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A New Synthesis of Thiacyclophanes from Thiolacetates

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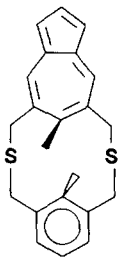
Abstract: A new cyclization to obtain good yields of thiacyclophanes is described, which is particularly useful when one of the components cannot be obtained as the halide.

Thiacyclophanes have proved remarkably useful intermediates to prepare a number of novel compounds,[1] in part for two main reasons: firstly they are much easier to prepare than the cyclophanes themselves and secondly, a number of routes have been developed to convert the C-S-C unit into either a C-C or C=C group. It is clear from Vogtle's review[2] that synthesis of medio- and macrocyclic compounds advanced much by making use of the nucleophilicity of thiolate. This, together with a choice for ring contraction routes,[3] which include (i) photochemical and thermal extrusion of sulfur or SO_2,[4] (ii) Stevens or Wittig rearrangement of the C-S-C unit into C-C(SCH_3), followed by Hofmann elimination of Me_2S,[5] (iii) Ramberg-Backlund type rearrangement,[6] has now made thiacyclophanes into one of the most popular intermediates for cyclophane synthesis.

The thiacyclophanes themselves have nearly all been made by one of two routes.[2] In one, two molecules of a bis-halide are reacted with Na_2S or thioacetamide. In the second, one molecule of bis-halide is first converted into a bis-thiol (usually using thiourea), and then the thiol is coupled with the other molecule of bis-halide in the presence of base. This latter approach is of course better for non-symmetrical thiacyclophanes, and as well in our opinion[1] is easier, since normally both the thiol and the halide can be placed in a single dropping funnel in equimolar amounts and then are added slowly to a dilute solution of base. The former method usually requires simultaneous addition from two dropping funnels or syringes. However, either method requires that the corresponding halide is available, either to couple directly or to covert to the thiol.

This point was brought home to us, when we were trying to synthesise the thiacyclophane **1**, as intermediate to the novel bridged annulene **2**. We were not able to convert the azulene-diol **3** into the dibromide **4**, by HBr or by PBr_3, or to the dichloride with $SOCl_2$ or even when the fairly mild Ph_3P/CCl_4 was used. Only tars were obtained. It is often difficult to isolate bromomethylaromatics in which the aromatic can easily self alkylate. We thought at first, that this problem might be overcome if the diol **3** could be



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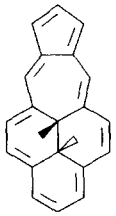

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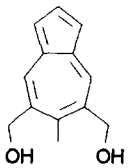

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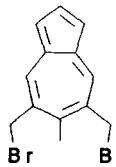

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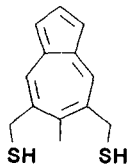

