Heteroaryl Radicals: A Furyl Radical in the Synthesis of the Tricyclic Framework of Eremophilane Sesquiterpenoids

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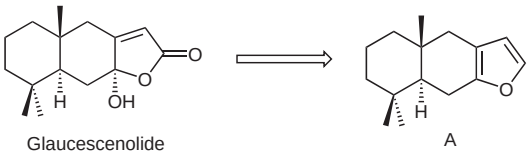
Abstract: Studies on the intramolecular addition of thieno and furan radicals to alkenyl groups are reported. The radicals undergo a *6-endo-trig* selective cyclization to alkenyl systems resulting in a linearly annulated tricyclic moiety.

Key words: radical reactions, cyclizations, furans, terpenoids

The use of radical reactions, and in particular a radical reaction cyclization sequence, has been of great interest to organic chemists.[1] Organotin-mediated intramolecular aryl–radical cyclizations have emerged as useful synthetic methods for benzo-fused ring structures.[2] Ring closures of aryl radicals, as in the case of alkyl radicals, readily proceed via 5-*exo* and 6-*exo* pathways, generating five- and six-membered rings.[3] Ghatak and co-workers[4a–e] reported a potentially useful route to certain linearly benzannulated six- to nine-membered ring structures through Bu_3SnH-induced *endo-trig* aryl–radical cyclizations. Pyridine-ring-fused six-, seven-, and eight-membered-ring annulated polycyclic compounds were also synthesized very recently;[4f] also homolytic reactions for the heteroaromatic series were investigated.[5] There is also precedent for radical *ipso*-type substitution onto aryl rings.[6]

The furanoeremophilanes, bearing a furan moiety fused to the decalin core, belong to a structurally diverse class of sesquiterpenoids. The linearly fused furan ring is embodied in a large number of natural products, particularly, in some insect anti-feeding compounds such as petasalbine, ligularone, atractylon etc.,[7] which possess unique structural features; this has triggered the synthesis of such compounds.[8,9] However, to date there have been no reports on the synthesis of furanoeremophilane frameworks through radical cyclization. In 2002 Perry et al.[10] isolated a bioactive natural product, *Glaucescenolide*, which contains a novel carbon skeleton. Very recently Takikawa et al.[11] have synthesized *Glaucescenolide* in vitro using tricyclic intermediate A (Scheme 1). Amongst various approaches aimed at the synthesis of these types of skeletons, we examined the possibilities of using radical reactions, as they usually avoid acidic or basic conditions, which is a prerequisite for handling such systems.

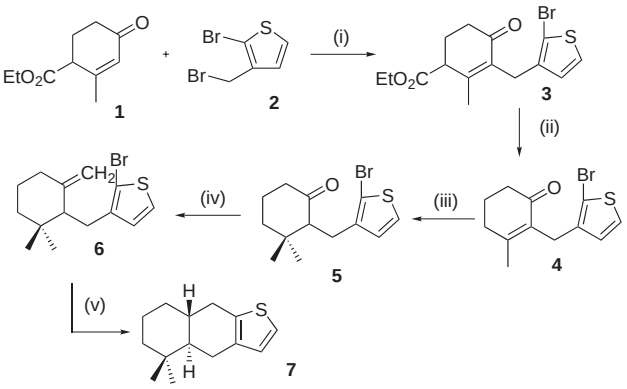


Scheme 1

As a part of our ongoing investigation into the generation and reactions of radicals formed from heteroaromatic compounds, we prepared 2-bromo-3-bromomethyl thiophene derivatives **2**, which could serve as radical precursors. Bromination of 2-bromo-3-methyl thiophene with NBS in carbon tetrachloride afforded compound **2** in very good yield.

The desired alkene **6** was derived from Hagemann's ester **1**. We initially converted **1** to **5** by adapting a known three-step procedure.[12] Wittig olefination of the ketone **5** with a phosphonium salt and BuLi in THF furnished compound **6** in 68% yield. The radical cyclization of **6** in refluxing benzene with Bu_3SnH and a catalytic amount of AIBN at high dilution afforded 5,5-dimethyl-4,4a,5,6,7,8,8a,9-octahydro-naphtho[2,3-*b*]thiophene (**7**) in 60% yield as the only isolable product (Scheme 2).

Unfortunately, when we attempted to convert 3-methylfuran to 2-bromo-3-bromomethylfuran by the same procedure we could not isolate the desired compound, as it



Scheme 2 *Reagents and conditions*: (All the reactions were carried under an argon atmosphere) (i) *t*-BuOK, *t*-BuOH, reflux, 10 h (63%); (ii) KOH, EtOH–H_2O, reflux, 8 h (49%); (iii) Me_2CuLi, $BF_3{\cdot}Et_2O$, Et_2O, –50 °C (15 min), then –30 °C (1 h) (71%); (iv) $Ph_3P^+CH_3I^-$, BuLi, THF, –30 °C to r.t. (3 h) (68%); (v) Bu_3SnH, AIBN, benzene, reflux, 8 h, (60%).

