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A NOVEL ROUTE TO LINEAR POLYCYCLIC COMPOUNDS. DIASTEREOSELECTIVE ALDOL-TYPE REACTIONS OF α-SULFONYL CARBANIONS

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Summary: Aromatic derivatives, bifunctionalized at vicinal benzylic positions with Br and SO_2Ph groups undergo one-pot annulations with unactivated cycloalkanones. The ring closure occurs by a diastereoselective aldol-type reaction of α-sulfonyl carbanions.

The development of new methods for the construction of carbocyclic rings is one of the most important challenges in organic synthesis. Within this context, new annulation processes by which more than one carbon-carbon bond are formed in one operation allow rapid and efficient elaborations of polycyclic systems.

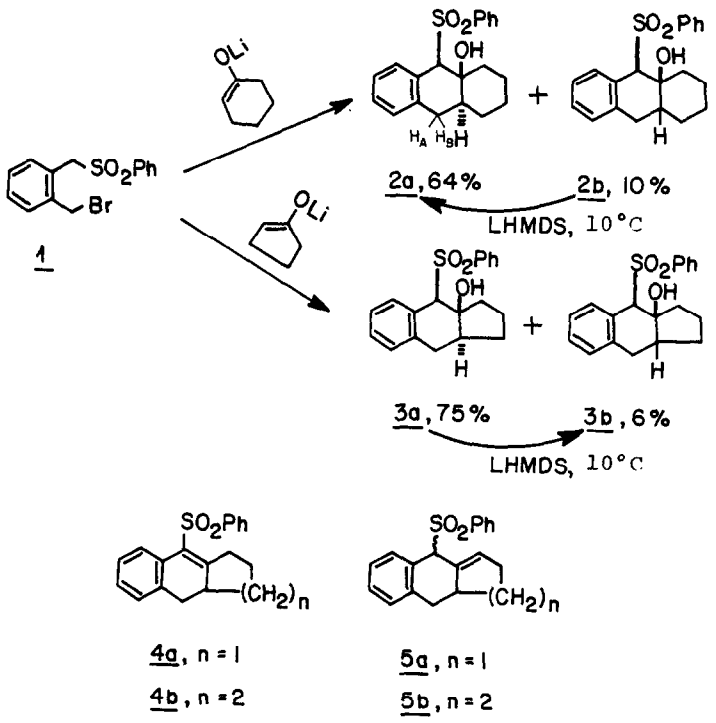
We have recently reported on annulations involving aromatic derivatives with two reactive sites at vicinal benzylic positions and various substrates, usually possessing an activated methine or methylene group[1] We now describe an extension of our strategy to provide the first examples of utilization of unactivated cycloalkanones for an effective one-pot generation of linear polycyclic systems.

Cyclic ketones, converted to their enolates by using lithium hexamethyldisilazide (LHMDS), underwent alkylation by 1-(bromomethyl)-2(phenylsulfonylmethyl) benzene **1** or other analogously substituted aromatics, followed by an intramolecular aldol-type ring closure to afford tricyclic or tetracyclic products (Scheme I, Table)[2]. The process is thus chemoselective despite the similar range of acidity of benzylic α-phenylsulfonyl methylene groups[3] as compared to α-keto methylene groups[4,5]. Utilization of other lithium bases resulted in lower annulation yields.

Only two diastereomeric products were obtained in all cyclizations involving the formation of compounds with three chiral centers (Table, entries 1-5) and the stereochemical implications of this noteworthy diastereoselectivity have been investigated in the reactions involving cyclohexanone and cyclopentanone. Scheme I shows the ratio of diastereomers which corresponds to kinetically controlled conditions: raising the temperature of the reaction mixture to 0°C after completion of the annulation resulted in a slow equilibration as determined from changes in the diastereomeric ratio. Moreover, exposure of **2b** to LHMDS[6], resulted in full conversion into **2a**, whereas the latter remained unchanged under the above conditions. Conversely, **3a** was completely isomerized into the minor diastereomer **3b**[7] under the same conditions.

