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Dearomatizing spirocyclization of thioureas, ureas and guanidines

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ABSTRACT

An investigation of the dearomatization reactions of benzylic thioureas, ureas and guanidines using hypervalent iodine reagents is described. Initial attempts to perform this reaction with methyl aryl ethers was compromised by electrophilic addition leading to the formation of benzo[*d*]thiazoles. However, inverting the direction of the process and oxidizing the corresponding phenol delivered the desired spiro fused heterocycles in moderate to good yields for all three families.

Dearomatization has emerged as a powerful strategy for the construction of highly functionalized frameworks which are primed for further elaboration [1–4]. In particular, oxidative methods to effect dearomatization have attracted significant attention; typically this involves the reaction of a phenol with a hypervalent iodine reagent followed by nucleophilic trapping thus generating a 4,4-disubstituted cyclohexadienone [1–3]. Most frequently amides, carboxylic acids, and alcohols have served as the trap, although alkynes [5,6] and alkenes [7] can also be used (Fig. 1a). When this reaction is conducted intramolecularly it gives rise to spiro fused derivatives. In connection with an approach to the *Leucetta* derived alkaloids [8], spirocalcaridines A (**1**) and B (**2**) [9], we have reported a tandem oxidative amination dearomatizing spirocyclization (TOADS) reaction of propargyl guanidines that leads directly to the complete framework of the natural products [10–12]. The use of alkynes had been reported previously in dearomatization reactions, but we were unaware of guanidines (or (thio)ureas) [13] participating in simple dearomatization reactions when we commenced this investigation [14]. Further, cyclic guanidines are prevalent structural motifs in marine derived natural products [15] and there are numerous examples of spiro fused systems [16–18]. One particularly attractive target, KB343 (**3**), contains two spiro fused guanidines that may be accessible by such a dearomatizing spirocyclization [19].

In our prior report, we employed propargyl guanidine and urea derivatives containing a *p*-methoxybenzene moiety and proposed

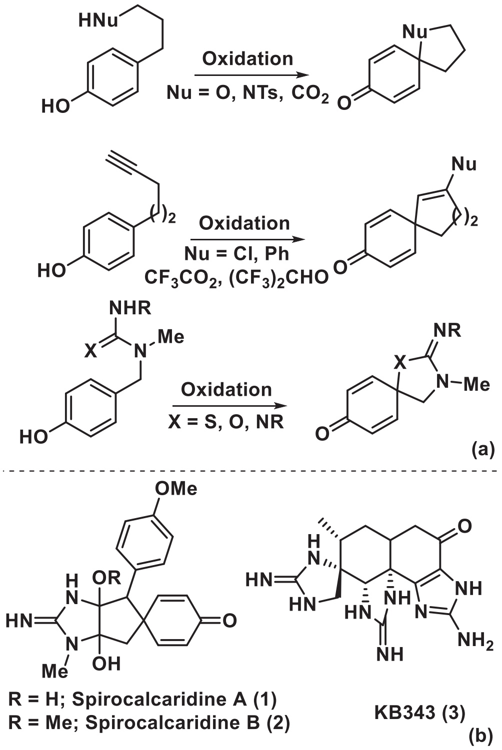

Fig. 1. Dearomatization reactions.

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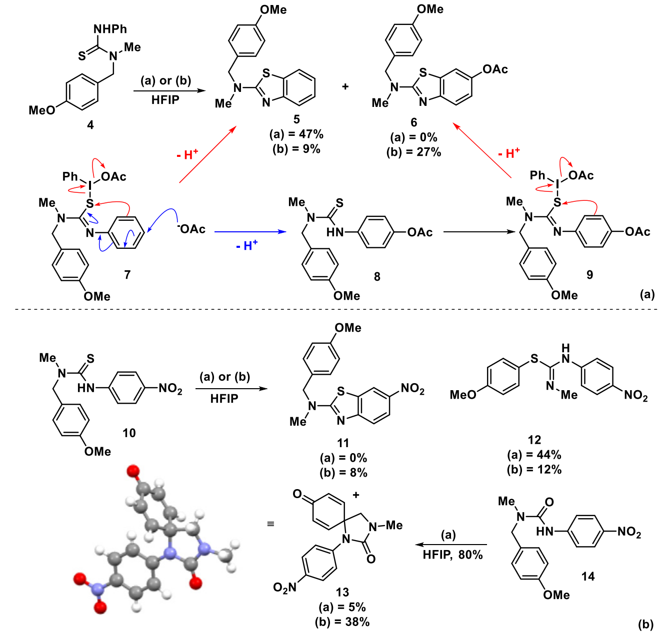