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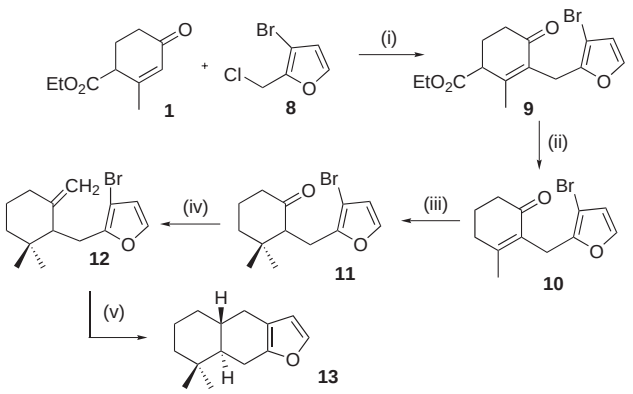
polymerized readily at room temperature.[13] The analogous 3-bromo-2-chloromethylfuran was stable and alkylation of Hagemann's ester **1** with 3-bromo-2-chloromethylfuran and *t*-BuOK in *t*-BuOH under reflux afforded compound **9** as a viscous yellow oil in 58% yield. Hydrolysis and decarboxylation of **9** with KOH/EtOH–H_2O furnished 2-(3-bromofuran-2-ylmethyl)-3-methylcyclohex-2-enone (**10**) in 48% yield. The saturated ketone **11** was synthesized from the cyclohexenone derivative **10** with Gilman's reagent (Me_2CuLi). Wittig olefination of the ketone **11** resulted in the formation of 3-bromo-2-(2,2-dimethyl-6-methylenecyclohexylmethyl)furan (**12**) in 67% yield.

Radical cyclization[14] of the unsaturated bromofuran **12** with Bu_3SnH initiated with a catalytic amount of AIBN in refluxing benzene at high dilution afforded exclusively the cyclohexane-ring-annulated furan **13** as the only isolable product (Scheme 3). The assigned structures of **7** and **13** were established by spectral and elemental analyses.[15] The *trans*-geometry of the newly generated ring junction was derived from the spectral data and by analogy with known compounds.[4e]



Scheme 3 *Reagents and conditions:* (All the reactions were carried out under an argon atmosphere) (i) *t*-BuOK, *t*-BuOH, reflux, 12 h (58%); (ii) KOH, EtOH–H_2O, reflux, 8 h (48%); (iii) Me_2CuLi, $BF_3{\cdot}Et_2O$, Et_2O, –50 °C (15 min), then –30 °C (1 h) (75%); (iv) $Ph_3P^+CH_3I^-$, BuLi, THF, –30 °C to r.t., 3 h (67%); (v) Bu_3SnH, AIBN, benzene, reflux, 8 h, (46%).

In conclusion, it has been shown that it is possible to generate radicals at the C-2 position of thiophene and C-3 position of the furan ring and for these to undergo intramolecular cyclization reactions to provide a quick access to a range of interesting natural and unnatural tricyclic frameworks. Further investigations on the generality of this type of *endo*-selective heteroaryl–radical cyclization, as a potential synthetic gateway to a variety of new ring-fused heterocyclic structures of general interest, are in progress.

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(14) **Radical cyclization of 6 and 12 with Bu_3SnH**
To a solution of **6** or **12** (50 mg, 0.227 mmol or 0.245 mmol) in degassed anhyd benzene (30 mL) heated under reflux were added Bu_3SnH (1.5 equiv) and AIBN (5 mg, 0.02 mmol) in degassed anhyd benzene (20 mL) slowly by syringe pump. The addition of Bu_3SnH was carried out over 2 h and the mixture was heated under reflux for 8 h. The solvent was removed under reduced pressure, Et_2O (20 mL) and a sat. aq solution of KF (20 mL) were added to the residue; the whole mixture was stirred at r.t. for 24 h. The organic phase was separated, washed with brine, dried, and concentrated. Purification was carried out by chromatography(hexane).

(15) Spectral data of representative compounds.
5,5-Dimethyl-4,4a,5,6,7,8,8a,9-octahydronaphtho[2,3-*b*]thiophene (7)
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.88 (s, 3 H), 0.96 (s, 3 H), 1.25–1.59 (m, 8 H), 2.27–2.41 (m, 2 H), 2.62–2.88 (m, 2 H), 6.73 (d, 1 H, *J* = 5.11 Hz), 7.02 (d, 1 H, *J* = 5.11 Hz); MS (EI, 70 ev): *m*/*z* = 220 (M^+); Anal. Calcd for $C_{14}H_{20}S$: C, 76.30; H, 9.15. Found: C, 76.45; H, 9.25.
8,8-Dimethyl-4,4a,5,6,7,8,8a,9-octahydronaphtho[2,3-*b*]furan (13)
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.88 (s, 3 H), 0.96 (s, 3 H), 1.21–1.58 (m, 8 H), 1.71–2.71 (m, 4 H), 6.15 (br s, 1 H), 7.22 (br s, 1 H); ESI-MS: *m*/*z* = 205.12 $[M + H]^+$; Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.65; H, 9.76.