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'Cascade' Radical Reactions in Synthesis : Condensed Thiophenes from Ketenethioacetals.

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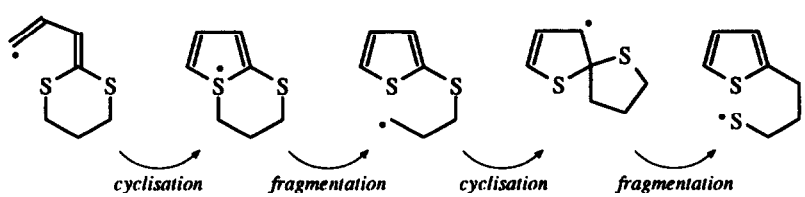
Abstract : *A novel radical centred tandem cyclisation - tandem fragmentation sequence is described for the direct convertion of ketenethioacetals e.g.* ***1, 6, 9, 12 and 16*** *into condensed thiophenes e.g.* ***2, 7, 10, 13 and 17.***

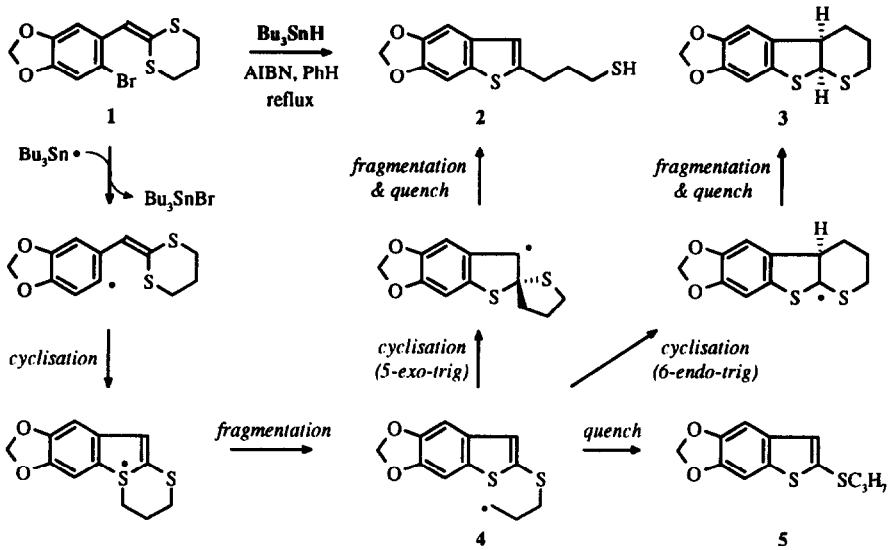
Illustrations of the explosive power and diverse application of radical centred reactions in organic synthesis abound in the contemporary literature. Recently, these studies have centred on various aspects of selectivity in radical mediated bond forming reactions[1] and the ability of such processes to promote, in a controlled manner, a series of such manipulations.[2] Our interest in the development of new *'tandem'* and *'cascade'* sequences[3] stems from the belief that they may offer a ready access to complex molecular architectures through the union of other, much simpler fragments.[4] During one study, on the addition of organolithium species to ketenethioacetals,[3b] our attention became focussed on the possible transformations that could occur through the addition of a carbon centred radical to this curious functional group.[5] We were particularly intreagued by the potential tandem cyclisation - tandem fragmentation sequence outlined in Scheme 1, as this would offer a concise and versatile entry to an array of highly substituted condensed thiophenes. In this letter we report the realisation of this objective.



Scheme 1

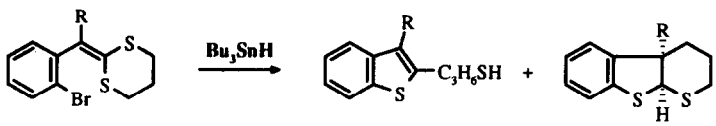
We first examined this reaction with the ketenethioacetal **1**; derived from 6-bromopiperonal *via* a Peterson olefination with 2-lithio-2-trimethylsilyl-1,3-dithiane (90%).[6] On exposure of this material **1** to standard radical forming conditions (Bu_3SnH, AIBN, PhH, reflux, N_2; $KF_{(aq)}$) we were pleased to observe that the

anticipated benzo[*b*]thiophene **2** was furnished in 72% yield.[7] Two minor components, the tetracyclic thioacetal **3** (12%) and the benzo[*b*]thiophene **5** (5%) were also isolated. These materials presumably arising *via* a 6-*endo*-trig cyclisation of the radical intermediate **4**, and the interception of this intermediate **4** by tributyltin hydride, respectively (Scheme 2).



