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Regioselective Unusual Formation of Spirocyclic 4-{2′-Benzo(2′,3′-dihydro)furo}-9-methyl-2,3,9-trihydrothiopyrano[2,3-*b*]indole by 4-*exo-trig* Aryl Radical Cyclization and Rearrangement

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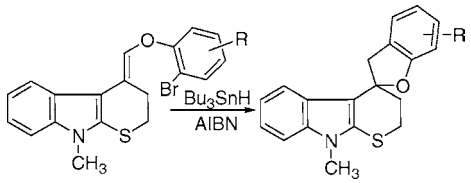
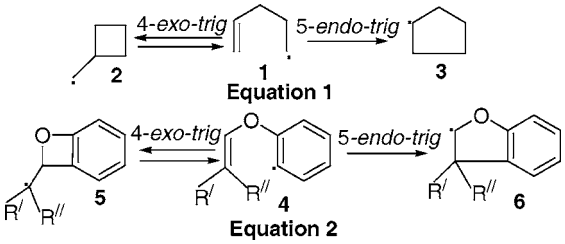
ABSTRACT



4-(2′-Bromoaryloxymethylene)-9-methyl-2,3,9-trihydrothiopyrano[2,3-*b*]indoles under tri-*n*-butyltin hydride mediated aryl radical cyclization furnished exclusively the 4-{2′-benzo(2′,3′-dihydro)furo}-9-methyl-2,3,9-trihydrothiopyrano[2,3-*b*]indoles in excellent yield (75–80%) via 4-*exo-trig* cyclization, opening of the oxetene ring, and 5-*endo-trig* cyclization.

The use of C−C bond forming aryl radical cyclization for the construction of heterocyclic rings is an important reaction in synthetic organic chemistry.[1] There are some reports on the synthesis of oxygen-containing heterocyclic compounds by aryl radical cyclization.[2] A pentenyl radical (**1**) can cyclize either in a 4-*exo-trig* manner or in a 5-*endo-trig* manner to give radicals **2** and **3**, respectively (eq 1, Scheme 1). In the 4-*exo-trig* process, however, the ring opening and cyclization between **2** and **1** is reversible due to the high degree of strain present in the four-membered ring **2**,[3] which usually shifts the equilibrium to the starting radical **1**. On the other hand, the 5-*endo-trig* process is recognized as a disfavored process due to stereoelectronic disadvantage in the attack of the

Scheme 1. Two modes of Cyclization of the Pentenyl Radical and the Related Aryl Radical



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(2) (a) Smith, T. W.; Butler, G. B. *J. Org. Chem.* **1978**, *43*, 6. (b) Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991. (c) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P.; Sarkar, S.; Ghosh, S. K.; Biswas, P. *Tetrahedron* **2003**, *59*, 2151. (d) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **2001**, *42*, 5613.

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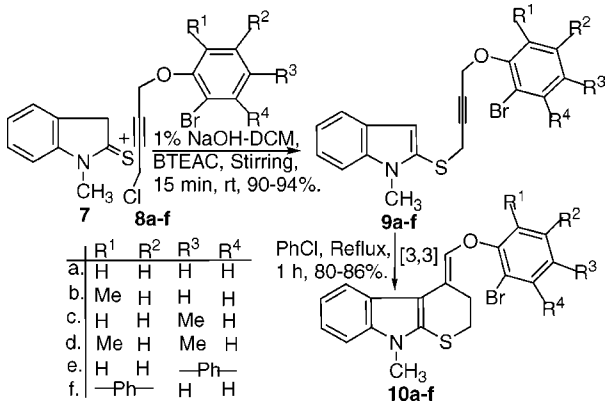
radical center of **1** at the alkenic bond.[4] So, there have been few reports on either 5-*endo-trig*[5] or 4-*exo-trig*[6] radical cyclization of the pentenyl radical and related species. The four-membered ring is known to possess a higher degree of strain and generally 5-*endo-trig* cyclization becomes facile over 4-*exo-trig* cyclization. The substituents and temperature also control the mode of cyclization.[7] But a higher degree of stability of the four-membered radical intermediate sometimes favors the 4-*exo-trig* cyclization.[8] Here we have examined whether 4-*exo-trig* or 5-*endo-trig* cyclization would be facile for an aryl radical of the type **4** (eq 2, Scheme 1).

The required precursors for our present study 4-(2′-bromoaryloxymethylene)-9-methyl-2,3,9-trihydrothiopyrano-[2,3-*b*]indoles (**10a**−**f**) were synthesized in 80−86% yield by the *thio*-Claisen rearrangement of 2-(4′-aryloxybut-2′-ynylthio)-1-methylindoles (**9a**−**f**). The compounds **9a**−**f** in turn were prepared in 90−94% yield by the reaction of 1-methylindoline-2-thione (**7**) and 1-aryloxy-4-chlorobut-2-yne (**8a**−**f**) under phase transfer catalysis conditions, using benzyltriethylammonium chloride (BTEAC) as a phase transfer catalyst (Scheme 2).

