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Regioselective synthesis of quinolone-annulated sulfur heterocycles by aryl radical cyclization

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Abstract—The tin hydride-mediated cyclizations of a number of sulfides and sulfones under mild, neutral conditions, have been investigated accompanied by some amount of β-scission product for sulfides. The sulfides were derived from 4-mercaptoquinolone and 2-bromobenzyl bromides by phase transfer catalyzed reaction and the corresponding sulfones were prepared by treatment of the sulfides with *m*-CPBA at room temperature. The sulfides and the corresponding sulfones were then reacted with $^{n}Bu_3SnH$-AIBN to give regioselective quinolone-annulated sulfur heterocycles.

Aryl radical cyclizations have been developed as a powerful method for constructing carbon–carbon bonds in organic synthesis.[1] These radical cyclization protocols commonly have several advantages over non-radical methods, for example, the radical cyclization can be carried out in neutral organic solutions. We have previously synthesized several novel heterocyclic systems containing sulfur by sigmatropic rearrangements.[2] During our studies, we observed the unusual formation of [6,6]pyranothiopyrans during the second Claisen rearrangement step.[3] The oxygen- and nitrogen-containing radical cyclizations have been studied intensively. However, an examination of the literature revealed only a few examples of the synthesis of sulfur-based heterocycles via radical methods. These include cyclizations where the sulfur functionality is in a hexenyl chain at the 3-[4] and 4-positions[5] and an example of a sulfonylated radical in the 2-position,[6] but these reactions were not regioselective. Several useful radical cyclizations with a sulfur functionality located α- to the radical centre have also been reported, however, these yielded a cyclic product with the sulfur external to the ring.[7] We have recently succeeded in the regioselective synthesis of [6,6] cyclic sulfur heterocycles by $^{n}Bu_3SnH$ mediated cyclization.[8] β-Scission is a competitive side reaction for thiyl radicals compared to hydrogen abstractions. The rate of β-scission[9] of the product radicals is high when the C-centred radical released is tertiary or resonance stabilized.[9b] However, when a highly electron-withdrawing SO_2 group is attached to the radical centre, it confers considerable stability (lowers the energy of the SOMO) to the intermediate radical and prevents the β-scission with an increase in the product yield. It was observed that alkyl radical cyclization predominantly gave the smaller five-membered ring rather than the larger six-membered ring owing to the stereoelectronically more favourable transition state during 5-*exo*-cyclization although it resulted in an unstable primary radical intermediate. For stabilized radicals,[10] this preference is found to be reversed. A study of the cyclization of R-sulfenyl-, R-sulfinyl- and R-sulfonyl-5-hexenyl and 5-methyl-5-hexenyl radicals revealed a unique contrast in the mode of ring closure of the radicals.[11] In this context, we undertook a study on the radical cyclization of the sulfides **3a**–**d**, sulfones **4a**–**d** and sulfoxides **5a**,**b**. Here we report the results.

The starting materials 4-(2′-bromobenzylsulfanyl)-1-alkyl-1*H*-quinolin-2-ones **3** (X = S) were prepared in 80–85% yield by the phase transfer catalyzed alkylation of 4-mercaptoquinolone **1** with either 2-bromobenzyl bromide (**2a**) or 2-bromo-5-methoxybenzyl bromide (**2b**) in chloroform and 1% aq NaOH solution in the presence of benzyltriethylammonium chloride (BTEAC) at room temperature for 3 h. The other starting materials 4-(2′-bromobenzylsulfonyl)-1-alkyl-1*H*-quinolin-2-ones **4** (X = SO_2) were synthesized from the

