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Hypervalent iodine oxidation of indolic 2-oxazolines

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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. © 1999 Elsevier Science Ltd. All rights reserved.

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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 nucleus¹ and by our own observation that reaction of 1 with DIB in CF₃CH₂OH (Kita conditions²) affords product 2. The latter reaction is noteworthy, in that 2 is the apparent result of nucleophilic capture of an electrophilic intermediate by CF₃CH₂OH. This seems to be the first example of allegedly nonnucleophilic CF₃CH₂OH 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. $5 \rightarrow 6$, 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 cyclization⁵ of intermediate amides 8 with the Burgess reagent. Reaction of 9a with DIB under Kita conditions⁶ 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% Et₂O). Reaction of tryptophane-derived 9b proceeded similarly to give a 1:1 mixture of 14 (faster, 5:1, Et₂O:hexane) and 15 (slower) in 42% chromatographed yield.⁷

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Scheme 2.

Interestingly, the 2-methyl indole derivative 9c reacted differently under the same conditions, producing quinonimine monoketals 17 (faster, 100% Et₂O) 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





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.



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 chemistry¹², 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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- 7. The balance of the starting material was converted to intractable mixtures of polymeric compounds, thus accounting for the moderate yields of desired products.
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- 10. All compounds were fully characterized [¹H, ¹³C, ¹⁹F NMR (CDCl₃), IR, MS, $[\alpha]_D^{20}$ (CHCl₃), 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); ¹³C: 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); ¹³C: 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: $R_f = 0.56$ (Et₂O), 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); ¹³C: 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: $R_f = 0.30$ (Et₂O). 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); ¹³C: 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: $R_f = 0.46$ (Et₂O), oil, ¹⁹F: -74.48 (br); $[\alpha] = -19.3$ (c 0.40). 18: $R_f = 0.21$ (Et₂O), oil, ¹⁹F: -74.40, -74.47; $[\alpha] = +13.3$ (c 0.67).
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