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REACTIVITY OF ETHANEDIYL S,S-ACETALS - 3[§]. RING AROMATIZATION IN CYCLOHEXANONE DERIVATIVES: A NOVELTY SYNTHESIS OF 1,4-BENZODITHIANS[1]

ROMUALDO CAPUTO, CARLA FERRERI, GIOVANNI PALUMBO*, FRANCESCO RUSSO

Dipartimento di Chimica Organica e Biologica dell'Università
Via Mezzocannone, 16 I-80134 Napoli (Italy)

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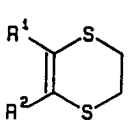
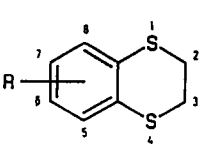
Abstract: Ethanediyl S,S-acetal derivatives of cyclohexanone and substituted cyclohexanones are reported to be fast and smoothly converted into 1,4-benzodithians, by concurrent aromatization of the six-member ring and expansion of the five-member sulfur-containing one, under simple treatment with bromine in anhydrous chloroform at room temperature. This conversion represents the first hitherto reported synthetic way leading to 1,4-benzodithians (2) variously substituted at the benzenoid ring. The ready availability of these latter makes the 1,4-benzodithian system itself being regarded as appealing intermediate to obtain, after sulfur replacement or removal, aromatic compounds that cannot be prepared under the usual electrophilic substitution conditions.

Pursuing our interest[2] in the chemistry of ethanediyl S,S-acetals (1,3-dithiolanes), we have recently reported[3] that 1,3-dithiolanes of enolisable aldehydes and ketones are smoothly converted into 5,6-dihydro-1,4-dithiins (1) by expansion of their five-member ring, under simple treatment with halogens (bromine preferably), in chlorinated solvents at room temperature. Further investigation then showed that 1,3-dithiolanes of cyclohexanone and substituted cyclohexanones as well, when treated under these experimental conditions, undergo a quite interesting aromatization of their six-member ring moiety that accompanies the above mentioned enlargement of the sulfur-containing ring, thus affording the 1,4-benzodithian[1] heterocyclic system (2).

This aroused our attention since such a conversion of cyclohexanones to 1,4-benzodithians, via their readily available ethanediyl S,S-acetals, does appear to be an

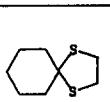
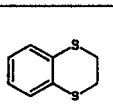
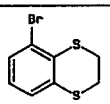
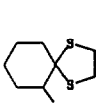
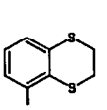
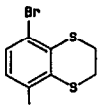
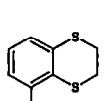
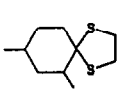
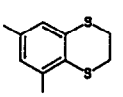
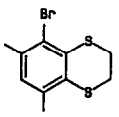
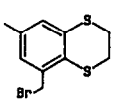
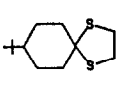
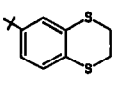
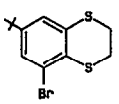
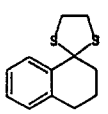
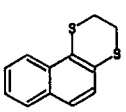
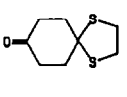
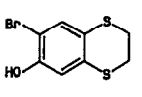
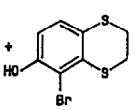
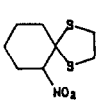
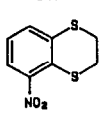


1



2

Table 1 - Synthesis of 1,4-Benzodithians from 1,3-Dithiolanes of Cyclohexanones, by Treatment with Br_2 (1:3) in Anhydrous Chloroform.

Substrate	Time	Product(s)	% Yield(s)
 3	50'	 4a +  4b	80 + 5
 5	30'	 6a +  6b +  6c	75 + 8 + 2
 7	40'	 8a +  8b +  8c	70 + 10 + 5
 9	40'	 10a +  10b	80 + 5
 11	30'	 12a	90*
 13	30'	 14b +  15b	80 + 10*
 16	15'	 17a	70

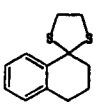
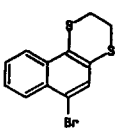
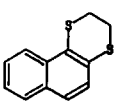
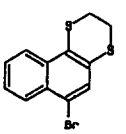
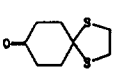
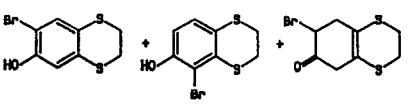
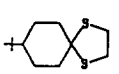
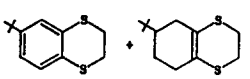
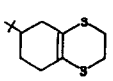
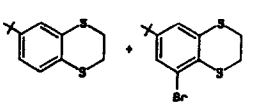
* Reaction carried out with 1:2 substrate:Br_2 ratio.

