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An Expedient Route to 2,3-Substituted and Fused Benzo[*a*]quinolizine-4-thione Framework via Ring Annulation with β-Oxodithioesters

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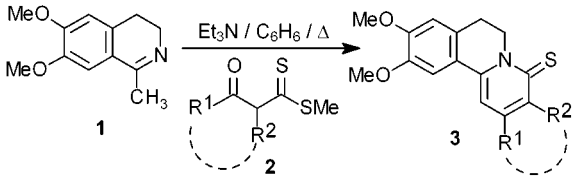
ABSTRACT



An efficient highly convergent route to hitherto unreported 2,3-substituted and annulated benzo[*a*]quinolizine-4-thiones 3 has been developed. The methodology involves ring annulation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline 1 with a variety of readily accessible acyclic and cyclic β-oxodithioesters 2 in the presence of triethylamine in refluxing benzene. These benzo[*a*]quinolizine-4-thiones can be readily converted to the corresponding benzo[*a*]quinolizine-4-ones 5 via dethiomethylative hydrolysis of the respective benzo[*a*]quinolizinium salts 4 obtained by alkylation of 3 with methyl iodide.

The tricyclic benzo[*a*]quinolizine[1−3] ring system constitutes the basic structural framework of various naturally occurring alkaloids and physiologically active drugs. Thus, the benzo[*a*]quinolizine structure is present in berberine,[4] emetine,[5] and related ipecac alkaloids with potent clinical activity and also in tranquilizer drugs such as tetrabenazine,[6a] benzquinamide,[6b] and analogues displaying reserpine type activity.[7] The benzo[*a*]quinolizinone derivatives such as Ro 41-3696 have been identified as promising nonsedative hypnotics for the induction and maintenance of sleep which has stimulated an extensive research program at Hoffmann La-Roche aimed at developing new class of nonbenzodiazepine heterocycles as benzodiazepine receptor ligands for treatment of anxiety and sleep disorders.[8] In light of this broad array

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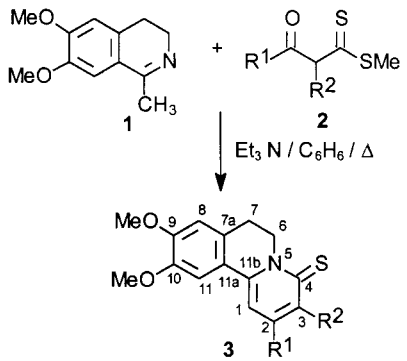
of biological activity, the development of new efficient and more viable routes for this class of compounds would be of great relevance to both synthetic and medicinal chemists. In this Letter we report a facile synthetic entry to substituted and fused benzo[*a*]quinolizine-4-thiones involving highly regioselective [3 + 3] annulation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **1** with *β*-oxodithioesters. The new methodology allows facile introduction of substituents in the C ring of the nitrogen heterocycle and flexibility for the construction of novel benzo[*a*]quinolizine fused ring systems.