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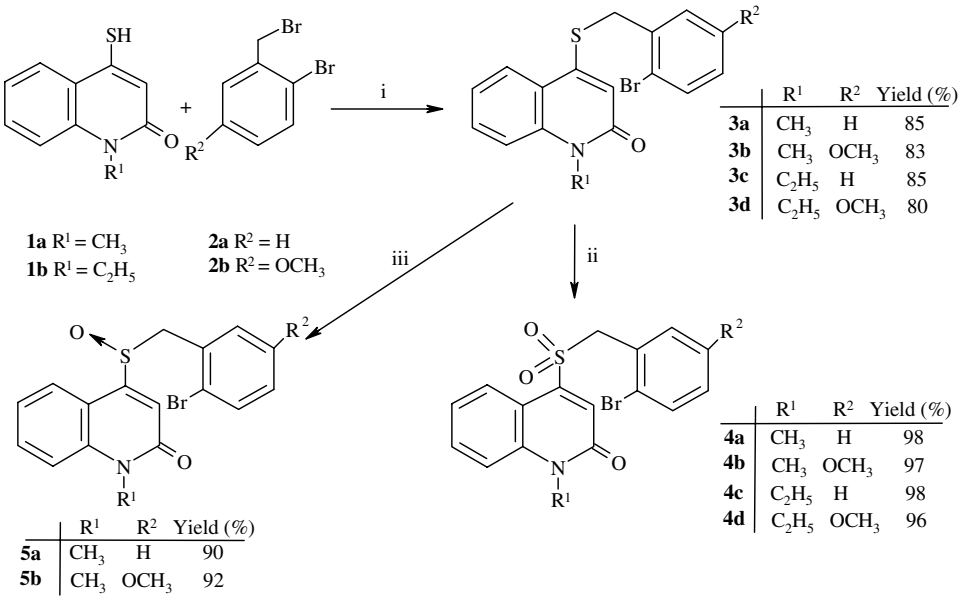


Scheme 1. Reagents and conditions: (i) 1% aq NaOH–$CHCl_3$, BTEAC, 3 h, rt; (ii) *m*-CPBA (2 equiv), CH_2Cl_2, stirring, 3–4 h, rt; (iii) *m*-CPBA (1 equiv), CH_2Cl_2, stirring, 1 h, 0–5 °C.

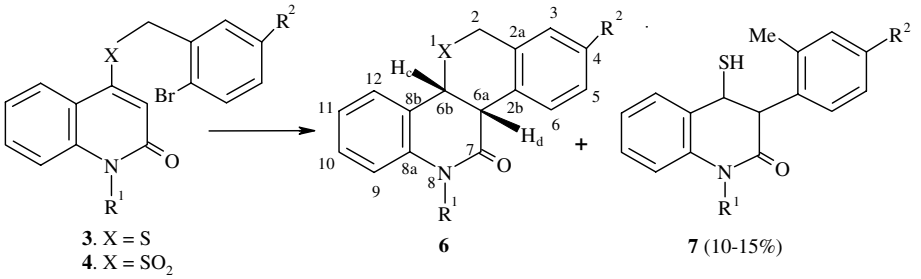
corresponding sulfides by treatment with *m*-CPBA at room temperature (Scheme 1).

Compounds **3** and **4** were characterized from their elemental analyses and spectroscopic data. The IR spectrum of compound **4a** showed characteristic S=O stretching frequencies at ν_{max} 1305 (sym.) and 1137 (asym.) cm^{-1}. The two proton singlet due to $-SCH_2$ protons of **3a** at δ 4.36 was shifted by 0.39 ppm downfield in **4a**. The substrate **3a** was refluxed in dry degassed C_6H_6 under a nitrogen atmosphere with $^nBu_3SnH$ in the presence of AIBN as an initiator for 1 h to give the cyclic product **6a**[12] (yield 65%) accompanied by a small quantity of the β-scission product. We were able to separate the β-scission product in the case of compound **3b** (12%). The β-scission is controlled by conversion of the sulfide to the sulfone. Exposure of the sulfone **4a** to $^nBu_3SnH$ under the same conditions as described above afforded the cyclized sulfone **6e**[13] ($X = SO_2$) in 90% yield. The structures of the compounds **6** ($X = S, SO_2$) were readily elucidated by ^1H NMR spectroscopy, which a exhibited one proton doublet at δ 4.21 ($J = 4$ Hz) and another one proton doublet at δ 4.42 ($J = 4$ Hz) due to ring junction protons H_d and H_c, respectively, for **6a** ($X = S$) where as the same two protons resonated at δ 4.44 ($J = 6$ Hz) and δ 4.54 ($J = 6$ Hz), respectively, for **6e** ($X = SO_2$). The stereochemistry of the ring fusion of the cyclic system can be surmised from the molecular model (Dreiding Model), which shows a strain free cis-arrangement and also from the small coupling constants **6a** ($X = S$, $J = 4$ Hz) and **6e** ($X = SO_2$, $J = 6$ Hz). The ^{13}C spectrum of **6** ($X = S, SO_2$) also supported the proposed structure. The ^{13}C NMR chemical shifts as well as the multiplicity of compound **6** was established by a DEPT experiment. There are eleven carbons carrying hydrogen atoms, one CH_3, one CH_2 and nine CH moieties. The mass spectra of compounds **6a** and **6e** showed molecular ion peaks at $m/z = 281$ and 313 (M^+), respectively. The other substrates **3b–d** and **4b–d** were also treated similarly with $^nBu_3SnH$ and AIBN to give exclusively the [6,6]thiopyranopyridone derivatives **6b–d**,**f**,**g** in 60–88% yields (Scheme 2).