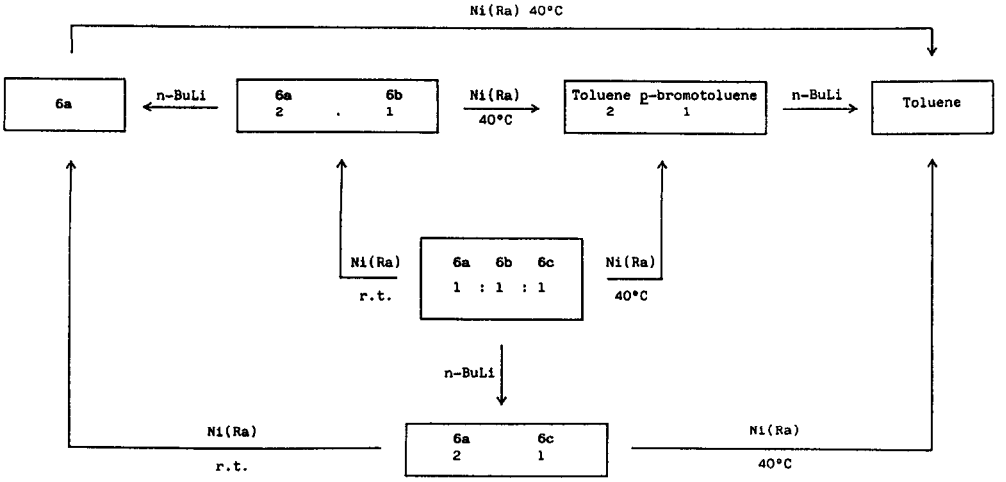
extremely convenient transformation: in order to understand the point, it may be indeed sufficient to consider the nearly total lack from the literature of any general methods for the synthesis of such heterocycles,[4,5] with apparently a sole, not very significant exception[6] when the disodium salt of o-dimercaptobenzene is cyclized with 1,2-dibromoethane to afford the parent compound in this series, 1,4-benzodithian (**4a**). Furthermore, to the best of our knowledge, 1,4-benzodithians carrying substituents on the benzenoid ring have never been prepared,[7] likely due to the intrinsic difficulty of ready availability of starting o-dimercaptobenzene properly substituted. The opportunity to have

a synthetic method leading to substituted 1,4-benzodithians becomes even more important if one considers that such substrates can be they themselves exploited conveniently for building up benzenoid systems with unusual substitution patterns, by replacement[8] of the sulfur (and/or bromine, as will be seen below) atoms resident on the aromatic ring.

For these reasons we planned to devise proper experimental conditions to optimize the conversion yields. The results obtained were satisfactory and are reported in Table 1. The reactions were carried out in anhydrous chloroform, between 0° C and room temperature, using a 3:1 bromine to substrate molar ratio. All the reactions were complete within 50'. As is shown in Table 1, frequently 1,4-benzodithians do not represent the sole reaction products, being accompanied by small to negligible amounts of their ring-brominated derivatives. This is due to side bromination reactions that occur either onto the dithians already formed[9] (e.g., 1,4-benzodithian **12a**, when treated with bromine in 1:1 molar ratio, as is shown in Table 2, affords quantitatively its brominated derivative **12b**) or onto the starting dithiolanes, as is the case of **13** the bromination of which takes place at both

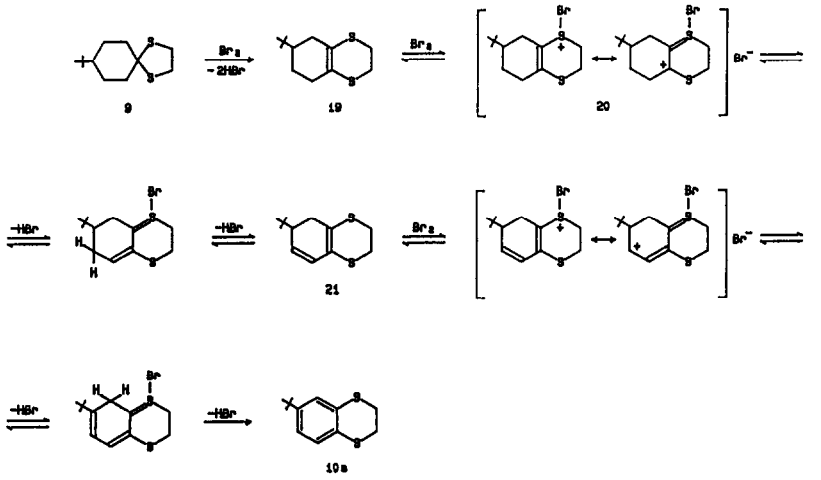
Table 2 – Miscellaneous Experiments Considered in the Explanation of the Conversion Pathway.