Several elegant approaches for the construction of benzo[*a*]quinolizine ring systems are described in the literature,[2] most of which involve closure of ring B by formation of the $C_{11a}-C_{11b}$ bond either by Bischler−Napieralski type[9] or by related palladium-catalyzed cyclization.[1a,b,2a] Other methods rely upon elaboration of the piperidine/pyridine (ring C) by formation of the C_1-C_{11b} bond via Mannich type cyclization of a dihydroisoquinolinium ion[10] or closure of ring B by formation of the C_2-C_{7a} bond[1c,3b] from appropriately N-substituted 2-arylpiperidine or pyridine derivatives. On the other hand, examples of direct synthesis of the benzo[*a*]-quinolizine framework utilizing the enamine character of easily accessible 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **1** in cyclocondensation with 1,3-bielectrophilic components are very few in the literature.[11−13] It should be noted that the imine **1** has been successfully employed as a useful precursor for the synthesis of protoberberine alkaloids via photochemical and thermal cyclization of *N*-aroylenamides.[14] During the course of our investigations on dihydroisoquinoline-derived enaminones[15] and enaminoesters,[16] we became interested in examining enamine reactivity of imine **1** toward unsymmetrical 1,3-bielectrophiles with a view to developing a facile one-pot synthesis of benzo[*a*]-quinolizines. Our initial efforts to react **1** with readily available *β*-ketoesters such as ethyl acetoacetate or ethyl *β*-benzoylacetate in the presence of various acidic and basic catalysts under different conditions did not meet with any success. However, to our surprise, when **1** was reacted with *β*-oxodithioester **2a** in refluxing benzene (12 h) in the presence of triethylamine, workup and column chromatography of the reaction mixture furnished only one product (66%) which was characterized as 6,7-dihydro-9,10-dimethoxy-2-methylbenzo[*a*]quinolizine-4-thione **3a** on the basis of spectral and analytical data.[17] The corresponding *β*-aroyl dithioesters **2b** and **2c** also reacted with **1** smoothly under identical conditions to afford the corresponding 2-arylbenzo-[*a*]quinolizine-4-thiones **3b** and **3c** in 80 and 71% yields, respectively (Scheme 1). Similarly, the 2,3-disubstituted benzo[*a*]quinolozine-4-thiones **3d** and **3e** could be easily synthesized in high yields from the respective α-methyl-*β*-acylidioates and **1**.

Scheme 1



2, 3	R^1	R^2	% yield	mp°C
a	CH_3	H	66	190-191
b	C_6H_5	H	80	192-193
c	4-$MeOC_6H_4$	H	71	186-187
d	CH_3	CH_3	60	180-181
e	C_6H_5	CH_3	72	253-254

To further demonstrate the scope of the reaction, the cyclic *β*-ketodithioesters **2f−h** derived from cyclohexanone, cyclopentanone, and *N*-benzylpiperidine-4-ones were chosen as cyclocondensation partners and reacted with **1** under similar conditions (Scheme 2). Thus, the dithioester **2f** afforded the hexahydrodibenzo[*a*,*g*]quinolizine-8-thione in high yield (70%) whereas the corresponding benzo[*a*]-quinolizine-4-thiones **3g** and **3h** were obtained in moderate yields from the respective dithioesters **2g** and **2h**.[18] The versatility of this novel cyclization reaction was further demonstrated by facile formation of novel pentacyclic benzo-[*a*]quinolizine frameworks **3i−j** in highly convergent fashion when the bicyclic *β*-oxodithioesters **2i−j** from tetralones

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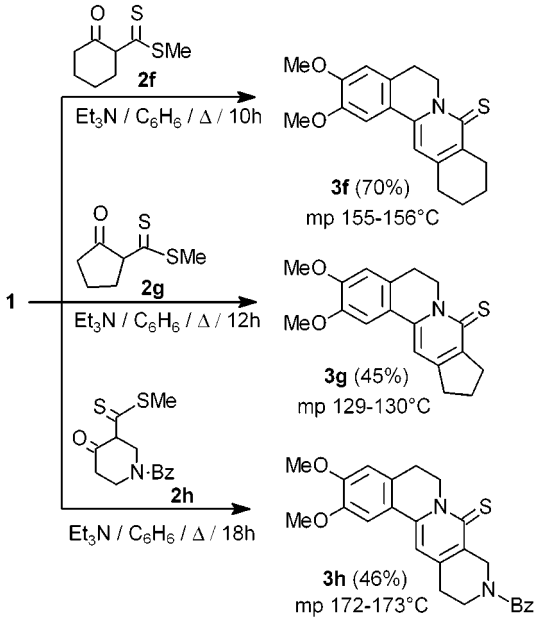
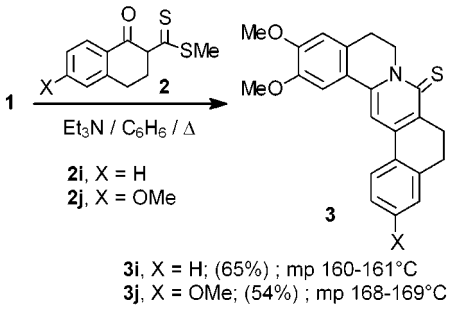
Scheme 2