Scheme 1. Preliminary dearomatization experiments. Reagents and conditions (a) = IBDA (1 equiv), Cs_2CO_3 (1.2 equiv), HFIP; (b) = IBDA (2 equiv), Cs_2CO_3 (1.2 equiv), HFIP.

that a nitrenium equivalent triggered the cascade process [12]. In addition, we had found in this earlier investigation that propargyl thioureas were prone to hydrothiolation [20,21] and did not participate in the TOADS chemistry; [12] thus our proposed study would permit us to establish the utility of thioureas in dearomatization processes. The investigation was initiated by examining *p*-methoxybenzyl derivatives. Accordingly, *N*-methyl *p*-methoxybenzylamine was treated with phenylisothiocyanate to afford the corresponding thiourea **4** (see ESI for details). The substrate was then treated with iodosobenzene diacetate (IBDA) under reaction conditions (Cs_2CO_3, hexafluoroisopropanol (HFIP)) previously utilized in TOADS chemistry. However, the desired dearomatized product was not obtained but rather benzothiazole **5** was formed via electrophilic aromatic substitution in 47% yield (Scheme 1a) [22,23]. Increasing the oxidant equivalents did not improve the yield but resulted in the formation of acetoxylation product **6** (see ESI for X-ray crystal structure) in addition to benzothiazole **5** (Scheme 1a). Presumably, this outcome is the result of activation

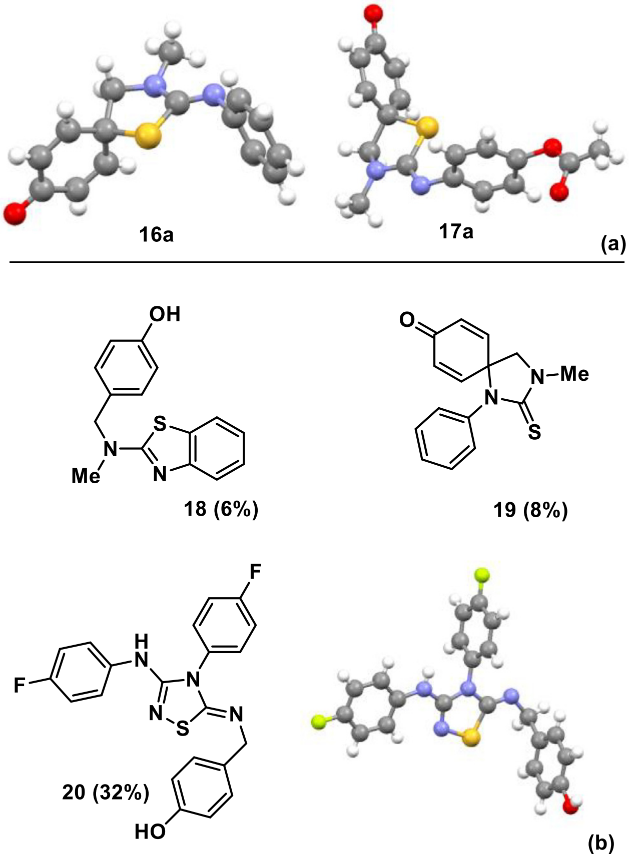
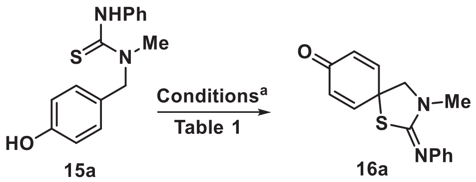


Fig. 2. (a) X-ray crystal structures of compounds **16a** and **17a**. (b) Additional products from the dearomatizing spirocyclization of phenolic thioureas.