Substrate	Br_2:Substr.	Product(s)	% Yield(s)
 11	1:3	 12b	70
 12a	1:1	 12b	96
 13	1:1	 14b + 15b + 16	40 + 5 + 10
 9	1:1.5	 10a + 19	10 + 30
 19	1:2	 10a + 10b	80 + 7



Scheme 1 - Experiments of Selective Removal of Sulfur and/or Bromine from 1,4-Benzodithians.

the alpha positions of the free keto group (see Table 2) prior to the formation of the 1,4-benzodithian system. However, provided that bromine as well as sulfur atoms can be selectively replaced[8] or removed from the aromatic ring, as is illustrated in Scheme 1, there are several cases in which it may result advantageous to enhance the above side bromination reactions (by using bromine in excess) in order to have a further substitution point and thus a major flexibility in the final elaboration of the aromatic ring.



Scheme 2 - Mechanistic Pathway of the Conversion of 1,3-Dithiolanes of Cyclohexanones into 1,4-Benzodithianes.

Mainly based on the experiments reported in Table 2, the mechanistic course of the conversion of 1,3-dithiolanes of cyclohexanones into 1,4-benzodithians can be confidently regarded as is illustrated in Scheme 2, where 1,3-dithiolane **9** is utilized as an example. The first step of the reaction consists[3] of the formation of 2,3-dihydro-1,4-dithiin **19**, involving consumption of one mol of bromine. The subsequent electrophilic attack by a second bromine molecule at one of the sulfur atoms in **19** then affords the bromosulfonium bromide **20** that, by loss of two molecules of hydrogen bromide, leads to the endocyclic diene **21**. Several efforts to quench the reaction at this point and isolate the latter were quite unsuccessful: only the appearance of transient ^{1}H NMR signals [δ 6.18 (d, 1H, J_{5-6} = 9.0 Hz, H-5), 5.98 (dd, 1H, J_{6-4} = 3.9 Hz, J_{6-5} = 9.0 Hz, H-6)] in some experiments was considered diagnostic for the intermediacy of **21**. Further electrophilic attack brought by a third bromine molecule onto **21**, followed by hydrogen bromide elimination, finally affords 1,4-benzodithian **10a**.

Successful work already in progress in our laboratory is aimed to exploit 1,4 benzodithians in the synthesis of naturally occurring benzenoid compounds with peculiar aromatic substitution patterns.

Acknowledgment: Financial support by Ministero della Ricerca Scientifica, to R.C., is gratefully acknowledged.

EXPERIMENTAL

Ethanediyl S,S-acetals were prepared from the parent ketones according to reported procedures.[10] Anhydrous chloroform was made from reagent grade solvent (Carlo Erba) according to literature procedures.[11] Commercially available bromine (Carlo Erba) was purified and dried immediately before use.[12] Flash-chromatography was performed on Merck silica gel 60 (400-230 mesh). Capillary column GLC was performed on a Carlo Erba FRACTOVAP 4160 [OV-1 column (25 m x 0.32 mm i.d., film thickness 0.1-0.5 m) at 100° C]. ^{1}H NMR spectra were recorded on a Bruker WH (270 MHz) instrument in $CDCl_3$ solutions.

Reaction of cyclohexanone 1,3-dithiolane (3) with bromine (1:3 molar ratio) - Typical procedure.

