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NEW ANNULATION METHODS OF AROMATIC RINGS. NEW SYNTHESES OF NAPHTHALENE, ANTHRACENE AND PHENANTHRENE STRUCTURES.

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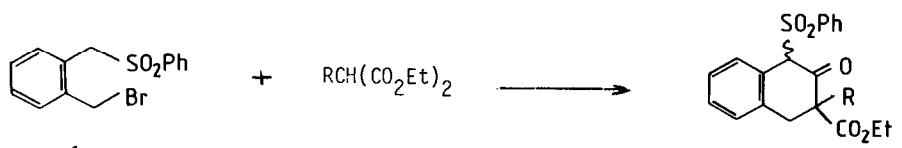
Summary: Condensation of 2-(phenylsulfonyl)methyl benzyl bromide and its derivatives with malonates, 1,3-ketoesters and lactones resulted in the regioselective formation of naphthalene derivatives and of other polycyclic systems.

Annulations of aromatic rings with carbocycles are utilized as pathways for the synthesis of various polycyclic systems including natural products. In this context, the recent utilization of o-quinodimethane species[1] and of Michael-induced ring closure (MIRC) reactions[2] provided annulation processes for aromatics in which two carbon-carbon ring bonds are formed in one operation. Difunctional aromatic reagents, containing both electrophilic and nucleophilic centers, may also serve as regioselective annulating agents, if undesired self-reactivity can be avoided. We recently used this approach in the synthesis of quinoline derivatives.[3] We report herein on the development of a regioselective one-pot annulating process for aromatic rings in which the presence of appropriate substituents (Br and SO_2Ph groups) in the benzylic positions of vicinal carbon side chains enables reactivity equivalent to a 1,4-dipole.

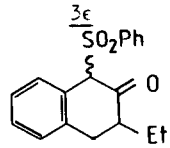
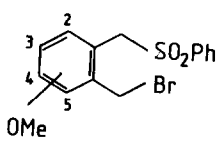
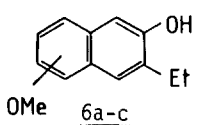
Bromosulfone (1)[4] reacted with deprotonated monosubstituted malonic esters by an alkylation-acylation sequence (Scheme I): the malonate (1.2 eq) dissolved in tetrahydrofuran (THF)[5] was added to a suspension of NaH (6 eq) in THF. After 30 min stirring at room temperature, compound 1 (1 eq) in THF was added, and the two consecutive reactions were followed by TLC monitoring (30-60 min). Quenching (aqueous NH_4Cl) and chromatography afforded bicyclic crystallizable diastereomeric mixtures (3a-e, Table).[6,7]



SCHEME I 1 2a-e 3a-e

TABLE

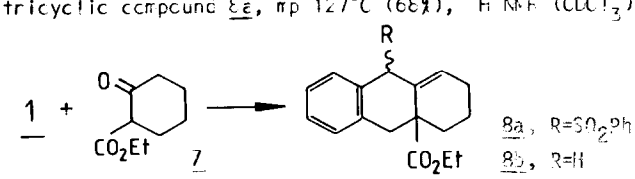
Reactions of annulating reagents with malonic esters

Entry	Annulating reagent	Malonic ester	Product	Yield, %
1	1	2a, R=Me	3a	80
2	1	2b, R=Et	3b	92
3	1	2c, R=$CH_2CH(OEt)_2$	3c	78
4	1	2d, R=$(CH_2)_2CH$	3d	87
5	1	2e, R=$CH_2CH=CH_2$	3e	82
6	1	$EtCH(CO_2Me)_2$	 4	78
7	 5a, 2-OMe			71
8	5b, 3-OMe	$EtCH(CO_2Me)_2$	 6a-c	72
9	5c, 4-OMe			69

One-pot annulation and decarboxylation was best carried out by using methyl malonates instead of the ethyl esters (Table, entry 6): after completion of cyclization (TLC), dimethyl sulfoxide was added (5% of amount of solvent in the reaction), and the reaction mixture was stirred at 70°C (30-60 min), to give 4. The base-induced desulfonylation and aromatization of the formed ring can be effected as was shown for 5a-c: the reaction mixture (cyclized and decarboxylated as for 4) was quenched (NH_4Cl), diluted with water, and stirred at room temperature for 15-30 min to give 6a, mp 97°C, 6b, mp 101°C and 6c, mp 87°C,[6] respectively.