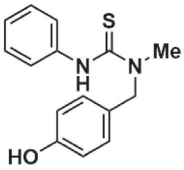
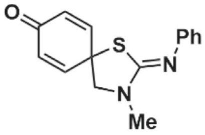
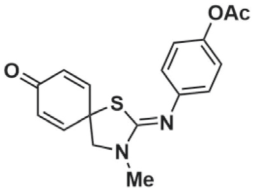
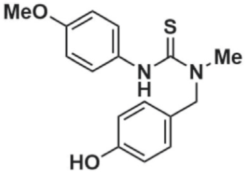
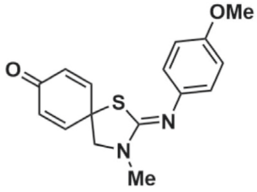
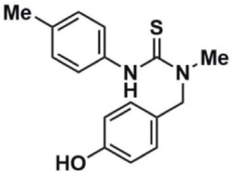
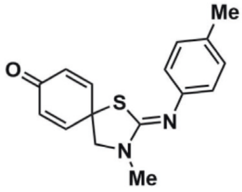
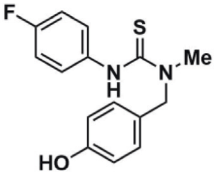
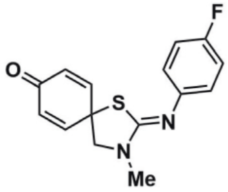
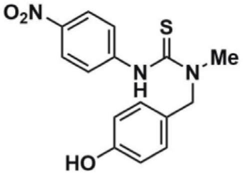
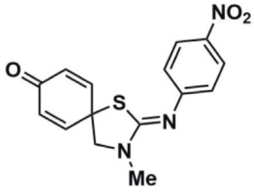
Table 1
Initial screening experiments.



Entry	Oxidant	Base	Solvent	Yield 16a (%)
1	IBDA	Cs_2CO_3	HFIP	$43^{b,c}$
2	IBDA	Cs_2CO_3	CH_2Cl_2	8^{b}
3	IBDA	Cs_2CO_3	MeCN	36^{b}
4	IBDA	NMM	HFIP	34^{b}
5	IBDA	NMM	CH_2Cl_2	ND
6	IBDA	NMM	MeCN	6^{b}
7	IBDA	$NaHCO_3$	HFIP	34^{b}
8	IBDA	$NaHCO_3$	CH_2Cl_2	10^{b}
9	IBDA	$NaHCO_3$	MeCN	11^{b}
10	IBDA	No base	HFIP	44^{c}
11	PIFA	No base	HFIP	10^{c}
12	PhI(OTs)OH	No base	HFIP	ND

[a] Reagents and conditions: **15a** (0.1 mmol), IBDA for entries 1–10 (0.1 mmol), for entries 11–12 (0.15 mmol), HFIP (7 mL), rt, 2 h.
[b] The yield of **16a** was determined by NMR spectroscopy using dibromomethane (1 equiv) as an internal reference.
[c] Isolated yield after chromatography

Table 2
Oxidative dearomatization of benzyl thioureas.

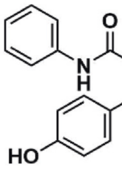
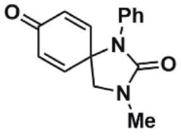
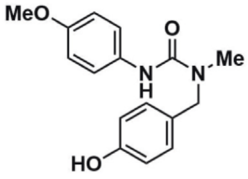
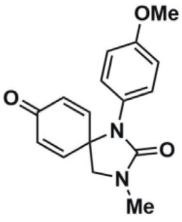
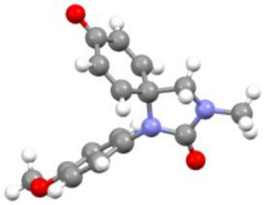
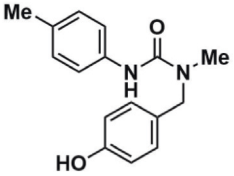
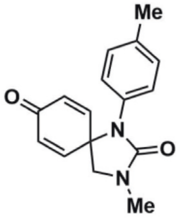
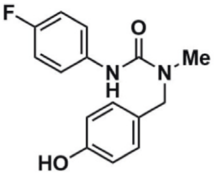
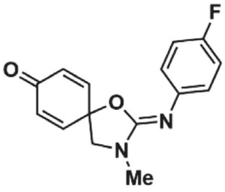
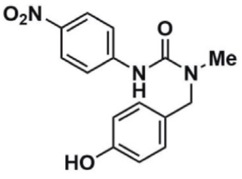
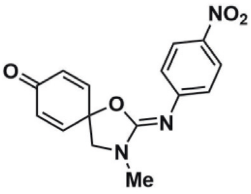
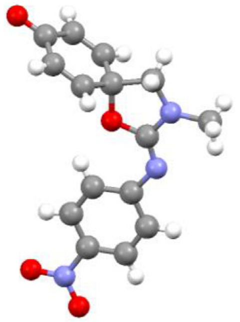
Entry	Substrate	Product	Yield (%)	Product	Yield (%)
					
1	**15a**[a]	**16a**	44	**17a**	0
2	**15a**[b]	**16a**	55	**17a**	15
3	**15a**[c]	**16a**	10	**17a**	31
4	 **15b**[b]	 **16b**	60		
5	 **15c**[b]	 **16c**	47		
6	 **15d**[b]	 **16d**	68		
7	 **15e**[b]	 **16e**	80		