We attempted to extend this reaction to 4-(2′-bromobenzylsulfinyl)-1-alkyl-1*H*-quinolin-2-ones (**5a**,**b**), but the starting materials decomposed and no cyclized products were obtained.

The formation of a six-membered sulfur heterocyclic ring in products **6** along with small amounts of β-scission products can be best explained by the addition of a hydrogen radical to the intermediate radical **9**, which in turn is formed from the aryl radical **8** by a '6-*endo*' ring closure. An alternative route, via '5-*exo*' ring closure to generate spiro heterocyclic radical[14] **10** with a subsequent neophyl rearrangement[15] has also been considered (Scheme 3).

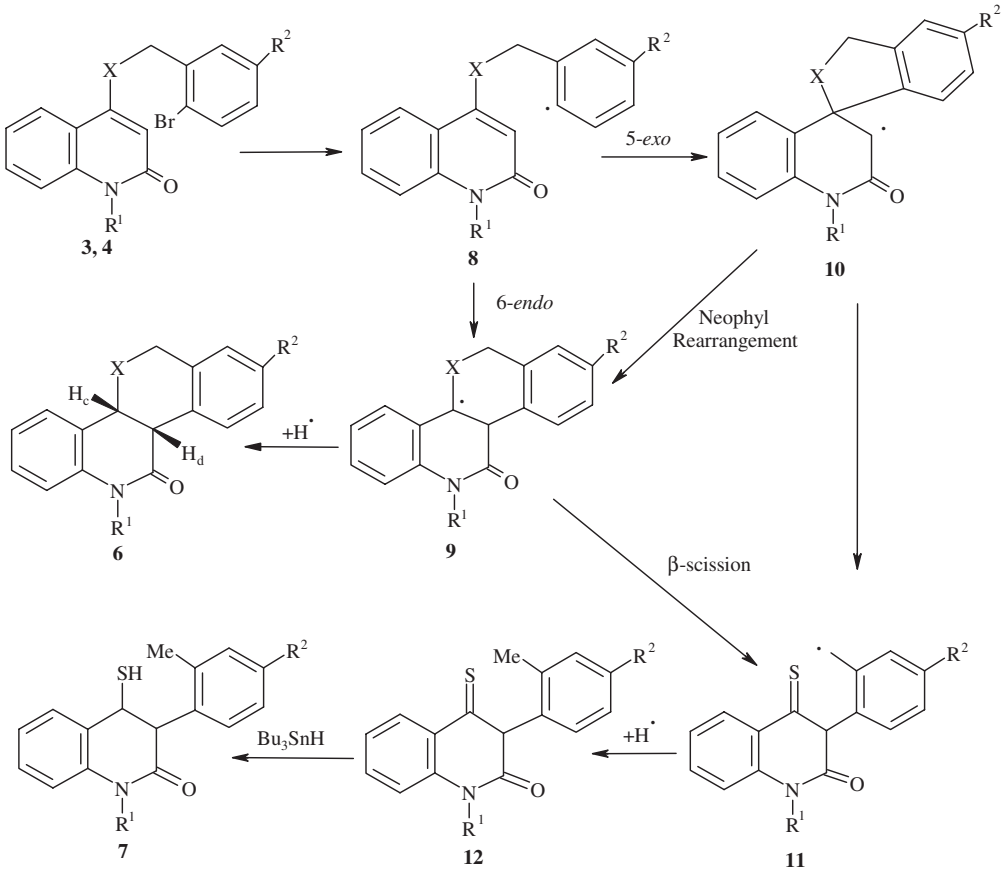
However, the 5-*exo*-cyclization to form the spiro heterocyclic radical **10** followed by a neophyl rearrangement is highly unlikely with the present systems. It is known that β-fragmentation of alkyl thiyl radicals is very fast[16] ($>10^8$ s^{-1}) compared to neophyl-type rearrangements, which are much slower[9a] (about 10^3–10^4 s^{-1}). Therefore, neophyl rearrangement of radical **10** cannot compete with the β-fragmentation reaction, which would lead to another product. The other reason is that the intermediate tertiary radical **9** is more stable than the spiro heterocyclic radical **10**. Inspection of molecular models indicate that the radical intermediate **9** should be more stable due to excellent overlapping of the p-orbital of the radical centre with the neighbouring aromatic π-system and also due to the greater polarization of the sulfur atom.[17] The stabilized conformational intermediate radical **9** gives preferably cis-products, the usual reduced product and the dihydro heterocyclic ring is isolated in good yield. All the starting materials gave the