To an ice cooled solution of the title dithiolane (0.174 g; 1.0 mmol) in anhydrous chloroform (20 ml), dry bromine (0.480 g; 3.0 mmol) dissolved in the same solvent (5 ml) was added dropwise, under magnetic stirring. The ice bath was then removed and the reaction monitored by TLC. After 50' the acidic chloroform solution was washed with saturated aq sodium hydrogen carbonate and water until neutral, then 5N aq sodium thiosulfate (2 x 5 ml), and water again. The evaporation in vacuo of the dried organic layer finally gave an oily residue that, after flash-chromatography, afforded: i) 1,4-benzodithian **4a** (yield 80%), oil, ^{1}H NMR: δ 3.19 (m, 4H, $-CH_2-CH_2-$), 6.95 (m, 2H, H-6 and H-7), 7.12 (m, 2H, H-5 and H-8); m/e = 168 (M^+). Found C, 57.22; H, 4.93; Calc. for $C_8H_8S_2$: C, 57.10; H, 4.79%. ii) 5-bromo-1,4-benzodithian **4b** (yield 5%), oil, ^{1}H NMR: δ 3.21 (m, 4H, $-CH_2-CH_2-$), 6.85 (t, 1H, H-7, J_{7-6} = J_{7-8} = 8.04 Hz), 7.09 (dd, 1H, H-8, J_{8-7} =

8.04 Hz, J_{8-6} = 1.35 Hz), 7.28 (dd, 1H, H-6, J_{6-7} = 8.04 Hz, J_{6-8} = 1.35 Hz); m/e = 247 (M^+). Found C, 38.70; H, 2.65; Calc. for $C_8H_7BrS_2$: C, 38.87; H, 2.85%.

Under the same conditions:

* **From 5:** i) **6a** (yield 75%), oil, ^1H NMR: δ 2.30 (s, 3H, $-CH_3$), 3.21 (m, 4H, $-CH_2-CH_2-$), 6.90 (m, 2H, H-6 and H-8), 7.00 (m, 1H, H-7); m/e = 183 (MH^+). Found C, 59.45; H, 5.65; Calc. for $C_9H_{10}S_2$: C, 59.30; H, 5.53%. ii) **6b** (yield 8%), oil, ^1H NMR: δ 2.40 (s, 3H, $-CH_3$), 3.20 (m, 4H, $-CH_2-CH_2-$), 6.88 (d, 1H, H-6, J_{6-7} = 8.41 Hz), 7.18 (d, 1H, H-7, J_{7-6} = 8.41 Hz); m/e = 262 (MH^+). Found C, 41.45; H, 3.52; Calc. for $C_9H_9BrS_2C$, 41.38; H, 3.47%. iii) **6c** (yield 2%), oil, ^1H NMR: δ 3.25 (m, 4H, $-CH_2-CH_2-$), 4.58 (s, 2H, $-CH_2Br$), 6.97 (d, 1H, H-8, J_{8-7} = 8.10 Hz), 7.10 (m, 2H, H-6 and H-7); m/e = 261 (M^+). Found C, 41.26; H, 3.35; Calc. for $C_9H_9BrS_2$: C, 41.38; H, 3.47%.

* **From 7:** i) **8a** (yield 70%), oil, ^1H NMR: δ 2.20 (s, 3H, $-CH_3$), 2.40 (s, 3H, $-CH_3$), 3.20 (m, 4H, $-CH_2-CH_2-$), 6.98 (s, 1H, aromatic H), 7.02 (s, 1H, aromatic H); m/e = 196 (M^+). Found C, 61.30; H, 6.21; Calc. for $C_{10}H_{12}S_2$: C, 61.17; H, 6.16%. ii) **8b** (yield 10%), oil, ^1H NMR: δ 2.31 (s, 3H, $-CH_3$), 2.45 (s, 3H, $-CH_3$), 3.21 (s, 4H, $-CH_2-CH_2-$), 6.96 (s, 1H, H-6); m/e = 275 (M^+). Found C, 43.70; H, 4.10; Calc. for $C_{10}H_{11}BrS_2$: C, 43.64; H, 4.03%. iii) **8c** (yield 5%), m.p. 64-5° C (n-hexane), ^1H NMR: δ 2.22 (s, 3H, $-CH_3$), 3.20 (m, 4H, $-CH_2-CH_2-$), 4.54 (s, 2H, $-CH_2Br$), 6.94 (s, 1H, aromatic H), 6.98 (s, 1H, aromatic H); m/e = 195 (M^+ - Br). Found C, 43.54; H, 3.94; Calc. for $C_{10}H_{11}BrS_2$: C, 43.64; H, 4.03%.