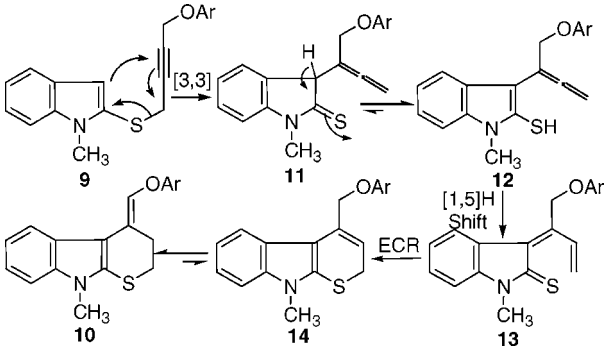
Scheme 2. Preparation of Sulfides and Enol Ethers



The sulfides **9a**−**f** contain the but-2-ynylindole-2-yl sulfide moiety as well as the arylprop-2-ynyl ether moiety. The *thio*-Claisen rearrangement[9] in the sulfide moiety may require lower activation energy perhaps due to lower aromaticity of the pyrrole ring of the indole moiety. The sulfides **9a**−**f** on refluxing in chlorobenzene (132 °C) for 1 h afforded the compounds **10a**−**f** (Scheme 2).

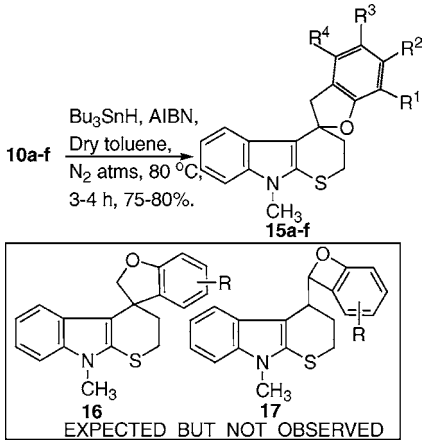
Formation of the products **10** may be explained[10] by an initial [3,3] sigmatropic rearrangement of the sulfide segment in substrates **9** followed by enolization to give the allenyl-ene-thiols (**12**) which may then undergo [1,5] H shift and 6π-electrocyclic ring closure to afford the endocyclic intermediate 4-aryloxymethyl-9-methyl-2,9-dihydrothiopyrano-[2,3-*b*]indole (**14**, not isolated). These may then undergo tautomerism to give the exocyclic double bonded[11] compound **10** (Scheme 3).

Scheme 3. Mechanism of *thio*-Claisen Rearrangement



The products **10** contain a suitably placed *o*-bromoaryl group with respect to the double bond of the enol ether. Therefore, compound **10a** was treated with Bu_3SnH (1.1 equiv) in toluene at 80 °C in the presence of a radical initiator (AIBN, 0.5 equiv) for 4 h. A white crystalline solid **15a**,[12] mp 156−158 °C, was obtained in 80% yield (Scheme 4).

Scheme 4. Aryl radical Cyclization of Enol Ethers



The structure of the product **15a** was confirmed by its single-crystal X-ray diffraction study (Figure 1) and was characterized as 4-{2′-benzo(2′,3′-dihydro)furo}-9-methyl-2,3,9-trihydrothiopyrano[2,3-*b*]indole.

