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ARTICLE TYPE

A facile approach to spirocyclic 2-azido indolines via azidation of indoles with ceric ammonium nitrate

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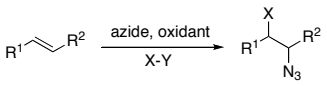
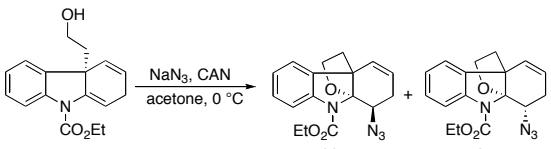
This paper describes azidation of indoles with NaN_3 and ceric ammonium nitrate (CAN), giving a variety of spirocyclic 2-azido indolines in good yields and moderate diastereoselectivities.

Azides are synthetically versatile intermediates.[1] Oxidative azidation of alkenes provides an effective strategy to introduce the azide group into organic molecules.[2-6] The reaction is believed to proceed via an azide radical, which adds to the C-C double bond. The resulting intermediate is usually intercepted by another heteroatom intermolecularly (Scheme 1). Oxidative azidation of alkenes followed by a ring closure with an internal heteroatom, however, is less well developed. Recently, we reported an intramolecular azidoalkoxylation of enecarbamate **1** with NaN_3 and ceric ammonium nitrate (CAN) to construct key intermediate **3** toward aspidophylline A (Scheme 2).[7-9] The synthetic potential of this type of process and our general interest in the area of alkene functionalization[10] prompted us to further explore such process with other systems. During these studies, we have found that indoles can be converted into the corresponding spirocyclic 2-azido indolines with NaN_3 and CAN.[11] Herein, we wish to report our preliminary studies on this subject.



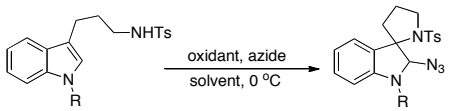
Scheme 1



Scheme 2

Indole **4a** was used as the substrate for our initial studies. Treating **4a** with NaN_3 (1.5 equiv) and CAN (3.0 equiv) in acetone at 0 °C gave spirocyclic 2-azido indoline **5a** in 57% yield and 5:1 dr (Table 1, entry 1). Among the solvents examined (Table 1, entries 2-6), CH_3CN gave the highest yield (77%) (Table 1, entry 2). A similar yield (78%) but with a slightly lower dr (3.5:1) was obtained with $TMSN_3$ (Table 1, entry 7). No reactions were observed with $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$ as oxidant using NaN_3 or $TMSN_3$ as azide source (Table 1, entries 8-11). Similar yield (73%) and dr (5:1) were obtained when the indole was protected with the Boc group (Table 1, entry 12). No desired product was formed for the methyl-protected substrate (Table 1, entry 13).

Table 1 Studies of reaction conditions.[a]



4 5

Entry	R	Solvent	Oxidant	Azide	Yield[b] (%)	dr[c]
1	CO_2Et (**4a**)	CH_3COCH_3	CAN	NaN_3	57	5:1
2	CO_2Et	CH_3CN	CAN	NaN_3	77	5:1
3	CO_2Et	EtOH	CAN	NaN_3	-	-
4	CO_2Et	DMF	CAN	NaN_3	-	-
5	CO_2Et	H_2O	CAN	NaN_3	-	-
6[d]	CO_2Et	CH_3CN/H_2O (10:1)	CAN	NaN_3	61	5:1
7	CO_2Et	CH_3CN	CAN	$TMSN_3$	78	3.5:1
8	CO_2Et	CH_3CN	PIDA	$TMSN_3$	-	-
9	CO_2Et	CH_3CN	PIDA	NaN_3	-	-
10	CO_2Et	CH_3CN	PIFA	$TMSN_3$	-	-
11	CO_2Et	CH_3CN	PIFA	NaN_3	-	-
12	Boc	CH_3CN	CAN	NaN_3	73	5:1
13	Me	CH_3CN	CAN	NaN_3	-	-

[a] All reactions were carried out with substrate **4** (0.250 mmol), NaN_3 (0.375 mmol), and oxidant (0.750 mmol) in solvent (11.9 mL) at 0 °C for 2 h unless otherwise noted. [b] Combined yields of the two isomers based on **4**. [c] The diastereoselectivity was determined by ^1H NMR of the crude reaction mixture. [d] The reaction was carried out in 2.5 mL solvent. CAN = $Ce(NH_4)_2(NO_3)_6$; PIDA = $PhI(OAc)_2$; PIFA = $PhI(OCOCF_3)_2$.