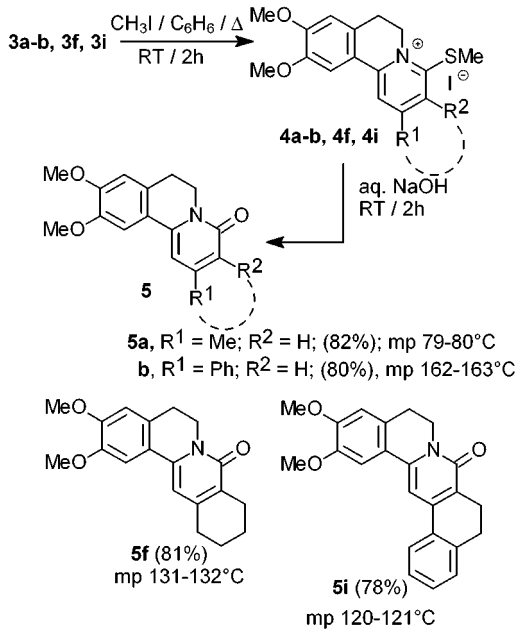
were subjected to cyclization with **1** under identical reaction conditions (Scheme 3).

Scheme 3

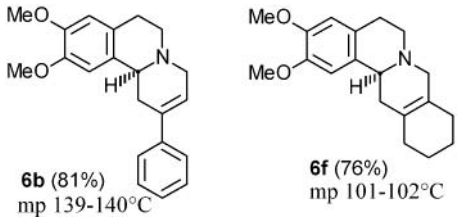


A few of the benzo[*a*]quinolzine-4-thiones **3a**,**b**, **3f**, and **3i** were converted to the corresponding 4-methylthiobenzoquinolizinium salts **4a**,**b**, **4f**, and **4i** on treatment with methyl iodide. These salts (**4a**,**b**, **4f**, **4i**) underwent facile dethiomethylative hydrolysis in the presence of dilute sodium hydroxide to afford the respective benzoquinolizine-4-ones **5a**,**b**, **5f**, and **5i** in high yields (Scheme 4). Thus, the method

Scheme 4



could be used for the synthesis of benzo[*a*]quinolizine-4-ones also. The salts **4b** and **4f** were reduced with some sodium borohydride to yield tetrahydrobenzo[*a*]quinolizines **6b** and **6f** in 81% and 76% yields, respectively.



