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Hypervalent iodine oxidation of indolic 2-oxazolines

Norbert A. Braun,[b] Jonathan D. Bray [a] and Marco A. Ciufolini [a,b,*]

[a] *Université Claude Bernard Lyon 1 et Ecole Supérieure de Chimie, Physique, Electronique de Lyon, 43, Boulevard du 11 Novembre 1918, 69622 Villeurbanne cedex, France*

[b] *Department of Chemistry, MS 60, Rice University, 6100 Main Street, Houston, Texas 77005-1892, USA*

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Abstract

A novel oxidation of indolic 2-oxazolines with iodobenzene diacetate leads to unusual spiroheterocycles of potential interest in synthetic and medicinal chemistry. In several instances, addition of 2,2,2-trifluoroethanol (the solvent for such oxidations) to the substrates was observed.

Keywords: indole; oxazolines; cyclization; oxidation; hypervalent iodine.

We report a new oxidative transformation of indoles that produces azaspirocyclic structures of interest as synthetic building blocks in alkaloid chemistry, as unusual glutamic acid analogs, and as unique templates for the preparation of novel bioactive molecules. This work was inspired by the well-documented ability of iodobenzene diacetate (DIB) to attack the indole nucleus[1] and by our own observation that reaction of **1** with DIB in CF_3CH_2OH (Kita conditions[2]) affords product **2**. The latter reaction is noteworthy, in that **2** is the apparent result of nucleophilic capture of an electrophilic intermediate by CF_3CH_2OH. This seems to be the first example of allegedly nonnucleophilic CF_3CH_2OH expressing nucleophilicity in Kita-type reactions. More importantly, this result suggested that an 'indolic' variant of our recently described oxidative cyclization of phenolic 2-oxazolines **3** to spirolactams **4** may be possible (cf. **5** → **6**, Scheme 1).[3] This proved to be the case.

Oxazolines **9** were prepared (Table 1) by coupling indolic acids **7**[4] with (*S*)-phenylalaninol under the influence of BOP-Cl, followed by Wipf-type cyclization[5] of intermediate amides **8** with the Burgess reagent. Reaction of **9a** with DIB under Kita conditions[6] proceeded with no stereoselectivity to provide a 1:1 mixture of **12** and **13**. These presumably arise from initially formed spiro-3*H*-indoles **11**, which subsequently undergo rapid intramolecular nucleophilic addition of the alcohol to the imino function of the indolenine (Scheme 2). Compounds **12** (faster on TLC) and **13** (slower) were readily separated by preparative TLC (100% Et_2O). Reaction of tryptophane-derived **9b** proceeded similarly to give a 1:1 mixture of **14** (faster, 5:1, Et_2O:hexane) and **15** (slower) in 42% chromatographed yield.[7]

* Corresponding author. Tel: +33 (0)4 72 43 29 61; fax: +33 (0)4 72 43 29 63; e-mail: ciufi@cpe.fr