* **From 9:** i) **10a** (yield 80%), oil, ^1H NMR: δ 1.25 (s, 9H, t-Bu), 3.21 (s, 4H, $-CH_2-CH_2-$), 7.07 (m, 2H, H-5 and H-6), 7.18 (s, 1H, H-8). m/e = 225 (MH^+). Found C, 64.36; H, 7.32; Calc. for $C_{12}H_{16}S_2$: C, 64.23; H, 7.19%. ii) **10b** (yield 5%), oil, ^1H NMR: δ 1.25 (s, 9H, t-Bu), 3.25 (m, 4H, $-CH_2-CH_2-$), 7.10 (d, 1H, H-8, J_{8-6} = 2.19 Hz) 7.30 (d, 1H, H-6, J_{7-8} = 2.19 Hz); m/e = 304 (MH^+). Found C, 47.65; H,5.05; Calc. for $C_{12}H_{15}BrS_2$: C, 47.52; H, 4.99%.

* **From 11 (2.0 mol of Br_2):** i) **12a** (yield 90%), oil, ^1H NMR: δ 3.31 (m, 4H, $-CH_2-CH_2-$), 7.18 (d, 1H, H-5, J_{5-6} = 8.41 Hz), 7.41 (m, 3H, H-6, H-8, and H-9), 7.69 (d, 1H, H-7, J_{7-8} = 8.41 Hz), 8.11 (d, 1H, H-10, J_{10-9} = 8.41 Hz); m/e = 218 (M^+). Found C, 66.16, H, 4.75; Calc. for $C_{12}H_{10}S_2$: C, 66.01; H, 4.62%.

* **From 13 (2.0 mol of Br_2):** i) **14b** (yield 80%), oil, ^1H NMR: δ 3.20 (m, 4H, $-CH_2-CH_2-$), 6.88 (s, 1H, H-5), 7.28 (s, 1H, H-8); m/e = 263 (M^+). Found C, 36.40; H, 2.50; Calc. for $C_8H_7OBrS_2$: C, 36.51; H, 2.68%. ii) **15b** (yield 10%), oil, ^1H NMR: δ 3.22 (m, 4H, $-CH_2-CH_2$), 6.74 (d, 1H, H-8, J_{8-7} = 8.53 Hz), 7.05 (d, 1H, H-7, J_{7-8} = 8.53 Hz); m/e = 263 (M^+). Found C, 36.60; H, 2.74; Calc. for $C_8H_7OBrS_2$: C, 36.51; H, 2.68%.

* **From 16:** i) **17a** (yield 70%), oil, ^1H NMR: δ 3.30 (m, 4H, $-CH_2-CH_2-$), 6.83 (t, 1H, H-7, J_{7-6} = J_{7-8} = 8.00 Hz), 7.10 (dd, 1H, H-8, J_{8-7} = 8.00 Hz; J_{8-6} = 1.01 Hz), 7.28 (dd, 1H, H-6, J_{6-7} = 8.00 Hz; J_{6-8} = 1.01 Hz); m/e = 213 (M^+). Found C, 44.90; H, 3.38; Calc. for $C_8H_7O_2NS_2$: C, 45.05; H, 3.30%.

Miscellaneous reactions carried out under the conditions described by the typical procedure, using different substrate:bromine molar ratios.

* **1,4-naphtodithian 12a** (1.2 mmol) and bromine (1.2 mmol) for 45': **12b** (yield 96%),

m.p. 84–85° C (from n-hexane), ^{1}H NMR: δ 3.36 (m, 4H, $-CH_2-CH_2-$), 7.53–8.13 (m, 5H, aromatic H); m/e = 297 (M^+). Found C, 48.57; H, 3.12; Calc. for $C_{12}H_9BrS_2$: C, 48.49; H, 3.05%

* **1,3-Dithiolane 13** (1.5 mmol) and bromine (1.5 mmol) for 30': **14b** (yield 40%) and **15b** (yield 5%), accompanied by starting **13** (30%) and 2,3-dihydro-6-oxo-7-bromo-1,4-dithiin **18** (yield 10%), oil, ^{1}H NMR: δ 3.19 (m, 4H, $-CH_2-CH_2-$), 4.75 (t, 1H, CH-Br); m/e = 265 (M^+). Found C, 36.05; H, 3.51; Calc. for $C_8H_9OBrS_2$: C, 36.23; H, 3.42%.

* **2,3-Dihydro-1,4-dithiin 19** (1.1 mmol) and bromine (2.2 mmol) for 50': 1,4-benzodithian **10a** (yield 80%), accompanied by its brominated derivative **10b** (yield 7%).

