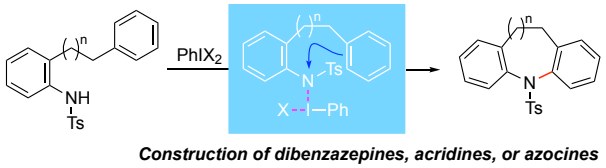
Iodine(III)-Mediated Oxidation of Anilines to Construct Dibenzazepines

Carmen Margaret White,[a] Naranchimeg Zorigt,[a] Tianning Deng,[a] and Tom G. Driver*[a]

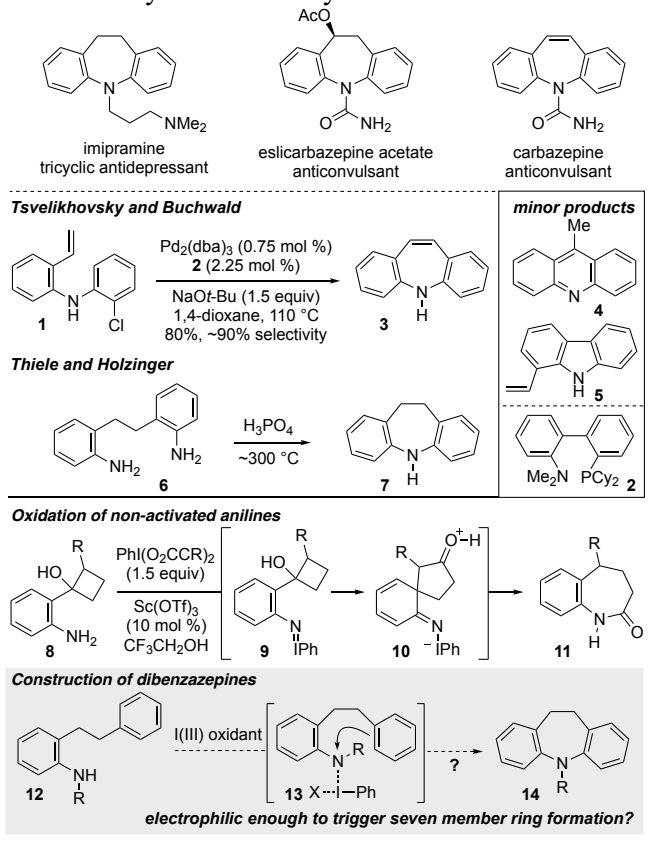
University of Illinois Chicago, Department of Chemistry, 845 West Taylor Street, MC 111, Chicago, Illinois, USA 60607
tgd@uic.edu

ABSTRACT. The development of an efficient process that produces bioactive medium-sized *N*-heterocyclic scaffolds from 2-substituted anilines using an iodine(III)-oxidant is reported. Construction of the medium-sized ring is mild, occurs at room temperature, and proceeds via cationic reactive intermediates.



Construction of dibenzazepines, acridines, or azocines

Despite their established and important bioactivity,[1] medium-sized *N*-heterocycles are underrepresented in pharmaceutical libraries.[2] Dibenzazepines and partially saturated dibenzazepines are important scaffolds,[3,4] which are found in the core of pharmaceutical agents, such as imipramine, eslicarbazepine acetate,[4] and carbamazepine (Scheme 1). While this bioactivity has spurred the development of methods to ease their synthesis,[5,6,7] the unfavorably high transition state energy barriers for medium-sized ring closure can limit the efficiency and selectivity of bond construction.[8] These weaknesses are illustrated in the common

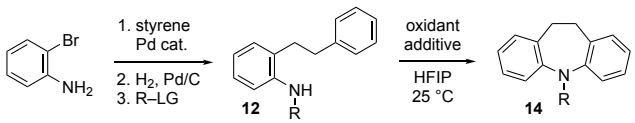


Scheme 1. Construction of the dibenzazepine scaffold.

approaches to this scaffold, which involve either creating a C–C bond through a cross-coupling reaction, which requires pre-existing functionality and can afford a mixture of *N*-heterocyclic products,[7] or a C–NAr bond through thermolysis of a symmetrical iminobibenzyl first reported by Thiele and Holzinger in 1899,[9] and is still widely employed for the synthesis of analogs.[10] This latter approach requires installation of functionality to occur post cyclization to differentiate the two sides of the dibenzazepine and can be non-selective.[11] In 2020, we reported that benzazepinones could synthesized from the room temperature oxidation of anilines that contain a strained *ortho*-cycloalkanol substituent,[12] and posited that the electrophilic nature of *N*-aryl nitrenoid triggered the ring-expansion-rearrangement sequence to provide **11**. We were curious if this electrophilicity could be harnessed to enable the synthesis of dibenzazepines by trapping **13** with a pendant arene. If successful, this approach would enable the synthesis of differentially substituted dibenzazepines under mild conditions through the construction of a C–NAr from a C–H bond and address the weakness in the traditional approach to this scaffold that requires a symmetrical substrate.