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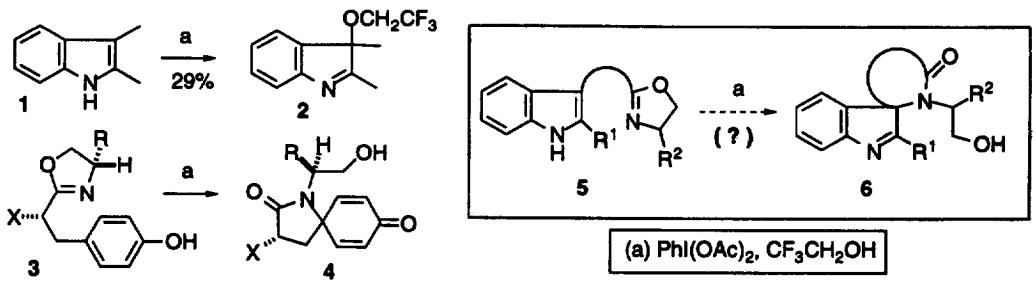
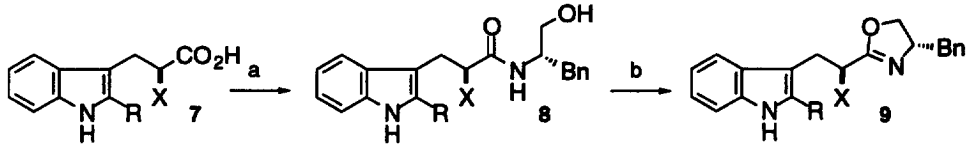
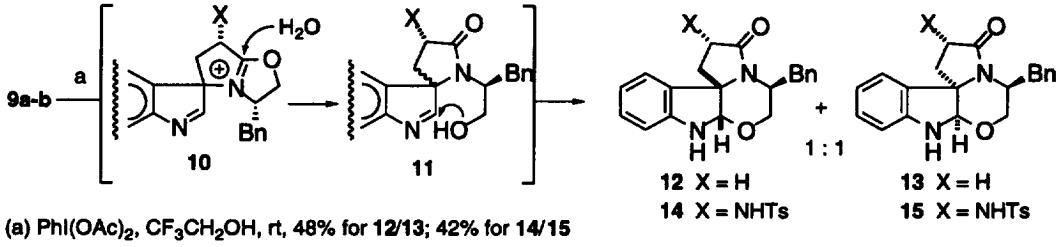


Scheme 1.

Table 1



entry	R	X	yield of 8	yield of 9
a	H	H	95	64
b	H	NHTs	51	53
c	Me	H	88	65

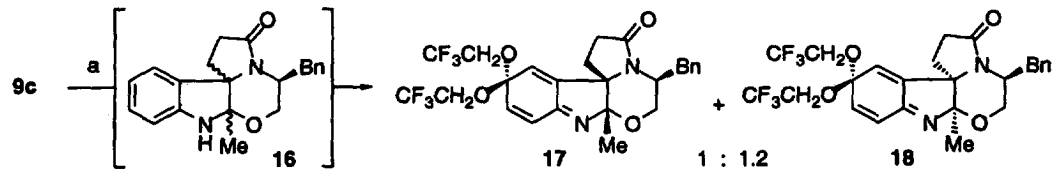


Scheme 2.

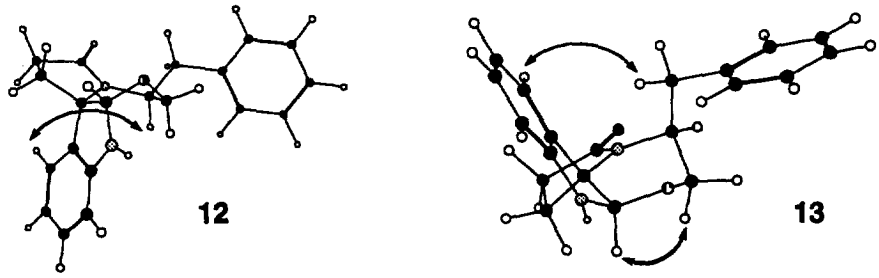
Interestingly, the 2-methyl indole derivative **9c** reacted differently under the same conditions, producing quinonimine monoketals **17** (faster, 100% Et_2O) and **18** (slower) in a 1:1.2 ratio (Scheme 3).[8] It appears that in this case further oxidation of the presumed primary products **16** occurs much faster than oxidative cyclization of the starting oxazoline **9c**. Indeed, control experiments in which only 0.8 equiv. of DIB were used relative to **9c** produced only **17/18**. It is noteworthy that trifluoroethanol again reacts as a nucleophile in these reactions. The conversion of **9c** to **17/18** corresponds to a six-electron oxidation. However, attempts to completely convert **9c** to **17/18** by using 3 equiv. of DIB gave the expected products in only 30% yield.

