Intramolecular Anionic Friedel-Crafts Equivalents. An Expeditious Synthesis of 4*H*-1,2-Benzothiazin-4-one 1,1-Dioxides from *N*-Arylsulfonylated Amino Acids

Wouter I. Iwema Bakker, O. B. Familoni, James Padfield and Victor Snieckus*

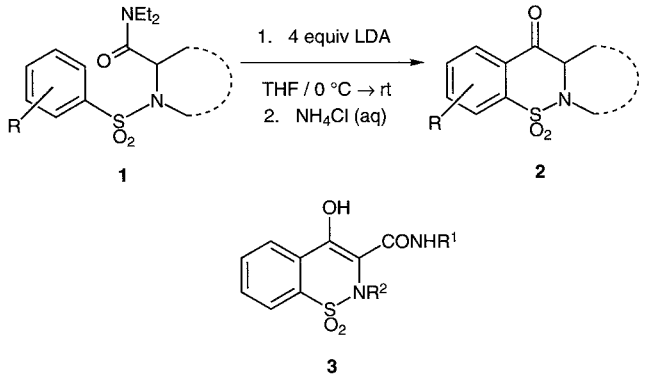
Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario, Canada, N2L 3G1

Fax: 519-746-5884; email: snieckus@buli.uwaterloo.ca

Received 17 June 1997

Abstract: Treatment of compounds **1**, readily available from amino acids, with excess LDA furnishes benzothiazinones **2** in modest to good yields (Table); variations of carbanion-mediated reactions lead to benzothiazepinones (Table, entries 12 and 13) and dibenzothiazepinone (**5**).

As a non-aromatic sequel to the Complex Induced Proximity Effect (CIPE)-assisted[1] carbanionic Friedel-Crafts equivalent, for the preparation of dibenzofused heterocycles,[2] we report on the convenient synthesis of 1,2-benzothiazin-4-one 1,1-dioxides **2** from readily available *N*-arylsulfonylated amino amides **1** using mild standard LDA conditions (Scheme 1). In the early 1970s, the discovery of potent anti-inflammatory activity by Lombardino[3] placed the 1,2-benzothiazine ring[4] into prominence and led to the development of a principal route[5] to this system based on alkoxide-mediated ring expansion of *N*-acyl saccharin derivatives, currently used for the production of commercial drugs (**3**).[6] The protocol reported herein allows ready access to simple and carbocycle-fused systems **2** which have not been reported to date.[7] As extensions, carbanion-mediated routes to benzothiazepinone and dibenzothiazepinone (**5**) systems are also described.



Scheme 1

Selected results (Table) indicate the scope and potential limitations of the excess LDA-promoted cyclization of *N*-arylsulfonylamino amides[8] to benzothiazinones.[9] *N*-Sulfonylated pipecolinamides (entries 1 and 2) provide respectable yields of products, whereas the corresponding pyrrolidinamides (entries 3 and 4) proceed poorly. Although *p*-methyl deprotonation occurs,[10] this comparison suggests that 5-fused ring products form with greater difficulty, perhaps owing to conformational (transition state) and/or strain (product) factors. Product stability appears not to be compromised by possible hydride delivery[11] from excess LDA as seen from comparable yields obtained with LiTMP (entry 3). In contrast to observations made for anionic xanthenone synthesis,[2b] a directed metalation group does not dictate the expected cyclization regiochemistry (entry 6). The detrimental effect of α-amide carbanion generation under excess LDA conditions is clearly evident (compare entries 4 and 5 with 7 and 8). Entries 7-9 illustrate the successful cyclization of secondary sulfonamides of acyclic amino amides, albeit in variable yields. Examination of entries 9 and 10 points to a potential conformational explanation for the lower yield in the latter case. Low-yield cyclization to heterocycle-fused sulfonamides (entry 11) may be due to metalation of other, more highly acidic sites. When the aryl C-H deprotonation is precluded by methyl substituents (entries 12 and 13), cyclization occurs *via* the acidic[10b] benzylic carbanion, to afford fused benzothiazepinones.[12] As a further extension of potential synthetic utility, the simple *N*-sulfonyl anthranilamide **4** afforded the known[13] dibenzothiazepinone (**5**) in low yield (Scheme 2).

