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Radical cyclizations to quinolone and isoquinolone systems under oxidative and reductive conditions

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Abstract—Radical cyclizations to quinolone and isoquinolone systems under Fenton-type and *n*-Bu_3SnH-mediated conditions are described. For *N*-iodoalkylquinolones, ca. 3:1 mixtures of oxidative cyclization products at C-2, and unexpectedly at C-8, were obtained under both conditions. Five- or six-membered oxidative cyclization products were obtained from *N*-iodoalkylisoquinolones under Fenton-type conditions, whereas *n*-Bu_3SnH-mediated reactions gave products of reductive cyclization in the five, six, and seven-membered series.

Heterocyclic moieties are an exceedingly frequently encountered structural feature of pharmacologically important compounds, and new synthetic routes to such substances, including radical based methods,[1] have received much attention. The intramolecular addition of carbon-centered radicals to an heteroaromatic nucleus followed by an in situ oxidative restoration of the double bond (oxidative radical cyclization), is a process, which has emerged as a powerful synthetic tool within this area.[2–4] Several methods have been devised to effect such radical cyclizations, with *n*-Bu_3SnH-mediated reactions being the most explored.[2] The highly toxic nature of the tin reagent, and the difficulties associated with the removal of its reaction products, have led synthetic organic chemists to find alternative methods to accomplish such reactions.[3,4] Some time ago, an efficient tin-free oxidative radical cyclization of (ω-iodoalkyl)-indoles and pyrroles using Fenton-type conditions was described,[5a] and more recently[5e] it was used in a tandem radical addition–oxidative cyclization sequence based on *N*-(2-iodoethyl)indoles and pyrroles. Implicit in this methodology is the resolution of the problem of the oxidative re-aromatization step, which arises in tin hydride mediated reactions.[5] The importance of the benzoindolizidine and benzoquinolizidine alkaloids[6] led us to consider the extension of this process to the radical cyclization of primary and secondary *N*-iodoalkylquinolones and isoquinolones. In this article we present some of our recent results on the cyclization of these compounds using the oxidative Fenton-type and the reductive *n*-Bu_3SnH-mediated conditions.

The radical precursors **2a–d** were synthesized in two steps by alkylation of the N-unsubstituted quinolones **1a–c** with the appropiate α,ω-dibromoalkane and subsequent halogen exchange with an excess of sodium iodide in acetonitrile (Scheme 1). The quinolones **1b** ($R = CO_2Et$) and **1c** ($R = CN$) were prepared by a thermal Gould–Jacobs cyclization of the corresponding anilinomethylenemalonates.[7] Preliminary attempts to effect the desired radical cyclization were carried out by dropwise addition of 30% hydrogen peroxide (10 equiv) to a sonicated[8] solution of **2a** in DMSO containing 3 equiv of heptahydrated ferrous sulfate. The mildly exothermic reaction was easily controlled at ca. 40 °C by the rate of the peroxide addition (~0.5 h). It was observed that after complete addition of hydrogen peroxide, some starting material remained and addition of further quantities of peroxide and/or Fe(II) failed to effect its consumption. Consequently, the desired product **3a** was isolated in a very low yield (Table 1, entry 1)