Scheme 2

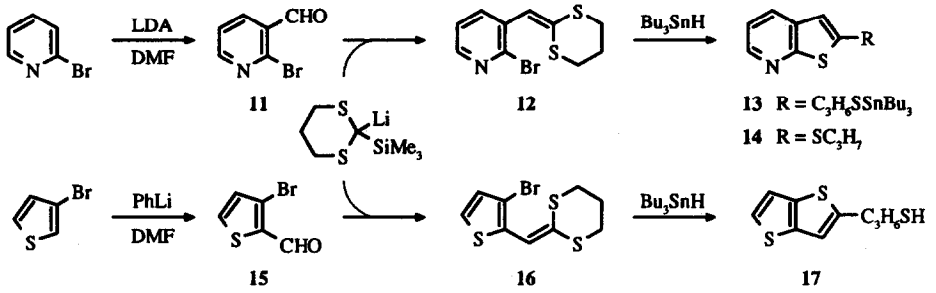
To further explore the scope of this methodology, we next examined the simple ketenethioacetal **6**. Treatment of this material as before produced the anticipated mixture of the benzo[*b*]thiophene **7** and the thioacetal **8**. However, when the methylated analogue **9** was examined, the only isolated component was the desired benzo[*b*]thiophene **10**. Presumably the increase in steric hinderence, engendered by the additional olefin substituent, hampers the 6-*endo*-trig mode of cyclisation.



Scheme 3

Our attention next turned to the construction of more novel heterocyclic materials using this protocol. To that end we prepared the ketenethioacetals **12** and **16**; derived from 2-bromopyridine and 3-bromothiophene respectivly (Scheme 4). Treatment of the pyridine **12** with tributyltin hydride under the above mentioned

conditions provided the thieno[2,3-*b*]pyridines **13** (62%) and **14** (12%), while the thiophene **16** yielded, as the sole isolated product, the thieno[3,2-*b*]thiophene **17** (74%). In each of these cases the dominance of the 5-*exo*-trig mode of cyclisation over the 6-*endo*-trig alternative is presumed to be electronic in nature.



Scheme 4

It is perhaps noteworthy that the sequence described here is initiated by the unusual, intramolecular addition of a carbon centred radical to a neighbouring sulfide[8] and that it is then propagated *via* the unprecedented addition of a carbon centred radical to a condensed thiophene.[9] We are currently investigating each of these processes independently, and in greater detail, to further delineate the scope and limitations of each for synthetic objectives since condensed thiophenes have been shown to display a wealth of therapeutically significant biological activity.[10]

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7. All new compounds gave satisfactory analytical and spectroscopic characteristics *e.g.* **2**: white solid; m.p. (ether/hexane) 52-53°C; FT-IR ($CHCl_3$) υ_{max} 2925m, 2850m, 2560w, 1475s, 1040s, 940s and 855s cm^{-1}; UV λ_{max} (ε) ($CHCl_3$) 317 (5100), 311 (4900), 306 (4400), 298inf (3100), 278 (11000), 268 (11000) and 244 (23000) nm; ^1H NMR (250MHz, $CDCl_3$) δ_H 7.16 (1H, s, Ar*H*), 7.07 (1H, s, Ar*H*), 6.88 (1H, s, Ar*H*), 5.99 (2H, s, OCH_2O), 2.98 (2H, t, *J* 7.2 Hz, $=CCH_2$), 2.60 (2H, q, *J* 7.2 Hz, CH_2SH), 2.02 (2H, quin, *J* 7.2 Hz, CH_2SH) and 1.39 (1H, t, *J* 7.3 Hz, S*H*) p.p.m.; $^m/_z$ (EI) found M^+, 252.0292 (44%); $C_{12}H_{12}S_2O_2$ requires 252.0279, 250 (87), 222 (58) and 191 (100) amu. **3**: white solid; m.p. (ether/hexane) 95-99°C; FT-IR ($CHCl_3$) υ_{max} 2915m, 2850m, 1465s, 940s and 865m cm^{-1}; UV λ_{max} (ε) ($CHCl_3$) 317 (2440) and 256 (2340) nm; ^1H NMR (250MHz, $CDCl_3$) δ_H 6.72 (1H, s, Ar*H*), 6.68 (1H, s, Ar*H*), 5.93 (2H, abq, OCH_2O), 4.99 (1H, d, *J* 5.2 Hz, SC*H*S), 3.25 (1H, app.dt, *J* 8.2, 5.0 Hz, $=CCH$), 2.73 (1H, ddd, *J* 14.7, 8.9, 2.6 Hz, SC*H*H), 2.55 (1H, ddd, *J* 14.7, 7.0, 2.9 Hz, SCH*H*), 1.95 (2H, m) and 1.78 (2H, m) p.p.m.; ^{13}C NMR (67.8MHz, $CDCl_3$) δ_C 147.1(s), 145.7(s), 135.5(s), 132.8(s), 105.2(d), 104.4(d), 101.3(t), 53.7(d), 47.7(d), 27.0(t), 26.3(t) and 23.3(t); $^m/_z$ (EI) found M^+, 252.0275 (5%); $C_{12}H_{12}S_2O_2$ requires 252.0279, 205 (41), 192 (100) and 191 (50) amu.

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