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The Addition Of Organolithiums to Ketenethioacetals: A New Cyclopentannulation Sequence Leading to Indanes.

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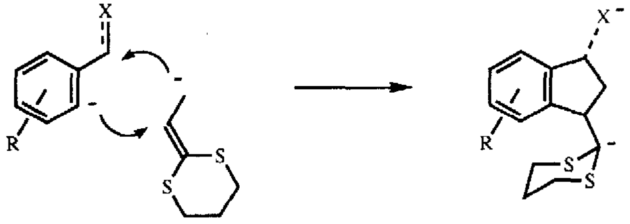
Key Words: Cyclopentannulation, Ketenethioacetal, Indane, 1,3-Dithiane, Tandem Reaction, Umpolung.

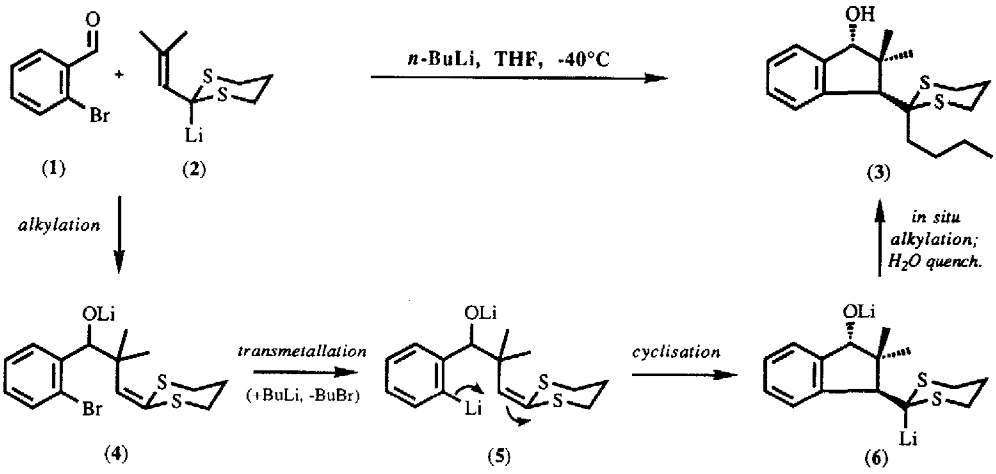
Abstract: *A new cyclopentannulation sequence leading to the rapid preparation of highly substituted indanes e.g. (3) is described. This novel cyclisation protocol is effected via the initial union of an aryl bromide such as (1) with a 2-lithio-2-vinyl-1,3-dithiane e.g. (2) leading to a ketenethioacetal e.g. (4). Transmetallation to the corresponding aryllithium e.g. (5), by addition of an alkyllithium reagent, next effects an intramolecular 5-exo-trig cyclisation onto the ketenethioacetal moiety, leading to an indane intermediate, e.g. (6). Subsequent in situ alkylation of this intermediate (6), with the alkyl bromide generated as a consequence of transmetallation, then completes the sequence.*

The widespread occurrence of cyclopentanes in biologically important natural products has resulted in the development of many exciting and diverse new strategies for their construction.[1] While many of these strategies typically involve the construction of a single carbon-carbon bond, interest in new cyclopentannulation sequences by multiple bond constructions has intensified since these processes often enable the rapid construction of complex molecular frameworks by the union of two usually much simpler fragments.[2]



