

## New synthesis of unsymmetrical dithia compounds

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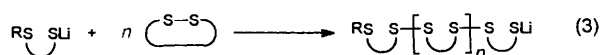
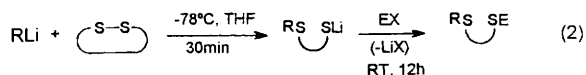
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1,2-Dithiacycloalkanes undergo nucleophilic ring-opening with organolithium reagents; the intermediates can be treated with electrophiles to provide unsymmetrical dithia compounds in high yields.

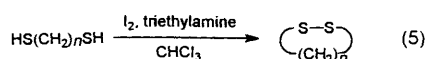
Organic thiols, sulfides and disulfides are important because of their physiological activity,<sup>1</sup> their auxiliary roles in a number of modern synthetic methods,<sup>2</sup> and their potential use in electronic and other modern materials.<sup>3</sup> Therefore, there is considerable interest in the development of novel syntheses of such compounds.<sup>4</sup> As part of our more general interests in sulfur compounds<sup>5</sup> and in lithiations<sup>6</sup> we have introduced processes for the elaboration of arenethiols by directed lithiation<sup>7</sup> and for the incorporation of a thiol equivalent into heterocyclic compounds by reaction of tetraisopropylthiuram disulfide with appropriate lithiated heterocycles.<sup>8</sup> This last reaction is a specific example of the well-established cleavage of an organic disulfide by an organometallic reagent to yield an unsymmetrical sulfide [eqn. (1)].<sup>9</sup>



In principle, application of this reaction to cyclic disulfides could provide potential access to unsymmetrical dithia compounds [eqn. (2)], but there are no such reactions in the literature. A possible complication is that a free metal thiolate formed in the initial step can react rapidly with further cyclic disulfide to produce oligomeric materials [eqn. (3)]<sup>10</sup> which could then give rise to symmetrical compounds [eqn. (4)]. It was therefore not clear whether the desired unsymmetrical compounds could be obtained selectively. However, we now report that reactions of 1,2-dithiacycloalkanes with organolithium reagents followed by trapping of the intermediates with certain electrophiles can indeed give unsymmetrical dithia compounds in high yields [eqn. (2)].



1,2-Dithiacycloalkanes of ring sizes from 5 to 12 are easily synthesised by oxidative cyclisation of the readily available dithiols.<sup>11</sup> The literature method,<sup>12</sup> with only minor modifications of concentration and purification procedure, was applied in the synthesis of 1,2-dithiane and 1,2-dithiacyclooctane [eqn. (5)]. These compounds tended to undergo oligomerisation on

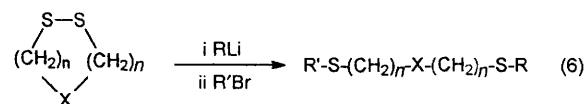


prolonged storage, so they were used relatively soon after purification.

The dithianes were treated first with an organolithium and then with an alkyl or acyl halide to give the corresponding products in good yield (see Table 1).

As the results in Table 1 show, the reaction was successful with a range of different organolithium reagents and with acetyl halides and primary alkyl halides as electrophiles, but alkylation did not take place under these conditions with tertiary alkyl halides which, after work-up, led instead to the corresponding thiols.

This work shows that the reaction of eqn. (2) is a fast and convenient way to synthesise a range of dithia compounds in high yields. Although the investigation was limited to dithiane and dithiacyclooctane, smaller and larger ring sizes and rings containing additional heteroatoms<sup>12</sup> or fused to aromatic or alicyclic rings<sup>13,14</sup> have been reported in the literature. This leads to possibilities for the synthesis of other unsymmetrical dithia compounds [eqn. (6), X = a heteroatom or a ring system].



