallyl anions.[38] Recently, Yang, Zhang, Walsh and co-workers applied this unique radical generation and coupling strategy in the synthesis of benzofurylethylamines , isochromenylethylamines and isoquinoline ethylamines using 2-iodo aryl allenyl ethers and amines as electron acceptors (Scheme 1c).[39-41] Cross-dehydrogenative coupling reactions were also introduced.[42, 43] Additionally, Nishikata, Yazaki, Ohshima and their coworkers used a copper catalyzed generation of 2-azaallyl radicals to develop a synthesis of hindered α-amino acid derivatives.[44, 45]

Given the high demand for tryptamine derivatives in drug discovery, and our experience with 2-azaallyl anions as SEDs, we became interested in expanding our ethylamine synthesis strategy to tryptamines (Scheme 1d).

We hypothesized that the aryl radical derived from SET between the 2-azaallyl anion and 2-iodoaryl allenyl amines would undergo radical cyclization to form the indolyl methyl radical, which we envisioned could be trapped by the newly formed 2-azaallyl radical to form tryptamines. Herein, we report an efficient transition-metal-free synthesis of tryptamine derivatives through a cascade protocol involving i. deprotonation of ketimines; ii. single electron transfer to the aryl iodide with subsequent loss of iodide; iii. radical cyclization and; iv. radical-

radical coupling (Scheme 1d). Interestingly, under basic conditions, the Boc group was deprotected in all cases, conveniently affording the free indoles. We note that in 2021 Wu, Zhang, Chruma and coworkers also reported the synthesis of tryptamine derivatives using 2-azaallyl anion nucleophiles.[46] This work is complementary to the method described herein, with reactions proceeding largely through 2-electron processes on preformed indole core structures (Scheme 1e).[46]

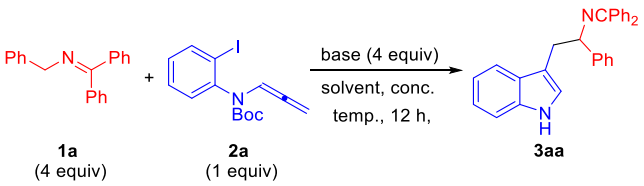


Scheme 1. Functionalization of azaallyl anions.

Results and Discussion

Based on our benzofurylethylamine synthesis (Scheme 1c), we selected Boc-protected 2-iodophenyl allenyl amine **2a** and ketimine **1a** as model substrates, dimethoxyethane (DME) as solvent and examined 6 different bases [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, LiO^tBu, NaO^tBu, and KO^tBu] at 0.1 M and room temperature. Interestingly, *in situ* Boc-deprotected product **3aa** was delivered by $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$ in 56, 74 and 26% assay yields (AY, as determined by ^1H NMR integration of the unpurified reaction mixtures against an internal standard, Table 1, entries 1–3). Traces of product were detected when LiO^tBu, NaO^tBu, and KO^tBu were used (entries 4–6). The conditions in entry 2 were next used to probe the impact of solvent as listed in entries 7–11. CPME, MTBE, dioxane, THF and toluene all gave decreased yields (<5–57% AY). Examination of concentration indicated that the reaction was most efficient at 0.2 M, leading to product **3a** in 80% isolated yield (entries 2, 12 and 13). Finally, increasing the reaction temperature to 60 and 80 °C led to slightly lower conversion to **3aa** (78 and 74% AY, respectively, entries 14 and 15).

Table 1. Optimization of coupling between ketimine **1a** and allenyl ether **2a**.[a,b]