The stereochemical assignment of compounds **12–15** and **17/18** rests on the NOE enhancements (2D NOESY)[9] observed as shown, for example, for **12** and **13** in Scheme 4.[10]

The foregoing results induced us to study the reaction of acid **19**, alcohol **20**, amine **21**, and amide **22** with DIB as an avenue to heterocycles **23–25**. It may be expected that both **19** and **22** should lead

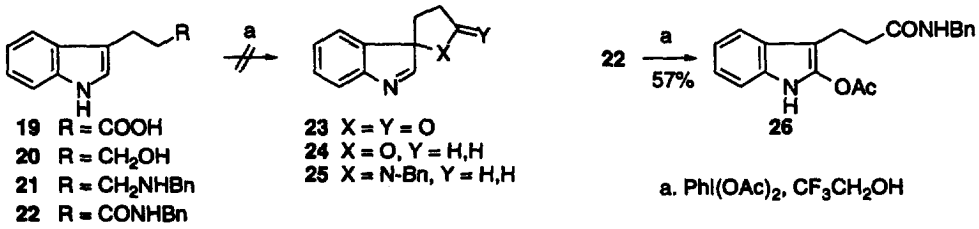


Scheme 3.



Scheme 4.

to lactone **23**.[11] Unfortunately, compounds **19–21** produced complex mixtures upon reaction with DIB. By contrast, amide **22** was converted to the acetoxylated derivative **26** in 57% chromatographed yield (Scheme 5). No identifiable materials arising through addition of trifluoroethanol were observed in these reactions. The reasons behind the variable reactivity of indolic substrates **19–22** remain unclear at this time.



Scheme 5.

In summary, an 'indolic' variant of our spirolactam synthesis has been developed and the oxidation of a number of indolic substrates with DIB has been examined. The transformations shown here embody a further aspect in the rapidly growing field of organic hypervalent iodine chemistry[12], and they should be quite useful in the synthesis of a range of nitrogenous substances. Synthetic applications of these reactions will be reported in due course.