To determine if dibenzazepines could be constructed from *ortho*-substituted anilines, the reactivity of **12** was investigated towards oxidants (Table 1). The substrate for our study was synthesized by a Heck cross-coupling reaction between 2-bromoaniline and styrene, followed by hydrogenation of the resulting stilbene, and terminating with a nitrogen-protection reaction. The optimization process began by submitting **12a** (R = H) to iodosobenzene (PhIO) in hexafluoroisopropanol (HFIP) with 4 Å molecular sieves as an additive to remove the water biproduct because we found this combination of solvent and oxidant to be effective in promoting RI-catalyzed oxidative cyclization-migration reactions.[13] In contrast to our previous work, a poor yield of **14a** was observed (entry 1). Consequently, a series of *N,N*-disubstituted substrates were screened to determine if the poor yield was due to the instability of the product or an *N*-H reactive intermediate to

Table 1. Development of optimal conditions for dibenzazepine formation.



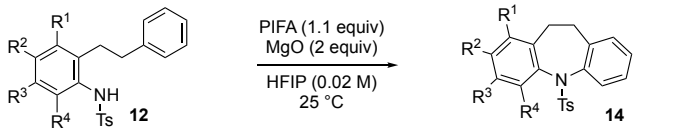
entry	**12**	R	oxidant (equiv)	additive[a]	time	yield **14**, %[b]
1	**a**	H	PhIO (1.1)	4Å MS	16 h	37
2	**b**	iPr	PhIO (1.1)	4Å MS	16 h	12
3	**c**	Boc	PhIO (1.1)	4Å MS	16 h	39
4	**d**	Ac	PhIO (1.1)	4Å MS	16 h	85
5	**e**	Ts	PhIO (1.1)	4Å MS	16 h	88
6	**e**	Ts	$PhI(O_2CCF_3)_2$ (1.1)	...	0.5 h	73
7	**e**	Ts	$PhI(O_2CCF_3)_2$ (1.1)	TFA	5 min	72
8	**e**	Ts	$PhI(O_2CCF_3)_2$ (1.1)	MgO	5 min	95
9	**e**	Ts	HTIB (1.1)	MgO	0.3 h	92
10	**e**	Ts	$PhI(O_2CCH_3)_2$ (1.1)	MgO	5 min	22
11	**e**	Ts	Selectfluor (1.1)	MgO	3 h	27
12	**e**	Ts	*m*-CPBA (1.1)	MgO	10 h	trace

[a] 200 wt % of 4Å MS, 2 equiv of TFA, or 2 equiv of MgO added; [b] As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. HFIP = hexafluoroisopropanol; Ac = acetyl; Ts = tosyl; TFA = trifluoroacetic acid; HTIB = [hydroxy(tosyloxy)iodo]benzene; *m*-CPBA = *meta*-chloroperbenzoic acid.

the oxidative conditions. While the use *N*-alkyl- or *N*-Boc-substrates did not improve the reaction outcome (entries 2 and 3), changing the *N*-substituent to a more robust electron-withdrawing protecting group significantly increased the yield of the transformation to afford *N*-Ac **14c** in 85% and *N*-Ts **14d** in 88% (entries 4 and 5). In attempt to increase the yield and reduce the reaction time, a stronger oxidant, $PhI(O_2CCF_3)_2$ (PIFA) was investigated. Using this oxidant enabled the reaction time to be reduced to 30 minutes and still afforded dibenzazepine **14d** in good yield (entry 6). Our next experiments focused on additives to further increase the yield of **14d**. No improvement in the reaction outcome was observed with the addition of trifluoroacetic acid (entry 7). In contrast, the addition of magnesium oxide to eliminate the acid byproduct gave quantitative yields of **14d** in as little as 5 minutes (entry 8). While [hydroxy(tosyloxy)iodo]benzene (HTIB) produced **14d** in great yield (entry 9), other oxidants screened (e.g. (diacetoxyiodo)benzene (PIDA), Selectfluor, on *m*-CPBA) gave poor yields of dibenzazepine (entries 10 – 12). These investigations revealed that benzazepines could be smoothly formed using either PhIO and 4Å MS (entry 5) or PIFA and MgO (entry 7).