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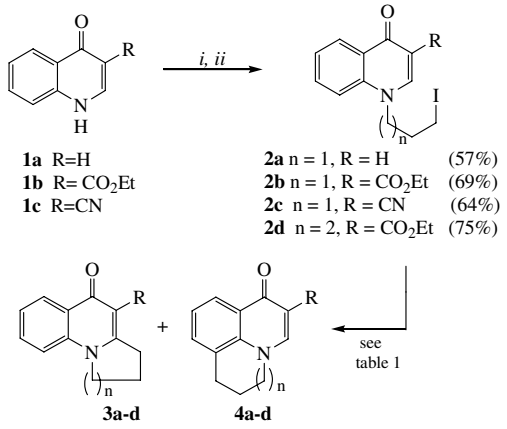
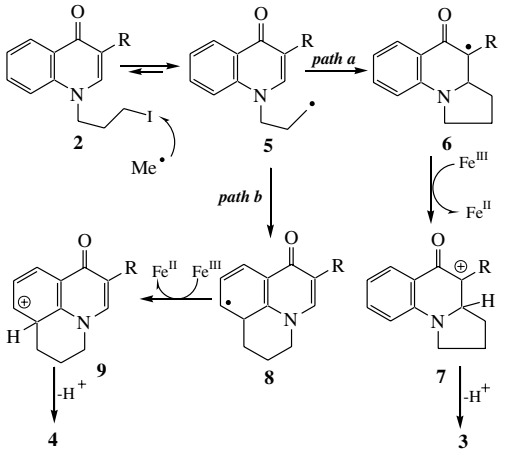


Scheme 1. Reagents and conditions: (i) NaH, DMF, $BrCH_2CH_2(CH_2)_nBr$; (ii) NaI, CH_3CN, reflux, 24 h.



Scheme 2. Proposed mechanism for the oxidative radical cyclizations.

Table 1. Radical cyclization

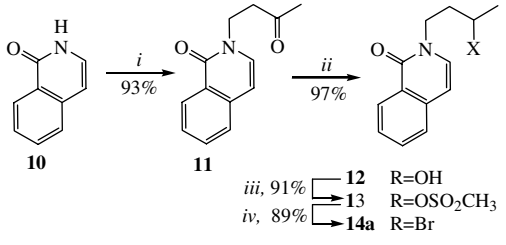
Entry	Substrate	*n*	R	Cond.	Product, yield (%)	
1	**2a**	1	H	A	**3a** (5)	**4a** (0)
2	**2b**	1	CO_2Et	A	**3b** (48)	**4b** (15)
3	**2c**	1	CN	A	**3c** (56)	**4c** (23)
4	**2d**	2	CO_2Et	A	**3d** (53)	**4d** (0)
5	**2b**	1	CO_2Et	B	**3b** (26)	**4b** (9)
6	**2b**	1	CO_2Et	C	**3b** (60)	**4b** (24)
7	**2c**	1	CN	C	**3c** (65)	**4c** (22)
8	**2d**	2	CO_2Et	C	**3d** (90)	**4d** (0)

Conditions: (A) $FeSO_4{\cdot}7H_2O$, H_2O_2, DMSO,))))); (B) n-Bu_3SnH (1.2 equiv), AIBN (0.4 equiv), benzene, reflux; (C) n-Bu_3SnH (1.2 equiv), AIBN (1.1 equiv), benzene, reflux.

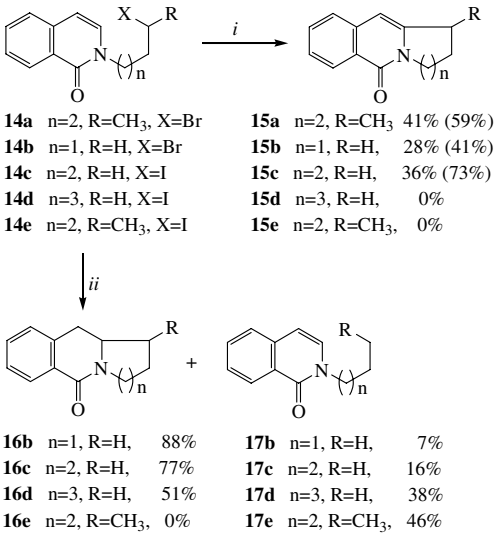
along with considerable starting material (~20%). In the light of this result, we turned our attention to the more electrophilic quinolones **2b–d** (Scheme 1) wherein the strongly electron attracting CO_2Et ($\sigma_m = 0.37$) and CN ($\sigma_m = 0.56$) groups were expected to decrease the SOMO–LUMO energy difference at C-3 and favor radical attack at this site relative to that found for **2a**. Indeed, when **2b** and **2c** were subjected to the above conditions, not only were the expected pyrrolo[1,2-*a*]quinolines **3b** and **3c** formed in quite acceptable yields (entries 2 and 3), significant amounts of the unexpected benzo[*ij*]quinolines **4b** and **4c**, derived from cyclization at C-8, were obtained as well. The observed preference for cyclization at C-2 (path a, Scheme 2) over C-8 (path b) is no doubt a consequence of the greater energetic cost of breaking resonance in the benzenoid ring. In contrast, under the same conditions **2d** gave the tricyclic compound **3d** as the sole product (entry 4). The failure to observe any of the seven-membered product **4d** stemming from cyclization at C-8 may well be due to an unfavorable entropic effect.[9]