(17) The structures of all the new compounds were confirmed with the help of spectral and analytical data. The regiochemistry of the product benzo[*a*]quinolizine-4-thiones was established on the basis of NOESY correlation spectra. **3a**: yellow solid; mp 190−191 °C; yield 0.96 g (66%); IR (KBr) 2930, 1604, 1506, 1229, 1120 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (s, 3H, CH_3), 2.96 (t, J = 6.5 Hz, 2H, CH_2), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.90 (t, J = 6.5 Hz, 2H, NCH_2), 6.78 (s, 1H, ArH), 6.85 (d, J = 1.6 Hz, 1H, H-1), 7.14 (s, 1H, ArH), 7.56 (d, J = 0.6 Hz, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.91, 27.53, 46.92, 56.15, 56.37, 108.24, 110.23, 112.36, 121.09, 129.46, 133.13, 145.42, 145.71, 148.65, 151.65, 179.12; MS *m/e* 287 (M^+, 100), 272 (45.0). Anal. Calcd for $C_{16}H_{17}NO_2S$ (287.39): C, 66.87; H, 5.96; N, 4.87. Found: C, 66.81; H, 5.97; N, 4.85. **3b**: yellow solid; mp 192−193 °C; yield 1.38 g (80%); IR (KBr) 2835, 1604, 1506, 1265, 1133 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.01 (t, J = 6.5 Hz, 2H, CH_2), 3.96 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.95 (t, J = 6.5 Hz, 2H, NCH_2), 6.80 (s, 1H, ArH), 7.20 (d, J = 2 Hz, 1H, H-1), 7.21 (s, 1H, ArH), 7.47−7.51 (m, 3H, ArH), 7.66−7.68 (m, 2H, ArH), 7.94 (d, J = 2.0 Hz, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.57, 47.12, 56.17, 56.43, 108.34, 109.31, 110.25, 121.32, 127.01, 129.18, 129.53, 129.79, 130.47, 137.01, 145.74, 146.54, 148.73, 151.81, 179.77; MS *m/e* 349 (M^+, 100), 334 (50.1). Anal. Calcd for $C_{21}H_{19}NO_2S$ (349.46): C, 72.18; H, 5.48; N, 4.01. Found C, 72.16; H, 5.50; N, 4.03. **3d**: yellow solid; mp 180−181 °C; yield 0.89 g (60%); IR (KBr) 2965, 1606, 1513, 1223, 1156 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.95 (t, J = 6.5 Hz, 2H, CH_2), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.04 (t, J = 6.5 Hz, 2H, NCH_2), 6.78 (s, 1H, ArH), 6.90 (s, 1H, H-1), 7.15 (s, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.76, 21.35, 27.68, 48.35, 56.09, 56.32, 107.94, 110.11, 112.55, 121.47, 129.05, 137.35, 143.08, 143.27, 148.55, 151.22, 178.60; MS *m/e* 301 (M^+, 100), 286 (55.2). Anal. Calcd for $C_{17}H_{19}NO_2S$ (301.42): C, 67.74; H, 6.35; N, 4.65. Found: C, 67.81; H, 6.30; N, 4.59. **3f**: yellow solid; mp 155−156 °C; yield 1.15 g (70%); IR (KBr) 2939, 1604, 1509, 1217, 1148 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76−1.79 (m, 2H, CH_2); 1.84−1.87 (m, 2H, CH_2), 2.72 (t, J = 6.1 Hz, 2H, CH_2); 2.93−2.97 (m, 4H, CH_2); 3.95 (s, 3H, OCH_3); 3.97 (s, 3H, OCH_3); 5.05 (t, J = 6.4 Hz, 2H, NCH_2); 6.77 (s, 1H, ArH); 6.80 (s, 1H, H-13); 7.14 (s, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.73, 23.08, 27.73, 30.31, 30.49, 47.77, 56.11, 56.34, 107.95, 110.15, 111.46, 121.63, 129.10, 138.01, 142.62, 144.59, 148.57, 151.14, 179.14; MS *m/e* 327 (M^+, 100); 312 (68.6). Anal. Calcd for $C_{19}H_{21}NO_2S$ (327.46): C, 69.69; H, 6.46; N, 4.28. Found: C, 69.71; H, 6.50; N, 4.29.

In conclusion, we have devised an efficient, highly convergent, and straightforward route to hitherto unreported benzo[*a*]quinolizine-4-thiones involving readily available *β*-oxodithioesters[19] in a cycloannulation process with 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline under mild and simple reaction conditions. A particularly attractive feature of this approach is that depending on the structure of *β*-oxodithioesters, different substituents can be incorporated in the 2,3 position in addition to the possibility of annulating various rings at this position. The 4-methylthiobenzo[*a*]-quinolizinium salts **4** derived from **3** can lend themselves to conversion to various products including benzoquinolizine-4-ones. We defer at this stage any definite statement regarding mechanism, which appears to be interesting since the corresponding *β*-oxoesters failed to cyclize with the imine **1** under varying reaction conditions. We are further probing into the reactivity profile of *β*-oxodithioesters toward bi-functional heteronucleophiles in addition to application of this methodology to related alkaloids and other biologically important benzo[*a*]quinolizine analogues.

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Supporting Information Available: Characterization data for products **3c**, **3e**, **3g**−**j**, **4a**, **4f**, **5a**,**b**, **5f**, **5i**, **6b**, and **6f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Yields of all the products have not been optimized.

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