(3) Ishibashi, H.; Kameoka, C.; Iriyama, H.; Kodama, K.; Sato, T.; Ikeda, M. *J. Org. Chem.* **1995**, *60*, 1276 and references therein.
(4) Baldwin, J. E. *J. Chem. Soc., Chem. Commun*. **1976**, 734.
(5) (a) Majumdar, K. C.; Sarkar, S.; Bhattacharrya, T. *Tetrahedron* **2003**, *59*, 4309. (b) Bommezijn, S.; Martin, C. G.; Kennedy, A. R.; Lizos, D.; Murphy, J. A. *Org. Lett.* **2001**, *3*, 3405. (c) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett*. **1991**, *32*, 1725. (d) Bogen, S.; Gulea, M.; Fensterbank, L.; Malacria, M. *J. Org. Chem*. **1999**, *64*, 4920. (e) Gao, J.; Rusling, J. F. *J. Org. Chem.* **1998**, *63*, 218. (f) Ishibashi, H.; Fuke, Y.; Yamashita, T.; Ikeda, M. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2531. (g) Goodall, K.; Parsons, A. F. *Tetrahedron Lett.* **1997**, *37*, 491.
(6) (a) Castle, K.; Hau, C.-S.; Sweeney, J. B.; Tindall, C. *Org. Lett*. **2003**, *5*, 757. (b) Piccardi, P.; Modena, M.; Cavalli, L. *J. Chem. Soc. C* **1971**, 3959. (c) Belletire, J. L.; Hagedorn, C. E.; Ho, D. M.; Krause, J. *Tetrahedron Lett.* **1993**, *34*, 797. (d) Ishibashi, H.; Kameoka, C.; Ueda, R.; Kodama, K.; Sato, T.; Ikeda, M. *Synlett* **1993**, 649. (e) Ishibashi, H.; Kameoka, C.; Kodama, K.; Ikeda, M. *Tetrahedron* **1996**, *52*, 489. (f) Ishibashi, H.; Kodama, K.; Kameoka, C.; Kawanami, H.; Ikeda, M. *Tetrahedron* **1996**, *52*, 13867. (g) Ishibashi, H.; Kameoka, C.; Kodama, K.; Kawanami, H.; Hamada, M.; Ikeda, M. *Tetrahedron* **1997**, *53*, 9611.

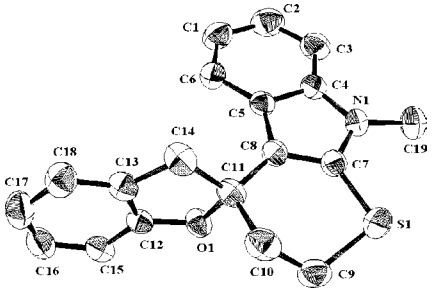
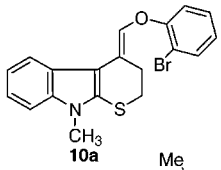
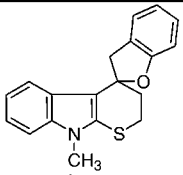
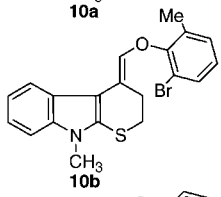
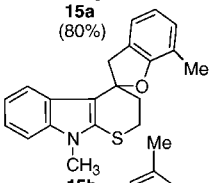
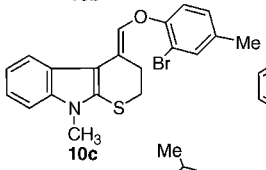
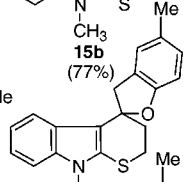
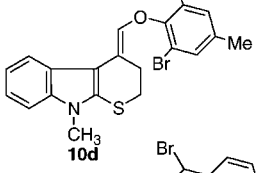
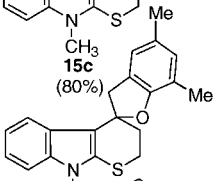
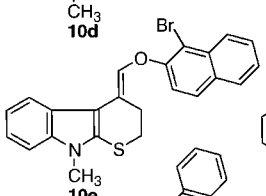
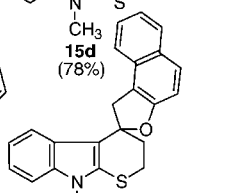
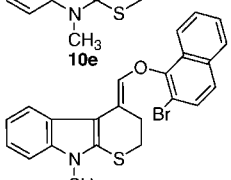
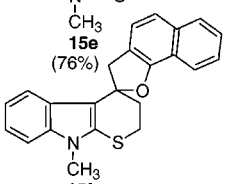


Figure 1. X-ray crystal structure of **15a**.

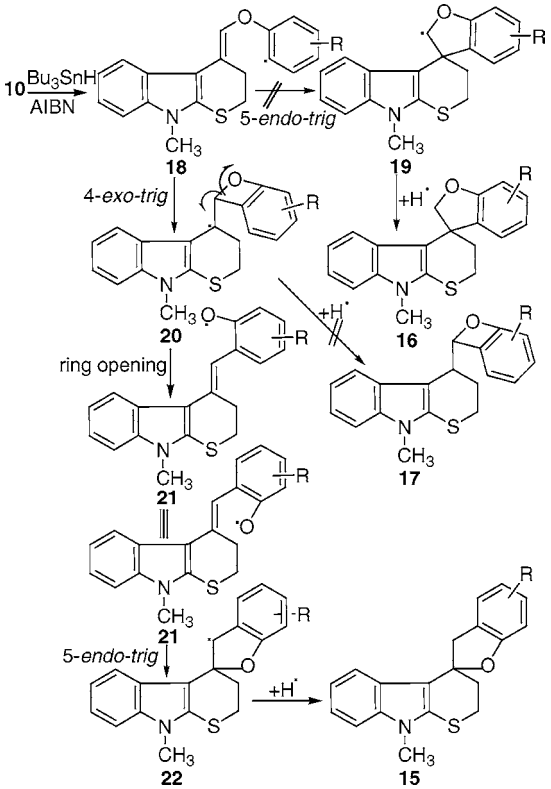
Substrates **10b**−**f** under similar treatment gave the products **15b**−**f** in 75−80% yield (Table 1). Surprisingly we failed to obtain here the expected product **16** and or **17** (Scheme 4) as **16** type product was obtained in the case of another enol ether.[5a]