* **1,3-Dithiolane 9** (1.0 mmol) and bromine (1.5 mmol) for 50': starting **9** (50%), pure 2,3-dihydro-1,4-dithiin **19** (ref. 3) (yield 30%), and 1,4-benzodithian **10a** (yield 10%).

Reductive desulfurization and benzylic bromine removal.

* A specially prepared equimolar mixture of compounds **6a**, **6b**, and **6c** (1.0 + 1.0 + 1.0 mmol) dissolved in glacial acetic acid (10 ml) was added in one portion to commercial (Fluka AG) Ni(Ra)-W2 (2.1 g; about three fold excess) suspended in the same solvent (5 ml), at r.t. and under magnetic stirring. The resulting suspension was heated at 40° C and stirred for 50'. After cooling in an ice bath, the solid was filtered off and washed with glacial acetic acid (3 x 5 ml). The filtrate was then neutralized with 5N aq NaOH and extracted with Et_2O. Careful distillation of the dried (Na_2SO_4) ethereal extract finally afforded a crude residue (average yield 92%) consisting of toluene and p-bromotoluene (2:1 molar ratio, determined by ^{1}H NMR and GLC on capillary column).

Under the same conditions:

* A specially prepared **6a** + **6b** mixture (2.0 + 1.0 mmol in 10 ml solvent) and Ni(Ra)-W2 (2.1 g in 5 ml solvent): toluene and p-bromotoluene (2:1 molar ratio; ^{1}H NMR and GLC on c.c.) (average yield 89%).

* A specially prepared **6a** + **6c** mixture (2.0 + 1.0 mmol in 10 ml solvent) and Ni(Ra)-W2 (2.4 g in 5 ml solvent): pure toluene (^{1}H NMR and GLC on c.c.) (average yield 89%).

* Pure **6a** (1.0 mmol in 8 ml solvent) and Ni(Ra)-W2 (0.8 g in 2 ml solvent): pure toluene (^{1}H NMR and GLC on c.c.) (yield 94%).

Selective benzylic bromine removal.

* A specially prepared equimolar mixture of compounds **6a**, **6b**, and **6c** (1.0 + 1.0 + 1.0 mmol) dissolved in glacial acetic acid (10 ml) was added in one portion to commercial (Fluka AG) Ni(Ra)-W2 (1.4 g; about two fold excess) suspended in the same solvent (5 ml), at r.t. and under magnetic stirring. The resulting suspension was kept at r.t. and stirring continued for 10'. The solid was then filtered off and washed with glacial acetic acid (3 x 5 ml). The filtrate was neutralized with 5N aq NaOH and extracted with Et_2O. Evaporation of the dried (Na_2SO_4) ethereal extract in vacuo finally afforded a crude residue (yield 95%) that by flash-chromatography gave pure **6a** and **6b** in a 2:1 molar ratio.

Under the same conditions:

* A specially prepared **6a** + **6c** mixture (2.0 + 1.0 mmol in 10 ml solvent) and Ni(Ra)-W2 (1.6 g in 3 ml solvent): pure **6a** (yield 92%).

Selective aromatic bromine removal.

* To a specially prepared equimolar mixture of compounds **6a**, **6b**, and **6c** (1.0 + 1.0 + 1.0 mmol) dissolved in anhydrous tetrahydrofuran (15 ml) a 1.2 M solution of n-butyllithium in n-hexane (0.83 ml; 1.0 mmol) was added under N_2 at -78° C. After 30' stirring at this temperature, the reaction was quenched by adding Et_2O (10 ml) and 10% aq NH_4Cl (5 ml). The ethereal layer was then separated, washed with water and dried (Na_2SO_4). Evaporation in vacuo finally afforded a crude product (yield 96%) that by flash-chromatography gave pure **6a** and **6c** in a 2:1 molar ratio.

Under the same conditions:

* A specially prepared **6a** + **6b** mixture (2.0 + 1.0 mmol in 10 ml solvent) and n-butyllithium (1.0 mmol): pure **6a** (yield 95%).

* A specially prepared toluene + p-bromotoluene mixture (2.0 + 1.0 mmol in 15 ml solvent) and n-butyllithium (1.0 mmol): pure toluene (^1H NMR and GLC on c.c.) (yield 94%).

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§ For part 2 in the same series, see ref. 3.

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