The same pattern of product formation was observed when **2b–d** were reacted with n-Bu_3SnH/AIBN in benzene solution at reflux temperature, but low product yields and incomplete consumption of the starting materials were observed using catalytic amounts of AIBN (e.g., entry 5). This situation was rectified by adding small incremental amounts of AIBN until 1.1 equiv had been reached. At this stage, the starting material had largely disappeared, and the above mentioned tricyclic products were formed in remarkably high yields (entries 6–8). That products of oxidative radical cyclization can form using n-Bu_3SnH is no longer unusual.[2] The large amounts of AIBN, which are required, however, for the reaction to proceed efficiently is consistent with this reagent functioning as the oxidant of the intermediate radical species **6** and **8** (Scheme 2).[10]

To extend the study to alkyl radical cyclizations in the isoquinolone series, the required halides **14b–e** were prepared following the same protocol as for compounds **2a–d,** but the secondary halo derivative **14a** had to be prepared by the reaction sequence shown in Scheme 3. When the Fenton-type conditions were applied to halides **14a–c**, the oxidative radical cyclization products benzo[1,2-*b*]indolizidinones **15a** and **15b**, and the benzo-[1,2-*b*]quinolizidinone **15c** were produced in modest yields (Scheme 4), and considerable amounts of the starting materials were recovered. Neither the primary alkyl iodide **14d** nor the secondary alkyl iodide **14e** gave the anticipated products. The failure to observe the formation of the seven-membered product **14d** is not surprising, but the negative result with **14e** was unanticipated, especially since oxidative radical annulation of **14a** to **15a** took place reasonably well.



Scheme 3. Reagents and conditions: (i) methyl vinyl ketone, C_6H_6, 120 °C; (ii) $NaBH_4$, CH_3OH; (iii) $MeSO_2Cl$, Et_3N; (iv) LiBr, THF, 0 °C.



Scheme 4. Reagents and conditions: (i) $FeSO_4 \cdot 7H_2O$, H_2O_2, DMSO,))))); (ii) n-Bu_3SnH (1.2 equiv), AIBN (0.4 equiv), benzene, reflux.

When compounds **14b–d** were subjected to standard n-Bu_3SnH/AIBN reaction conditions, the reductive cyclization products **16b–d** were obtained in good yields with even the seven-membered compound **16d** being formed quite efficiently (Scheme 4).[11] Significant amounts of the reductively dehalogenated compounds **17b–d** were formed in each case, the amount thereof increasing in parallel with the increasing ring size of the cyclization products **16b–d**. These reactions were all effected using catalytic AIBN; even large concentrations of this reagent did not divert the reactions away from the observed reductive cyclization products. Finally, both of the secondary halides **14a** and **14e** failed to give reductive cyclization products. Only the reductive dehalogenation product **17e** was obtained from **14e**, while **14a** underwent cyclization to the isoquinolinium salt **18**, the structure of which was established by X-ray crystallography (Fig. 1, Br omitted for simplification purposes). Interestingly, **14a** did undergo cyclization under Fenton-type conditions, presumably at least in part, because of the lower reaction temperature.