Table. Synthesis of 4H-1,2-Benzothiazin-4-one 1,1-Dioxides

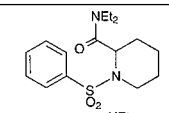
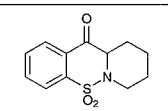
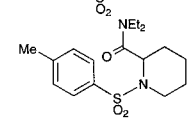
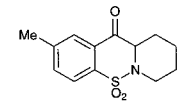
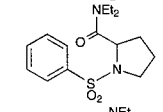
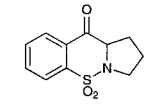
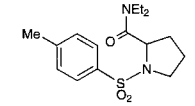
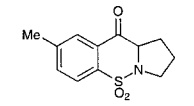
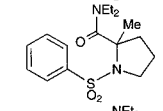
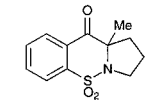
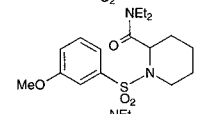
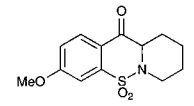
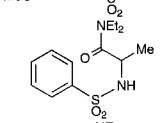
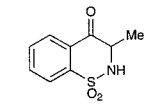
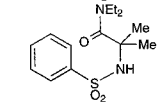
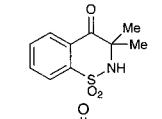
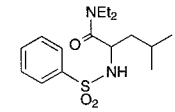
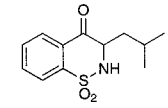
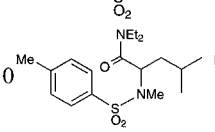
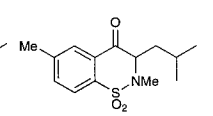
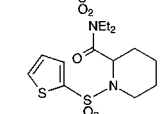
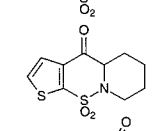
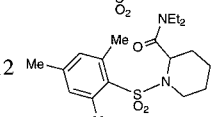
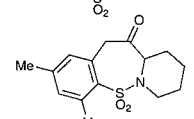
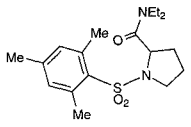
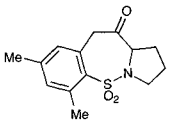
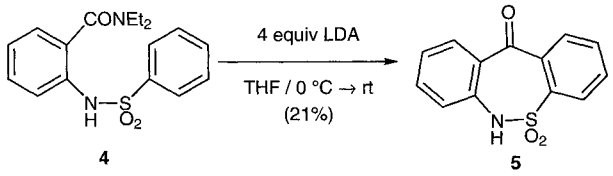
Entry	Amide[a]	Product[a]	Yld[b], %	mp °C
1			68	115 - 117
2			60	152 - 154
3			25 (27)[c]	76 - 78
4			24	88 - 90
5			69	130-131
6			29	148-150
7			20	151-154
8			85	72 - 74
9			57[d]	120-121
10			29	64-66
11			22	97 - 98
12			32	132 - 134

Table. (continued)

Entry	Amide[a]	Product[a]	Yld[b], %	mp °C
13			20	101-104

[a]All compounds show spectral (NMR, IR, MS) and analytical and/or HRMS data consistent with their structure. [b]Yields correspond to isolated chromatographed/recrystallized materials. [c]Using LiTMP as base. [d]Shows enol-keto tautomerism in solution, a well known phenomenon of benzothiazinones.[4a]



Scheme 2

Although competitive α-amide carbanion formation appears problematical, the excess LDA undoubtedly also serves to drive the equilibrium to the enolate of the product **2**. While the scope of this reaction for other DMGs and internal electrophiles remains to be established, the preliminary results reported here and elsewhere[2b] attest, with substrate modification (α-amide and heterocyclic higher acidity C-H protection, e.g. TMS) to the potential synthetic value of the concept as an anionic complement to Friedel-Crafts chemistry.[14] Cyclization mediated by lateral deprotonation (Table, entries 12 and 13) anticipates additional synthetic possibilities.

Acknowledgements. We are grateful to NSERC Canada and Monsanto/Searle for support of our research under the Industrial Research Chair and Research Grant Programs. OBF thanks NSERC/CIDA for a Fellowship which resulted in the work reported herein. VS thanks Glaxo Wellcome for a Visiting Professorship at Duke University and Michael Pirrung and Ned Porter for a peaceful environment for the preparation of this manuscript.

References and Notes

(1) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(2) a) Thioxanthenones (Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 6508); b) xanthenones (Familoni, O. B.; Ionica, I.; Bower, J. F.; Snieckus, V. *Synlett* **1997**, 1081); c) acridones (Gray, M.; MacNeil, S.; Glaenzer, J.; Snieckus, V. work in progress); d) dibenzophosphorinones (Gray, M.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1558).

(3) Lombardino, J. G.; Wiseman, E. H.; Chiaini, J. *J. Med. Chem.* **1973**, *16*, 493.