[a] IBDA (1.0 equiv), HFIP, rt. b. IBDA (1.5 equiv), HFIP, rt. c. IBDA (2.0 equiv), HFIP, rt.

of the sulfur of the thiourea via **7** which can then undergo electrophilic aromatic substitution to afford **5** or alternatively addition of acetate followed by rearomatization to afford **8** (Scheme 1a) [24]. The acetyloxylated derivative undergoes a second oxidation at sulfur to trigger the formation of the thiazole. To circumvent this possibility, a thiourea derivative was prepared in which electrophilic substitution was less likely (Scheme 1b). Specifically, a deactivated aromatic was employed and, in this case, a spiro fused product was obtained, but interestingly it was the cyclic urea **13** (confirmed by an X-ray crystal structure, see Scheme 1b) rather than the expected thiourea or thiazole. Presumably, oxidation of thiourea **10** to urea **14** precedes oxidative dearomatization. A control reaction with the corresponding urea derivative **14** confirmed that it was at least a competent substrate. In addition to the urea, two further products were obtained from the oxidation of **10** including benzothiazole **11** and isothio urea **12** (see ESI for X-ray crystal structure) [25].

Given that oxidation to form nitrenium-like intermediates was compromised by addition to the *N*-aryl substituent we considered changing the role of the thiourea to serving as a nucleophilic trap and oxidizing the phenol, essentially employing an umpolung tactic. Accordingly, the corresponding phenol derivative **15a** was constructed and subjected to attempted oxidative dearomatization with IBDA and Cs_2CO_3 in HFIP [12]. We were gratified to observe that the dearomatization occurred in moderate yield (Table 1, entry 1).

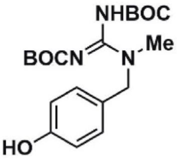
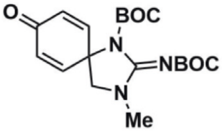
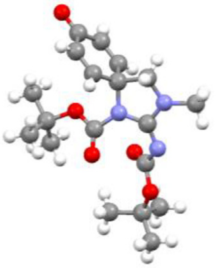
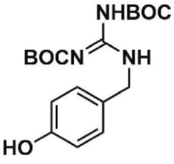
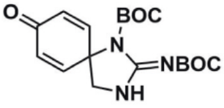
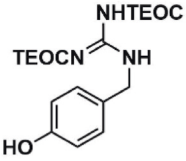
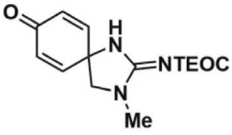
Table 3
Oxidative dearomatization of benzyl ureas.

Entry	Substrate	Product[a]	Yield (%)	
1	 **21a**	 **22a**	36	
2	 **21b**	 **22b**[b]	16	
3	 **21c**	 **22c**	56	
4	 **21d**	 **23d**	37	
5	 **21e**	 **23e**	95	

a. IBDA (1.0 equiv), Cs_2CO_3 (1.2 equiv), HFIP, rt. b. An additional 0.2 equiv of IBDA was added after 5 h.

Optimization of the reaction was conducted by investigating inorganic bases (Cs_2CO_3, $NaHCO_3$), an organic base (*N*-methylmorpholine = NMM) and different solvents (Table 1, entries 1–9). The influence of reaction solvents mirrored that observed in TOADS chemistry; [12] broadly speaking, reactions conducted in HFIP provided better yields than dichloromethane or acetonitrile (Table 1, entries 2–3). Out of the three bases evaluated, Cs_2CO_3 delivered the best yields, but ultimately it was determined that base was not required (Table 1, entry 10). Under these conditions, the desired spiro thiazoline **16a** (for X-ray crystal structure, see Fig. 2a) was obtained in 44% isolated yield (Table 2, entry 1) along with small amounts of benzothiazole **18** (for X-ray crystal structure, see ESI) and thioimidazoline **19** (Fig. 2b). Upon increasing the oxidant to 1.5 equivalents **16a** was obtained in 55% yield (Table 2, entry 2), along with small amounts of the 4-acetoxy adduct **17** (for X-ray crystal structure, see Fig. 2a). When the reaction was conducted with 2 equivalents of IBDA, the spiro 4-acetoxylated product **17** was now isolated as the major product

Table 4
Dearomatization of benzyl guanidines.[a]

Entry	Substrate	Product[a]	Yield (%)
1	 **24** **24**	 **25** **25**	25 
2	 **26** **26**	 **27** **27**	15
3	 **28** **28**	 **29** **29**	9

[a] IBDA (1.0 equiv), Cs_2CO_3 (1.2 equiv), HFIP, rt.