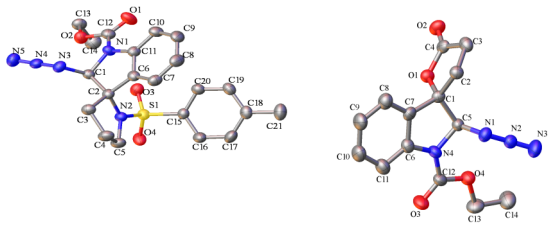


Fig. 1 The X-ray structures of compounds *anti*-**5a** and *anti*-**5h**.

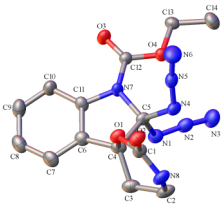


Fig. 2 The X-ray structure of compound **5i**.

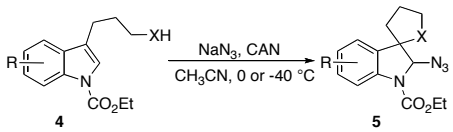
As shown in Table 2, the reaction process can be extended to tosyl protected homotryptamines (Table 2, entries 1-3), 3-indolepropanols (Table 2, entries 4-7), and 3-indolepropanoic acid (Table 2, entry 8), giving spirocyclic 2-azido indolines as two diastereomers in good yields. Except for entries 4 and 5, both diastereomers can be isolated. It appeared that a slightly higher diastereoselectivity was obtained for substrates with electron-donating groups (Table 2, entries 4-7). In the cases of entries 1 and 8, the indicated stereochemistry of the major isomer was determined by the X-ray structure (Fig. 1). The *syn*-isomer is disfavored likely due to the unfavorable hindrance between the azide group and the nucleophile. Interestingly, spirocyclic 2,2-diazido indolines were obtained when Boc protected tryptamines were subjected to the reaction conditions (the X-ray structure of **5i** is shown in Fig. 2).

While a precise understanding of the reaction mechanism awaits further study, a plausible pathway for the bisazidation is shown in Scheme 3. An azidyl radical, generated from the oxidation of sodium azide by CAN, added to indole **4i** at C-2 position to form radical **6**, which was converted to 2-azido indole **8** via H-abstraction of **6** or via loss of a proton from cation **7** (for this cation, the cyclization was relatively slower). The azidyl radical added to indole **8** again to form radical **9**, which was oxidized by CAN to cation **10**. The subsequent capture of the cation by the Boc group to form diazido indoline product **5i**. For entries 1-8 in Table 2, cation **7** was effectively intercepted by the nucleophile to form monoazido indolines due to the facile formation of the 5-membered ring.[12]

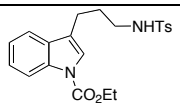
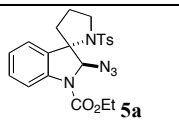
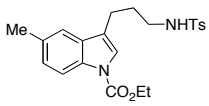
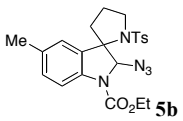
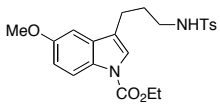
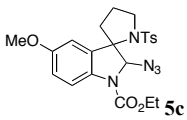
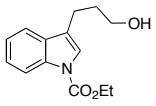
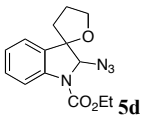
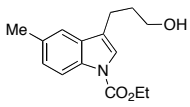
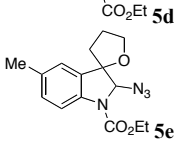
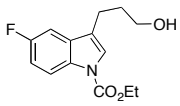
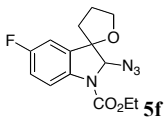
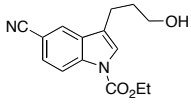
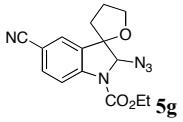
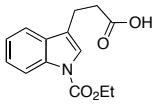
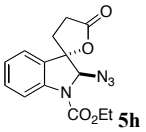
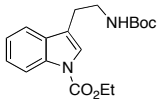
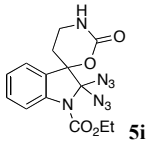
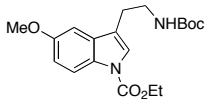
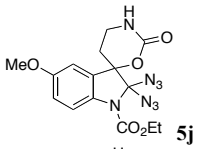
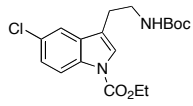
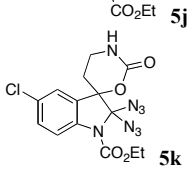
Conclusion

In summary, we have shown that indoles can be effectively azidated with NaN_3 and CAN to form various spirocyclic 2-azido indolines in good yields and moderate diastereoselectivities. In some cases, spirocyclic 2,2-diazido indolines have been obtained.