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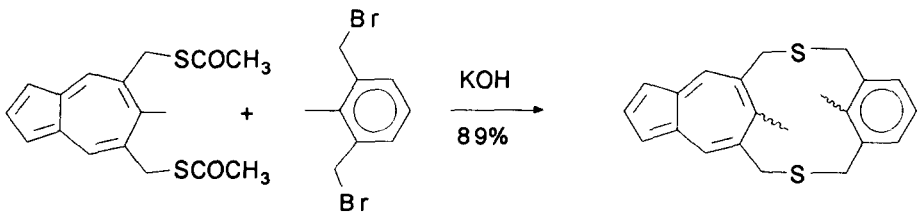
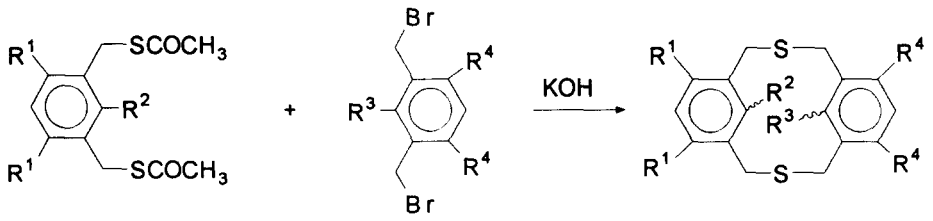
directly converted to the dithiol **5**, since that could then be coupled with stable 2,6-bis(bromomethyl)toluene to give **1**. In fact only recently has a good method of directly converting alcohols to thiols been reported.[7] This uses commercially available Lawesson's reagent, which at room temperature in dimethoxyethane with **3** gave a 70% yield of the bis-thiol **5**. Unfortunately, however, **5** is a rather unstable compound,[8] which quite quickly decomposes. Since in the coupling reaction, a 1:1 ratio of bis-thiol to bis-bromide is required to get good yields of cyclic dimer, this was a serious impediment to obtaining a good yield of **1**. This problem was solved by using the bis-thiolacetate **6**. Volante[9] has shown that alcohols can be directly converted into thiolacetates using a modified Mitsunobu reaction under mild conditions, and that the thiolacetates are readily cleaved to thiolate anions by base. Since thiolacetates are stable to air, and do not directly react with halides, the possibility existed that they might be suitable for coupling directly with the halide in the presence of KOH. In the event, dialcohol **3** was converted in 62% yield to bis-thiolacetate **6** using a slightly modified Volante method in which alcohol **3** (1 mmol) and thiolacetic acid (4 mmol) in THF are added to diethyl azodicarboxylate-triphenylphosphine adduct (4 mmol) in THF at room temperature. The thiolacetate proved to be isolable.[10]

Coupling **6** with bromide **7** by dropwise addition of a 1:1 mixture in benzene into an ethanolic dilute solution of KOH gave an 89% yield of the desired cyclic dimer **1** as a 60:40 *anti/syn* mixture.[11]



6 **7** **1**

This new thiacyclophane coupling was then tested with other examples:



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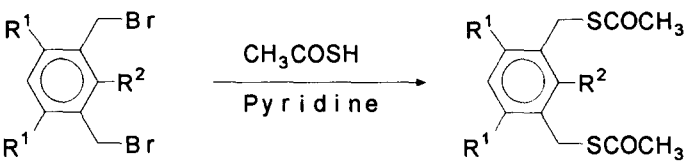
Entry	R^1	R^2	R^3	R^4	Yield of **10**	*Anti/syn ratio*	mp[12] °C (ref)
A	H	H	H	H	78%	*syn*	120-121 (5)
B	H	CH_3	CH_3	H	68%	87:13	260-262(5)
C	CH_3	CH_3	CH_3	CH_3	48%	98:2	258-260 (13)
D	H	H	CH_3	CH_3	83%	1:1	(14)
E	CH_3	CH_3	H	H	85%	1:1	(14)

Clearly this coupling is an attractive alternative to the more common thiol-bromide coupling, and it gives very good yields, and may be especially useful where the thiol is hard to isolate pure, or one component of the coupling is not accessible as the bromide. It is noteworthy that couplings **D** and **E**, which both give the same product, proceed in the same yield despite the rather different steric bulk of the reactant pairs.

Because the thiolacetates are easy to purify and are stable in air, it is possible to easily maintain a 1:1 ratio between thiolacetate and bromide, and this may account for the relatively good yields obtained in the coupling reaction. This may make the reaction attractive for other cases, especially since if the bromide is accessible, then it may be converted to the *non-smelly* thiolacetate cheaply using thiolacetic acid and pyridine:



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Yields: a) $R^1 = R^2 = H$, 86%; b) $R^1 = H$, $R^2 = CH_3$, 75%; c) $R^1 = R^2 = CH_3$, 72%

General Procedure

A solution of the bromide **9** (4 mmol) and thiolacetate **8** (4 mmol) in N_2 flushed benzene (200 mL) was added dropwise slowly (24-36 h) to a well stirred N_2 flushed solution of KOH (10 mmol) in water (10 mL) and ethanol (600 mL). After stirring an additional 12 h, the solvent was removed and water and dichloromethane were added. The organic extract was washed, dried and evaporated, and the residue was chromatographed over silica gel to yield thiacyclophane, which was recrystallized from cyclohexane.