Under slightly modified conditions[6] bromosulfone 1 reacted with cyclohexanone-2-carboxylate 7 by preferential attack of the α-sulfonyl carbanion on the ketone group to give the stereohomogeneous tricyclic compound 8a, mp 127°C (68%),[6] ^1H NMR ($CDCl_3$) δ 5.03 (1H, s,

SCHEME II

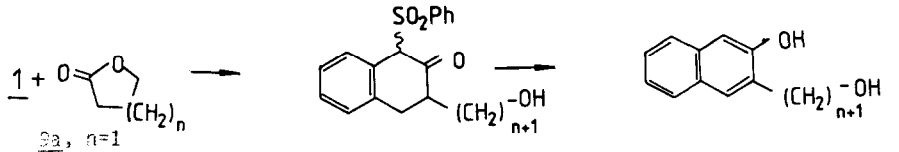


8a, R=SO_2Ph
8b, R=H

CHSO$_2$Ph), 6.58 (1H, brs, CH=C). Reductive desulfonylation[9] to 8b, δ 5.77 (1H, brs, CH=C), confirmed the structural assignments (Scheme II).

The reactions of annulating reagents with lactones were based on the well known ability of the latter to undergo alkylations by use of lithium bases and to acylate α-sulfonyl carbanions in similar conditions.[10] Lactones (9a-b, 1.2 eq) in THF[5] were deprotonated at -78°C using excess (4 eq) of lithium diisopropylamide (for 9a) or lithium dicyclohexylamide (for 9b). Addition of 1 (1 eq) in THF resulted in the formation of a polar compound (ca. 30 min, -78°C, TLC monitoring). Quenching (NH_4Cl) extraction, and chromatography, provided diastereomeric mixtures of 10a-b.[11] Aromatization of the formed ring was achieved by pouring the above reaction mixture into water and stirring the resulting basic aqueous mixture for 3h, to give 11a, mp 109°C (68%)[12] and 11b, mp 81°C (66%),[12] respectively. Similarly, utilization of 5a-c as annulating reagents gave, with lactone 9a, the methoxy substituted analogs of 10a (ca. 70%).

SCHEME III

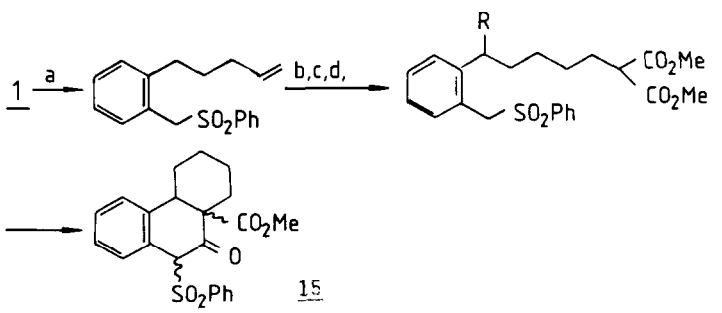


9a, n=1
9b, n=2

10a-b

11a-b

The effectiveness of the annulation route in an intramolecular process has been demonstrated by the utilization of compound 13, prepared as shown in Scheme IV. Selective bromination[4] gave 14, mp 83°C (91%), which readily underwent a double cyclization, on treatment with t-BuOK,[13] to the tricyclic compound 15 (71% yield, 95% one diastereomer) mp 199-200°C, ^{1}H NMR δ 1.32-2.40 (8H, m), 3.26 (3H, s) 3.41 (1H, dd), 5.04 (1H, s), 7.09-7.81 (9H, m).[6]



13, R=H
14, R=Br

15

SCHEME IV a)  MgBr (excess), THF, reflux (53%); b) BH_3, THF; NaOH, H_2O_2 (77%), c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C (92%); c) NaI, acetone; $CH_2(CO_2Me)_2$, NaH, DMF (76%).