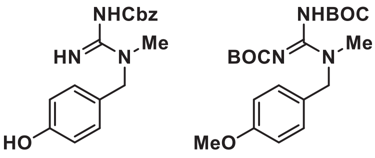
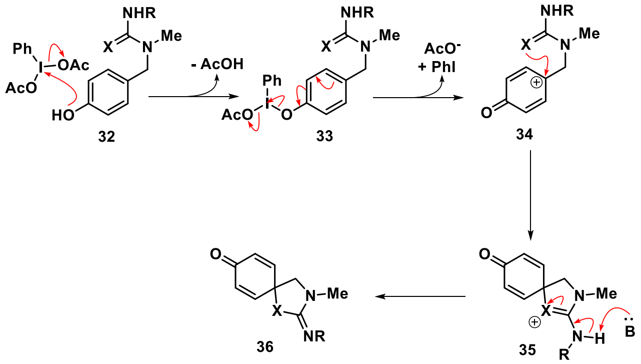

30 **31**

Fig. 3. Unsuccessful guanidine substrates.



Scheme 2. Putative mechanism for the dearomatization.

(Table 2, entry 3). Extension to other thioureas containing various aryl-substituents using 1.5 equivalents of IBDA delivered the corresponding spiro derivatives in moderate yields (Table 2, entries 4–7). An attempt to extend the spirocyclization to a thiourea lacking the *N*-methyl substituent resulted in the formation of thiadiazole **20** (for X-ray crystal structure, see Fig. 2) rather than the desired spiro derivative.

With this generally positive outcome, the corresponding urea derivatives **21a-e** were prepared (see ESI) and evaluated. In this case, however, the reactions proceeded better in the presence of Cs_2CO_3. All five derivatives produced spiro fused cyclohexadienones **22a-c**, **23d-e** but interestingly, they did not all cyclize to form the same heterocycle. Ureas **21a-c** with electron-rich aryl groups provided the corresponding imidazolones **22a-c** (Table 3, entries 1–3) whereas those with electron-poor aryl groups **21d-e** cyclized *via* the oxygen affording oxazolines **23d-e** (Table 3, entries 4–5). Connectivities were established either through X-ray crystallography (**22c** and **23e**) or by comparison of the ^{13}C NMR chemical shifts of the spiro carbon (δ_C = 59 ppm (imidazolone) vs δ_C = 75 ppm (oxazole)).

As noted in the introduction, the primary motivation for this study was to apply the chemistry towards the total synthesis of spiroguanidines such KB434 (**3**) and thus we examined the possibility of using guanidines in this reaction. It was found that the *N*-methyl bis Boc guanidine **24** underwent dearomatization to afford spirocyclic derivative **25** (Table 4, entry 1) in modest yield (confirmed by X-ray crystallography). Interestingly, the corresponding NH derivative **26** also provided the desired spirocyclic derivative **27** in low yield (Table 4, entry 2). Three other derivatives were evaluated, the Teoc-protected congener **28** (Table 4, entry 3), the mono Cbz adduct **30** and the anisole precursor **31** (Fig. 3). Teoc derivative **28** afforded spirocyclic product **29** but it underwent mono deprotection whereas the other two substrates did not afford the spirocyclic derivatives but rather complex reaction mixtures.

We assume mechanistically that these dearomatization reactions proceed *via* the accepted pathway involving reaction of the phenolic oxygen *via* substitution of one of the acetates **32** → **33** on the iodine(III) center (Scheme 2). There is some debate whether ionization to the phenoxonium ion followed by nucleophilic attack (shown **33** → **34**) or a concerted process ensues [26–29] whichever sequence is followed, the spirocyclic derivative is formed by intramolecular nucleophilic attack and proton transfer [30]. One observation that requires further comment is the divergent activity of ureas which deliver different heterocycles depending on the electronic character of the urea nitrogen substituent. Presumably, the nitrogen atom of the urea is rendered more electron rich with electron donating substituents on the aromatic moiety thus facilitating attack by nitrogen and formation of the imidazolone. Whereas with the electron withdrawing groups deprotonation of the aniline nitrogen may occur prior to cyclization thus resulting in negative charge character on oxygen resulting in the formation of the oxazoline. It is also conceivable in latter case there is a mechanistic changeover such that with electron withdrawing substituents activation of the urea occurs rather than the phenol. Oxazolines are formed in TOADS chemistry where it is likely that activation of the urea occurs which may also be operative in the present case for some substrates [12].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153054.

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