Since the α-sulfonyl carbanion preserves its configuration during the retro-aldol reaction[8], the diastereomerism should be related to the centers at the ring junction. We assumed a *cis* arrangement of the heterogroups in both diastereomeric products, which can be rationalized in terms of diastereotopic lithiation of the α-sulfonyl methylene group due to coordination of the

SCHEME I

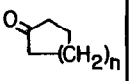
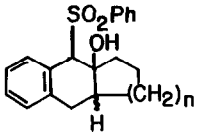
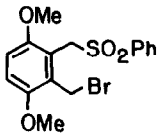
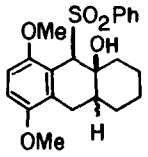
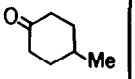
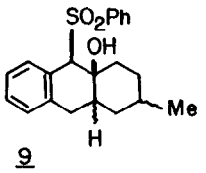
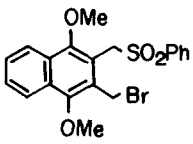
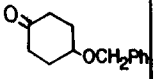
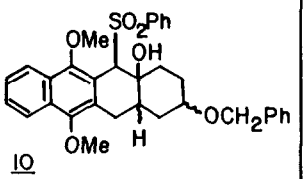


Li counterion with oxygens of both sulfone and ketone groups prior to ring closure[9]. Confirmation of this assumption was obtained by effecting the annulation in the presence of hexamethylphosphoramide (HMPA, 1.5 equiv. added prior to **1**) which resulted in the isolation of an additional diastereomer (**2c** and **3c**, respectively) from each cyclization[7,10]. The presence of a solvating agent (HMPA) has a dissociating effect on coordination, hence the decreased diastereoselectivity of the aldol-type condensation. The assignment of a *trans* ring junction in the main diastereomers (**2a**, and **3a**, Scheme 1), is based, for **2a**, on a preferential equatorial attack on the ketone, as in related kinetically controlled aldol additions[11] and for **3a** on the similarity of NMR data (H_A and H_B benzylic protons) in both above compounds, which are very different from those of **2b** and **3b**, of presumed *cis*-fused configuration[10,12]. These assignments are consistent with the results obtained under equilibrating conditions giving the energetically preferred *trans*-decalin and *cis*-hidrindane systems.

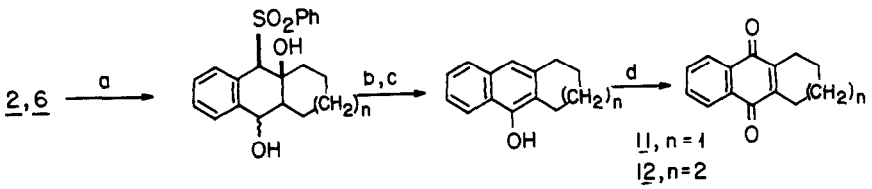
When the basic reaction mixture was further warmed after cyclization (50°C, 2 h), dehydration with complete or partial shift of the double bond occurred. Thus 75% of **5b** (separable mixture of stereoisomers) was obtained from the annulation of cyclohexanone and 83% of **4a** and **5a** (6:4) from the five-membered analog.

The synthetic utility of the described annulation was shown in the effective formation of **10**, a potential intermediate for the synthesis of bioactive anthracycline derivatives. Within this context, we have developed a general route for the oxidation of the sulfone-containing ring as shown for compounds **2** and **6** (Scheme II)[13] to give **11** and the novel quinone **12**, respectively[14].

TABLE

entry	bromosulfone	Ketone	product	yield (%)
				
1			2, n=2	74
2			3, n=1	81
3			6, n=3	75
4			7, n=4	42
5			 8	72
6	1		 9	62
7			 10	85

SCHEME II



(a) NBS/CCl_4, then H_2O-THF, (1:1), 30h r.t. 92% (n=1); 88% (n=2). (b) Jones oxidation, 92% (n=1); 87% (n=2). (c) Na, THF-EtOH (20:1) 0°C[15], 68% (n=1); 58% (n=2). (d) *t*-Butylhydroperoxide, $RhCl(PPh_3)$, C_6H_6, 70°C, 20h[16], 68% (n=1); 72% (n=2).

Acknowledgements: This research was assisted financially by the Israel Academy of Sciences.