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6. Attempts to induce oxidative cyclization in solvents other than trifluoroethanol or hexafluoroisopropanol (e.g. MeCN, $MeNO_2$, DMF, CH_2Cl_2) have so far been unsuccessful. This is in accord with observations reported by Kita: Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684–3691. See also reference 3.
7. The balance of the starting material was converted to intractable mixtures of polymeric compounds, thus accounting for the moderate yields of desired products.
8. For a related quinonimine synthesis see: (a) Barret, R.; Daudon, M. *Tetrahedron Lett.* **1991**, *32*, 2133–2134. (b) Kita, Y.; Egi, M.; Okajima, A.; Ohtsubo, M.; Takada, T.; Tohma, H. *Chem. Commun.* **1996**, 1491–1492. (c) Spirocycles related to **12–18** formally derived from indoles: Rodriguez, J. G.; Urrutia, A.; de Diego, J. E.; Martinez-Alcazar, M. P.; Fonseca, I. *J. Org. Chem.* **1998**, *63*, 4332–4337.
9. We are grateful to our colleague, Dr. Bernard Fenet, for his assistance with the 2D NOESY measurements.
10. All compounds were fully characterized [^1H, ^{13}C, ^{19}F NMR ($CDCl_3$), IR, MS, $[\alpha]_D^{20}$ ($CHCl_3$), HRMS]. Data for representative compounds: **8a**: foam. ^1H: 2.46 (t, 7.4 Hz, 2H), 2.66 (dd, 7.4, 13.5 Hz, 1H), 2.72 (dd, 6.6, 13.5 Hz, 1H), 3.01 (t, 7.4 Hz, 2H), 3.39 (dd, 5.1, 11.4 Hz, 1H), 3.47 (dd, 3.7, 11.4 Hz, 1H), 4.09 (m, 1H), 6.03 (d, 8.1 Hz, 1H), 6.80 (d, 2.2 Hz, 1H), 7.04–7.21 (m, 7H), 7.30 (d, 8.1 Hz, 1H), 7.54 (d, 7.4 Hz, 1H), 8.54 (s, 1H); ^{13}C: 21.17 (t), 36.65 (t), 37.13 (t), 52.51 (d), 63.43 (t), 111.30 (d), 114.14 (s), 118.41, 119.04, 121.71, 121.84 and 126.38, 126.92 (s), 128.37 and 129.06 (d), 136.21 and 137.51 (s), 173.59 (s); $[\alpha]=-16.1$ (*c* 4.98). **9a**: oil, ^1H: 2.60 (dd, 8.1, 13.2 Hz, 1H), 2.67–2.72 (m, 2H), 3.07 (dd, 5.2, 13.2 Hz, 1H), 3.10–3.15 (m, 2H), 3.97 (dd, 7.1, 8.3 Hz, 1H), 4.17 (dd, 8.3 Hz, 1H), 4.38 (m, 1H), 6.99 (d, 2.2 Hz, 1H), 7.11–7.37 (m, 8H), 7.63 (d, 7.4 Hz, 1H), 8.24 (s, 1H); ^{13}C: 21.70 (t), 28.94 (t), 41.70 (t), 67.10 (d), 71.55 (t), 111.09 (d), 114.97 (s), 118.71, 119.19, 121.36, 121.92 and 126.41 (d), 127.23 (s), 128.45 and 129.21 (d), 136.21 and 137.87 (s), 167.82 (s); $[\alpha]=-11.1$ (*c* 1.16). **12**: R_f=0.56 (Et_2O), oil, ^1H: 2.16 (m, 1H), 2.30 (ddd, 9.6, 11.8 Hz, 1H), 2.53 (m, 1H), 2.72–2.85 (m, 2H), 3.36–3.46 (m, 2H), 3.68 (m, 1H), 3.96 (dd, 3.7, 13.2 Hz, 1H), 4.53 (s, 1H), 5.08 (s, 1H), 6.63 (d, 8.1 Hz, 1H), 6.74 (dd, 7.4 Hz, 1H), 7.06 (d, 7.4 Hz, 1H), 7.11 (dd, 7.4, 8.1 Hz, 1H), 7.15–7.28 (m, 5H); ^{13}C: 29.67 (t), 34.23 (t), 35.00 (t), 53.35 (d), 60.92 (t), 67.19 (s), 93.31 (d), 109.13, 119.40, 121.75, 126.34, 128.37, 129.56 and 129.63 (d), 130.21, 138.03 and 147.66 (s), 175.27 (s); $[\alpha]=-53.3$ (*c* 1.61). **13**: R_f=0.30 (Et_2O). Crystals, mp 209–211°C; ^1H: 2.05 (ddd, 3.0, 8.9, 12.5 Hz, 1H), 2.27 (ddd, 9.6, 10.3, 12.5 Hz, 1H), 2.41–2.51 (m, 2H), 2.68–2.81 (m, 2H), 3.40 (dd, 4.0, 12.1 Hz, 1H), 3.56 (dd, 3.3, 12.1 Hz, 1H), 4.28 (m, 1H), 4.56 (s, 1H), 4.71 (s, 1H), 6.75 (d, 8.1 Hz, 1H), 6.83 (dd, 7.4 Hz, 1H), 7.11–7.26 (m, 7H); ^{13}C: 29.16 (t), 33.43 (t), 36.94 (t), 50.30 (d), 61.96 (t), 66.74 (s), 93.57 (d), 110.17, 119.95, 122.83, 126.44, 128.42, 129.38 (d), 130.86, 137.66 and 147.45 (s), 174.67 (s); $[\alpha]=+16.0$ (*c* 0.78). **17**: R_f=0.46 (Et_2O), oil, ^{19}F: –74.48 (br); $[\alpha]=-19.3$ (*c* 0.40). **18**: R_f=0.21 (Et_2O), oil, ^{19}F: –74.40, –74.47; $[\alpha]=+13.3$ (*c* 0.67).
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