The effect of changing the substituents on the aniline portion of **12** was investigated (Table 2). The impact of changing the electronic nature of the aryl amine was assayed by changing the identity of the R^2- or R^3-substituent. While significant decomposition was obtained with an electron-donating methoxy R^2-group (entry 1), the yield of dibenzazepine **14** increased as R^2 became more electron-withdrawing (entries 2 – 9). Aniline **12k**, however, required the use of PhIO to minimize decomposition biproducts. To determine the effect of increasing the steric environment around either the nitrogen- or the *ortho*-phenethyl substituent, a methyl group was placed at either the R^1- or R^4-position (entries 10 and 11). While increasing the steric environment around the nitrogen decreased the yield of **14o** (entry 10), the presence of an R^4-methyl did not negatively affect the reaction outcome to provide **14p** in 70% provided that PhIO was used as the oxidant.

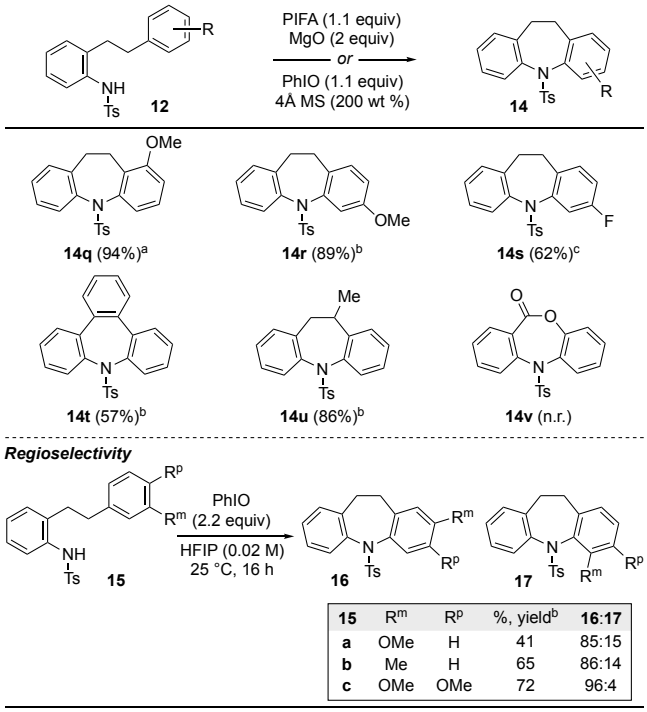
Table 2. Scope and limitations with regards to the aniline portion.



entry[a]	**12**	R^1	R^2	R^3	R^4	time	yield, %[b]
1	**f**	H	OMe	H	H	10 min	dec
2	**g**	H	Me	H	H	10 min	50
3	**h**	H	F	H	H	10 min	85
4	**i**	H	I	H	H	1 h	83
5	**j**	H	OCF_3	H	H	1 h	82
6	**k**	H	CO_2Me	H	H	1 h	50 (78)[c]
7	**l**	H	CF_3	H	H	1 h	73
8	**m**	H	H	F	H	24 h	81[d]
9	**n**	H	H	CF_3	H	4 h	52
10	**o**	H	H	H	Me	28 h	40
11	**p**	Me	H	H	H	2 h	47 (70)[e]

[a] Conditions: 0.1 mmol of **12**, 0.11 mmol of PIFA, and 0.2 mmol of MgO in 2 mL of HFIP; [b] Isolated yield after silica gel chromatography. [c] 0.22 mmol of PhIO, 200 wt % of 4 Å MS used; [d] 2.5 mL HFIP used; [e] 0.11 mmol of PhIO, 200 wt % of 4 Å MS used.

Next, changing the identity of the *ortho*-phenethyl substituent was surveyed (Scheme 2). In contrast to the reactivity of **12f**, the addition of a methoxy substituent did not hinder the reaction: exposure of **12q** to reaction conditions provided **14q** in 94%. This reversal of the electronic preference was also observed in substrates that varied the identity of the 4-substituent; higher yields were observed with electron-donating substituents (e.g. **14q** and **14r**) than **12s** bearing an electron-withdrawing 4-fluorine substituent. Our next investigations focused on the effect of changing the identity of the tether. While terphenyl amine **12t** and methyl-substituted **12u** were smoothly converted *N*-heterocycles **14t** and **14u**, benzoate **12v** proved to be recalcitrant towards the reaction conditions. To determine if the reaction was site selective, **15a** and **15b** were subjected to reaction conditions to provide dibenzazepines as an 85:15 mixture of regioisomers. Improved selectivity was observed from dimethoxy-substituted **15c** to provide a 96:4 mixture of dibenzazepines.

