γ- *versus* α-Substitution in Dihydronaphthalene Sulphonamides. A Novel Approach to (±)-Naproxen

H. J. E. Loewenthal

Department of Chemistry, Technion - Israel Institute of Technology, Haifa 32000, Israel

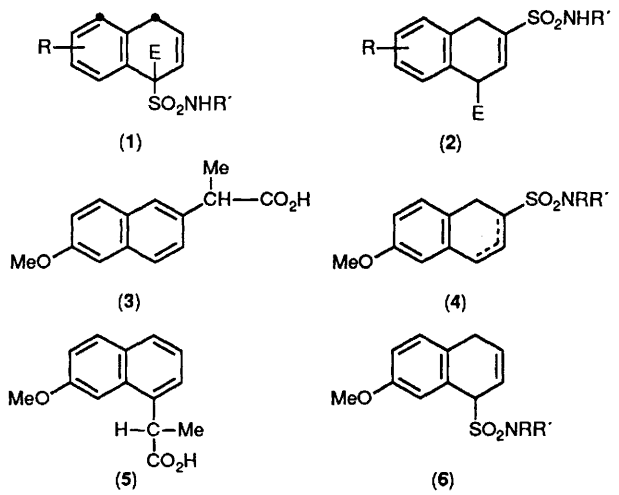
Alkylation of *N*-alkyl dihydronaphthalene-1-sulphonamides, derived by reduction with Li/liq. NH_3, can be directed in certain cases to the naphthalene 3-position, depending mainly on the steric bulk of the *N*-alkyl group(s).

We have recently reported[1] that reductive alkylation of *N*-lithio *N*-alkyl naphthalene-1- or -3-sulphonamides with lithium in liq. NH_3, using simple non-functionalised alkyl halides (E-Hal) occurs exclusively at the 1-position to give products of types (**1**) and (**2**). This was not surprising since in the hybrid allylic dianion intermediate formed in the reduction step that position would most likely be favoured, being both allylic and benzylic. However, this finding appeared to rule out the possibility of arriving by this kind of reaction at a 2- (or 3-) substituted naphthalene from the corresponding

Table 1. Production of Naproxen (**3**) and regioisomer (**5**) from (**6**).

Entry	R	R′	Reaction conditions[a]	Total yield of acidic product	Ratio[b] (**3**) : (**5**)
1	Me	Me	A	60.7%	50 : 50
2	Et	Et	A	48%	66 : 34
3	Bu^t	Me	A	49.5%	84 : 16
4	Bu^t	$-CH_2OMe$	A	24%	82 : 18
5	Bu^t	Me	B	44%	90 : 10
6	Me	H	C	29%	62.5 : 37.5
7	Bu^t	H	C	47.8%	87.5 : 12.5
8	$-C(Me_2)CH_2Me$	H	C	56.7%	85 : 15
9	$-C(Me_2)CH_2CMe_3$	H	C	30.4%	>99 : <1

[a] A: NaH/dimethylformamide (DMF)/$MeCHBrCO_2Me$, −60 to 20 °C, alkaline hydrolysis, sublimation of acidic fraction; B: as for A, except using HMPA–DMF (2.5 : 1 v/v) as solvent, reaction between −25 and 20 °C; C: (**6**) added at −70 °C to tetrahydrofuran (THF) containing 2.4 equiv. of Bu^{n}Li–TMEDA complex, when (**6**) dissolved $MeCHBrCO_2Me$ added at −100 °C, then warmed to 25 °C, alkaline hydrolysis, sublimation of acidic fraction. [b] Determined by integration (400 MHz) of methyl doublets in the ^1H NMR spectrum of mixture; [(**3**): δ 1.57, (**5**): δ 1.67 relative to Me_4Si].



naphthalene-2-sulphonic acid; for example obtaining the important anti-inflammatory drug Naproxen (**3**) from 2-hydroxynaphthalene-6-sulphonic acid, a dyestuff intermediate obtainable directly from 2-naphthol.[2] In fact, all attempts to alkylate intermediate dihydrosulphonamides (**4**) *via* a hybrid mono-anion (R = R′ = alkyl) or dianion (R = alkyl, R′ = H) with derivatives of 2-bromo- or 2-iodopropanoic acids (methyl or ethyl esters, sodium or lithium salts) led exclusively (after re-aromatisation brought about by alkaline hydrolysis and distillation) to the regio-isomer (**5**), irrespective of the nature of R and R′ and of the base or solvent system employed.

It has now been found that with sulphonamides derived from 2-hydroxy-naphthalene-8-sulphonic acid (croceic or Bayer acid), also directly accessible from 2-naphthol,[3] this trend can be changed to afford a concise approach to a product such as (**3**). This can proceed *via* dihydrosulphonamides (**6**) (R = alkyl, R′ = H) obtainable from croceic acid K salt in 54—74% overall yields; and then *via* a hybrid mono-anion derived from products of further alkylation (**6**) (R = R′ = alkyl) (produced by a simple titration process using Bu^{n}Li and then R′–Hal), or, shorter still, *via* a hybrid dianion formed directly from (**6**) (R = alkyl, R′ = H). The conditions used and results obtained are summarised in Table 1.

Table 1 shows that with methyl 2-bromopropanoate as alkylating agent the important factor responsible for directing alkylation to the desired 3-position with either intermediate is the steric bulk of the *N*-alkyl group(s). All told, the best route to (**3**) is indicated by entry 8, separation of (**3**) from (**5**) being easily accomplished by crystallisation. Hexamethylphosphoric triamide (HMPA), used extensively because of its reported effectiveness in changing regio- (and stereo-) chemistry in allylic carbanion substitution,[4—6] was tried instead of *N*,*N*′-tetramethylethylenediamine (TMEDA) in entries 6 to 9, but was found not to influence significantly the (**3**) : (**5**) ratio and to lead to side reactions.

The results here described are a further illustration of the usefulness of the dihydrosulphonamide route for directed substitution in naphthalenes.[1] They may be of wider relevance in the context of continuing interest in the regiochemistry of substitution of allylic carbanions,[7] with the distinction that sulphonamides as activating electron-withdrawing groups are largely inert to nucleophilic attack.

Received, 19th January 1990; Com. 0/00307G

References

1 L. Gottlieb and H. J. E. Loewenthal, *Tetrahedron Lett.*, 1988, **29**, 4473.
2 H. E. Fierz-David and L. Blangey, 'Fundamental Processes of Dye Chemistry,' Interscience, London and New York, 1949, p. 194.
3 F. Muth, in 'Methoden der Organischen Chemie' (Houben–Weyl), ed. E. Müller, Georg Thieme, Stuttgart, 1955, vol. 9, p. 487.
4 R. Graefing and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, 1978, **97**, 209.
5 E. Vedejs and D. M. Gapinski, *Tetrahedron Lett.*, 1981, **22**, 4913.
6 K. Yamada, S. Tanaka, S. Kohmoto, and M. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1989, 110.
7 (a) α,β-Unsaturated carboxamides and other carbonyl compounds: see M. Majewski, G. B. Mpango, M. T. Thomas, A. Wu, and V. Snieckus, *J. Org. Chem.*, 1981, **46**, 2029, and references cited therein; (b) allyl 1,3-dithians: J. M. Fang, B. C. Hong, and L. F. Liao, *J. Org. Chem.*, 1987, **52**, 855; (c) β,γ-unsaturated aminonitriles: J. M. Fang and C. J. Chang, *J. Chem. Soc., Chem. Commun.*, 1989, 1787; (d) nitronate dianions: see ref. 6.