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# METAL-AMMONIA REDUCTION AND REDUCTIVE ALKYLATION OF NAPHTHALENE SULPHONAMIDES. A NEW ROUTE TO SUBSTITUTED NAPHTHALENES.

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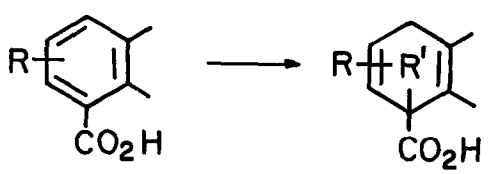
Summary: Conditions have been found for the successful Birch reduction and reductive alkylation of N-alkyl arylsulphonamides, specifically in the naphthalene series. The derived C-alkylation products smoothly fragment on heating with re-aromatisation, affording a new specific route to 1-substituted naphthalenes starting from the 1-sulphonamides, and to both 2-mono-substituted and 2,4- (or 1,3-) disubstituted naphthalenes from the corresponding 2-sulphonamide.

Since we first demonstrated the fact that carboxyl-substituted aromatic rings can be preferentially reduced to 1,4-dihydro compounds by metals in liquid ammonia and that under suitable conditions the intermediate dianion can be alkylated in situ[1] this type of sequence, generally formulated as in Scheme 1, has been used widely, in the main as a key step in




R= H, o- or m-methoxyl
= H, alkyl, hydroxymethyl, ß-hydroxy =alkyl, ß-alkoxycarbonylalkyl

SCHEME 1.

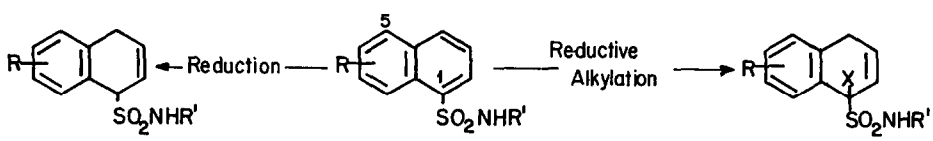
natural product synthesis[2]. Furthermore, this process has been extended to other electron-withdrawing groups attached to an aromatic ring such as alkoxycarbonyl[3], carboxamide[4,5] and nitrile[6]. A particularly important extension which has pioneered a number of approaches to otherwise difficulty accessible compounds[7] has been to aromatic ketones[8].

One type of electron withdrawing group which does not seem to have been considered in this regard is that derived from aromatic sulphonic acids. Presumably this is because of a natural assumption that reductive cleavage of the Ar-S bond or reduction to a lower-valent sulphur compound would precede any other type of reaction course, and this is indeed supported (and the results synthetically utilised) in a number of reports by previous workers[9,10,11]. Nonetheless we decided to devote some effort to re-investigation of this possibility, in the

main because of the very large number of known substituted naphthalenesulphonic acids of rigorously established orientation[12], and also because N-alkyl and N,N-dialkylsulphonamide groups in particular exhibit synthetically useful attributes. These include a powerful ortho-metalating aptitude on the one hand,and on the other a relative indifference to nucleophilic ttack when compared to e.g., carboxamides[13]. This communication describes some useful and encouraging results in this direction.

Preliminary work on N,N-dialkylsulphonamides, done because of possible analogy with the corresponding carboxamides[4], was quite unsuccessful, resulting in formation of either polymeric material or completely hydrogenolysed product under all conditions tried. On the other hand we have found that N-monoalkyl (preferably N-t-butyl) sulphonamides in the form of their lithium salts formed under strictly aprotic conditions (n-butyl lithium in THF to incipient orange colour due to lateral metalation), with liquid ammonia added subsequently, take up[14] 2.1-2.4 equivalents of lithium at -55° to 65° [15]. Subsequent quenching with a large excess of ammonium chloride followed by removal of both solvent and ammonia in vacuo gave the corresponding 1,4-dihydro compounds (from naphthalene-1-sulphonamides) in good to excellent yield. Alternatively the intermediate dianion could be $C_1$-alkylated in situ by adding an alkyl halide at below -65° [15], again followed by ammonium chloride quench and evaporation in vacuo (see SCHEME 2).

SCHEME 2. Reduction and Reductive Alkylation of Naphthalene 1-sulphonamides. (in parentheses: yields, m.p.) For conditions see text.