### Experimental

#### General procedure

The dithiacycloalkane was dissolved in dry THF and the solution cooled to  $-78^\circ\text{C}$ . An equimolar amount of organolithium compound in hexane or diethyl ether was added to the solution and the mixture stirred for 30 min; it was then allowed to warm to room temperature before addition of an equimolar amount of the electrophile. The mixture was stirred at ambient temperature overnight after which it was washed with water, dried, concentrated under reduced pressure and purified by bulb-to-bulb distillation. The products and yields obtained are those shown in Table 1.

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**Table 1** Products synthesised according to eqn. (2)

| RLi                | Disulfide             | EX                                | Product  | Yield (%) <sup>a</sup> |
|--------------------|-----------------------|-----------------------------------|--|------------------------|
| MeLi               | 1,2-Dithiane          | MeI                               | MeS(CH <sub>2</sub> ) <sub>4</sub> SMe                             | 86                     |
| MeLi               | 1,2-Dithiane          | MeBr                              | MeS(CH <sub>2</sub> ) <sub>4</sub> SMe                             | 55                     |
| MeLi               | 1,2-Dithiane          | BuBr                              | MeS(CH <sub>2</sub> ) <sub>4</sub> SBu                             | 74                     |
| BuLi               | 1,2-Dithiane          | EtBr                              | BuS(CH <sub>2</sub> ) <sub>4</sub> SEt                             | 97                     |
| BuLi               | 1,2-Dithiane          | BuBr                              | BuS(CH <sub>2</sub> ) <sub>4</sub> SBu                             | 87                     |
| Bu <sup>t</sup> Li | 1,2-Dithiane          | BuBr                              | Bu <sup>t</sup> S(CH <sub>2</sub> ) <sub>4</sub> SBu               | 98                     |
| Bu <sup>t</sup> Li | 1,2-Dithiane          | Bu <sup>t</sup> Br                | Bu <sup>t</sup> S(CH <sub>2</sub> ) <sub>4</sub> SH                | 77                     |
| BuLi               | 1,2-Dithiane          | PhCH <sub>2</sub> Br              | BuS(CH <sub>2</sub> ) <sub>4</sub> SCH <sub>2</sub> Ph             | 78                     |
| BuLi               | 1,2-Dithiane          | AcCl                              | BuS(CH <sub>2</sub> ) <sub>4</sub> SAc                             | 80                     |
| PhLi               | 1,2-Dithiane          | BuBr                              | PhS(CH <sub>2</sub> ) <sub>4</sub> SBu                             | 77                     |
| PhLi               | 1,2-Dithiane          | PhCH <sub>2</sub> Br              | PhS(CH <sub>2</sub> ) <sub>4</sub> SCH <sub>2</sub> Ph             | 98                     |
| PhLi               | 1,2-Dithiane          | AcBr                              | PhS(CH <sub>2</sub> ) <sub>4</sub> SAc                             | 71                     |
| MeLi               | 1,2-Dithiacyclooctane | MeI                               | MeS(CH <sub>2</sub> ) <sub>6</sub> SMe                             | 67                     |
| BuLi               | 1,2-Dithiacyclooctane | BuBr                              | BuS(CH <sub>2</sub> ) <sub>6</sub> SBu                             | 85                     |
| BuLi               | 1,2-Dithiacyclooctane | C <sub>7</sub> H <sub>15</sub> Br | BuS(CH <sub>2</sub> ) <sub>6</sub> SC <sub>7</sub> H <sub>15</sub> | 82                     |
| BuLi               | 1,2-Dithiacyclooctane | PhCH <sub>2</sub> Br              | BuS(CH <sub>2</sub> ) <sub>6</sub> SCH <sub>2</sub> Ph             | 86                     |
| BuLi               | 1,2-Dithiacyclooctane | AcBr                              | BuS(CH <sub>2</sub> ) <sub>6</sub> SAc                             | 69                     |

<sup>a</sup> Yield of isolated, purified product. All the products were confirmed by spectroscopic and analytical data.

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