References and Notes

1. E. Ghera and Y. Ben-David, *Tetrahedron Letters*, 1983, 3533; E. Ghera and Y. Ben-David, *J. Org. Chem*, 1985, In press.
2. A typical experimental procedure involves adding, during 10 min, the ketone (1 mmol) in dry THF (4 ml) to a stirred solution of 2.5 mmol LHMDS in THF (8 ml) at -78°C under argon. After 1h the bromosulfone (1.25 mmol) in THF (30 ml) was added dropwise via motor-driven syringe during 0.5h. After additional 0.5h stirring at -78°C, 0.5 mmol LHMDS was added dropwise, in order to complete the conversion of the bromosulfone (TLC). Quenching (ice, 5% HCl), standard work-up and chromatography gave the separated diastereomers. For entry 7, the above conditions were modified as follows: to the bromosulfone (1 mmol) and cyclohexanone (1.3 mmol) dissolved in THF (40 ml) under argon was added dropwise at -78°C, a solution of LHMDS (3.5 mmol) in THF (12 ml) during 45 min. After stirring 1h at -78°C and 1h at 0°C, standard work and chromatography gave **10** (diastereomeric mixture).
3. F.G. Bordwell, W.S. Matthews and N.R. Vanier, *J. Amer. Chem. Soc.*, 1975, **97**, 442.
4. H.D. Zook, W.L. Kelly, I.Y. Posey, *J. Org. Chem.*, 1968, **33**, 3477.
5. Prior formation of the α-phenylsulfonyl carbanion may result in the polymerization of the bromosulfone. See B.D. Gowland and T. Durst, *Can. J. Chem.*, 1979, **57**, 1462.
6. To a stirred solution of each diastereomer in THF at -10°C, under argon, 1.5 equiv of LHMDS in THF was added dropwise, and stirring was continued for 2h at 10°C (TLC monitoring). Small amounts of olefins (> 10% **4a** and **4b**, respectively) were also formed.
7. All new compounds gave satisfactory analytical or mass spectral data.
8. See e.g. E.J. Corey and T.H. Lowry, *Tetrahedron Letters* 1965, 793.
9. Diastereoselection is not observed in analogous intermolecular reactions of α-sulphonyl carbanions; see e.g. M. Julia, M. Launay, J.-P. Stacino and J.-N. Verpeaux, *Tetrahedron Letters*, 1982, 2465.
10. Representative data for compounds **2a-c** and **3a-c**. **2a**: mp 154-155°C, NMR ($CDCl_3$) δ 2.77-2.99 (2H, m, H_A and H_B) 4.16 (1H, s, $CHSO_2Ph$); **2b**: mp 116-117°C, ^1H NMR ($CDCl_3$) δ 2.61 (1H, dd, J = 16.2, 6.1 Hz, H_A), 3.24 (1H, d, J = 16.2, 11.2 Hz, H_B), 4.99 (1H, s, $CHSO_2Ph$); **2c**: mp 156°C, ^1H NMR ($CDCl_3$) δ 2.40 (1H, dd, J = 16.6, 8.8 Hz, H_A), 3.03 (1H, dd, J = 16.6, 8.2 Hz, H_B) 4.16 (1H, s, $CHSO_2Ph$); **3a**: mp 125-126°C, NMR ($CDCl_3$) δ 2.76-2.92 (2H, m, H_A and H_B), 4.53 (1H, s, $CHSO_2Ph$); **3b**: mp 168-169°C, NMR ($CDCl_3$) δ 2.39 (1H, dd, J = 16.1, 3.0 Hz, H_A), 3.50 (1H, dd, J = 16.1, 8 Hz, H_B), 4.58 (1H, s, $CHSO_2Ph$); **3c**: mp 130-131°C, ^1H NMR ($CDCl_3$) δ 2.36 (1H, dd, J = 14.4, 6.7 Hz, H_A), 2.97 (1H, dd, J = 14.4, 4.5 Hz, H_B), 4.43 (1H, s, $CHSO_2Ph$).
11. J.A. Marshall and W.I. Fanta, *J. Org. Chem.*, 1964, **29**, 2501; See also M. Hannaby and S. Warren, *Tetrahedron Letters*, 1985, 3133; M.E. Garst and P. Arhenius, *J. Org. Chem.*, 1983, **48**, 16.
12. For NMR data of a related *cis*-benz(f)indene derivative, see R.J. Moss and B. Rickborn, *J. Org. Chem.*, 1984, **49**, 3694.
13. Reactions in Scheme II were performed on the thermodinamically stable (*trans*-fixed) diastereomers of **2** and **6**.
14. **11**: mp 157-158°C; **12**: mp 108-109°C.
15. Y. Fujita, M. Ishiguro, T. Onishi and T. Nishida, *Bull. Chem. Soc. Jpn.* 1982, **55**, 1325.
16. P.M. Müller and C. Bobillier, *Tetrahedron Letters* 1983, 5499.

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