In closing, radical cyclizations to quinolone and isoquinolone systems under both Fenton-type and n-Bu_3SnH-mediated conditions are described. When successful, *N*-haloalkylquinolones gave products of oxidative cyclization under both conditions, whereas *N*-haloalkylisoquinolones afforded oxidative cyclization products under Fenton-type conditions and reductive cyclization products under n-Bu_3SnH/AIBN mediated conditions.

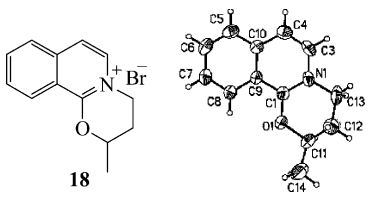


Figure 1. ORTEP drawing of the isoquinolinium salt **18**.

Acknowledgements

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References and notes

1. Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1–14.
2. (a) Studer, A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley VCH: Weinheim, 2001; Vol. 2, pp 62–76; (b) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077; (c) Suzuki, F.; Kuroda, K. *J. Heterocycl. Chem.* **1993**, *30*, 811; (d) Antonio, Y.; de la Cruz, E.; Galezzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15; (e) Tim, C. T.; Jones, K.; Wilkinson, J. *Tetrahedron Lett.* **1995**, *36*, 6743; (f) Osaki, S.; Mitoh, H.; Ohmori, H. *Chem. Pharm. Bull.* **1996**, *44*, 2020; (g) Dobbs, P. A.; Jones, K.; Veal, K. T. *Tetrahedron* **1997**, *53*, 8287; (h) Aldabbagh, F.; Bowman, W. R.; Mann, E. *Tetrahedron Lett.* **1997**, *38*, 7937; (i) Hagan, D. J.; Giménez-Arnau, E.; Schwalbe, C. H.; Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2739; (j) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639; (k) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S.; Pereira, A. M. D. L. *Tetrahedron* **1997**, *53*, 269; (l) Harrowen, D.; Nunn, M. I. T. *Tetrahedron Lett.* **1998**, *39*, 5875; (m) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111; (n) Nadin, A.; Harrison, T. *Tetrahedron Lett.* **1999**, 4073; (o) Marco-Contelles, J.; Rodríguez-Fernández, M. *Tetrahedron Lett.* **2000**, *41*, 381; (p) Bowmann, W. R.; Mann, E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991; (q) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, *43*, 4191.
3. (a) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345; (b) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 1719; (c) Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759; (d) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 7295; (e) Ly, T. M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533.
4. (a) Mohan, R.; Kates, S. A.; Dombroski, M. A.; Snider, B. B. *Tetrahedron Lett.* **1987**, *28*, 845; (b) Snider, B. B.; Buckman, B. O. *Tetrahedron* **1989**, *45*, 6969, and references cited therein; (c) Aidhen, I. S.; Narasimhan, N. S. *Tetrahedron Lett.* **1989**, *30*, 5323; (d) Artis, D. R.; Cho, I.-S.; Muchoswki, J. M. *Can. J. Chem.* **1992**, *70*, 1838.
5. (a) Artis, D. R.; Cho, I.-S.; Figueroa, S. J.; Muchoswki, J. M. *J. Org. Chem.* **1994**, *59*, 2456; (b) Bertilsson, B.-M.; Gustafsson, B.; Kuhn, I.; Torsell, K. *Acta Chem. Scand.* **1970**, *24*, 3590; (c) Minisci, F.; Vismara, E.; Fontana, F. *J. Org. Chem.* **1992**, *57*, 6817; (d) Bacciochi, E.; Muraglia, E.; Sleiter, G. *J. Org. Chem.* **1992**, *57*, 6817; (e) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M. *ARKIVOC* **2002**, 15.
6. For extensive lead references to benzoindolizidine and benzoquinolizidine alkaloids, see: *The Alkaloids, A Specialist Periodical Report*; The Royal Society of Chemistry: London; Vol. 1-13.
7. Gould, R. G., Jr.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890–2895.
8. Branson Models B-2200R-B ultrasonic bath type cleaners were used.

9. Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731–733, These authors highlight the difficulty of construction of seven-membered rings adjoining aromatic rings by radical chemistry.
10. (a) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1337; (b) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 70, and references cited therein.
11. Typical experimental procedure: *n*-Bu_3SnH-mediated conditions: A solution of AIBN (0.24 mmol, 0.4 equiv), Bu_3SnH (0.72 mmol, 1.2 equiv) in benzene (3.5 mL, 5 mL/mmol) was added dropwise (syringe pump) to a degassed solution of the halide (0.6 mmol, 1 equiv) in refluxing benzene (0.02 M) over 6 h. The reaction mixture was then cooled and the solvent removed under reduced pressure. The residue was partitioned between hexane (10 mL) and acetonitrile (5 mL). The polar layer was washed with hexane (4×10). The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane/EtOAc). *Selected spectral data*: **16c** as a white solid, mp 95–97 °C (lit.[12] 92–93 °C), IR (KBr, cm^{-1}): 2943, 1635, 1604, 1581; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.45–1.56 (m, 3H), 1.77–1.87 (m, 3H), 2.65–2.74 (m, 1H), 2.83 (dd, $J = 9.5$, 16.0 Hz, 1H), 3.06 (dd, $J = 5.5$, 16.0 Hz, 1H), 3.53–3.59 (m, 1H), 4.70–4.73 (m, 1H), 7.31 (d, $J = 7.5$ Hz, 1H), 7.38–7.41 (m, 2H), 8.11 (d, $J = 7.5$ Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ ppm 23.6, 24.8, 33.2, 34.7, 43.6, 55.1, 126.8, 127.5, 128.4, 130.2, 131.6, 136.6, 165.1; HRMS (FAB+): calcd for $C_{13}H_{16}NO$: 202.1232, found: 202.1239. **16d** as a white solid, mp 77–78 °C, IR (KBr, cm^{-1}): 2957, 1646, 1627, 1597; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.53–1.75 (m, 8H), 2.78 (dd, $J = 4.5$, 15.6 Hz, 1H), 2.98 (ddd, $J = 4.5$, 9.2, 14.0 Hz, 1H), 3.24 (dd, $J = 5.6$, 15.6 Hz, 1H), 3.74–3.82 (m, 1H), 4.53 (dt, $J = 5.6$, 14.0 Hz, 1H), 7.14 (d, $J = 7.5$ Hz, 1H), 7.29–7.42 (m, 2H), 8.06 (d, $J = 7.5$ Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ ppm 26.1, 26.4, 28.0, 33.6, 34.1, 46.1, 57.2, 126.8, 127.5, 128.4, 129.1, 131.4, 136.6, 163.7; HRMS (EI+): calcd for $C_{14}H_{17}NO$: 215.1310, found: 215.1324. **18** as a white solid, mp 120–122 °C; IR (KBr, cm^{-1}): 2984; 1648, 1583; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.73 (d, $J = 6.6$ Hz, 3H), 2.24–2.38 (m, 1H), 2.70–2.78 (m, 1H), 5.06 (ddd, $J = 2.7$, 5.1, 14.1 Hz, 1H), 5.29 (ddd, $J = 5.1$, 11.5, 14.1 Hz, 1H), 5.43–5.54 (m, 1H), 7.69 (d, $J = 7.0$ Hz, 1H), 7.76–7.81 (m, 1H), 7.96–7.98 (m, 2H), 8.34–8.39 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ ppm 20.3, 27.0, 50.3, 78.1, 117.3, 119.6, 125.5, 127.4, 129.8, 132.3, 135.7, 137.7, 158.1; HRMS (FAB+) calcd for $C_{13}H_{15}NOBr$: 280.0337, found: 280.0342.
12. Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Tetrahedron Lett.* **1996**, *37*, 7749.