	X	R^1	R^2	Yield(%)
6a	S	CH_3	H	65
6b	S	CH_3	OCH_3	63
6c	S	C_2H_5	H	65
6d	S	C_2H_5	OCH_3	60

	X	R^1	R^2	Yield(%)
6e	SO_2	CH_3	H	90
6f	SO_2	CH_3	OCH_3	88
6g	SO_2	C_2H_5	H	85
6h	SO_2	C_2H_5	OCH_3	80

Scheme 2. Regents and conditions: ^{n}Bu$_3$SnH, AIBN, benzene, reflux, 1–4 h.



Scheme 3.

reduced six-membered heterocyclic ring regioselectively via ^{n}Bu$_3$SnH mediated cyclization.[18] The methodology described here is mild and interesting by its simplicity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.151.

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12. Compound **6a**: Yield: 65%; white solid; mp 144–146 °C. IR (KBr): $\nu_{max} = 753$, 1602, 1674, 2923 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 3.45$ (s, 3H, –N**C**H_3), 3.88 (d, $J = 16$ Hz, 1H, –SC**H**), 4.06 (d, $J = 16$ Hz, 1H, –SC**H**), 4.11 (d, $J = 4$ Hz, 1H, –CC$\mathbf{H}_d$), 4.42 (d, $J = 4$ Hz, 1H, –CC$\mathbf{H}_c$), 7.06 (m, 2H, Ar**H**), 7.20 (m, 6H, Ar**H**). ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta_C = 30.1$ (C-2), 30.27 (–N**C**H_3), 40.7 (C-6b), 47.7 (C-6a), 115.3 (C-9), 123.1 (C-12), 124.9 (C-8b), 126.5 (C-11), 127.7 (C-6), 128.2 (C-4), 128.3 (C-3), 129.0 (C-5), 132.2 (C-10), 132.5 (C-2a), 133.0 (C-2b), 139.8 (C-8a), 168.2 (C-7). MS: $m/z = 281$ (M^+). UV (EtOH): $\lambda_{max} = 211$, 216, 233, 359 nm. Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57, H, 5.37, N, 4.98. Found: C, 72.79, H, 5.20, N, 5.27.
13. Compound **6e**: Yield: 90%; white solid; mp 170–172 °C. IR (KBr): $\nu_{max} = 754$, 1113, 1308, 1602, 1673, 2931 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 3.44$ (s, 3H, –N**C**$\mathbf{H}_3$), 4.33 (d, $J = 15$ Hz, 1H, –SO_2C**H**), 4.42 (d, $J = 15$ Hz, 1H, –SO_2C**H**), 4.44 (d, $J = 6$ Hz, 1H, –CC$\mathbf{H}_d$), 4.54 (d, $J = 6$ Hz, 1H, –CC$\mathbf{H}_c$), 7.13 (m, 3H, Ar**H**), 7.34 (m, 5H, Ar**H**). ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta_C = 30.9$ (C-2), 48.2 (–N**C**H_3), 65.3 (C-6b), 62.5 (C-6a), 115.6 (C-9), 116.3 (C-12), 123.9 (C-8b), 128.6 (C-11), 129.0 (C-6), 129.3 (C-4), 130.4 (C-3), 131.3 (C-5), 131.4 (C-10), 131.7 (C-2a), 132.1 (C-2b), 141.3 (C-8a), 166.1 (C-7). MS: $m/z = 313$ (M^+). UV (EtOH): $\lambda_{max} = 214$, 258, 285 nm. Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.18, H, 4.79, N, 4.47. Found: C, 65.35, H, 4.55, N, 4.24.
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