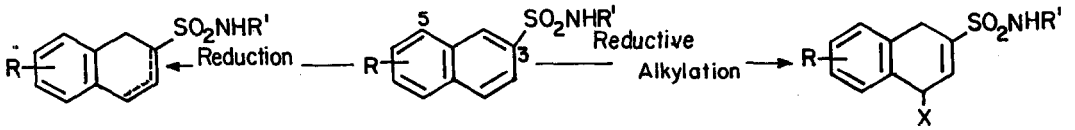

| | | | | | |
|---|---|---|---|---|---|
| 5 | R=H, R'=t-Bu (81%, 108°) | <------- | 1 | R=H, R'=t-Bu | |
| 6 | R=7-OMe, R'=Me (82%, 81-81.5°) | <------- | 2 | R=7-OMe, R'=Me (178-178.5°) | |
| 7 | R=7-OMe, R'=t-Bu (89%, 151.5-152°) | <------- | 3 | R=7-OMe, R'=t-Bu (178-178.5°) | ------> R=7-OMe R'=t-Bu, X=allyl (61.5% 129-130°) 9 |
| | | | | " " | -------> R=7-OMe, R'=t-Bu, X=Me (58%, 136-136.5°) 10 |
| 8 | R=5-OMe, R'=t-Bu (64%, 125-128°) | <------- | 4 | R=5-OMe, R'=t-Bu (166.5-167°) | -------> R=5-OMe, R'=t-Bu, X=$CH_2Ph$ (35%, 128° decom.) 11 |

With N-alkyl naphthalene-2-sulphonamides (shown here as 3-sulphonamides for consistency in numbering) somewhat different behaviour was observed. Simple reduction under conditions described above gave an inseparable mixture of double bond isomers of the dihydro compound. On the other hand, and more surprisingly, reductive alkylation gave in the main the 4- (shown here as the 1-)alkyl dihydro product as main product (see SCHEME 3).

The above dihydrosulphonamides could be further N-alkylated, or further N,C-dialkylated (where the sulphonamide carbon was unsubstituted) under a variety of conditions (see SCHEME 4). When n-butyl lithium was used here for deprotonation the reaction in appropriate cases was

again a simple titration since formation of a dianion was in all cases indicated by a colour change. In this alkylation the double bond isomer mixture mentioned above gave a single product.

SCHEME 3. Reduction and Reductive Alkylation of Naphthalene 2-sulphonamides. (in parentheses: yields, m.p.) For conditions see text.




15 R=7-OMe, R'=Me (78%, 82-92°) <------ 12 R=7-OMe, R'=Me (139.5-140)

16 R=7-OMe, R'=t-Bu (84.5%, 82-88°) <------ 13 R=7-OMe, R'=t-Bu (113-113.5°) ------> R=7-OMe, R'=t-Bu, X=Me (70%, 138-139°) 17

" " ------> R=7-OMe, R'=t-Bu, X=allyl (40%, 86-87°) 18

14 R=H, R'=t-Bu (147.5°) ------> R=H, R'=t-Bu, X=$CH_2Ph$ (76%, non-cryst.) 19

SCHEME 4. Further Alkylation of Dihydrosulphonamides. (in parentheses: yield, m.p)


6 -- a --> R= 7-OMe, R'R"=Me, X=H (80%, 109-111°) 20

7 -- b --> R= 7-OMe, R'=Me, R"= t-Bu, X= H (62.5%, 111-112°) 21

20 -- c --> R= 7-OMe, R'=R"=Me, X=$CO_2Me$ (73%, 89.5-91°) 22

21 -- c --> R= 7-OMe, R'=Me, R"=t-Bu, X= $CO_2Me$ (90-92°) 23

15 -- d --> R= 7-OMe, R'=R"=Me, X=Y=H (80%, 116-118°) 24

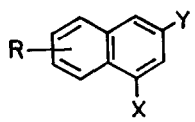
15 -- e --> R=7-OMe, R'=R"=Y=Me, X= H (85%, 109.5-110°) 25

16 -- d --> R= 7-OMe, R'=Me, R"=t-Bu, X=Y=H (68%,94-94.5°) 26

17 -- f --> R= 7-OMe, R'= t-Bu, R"=Y=allyl, X=Me (not isolated) 27

*Conditions:* a: NaH (1.5 equiv.), DMF, MeI; b: Na-t-AmO/toluene (1.1 equiv.), MeI; c: BuLi (1.05 equiv.), THF, -50°, $ClCO_2Me$; d: BuLi (1.05 equiv.), THF, -50°, MeI; e: NaH (2.7 equiv.), DMF, MeI (excess); f: NaH (2.7 equiv.), DMF, allyl bromide (excess).