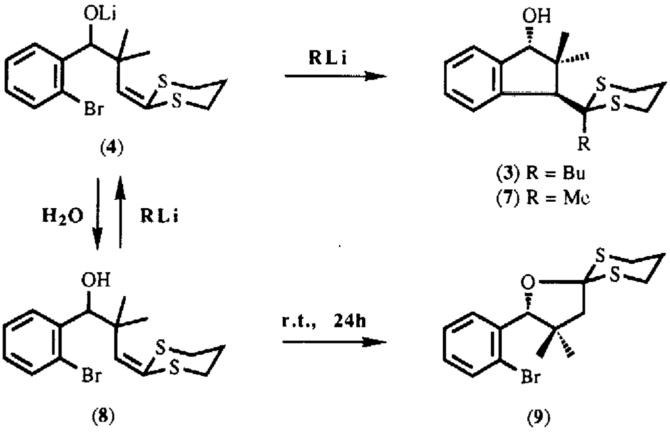
Scheme 1

During recent studies directed towards the synthesis of lignan natural products,[3] we became interested in the construction of the indane ring system. We envisaged a novel and simple 'one pot' annulation sequence based on the tandem alkylation protocol outlined in Scheme 1. The approach centred on the initial union, by γ-alkylation, of a metallated 2-vinyl-1,3-dithiane with an aryl bromide, leading to an intermediate ketenethioacetal.[4] A subsequent transmetallation of the aryl bromide might then effect 5-*exo*-trig ring closure by the intramolecular nucleophilic addition of the aryl anion to the proximate ketenethioacetal moiety.[5]



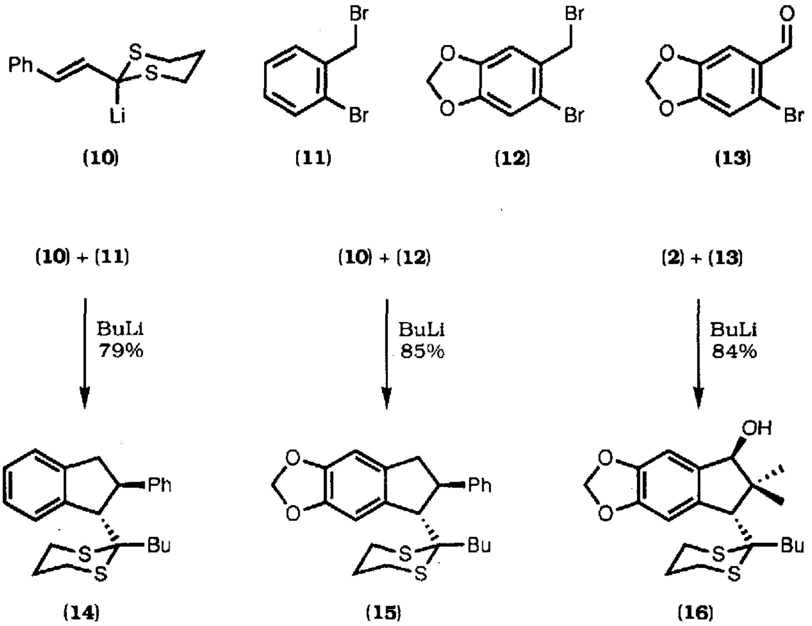
Scheme 2

Indeed, when a solution of the 2-lithio-2-vinyl-1,3-dithiane (**2**)[6] in THF was treated sequentially with 2-bromobenzaldehyde (**1**) and then *n*-butyllithium the indane (**3**) was produced as a single diastereoisomer,[7] [presumably *via* the intermediate aryllithium species (**5**)] in a satisfying 89% overall yield (Scheme 2). In addition, treatment of the intermediate (**4**) with methyllithium (THF, 0°C, 24h) furnished a single diastereoisomer of the corresponding indane (**7**, 72%). The intermediate (**4**) could also be quenched, by the addition of water, to give the ketenethioacetal (**8**, 91%). Immediate treatment of (**8**) with 2.2 equivalents of either *n*-butyllithium or methyllithium then smoothly effected the anticipated annulations to give the indanes (**3**) and (**7**), respectively. However, on leaving to stand at ambient temperature for 24h the ketenethioacetal (**8**) isomerised, in near quantitative yield, to the substituted tetrahydrofuran (**9**) (Scheme 3).[8]