(4) a) Lombardino, J. G.; Kuhla, D. E. *Advan. Heterocyl. Chem.* **1981**, *28*, 73; b) Catsoulacos, P.; Camoutsis, Ch. *J. Heterocycl. Chem.* **1979**, *16*, 1503; c) Ansell, M. F. Ed. *Rodd's Chemistry of Carbon Compounds*, Vol IV, Pt H, Elsevier, Amsterdam, 1987, p 239.

(5) Zinnes, H.; Comes, R. A.; Zuleski, F. R.; Caro, A. N.; Shavel, J. Jr. *J. Org. Chem.* **1965**, *30*, 2241. For an effective but rarely applied synthesis *via* lateral metalation of *o*-tolylsulfonamides, see Watanabe, H.; Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Org. Chem.* **1969**, *34*, 919.

(6) Allen, R. C. Ed. *Ann. Rep. Med. Chem.* **1989**, *24*, 309.

(7) However, many similar systems have been reported. In addition to reference 4, see also Zinnes, H.; Comes, R. A.; Shavel, J. Jr. *J. Med. Chem.* **1967**, *10*, 223.

(8) Prepared by standard procedures from commercial racemic and chiral amino acids and arylsulfonyl chlorides: a) Maurer, P. J.; Takahata, H; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095; b) Izumiya, N. *Bull. Chem. Soc. Jpn.* **1953**, *26*, 53; c) Moss, W. O.; Wakefield, E; Mahon, M. F.; Molloy, K. C.; Bradbury, R. H.; Hales, N. J.; Gallagher, T. *Tetrahedron* **1992**, *48*, 7551.

(9) *Typical Experimental Procedure:* **7,8,9,10-tetrahydro-pyrido[1,2-b][1,2]benzothiazin-10-one 5,5-dioxide** (entry 1). To a solution of LDA (freshly prepared from *i*-Pr_2NH (0.56 mL, 4 mmol) and *n*-BuLi (2.5 mL of a 1.60 M solution, 4 mmol) in THF (20 mL) at 0 °C was added a solution of *N,N*-diethyl *N*-phenylsulfonyl pipicolinamide (325 mg, 1.0 mmol) in THF (5 mL). The ice-bath was immediately removed, the solution was stirred at rt for 30 min, and quenched with satd aq NH_4Cl (5 mL). The reaction mixture was evaporated to dryness, H_2O (30 mL) was added and the whole was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2, EtOAc/hexane 3:7 eluent) to afford 172 mg (68%) of product as colorless crystals. An analytically pure sample was obtained by recrystallization from *i*-Pr_2O: mp 115-117 °C. ^{1}NMR (250 MHz, $CDCl_3$) δ 8.2-8.1 (m, 1H, Ar**H**), 7.9-7.7 (m, 3H, Ar**H**), 5.01 (t, *J* = 3.7, 1H, NC**H**CO), 3.72 (dt, *J* = 11.7, 3.6, 1H, NCH_2), 2.8-2.5 (m, 2H, CH_2), 1.9-1.6 (m, 4H, CH_2), 1.5-1.2 (m, 1H, CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 192.9, 138.2, 135.2, 132.9, 129.1, 128.1, 125.1, 63.9, 46.1, 24.3, 24.2, 20.1; IR (KBr disc) 2928, 2842, 1694, 1588, 1449, 1342, 1192, 1171, 1126, 1042, 1006, 927, 833, 770, 749, 578; Anal Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.17; H, 5.39; N, 5.50.

(10) For entry 2, the reaction mixture was quenched with MeI giving the *p*-ethyl derivative of the product (approx 65% by NMR). *o*- and *p*-Me metalation of secondary and tertiary benzenesulfonamides may be selectively achieved: a) Clark, R. D.; Jahangir, *Org. React.* **1995**, *47*, 29; b) Familoni, O. B.; Snieckus, V. unpublished results.

(11) Majewski, M.; Gleave, D. M. *J. Organometal. Chem.* **1994**, *470*, 1.

(12) The 2-methyl derivative corresponding to substrate of entry 13 led only to the normal benzothiazolinone product (12% yld).

(13) Abramovitch, R. A.; Azogu, C. I.; McMaster, I. T.; Vanderpool, D. P. *J. Org. Chem.* **1978**, *43*, 1218.

(14) When the carboxylic acid of entry 1 was treated under Friedel-Crafts conditions (reflux in heptafluorobutyric acid for 36 h) decomposition of the acid occurred, and none of the desired cyclization product was observed.