To prepare thiolacetate **8**: dibromide **11** (10 mmol) in THF (30 mL) was added to a refluxing well stirred solution of thiolacetic acid (22 mmol) and pyridine (22 mmol) in THF (30 mL), and reflux was continued for 4-12 h (a white ppt forms). The mixture was cooled, 5% aq. HCl was added, and extracted with dichloromethane. The organic layer was washed with aq. NaCl, dried and concentrated and was filtered through silica gel to yield product.

References and notes

1. Mitchell, R. H. *Heterocycles* **1978**, *11*, 563-586.
2. Vogtle, F. *Top. in Curr. Chem. (Springer-Verlag)*, **1983**, *113*, 1-185.
3. Block, E. *J. Chem. Educ.* **1971**, 814-824.
4. Boekelheide, V.; Reingold, J. D.; Tuttle, M. *J. Chem. Soc.* **1973**, 406-407; Vogtle, F. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 274-274.
5. Mitchell, R. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1547-1557.
6. Au, M. K.; Siu, T. W.; Mak, T. C. W.; Chan, T. L. *Tetrahedron Lett.* **1978**, *19*, 4269-4272.
7. Nishio, T. *J. Chem. Soc., Perkin I* **1993**, 1113-1117.
8. Unstable in air forming brown tars; blue, mp (dec) 29-30°C.
9. Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119-3122.
10. ^{1}H NMR (360MHz): δ 8.35 (s, Az-4,8-H), 7.80 (t, J = 3.7Hz, Az-2-H), 7.26 (d, Az-1,3-H), 4.40 (s, 4, -CH_2S-), 2.53 (s, 3, Az-CH_3), 2.35 (s, 6, -$COCH_3$); mp 94-95°C.
11. By ^{1}H NMR. We have not yet been able to separate the isomers, though can easily assign their ^{1}H NMR (360 MHz) peaks: *anti*: δ 8.48 (s, Az-4,8-H), 7.73 (t, J = 3.6 Hz, Az-2-H), 7.38(d, J = 7.4 Hz, Bz-4,6-H), 7.19 (d, Az-1,3-H), 7.19 (t, Bz-5-H), 1.52 (s, Az-CH_3), 1.05 (s, Bz-CH_3) ; *syn*: δ 7.96 (s, Az-4,8-H), 7.69 (t, J =3.7 Hz, Az-2-H), 7.09 (d, Az-1,3-H), 6.29 (d, J = 7.6 Hz, Bz-4,6-H), 5.51 (t, Bz-5-H), 2.67 (s, Az-CH_3), 2.53 (s, Bz-CH_3). The -CH_2S- protons for both isomers appeared at δ 4.3-3.6 as a series of AB's. Note the extraordinary shielding of the benzene ring in the *syn*-isomer of **1**.
12. The mp given is for the major isomer. All new compounds in this report gave satisfactory proton and carbon nmr spectra, and mass spectra, and where new and stable, satisfactory elemental analyses.
13. Sato, T.; Wakabayashi, M.; Hata, K.; Kainosho,M. *Tetrahedron*, **1971**, *27*, 2737-2755.
14. Two isomers: less soluble, mp 244-246°C, ^{1}H NMR (360MHz) δ 7.25-7.17 (m, 4H), 6.78 (s, 1H), 3.69 (s, 4H), 3.59 (s, 4H), 2.32 (s, 6H), 1.97 (s, 3H); more soluble, mp 115-117°C, δ 7.06-6.94 (m, 3H), 6.72 (s, 1H), 5.66 (t, J = 1 Hz, 1H), 4.00, 3.79, 3.62, 3.34 (AB, 8H), 2.32 (s, 6H), 1.92 (s, 3H).

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