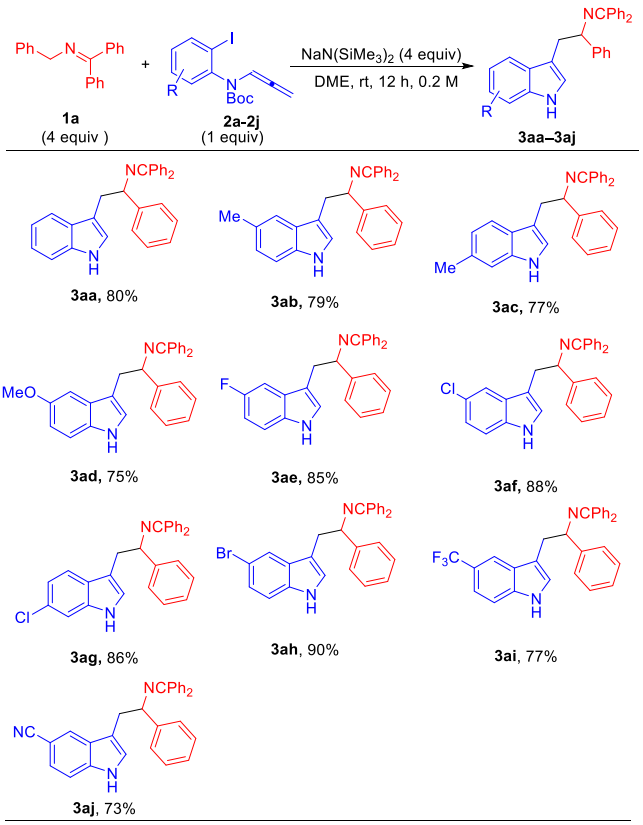


Entry	Base	Sol.	Conc. [M]	Temp. [°C]	AY [%]
1	$LiN(SiMe_3)_2$	DME	0.1	rt	56
2	$NaN(SiMe_3)_2$	DME	0.1	rt	74
3	$KN(SiMe_3)_2$	DME	0.1	rt	26
4	LiO^tBu	DME	0.1	rt	<5
5	NaO^tBu	DME	0.1	rt	<5
6	KO^tBu	DME	0.1	rt	<5
7	$NaN(SiMe_3)_2$	CPME	0.1	rt	38
8	$NaN(SiMe_3)_2$	MTBE	0.1	rt	40
9	$NaN(SiMe_3)_2$	Dioxane	0.1	rt	<5
10	$NaN(SiMe_3)_2$	THF	0.1	rt	57
11	$NaN(SiMe_3)_2$	Toluene	0.1	rt	12
12	$NaN(SiMe_3)_2$	DME	0.2	rt	80[c]
13	$NaN(SiMe_3)_2$	DME	0.05	rt	51
14	$NaN(SiMe_3)_2$	DME	0.2	60	78
15	$NaN(SiMe_3)_2$	DME	0.2	80	74

[a]Reaction conditions: **1a** (0.4 mmol, 4.0 equiv), **2a** (0.1 mmol, 1.0 equiv), base (0.4 mmol, 4.0 equiv), 12 h. [b]Assay yields (AY) determined by ^1H NMR spectroscopy integration of the crude reaction mixtures using CH_2Br_2 as an internal standard. [c]Isolated yield after chromatographic purification.

With the optimized conditions in hand (Table 1, entry 12), we evaluated various 2-iodoaryl allenyl amines with diverse substituents (Table 2). In general, all tryptamine products were isolated as free indoles and in good to excellent yield regardless of the substituents on the aniline core. Coupling of ketimine **1a** with phenyl substrate **2a** afforded product **3aa** in 80% yield. Methyl groups *para* or *meta* to the nitrogen of **2** provided products **3ab** and **3ac** in 77–79% yield. Methoxy situated *para* to the nitrogen gave 75% yield. Representative substrates with F, Cl, or Br *meta* or *para* to the nitrogen exhibited increased yields (85–90%). These results suggest that the SET between the 2-azaallyl anion and aryl iodide is highly chemoselective toward loss of iodide. Substrates carrying strongly electron-withdrawing CF_3 and CN *para* to the nitrogen also perform well, providing tryptamine derivatives in 77 and 73% yield, respectively.

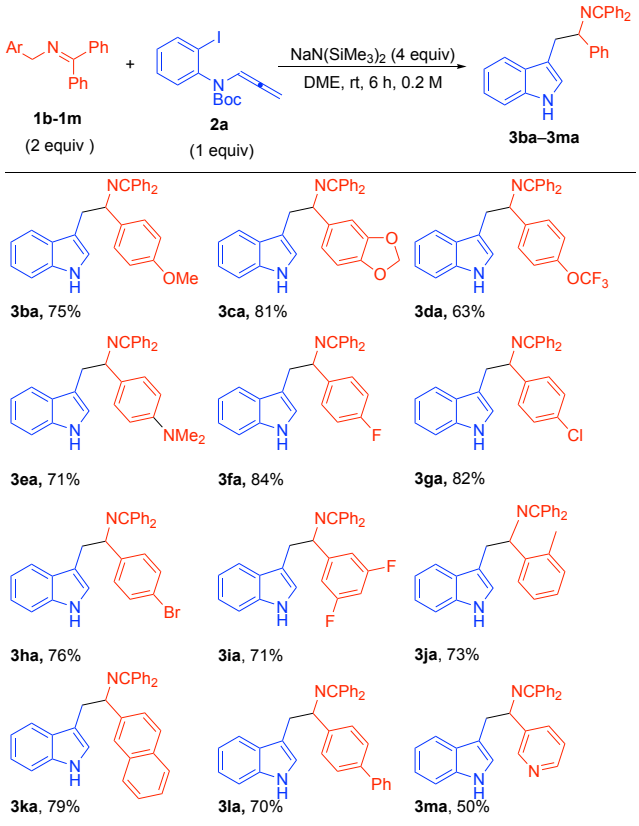
Table 2. Scope of 2-iodoaryl allenyl amines.



[a]Reaction conditions: **1a** (0.4 mmol, 4.0 equiv), **2a-2j** (0.1 mmol, 1.0 equiv), base (0.4 mmol, 4.0 equiv), rt, 12 h. [b]Isolated yield after chromatographic purification.