SCHEME 5. Substituted Naphthalenes by Pyrolysis of Alkyl Dihydronaphthalenesulphonamides. (in parentheses: yields, m.p. or b.p.)




10 ---------> R= 7-OMe, X= Me, Y= H (77.5%, m.p. 45.5-46.6°) (lit.[16]: 47-48°) 28

9 ---------> R= 7-OMe, X= allyl, Y = H (80%, b.p. 100°/oven/0.1 mm) 29

22 ---------> R= 7=OMe, X= $CO_2Me$, Y= H (95%, m.p. 41°) 30

11 ---------> R= 5-OMe, X= $CH_2Ph$, Y= H (84.7%, m.p. 106-108°) 31

4 - via 11 --> " , 52.6% overall

17 - via 27 -->R= 7-OMe, X= Me, Y= allyl (65.6%, b.p. 120°/oven/0.1 mm) 32

All the above dihydrosulphonamides, and in particular the C-alkylated ones, decomposed smoothly on heating above their melting points with re-aromatisation to give the corresponding substituted naphthalenes in high yield (see SCHEME 5). In some cases isolation of the intermediate alkylation stage (whether by reductive or subsequent alkylation, see above) was unnecessary, and the substituted naphthalene could be obtained by direct distillation of the total product.

These findings appear to indicate a new and specific route (in essence via a nucleophilic rather than electrophilic pathway) to 1-substituted and 1,3-disubstituted naphthalenes. The only exceptions we have found so far are in the case of N-alkyl 3-methoxy-1-sulphonamides and -2-methoxy-1-sulphonamides. The former were recovered unchanged under the conditions described. The latter were completely hydrogenolysed, but when allowed to react with 2.1 equivalents of n-butyl lithium (in an attempt to effect peri-metalation) the methoxyl group was replaced by n-butyl[17], indicating yet another possibility: that leading to specifically 1,2-disubstituted naphthalenes.

With benzenesulphonamides results so far have been disappointing. N-t-butyl benzene sulphonamide gave a crystalline 1,4-dihydro derivative in ca. 25% yield.

We wish to express our gratitude to Bayer AG (Leverkusen) for the generous gift of various substituted naphthalenesulphonic acid salts, and to Prof. D. Becker for N.O.E. studies.

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15. All these temperatures were measured within the reaction medium.
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18. Representative and significant $^1$H N.M.R. data (400 MHz, p.p.m. downfield from TMS, $CDCl_3$):
5: 1.23 (9H, s, N-t-Bu), 3.31 (1H, bd.d, C-4 H), 3.60 (1H, bd.d, C-4 H),4.00 (1H, s, -NH-), 4.83 (1H, bd.s, C-1 H), 6.12 (1H, m, olef. H), 6.38 (1H, m, olef. H), signals at 7.25 and 7.50 (3H, arom. H).
10: 1.05 (9H, s, N-t-Bu), 1.90 (3H, s, C-1 Me, 3.45 (2H, m, C-4 H), 3.80 (3H, s, OMe), 5.85 (1H, m, -NH-), 6.27 (1H, m, olef. H), signals at 6.85, 7.10 and 7.22 (4H, olef. H + arom. H)
17: 1.30 (9H, s, N-t-Bu), 1.37 (3H, d, J 8, C-1 Me, collapses on irradiation at 3.62 to s), 3.62 (3H, s, C-1 H and C-4 2H, coincidental equivalence), 3.78 (3H, s, OMe), 4.39 (1H, s, -NH-), signals at 6.95, 6.90 and 7.10 (4H, olef. H + arom. H).
20: 2.65 (6H, s, $-NMe_2$), 3.43 (2H, m, C-4 H), 3.80 (3H, s, OMe), 4.92 (1H, m, C-1 H), 6.10 (1H, m, olef. H), 6.31 (1H, m, olef. H), signals at 6.86 and 7.07 (3H, arom. H).
24: 2.57 (6H, s, $-NMe_2$), 3.18 (1H, dd, C-4 H), 3.37 (1H, dd, C-4 H), 3.80 (3H, s, OMe), 4.04 (1H, m, C-3 H), 6.05 (1H, m, olef. H), signals at 6.70, 6.78 and 7.10 (4H, olef. H and arom. H).
32: Multiple N.O.E. measurement shows one aromatic H (at C-2) interacting with both Me and allyl groups, hence 1,3-relationship between these and hence (via intermediacy of 27) correct structure of 17.

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