The described annulations have noteworthy advantages: 1) the reagents are readily prepared[4], 2) absence of self-annihilating reactivity of reagents in presence of bases, and 3) the functionality on the formed rings makes them useful synthetic intermediates. Further extensions and applications of the annulation pathway are under investigation.

References and Notes

1. For relevant references see: Y. Ito, M. Nakatsuka and T. Saegusa, J. Am. Chem. Soc., 104, 7609 (1982); W. Oppolzer, Pure and Applied Chemistry, 53, 1181 (1981); T. Kametani and K. Fukumoto Heterocycles, 8, 465 (1977).

2. See e.g. F.M. Hauser and R.P. Rhee, J. Org.Chem., 43, 178 (1978); J. Wildeman, P. Borgen, H. Pluim, F. Rouwette and A. van Leusen, Tetrahedron Lett., 2213, (1978); C.A. Kraus and H. Sugimoto, ibid., 2263, (1978); N.J.F. Broom and F.G. Sammes, J. Chem. Soc., Perkin I, 465 (1981)., For the definition of MIRC reactions see R.D. Little and J.R. Dawson, Tetrahedron Lett., 2609 (1980).

3. E. Ghera, Y. Ben-David and H. Rapoport, J. Org. Chem., 46, 2059 (1981); E. Ghera, Y. Ben-David and H. Rapoport, ibid., in press; one-pot annulations were, however, precluded because of the instability to base of pyridine-derived heteroaromatic annulating agents.

4. Compound 1, as well as other bromosulfones used in this work (5a-c) were prepared by regioselective benzylic bromination[3] (NBS, azobisisobutyronitrile, reflux in CCl_4) of the corresponding 2-(phenylsulfonyl)methyl toluene derivative.

5. About 5 ml of THF to mmol of each substrate were used in anhydrous conditions, under argon.

6. All new compounds were characterized by elemental and spectral analyses.

7. Characteristic chemical shift in ^1H NMR for 3a-e: δ 4.99-5.01 (1H, s, $CHSO_2Ph$).

8. To a mixture of cyclohexanone 2-carboxylate (1.5 mmol) in THF-DMSO (10:1, 22 ml) and NaH (0.36g), stirred for 30 min at room temperature, was added 1 (1 mmol in 25 ml THF), and stirring continued until completion of the alkylation step (ca 30 min, TLC). The mixture was then warmed (60°C, ca 1.5 h) to give a less polar product (6a). The increased dilution in the above reaction was found necessary to avoid intermolecular reactivity of the alkylated intermediates.

9. Y. Fujita, M. Ishiguro, T. Onishi and T. Nishida, Bull. Chem.Soc. Jpn., 55, 1325 (1982).

10. M.C. Musetto, D. Savoia, C. Trombini and A. Umani-Ronchi, J. Org. Chem., 45, 4002 (1980).

11. Partial retroacylation occurs on purification of the intermediate 10b (but not of 10a) when using a silica column.

12. ^1H NMR of 11a ($CDCl_3$): δ 3.03 (2H, t), 4.00 (2H, t), 7.16-7.86 (6H, m); 11b: δ 1.92 (2H, t), 2.91 (2H, t) 3.85 (2H, t), 7.15-7.73 (6H, m).

13. Compound 14 (50 mg) in 4 ml THF was added, in 3 portions, during 15 min, to freshly prepared t-BuOK (from 25 mg K and 3 ml t-BuOH) at room temperature. After additional 5 min, the mixture was diluted (CH_2Cl_2, aqueous NaCl) and extracted.

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