We next subjected various substituted *N*-benzyl ketimines to the optimized conditions using **2a** as a representative allenyl amine (Table 3). It was observed that the electronic properties of the *N*-benzyl group did not significantly impact the tryptamine synthesis, with most yields above 70%. Electron rich substrates (**2b**, 4-OMe; **2c**, 3,4-methylenedioxy; **2d**, 4-OCF_3 and **2e**, 4-NMe_2) afforded tryptamine products **3ba–3ea** in 75 , 81, 63 and 71% yields, respectively. The *N*-benzyl groups possessing 4-F, 4-Cl and 4-Br substituents gave the desired products (**3fa–3ha**) in 76–84% yields. An *N*-benzyl ketimine bearing a 3,5-difluoro phenyl group reacted to provide the product **3ia** in 71% yield. Increased steric hindrance from a 2-methylbenzyl group minimally impacted the reaction and provided product **3ja** in 73% yield. Extended π–systems were also tolerated: 2-naphthyl- and biphenyl containing-ketimines gave the corresponding products **3ka** and **3la** in 79 and 70% yields, respectively. Notably, a ketimine with a 4-pyridylmethyl group was also tolerated, albeit with 50% yield of the product **3ma**.

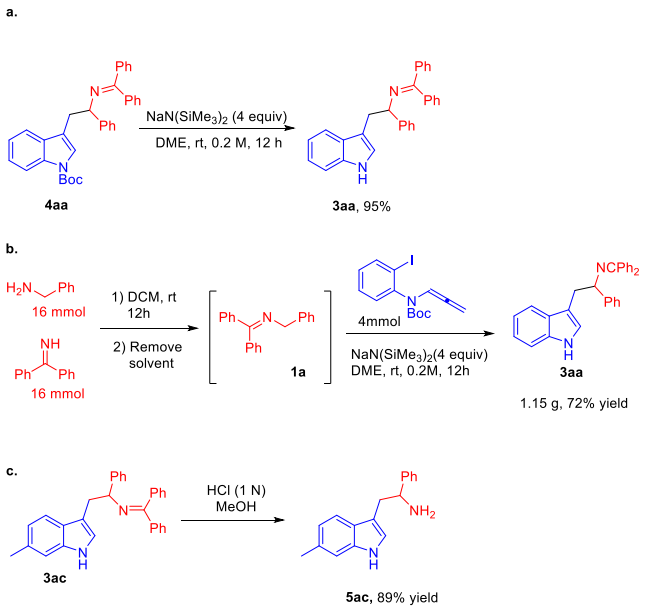
Table 3. Scope of ketimines as SED precursors and radical coupling partners.[a,b]



[a]Reaction conditions: **1b-1m** (0.4 mmol, 4.0 equiv), **2a** (0.1 mmol, 1.0 equiv), base (0.4 mmol, 4.0 equiv), rt, 12 h. [b]Isolated yield after chromatographic purification.

As noted above, the indole *N*-Boc groups were fully deprotected under the reaction conditions. Boc deprotection of nitrogen-containing heterocycles under basic conditions has been reported.[47] We probed the deprotection of the *N*-Boc group by subjecting Boc-**3aa** to 4 equiv of $NaN(SiMe_3)_2$ in DME solvent. Deprotected product **3aa** was isolated in 95% yield (Scheme 2a), which indicated that the deprotection proceeded by an anionic pathway rather than SET from the 2-azaallyl anion. We note that in all reactions using 2-azaallyl anions as SED's, some ketimine starting material is converted to diimine coupling products formed from dimerization of the 2-azaallyl species.

Scaleup was conducted by telescoping the imine synthesis by combining the benzophenone imine (16 mmol) and benzylamine (16 mmol) in dichloromethane at rt to form the *N*-benzylimine **1a** (Scheme 2b). Removal of the volatile materials under reduced pressure and addition of allene **2a** (4 mmol), DME, and $NaN(SiMe_3)_2$ resulted in a dark purple solution that faded as the reaction progressed. After stirring for 12 h at rt, the reaction was worked up to provide **3aa** in 72% yield (1.15 g product). Finally, we also performed the hydrolysis of the indole-imine **3ac** to afford the corresponding indole-amine **5ac** in 89 % yield (Scheme 2c).



Scheme 2. a. Probing the Boc group deprotection; **b.** Gram scale synthesis of **3aa**; **c.** Hydrolysis of imine **3ac**.

Conclusions

In summary, we successfully extended our SED chemistry of 2-azaallyl anions to the medicinally important indolamines, a well-known class of neurotransmitters. Our cyclization/radical-radical coupling strategy relies on the persistent radical effect of the 2-azaallyl radical.[48] This method provides a straightforward route to accesses tryptamines from radical cyclization of allenyl amine precursor. Notably, all the products obtained under the reaction conditions are free indoles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for all new compounds [**2**–**5**]. Copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF).

AUTHOR INFORMATION

Corresponding Authors

pwalsh@sas.upenn.edu

2014026@cau.edu.cn

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