In case of the aryl radical cyclization of **10**, formation of the products **15** is quite unusual. It may be noted that initially

Table 1. Yield of Aryl Radical Cyclization Products **15a**−**f**

Entry	Starting materials	Products
1	 **10a**	 **15a** (80%)
2	 **10b**	 **15b** (77%)
3	 **10c**	 **15c** (80%)
4	 **10d**	 **15d** (78%)
5	 **10e**	 **15e** (76%)
6	 **10f**	 **15f** (75%)

Scheme 5. Mechanism of Aryl Radical Cyclization



generated aryl radical **18** could have undergone either 5-*endo-trig* or 4-*exo-trig* cyclization at the enol ether part of the diene **10**. The 5-*endo-trig* cyclization would have generated the radical **19**, which would have provided **16**, or 4-*exo-trig* cyclization could have generated the four-membered radical intermediate **20**, which could have yielded **17**. The other less probable options were 6-*exo-trig* versus 7-*endo-trig* onto the ene-amine part of the diene **10**. However, none of these options can explain the formation of **15**.

(7) (a) Ikeda, M.; Ohtani, S.; Yamamoto, T.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1763. (b) Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1998**, *39*, 75. (c) Ponaras, A. A.; Zaim, O. *Tetrahedron Lett.* **1993**, *34*, 2879.

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(9) (a) Majumder, K. C.; Kundu, U. K.; Ghosh, S. K. *Org. Lett.* **2002**, *4*, 2629. (b) Majumdar, K. C.; Bandyopadhyay, A.; Biswas, A. *Tetrahedron* **2003**, *59*, 5289.

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(12) ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 2.15−2.25 (dt, 1H, J = 13, 2.1 Hz, −SCH_2CH_2), 2.66−2.73 (ddd, 1H, J = 13.4, 6, 1.6 Hz, −SCH_2SCH_2), 3.03−3.10 (ddd, 1H, J = 12.7, 6, 2.1 Hz, −SCH_2CH_2), 3.17−3.22 (d, 1H, J = 16.3 Hz, $ArCH_2$), 3.38−3.47 (dt, 1H, J = 12.8, 1.6 Hz, −SCH_2CH_2), 3.63 (s, 3H, −NCH_3), 3.98−4.04 (d, 1H, J = 16.3 Hz, $ArCH_2$), 6.75−7.38 (m, 8H, Ar**H**).^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 25.66, 30.28, 39.31, 42.10, 84.97, 108.84, 109.41, 110.08, 118.87, 120.39, 120.75, 121.34, 125.43, 126.48, 126.96, 128.79, 133.38, 138.00, 159.06. MS: *m*/*z* 307 (M^+).

The formation of **15** is explicable by a 4-*exo-trig* cyclization of the initially generated aryl radical **18** at the enol ether part of the diene to give the more stable radical **20** rather than radical **19**. The stability is due to the overlapping of the p-orbital of the radical center of **20** with the neighboring π-system of the indole moiety. The highly strained oxetene ring may undergo ring opening leading to the formation of a resonance stabilized aryloxy radical **21** rather than aryl radical **18**. The aryloxy radical **21** may then undergo 5-*endo-trig* cyclization to give stable benzylic radical **22** followed by abstraction of a hydrogen radical to afford the unusual product **15** (Scheme 5).

It may therefore be concluded that the furan ring in **15** is formed not via initial 5-*endo-trig* cyclization but through the occurrence of an initial 4-*exo-trig* cyclization followed by 5-*endo-trig* cyclization of the resultant aryloxy radical intermediate formed by the opening of the oxetene ring of the radical intermediate. We have been able to achieve the successful synthesis of spirocyclic indole annulated oxygen heterocyclic compounds in excellent yield by aryl radical cyclization. The methodology described here is mechanistically interesting and synthetically useful and exhibits appreciable regioselectivity.

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Supporting Information Available: ^{1}H NMR spectra for compounds **15a**−**f**, ^{13}C NMR spectra for compounds **15a**,**b**, mass spectra for compounds **15a**,**b**,**d**,**e**, and crystallographic information files (in CIF firmat) for compound **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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