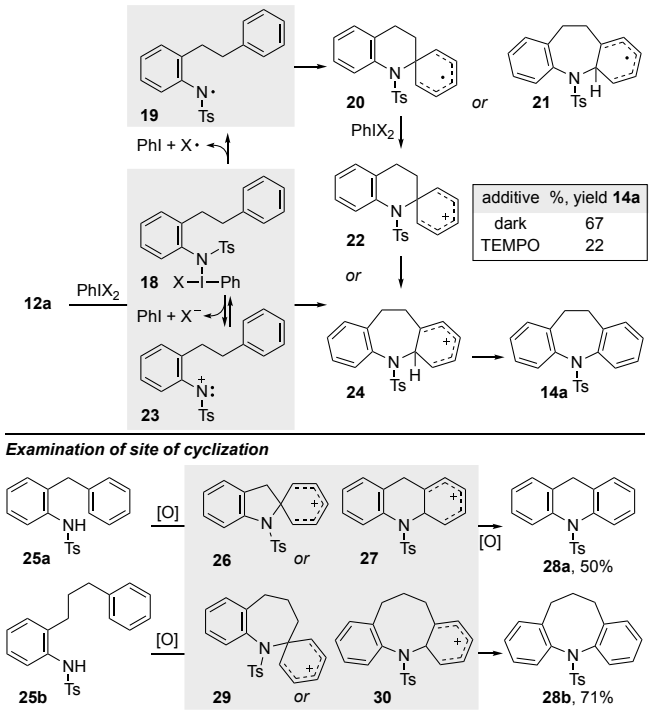


15	R^m	R^p	%, yield[b]	16:17
a	OMe	H	41	85:15
b	Me	H	65	86:14
c	OMe	OMe	72	96:4

[a] conditions: 0.1 mmol of **12**, 0.11 mmol of PIFA, and 0.2 mmol of MgO in 2 mL of HFIP; [b] conditions: 0.1 mmol of **12**, 0.11 mmol of PhIO, and 200 wt % of 4Å MS in 2 mL of HFIP; [c] conditions: 0.1 mmol of **12**, 0.11 mmol of PhIO, and 200 wt % of 4Å MS in 4 mL of HFIP.

Scheme 2. Effect of changing the *ortho*-substituent identity.

Dibenzazepine formation could occur via the cyclization of radical- or cationic reactive intermediates (Scheme 3).[14] *N*-Iodination of **12a** with $PhIX_2$ generates intermediate **18**. Homolysis of the C–N bond in **18** produces *N*-centered radical **19**,[15, 16] which cyclizes with the pendant arene to produce either spirocycle **20** through a 5-*exo*-trig cyclization or **21** through a kinetically less favorable 7-*exo*-trig cyclization.[17,18] Oxidation of cyclohexadienyl radical **20** then produces **22**. This mechanism, however, would require two equivalents of the iodine(III) oxidant for success. Alternatively, this spirocycle could be directly formed from nucleophilic attack of the arene on **18** or nitrenium ion **23**, which could be produced from elimination of PhI from **18**.[19] Ring-expansion of spirocycle would form **24**,[20] which upon deprotonation forms dibenzazepine **14a**.



Scheme 3. Distinguishing between radical- or cation-mediated mechanisms.

To distinguish between these mechanisms, a series of experiments were executed (Scheme 3). To determine if radical intermediates were formed in the reaction, the cyclization of **12a** was performed in the dark and separately in the presence of TEMPO because these modifications were reported to completely inhibit the reaction of nitrogen-centered radicals in iodine(III)-mediated reactions.[15] While each of these attenuated the yield of *N*-heterocycle formation, dibenzazepine **14a** was still formed. These results combined with the requirement of only 1.1 equivalents of oxidant suggest that radical species are not reactive intermediates in the formation of dibenzazepine **14a**. To provide more insight into the mechanism of C–N bond formation, **25a** and **25b** were synthesized. We anticipated that if formation of the spirocycle was critical that oxidation of **28b** would result in a poor reaction outcome because it requires a less favorable 7-*exo*-trig cyclization. In contrast to our expectation, submission of **25a** and **25b** to reaction conditions produced dihydroacridine **28a** in 50% and dibenzazocine **28b** in 71% yield. The successful formation of dibenzazocine **28b** suggests that *N*-heterocycle formation occurs through attack at the *ortho*-position to directly form the tertiary carbocation intermediates **27** or **30**.

In conclusion, we have discovered a mild iodine(III)-mediated oxidation reaction to construct dibenzazepines. Our reaction requires only a slight excess of oxidant, tolerates a broad range of functionality, and is chemoselective for reaction with the pendant arene irrespective of its distance to the aryl amine. Our preliminary mechanistic investigations reveal that the oxidation of the nitrogen-atom forms an electrophilic *N*-aryl cationic intermediate, which is captured by the arene in a 7-*exo*-trig cyclization. Our future work is aimed at further study of the mechanism and exploiting this reactivity to access other *N*-heterocycles.

Acknowledgments

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