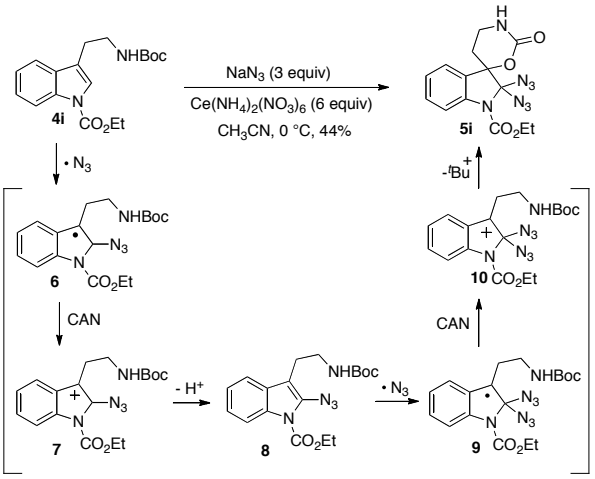
Table 2 CAN-mediated azidation of indoles.[a]



4 **5**

Entry	Substrate (**4**)	Product (**5**)	Yield[b]
1	 **4a**	 **5a**	major: 63% minor: 20%
2	 **4b**	 **5b**	major: 62% minor: 23%
3	 **4c**	 **5c**	major: 54% minor: 7%
4	 **4d**	 **5d**	71% (5:1)
5	 **4e**	 **5e**	81% (5:1)
6	 **4f**	 **5f**	major: 65% minor: 26%
7	 **4g**	 **5g**	major: 41% minor: 25%
8	 **4h**	 **5h**	major: 67% minor: 27%
9[c]	 **4i**	 **5i**	44%
10[c]	 **4j**	 **5j**	45%
11[c]	 **4k**	 **5k**	42%

[a] The reactions were carried out with **4** (0.50 mmol), NaN_3 (0.75 mmol), and CAN (1.50 mmol) in acetonitrile (24 mL) at 0 °C for 2 h unless otherwise noted. For entries 4-7, the reactions were carried out at -40 °C. [b] Isolated yields based on **4**; For entries 4 and 5, the yield is the mixture of two isomers. [c] With NaN_3 (1.50 mmol) and CAN (3.00 mmol).



Scheme 3

Further understanding of the reaction mechanism and expanding the scope of the oxidative azidation process are currently underway.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental, characterization data, X-ray structures of compounds *anti*-**5a** (CCDC 1015375), *syn*-**5a** (CCDC 1015319), *anti*-**5h** (CCDC 1015318), *syn*-**5h** (CCDC 1015320), **5i** (CCDC 1015373), and NMR spectra. See DOI: 10.1039/b000000x/

1 For leading reviews on organic azides, see: (a) S. Bräse and K. Banert, *Organic Azides: Syntheses and Applications*, John Wiley & Sons: Chichester, U. K., 2010; (b) S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem. Int. Ed*., 2005, **44**, 5188; (c) M. Minozzi, D. Nanni and P. Spagnolo, *Chem. Eur. J*., 2009, **15**, 7830.

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8 For related intramolecular azidoalkoxylations, see: (a) W. Ren, Q. Wang and J. Zhu, *Angew. Chem. Int. Ed*., 2014, **53**, 1818; (b) L. Zhu, H. Yu, Z. Xu, X. Jiang, L. Lin and R. Wang, *Org. Lett*., 2014, **16**, 1562.

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10 (a) Y. Shi, *Acc. Chem. Res*., 2004, **37**, 488; (b) H. Du, B. Zhao and Y. Shi, *J. Am. Chem. Soc*., 2007, **129**, 762; (c) D. Huang, X. Liu, L. Li, Y. Cai, W. Liu and Y. Shi, *J. Am. Chem. Soc*., 2013, **135**, 8101.

11 For an intramolecular azidoalkoxylation of indoles to fused indolines, see: H. Yin, T. Wang and N. Jiao, *Org. Lett*., 2014, **16**, 2302.

12 The azidation reaction of **4a** was also examined in the presence of a radical scavenger. No desired product was formed when 2,6-*tert*-butyl-4-methylphenol (BHT) was added.