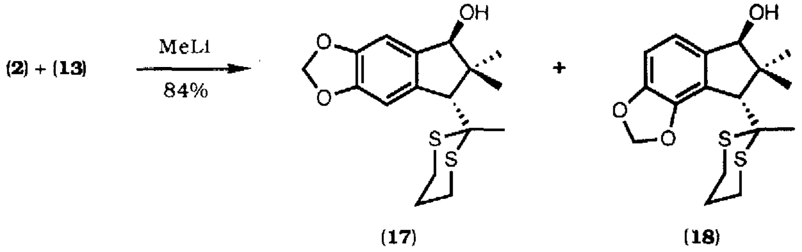
Scheme 3

We have also applied this novel annulation sequence to the synthesis of the indanes (**14**), (**15**) and (**16**) form the dithianes (**2**) and (**10**) and the aryl bromides (**11**), (**12**) and (**13**) respectively. In all these cases the indanes were produced in high yields and as single diastereoisomers (Scheme 4).



Scheme 4

Surprisingly however, when piperonal bromide (**13**) was coupled with the lithiodithiane (**2**) and then treated with methyllithium, a single diastereoisomer of the anticipated product, the indane (**17**, 52%) was produced together with its *positional* isomer, the indane (**18**, 32%). The precise mechanism by which the indane (**18**) is formed remains uncertain (Scheme 5).



Scheme 5

It is perhaps noteworthy that phenyllithium has previously been shown to be chemically inert towards ketenethioacetals.[5] Indeed, reports on the addition of organometalic reagents to ketenethioacetals are scarce and usually only proceed under special circumstances.[9] It is therefore interesting that the sequence described here is apparently quite straightforward. We are currently investigating the generality of this process for the construction of other ring systems and application in target orientated synthesis.

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5. For overviews of the chemistry of ketenethioacetals see: **a.** M. Kolb in 'The chemistry of ketenes, allenes and related compounds', pt. 2, chapter 16, ed. S. Patai, Wiley, Chichester, **1980**; **b.** M. Kolb; *Synthesis*, **1990**, 171.
6. The dithianes were all prepared from the corresponding aldehydes in >90% yield by treatment with 1,3-propanedithiol, catalytic *p*-TsOH in benzene at ambient temperature. Deprotonation was effected by *n*-BuLi at -78°C to -20°C in THF.
7. All new compounds gave satisfactory spectral and/or analytical data *e.g.* (**16**): foam, **m.p.** 48-52°C (ether/petrol); **UV** ($CHCl_3$) μ_{max} (ε) 242 (6630), 246 (6210), and 295 (5970) nm; **FT-IR** ($CHCl_3$) λ_{max} 3420brm, 2960s, 2770w, 1475s, 1275s, 1040s, 910s, and 730s cm^{-1}; **^{1}H NMR** (270 MHz, $CDCl_3$) δ 7.14 (1H, s), 6.82 (1H, s), 5.97 (2H, abq), 5.09 (1H, brd, J = 7.9Hz), 3.31 (1H, brs), 2.91 (2H, m), 2.70 (2H, m), 2.22 (1H, m), 1.97 (3H, m), 1.60 (3H, m), 1.53 (3H, s), 1.36 (2H, sextet, J = 7.6Hz), 1.00 (3H, s), and 0.97 (3H, t, J = 7.6 Hz) ppm; **n.O.e.** Irradiation of the signal at δ 1.60 ppm caused an n.O.e. enhancement at δ 5.09 ppm (14%) while irradiation of the signal at δ 1.00 ppm caused an n.O.e. enhancement at δ 3.31 ppm (10%); **^{13}C NMR** (67.8 MHz, $CDCl_3$) δ 147.1 (s), 146.4 (s), 138.9 (s), 134.3 (s), 109.4 (d), 103.9 (d), 100.9 (t), 81.9 (d), 58.3 (d), 58.2 (s), 50.5 (s), 36.7 (t), 27.3 (t), 26.4 (t), 25.9 (t), 25.2 (q), 24.3 (t), 23.8 (q), 22.8 (t), and 14.0 (q); **m/z** (EI) 362.1423 (M^+-H_20, 70%): $C_{20}H_{26}S_2O_2$ requires 362.1374; 241 (38), 213 (39), 199 (55), and 175 (100).
8. A.P. Kozikowski, and Y.-Y. Chen; *J. Org. Chem.*, **1980**, *45*, 2236.
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