α,N-Alkanesulfonamide Dianions: Formation and Chemoselective C-Alkylation

Mark E. Thompson

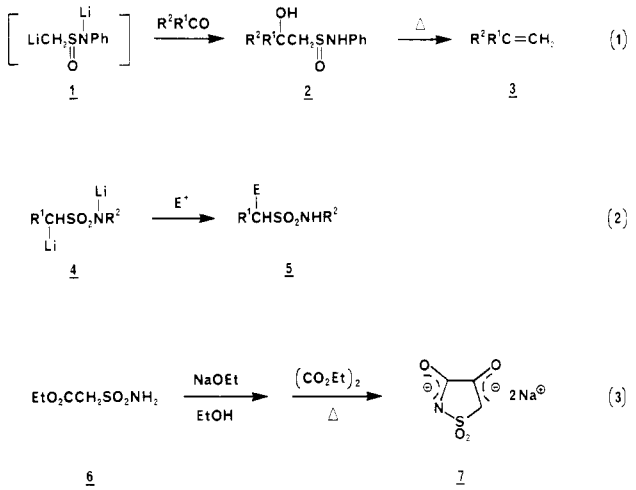
Agricultural Chemicals Department, E. I. Du Pont de Nemours & Co., Experimental Station, Wilmington, Delaware 19898

Received December 2, 1983

Mono-N-substituted alkanesulfonamides such as **11** (Scheme I) can be treated with 2 equiv of a strong base (*n*-butyllithium or LDA) to generate the hitherto unreported dianionic species **12**. Addition of electrophiles (alkyl halides, aldehydes, ketones, nitriles) to THF solutions of these dianions results in clean, chemoselective reaction on the carbon atom. Removal of the "protecting" group from nitrogen releases a primary sulfonamide, which may then be selectively functionalized. This method permits the preparation of a wide variety of substituted sulfonamides that might otherwise prove difficult to synthesize. As demonstration of the further utility of these adducts, β-hydroxy sulfonamides such as **14** were converted to either β-styrenesulfonamides **15** (and **16**) or 1,2-thiazetidine 1,1-dioxides (**18**) (Scheme II).

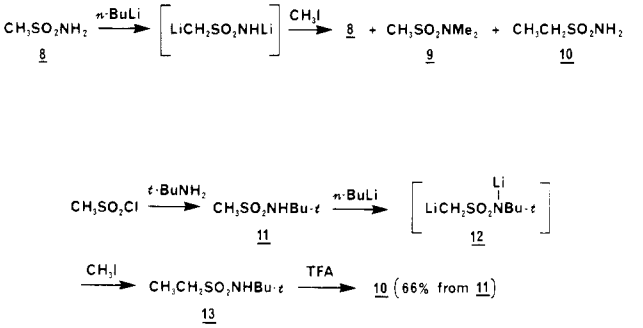
In connection with a program directed toward the preparation of highly substituted sulfonamides, we required a means for achieving selective C-alkylation of methanesulfonamide derivatives. Furthermore, it was essential that the sulfonamide portion of the products be available for subsequent functionalization on nitrogen. A search of the literature indicated that no methodology existed for effecting such a transformation.

It has been known for some time that the dianion **1** of methanesulfinanilide can be readily formed and treated with aldehydes and ketones to afford β-hydroxy sulfinamides **2** (eq 1); these adducts may then be converted to



olefins by thermolysis.[1] It therefore seemed plausible that α,N-alkanesulfonamide dianions of general structure **4** should form under similar conditions and might react with electrophiles in a chemoselective manner on the carbon atom (presumably the center of highest charge density[2]) to yield more highly functionalized sulfonamides **5** that might otherwise prove difficult to synthesize (eq 2).[3] Recently, Britcher has reported a synthesis of isothiazole 1,1-dioxides **7** via condensation of a substituted methanesulfonamide **6** with diethyl oxalate by employing sodium ethoxide as base (eq 3).[4] In view of this publication, we disclose the results of our work in this area.

Scheme I



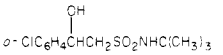
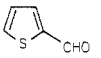
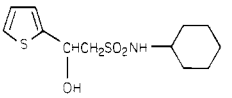
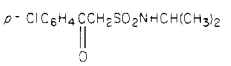
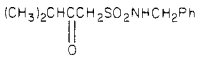
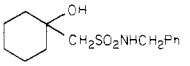
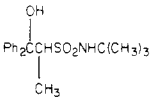
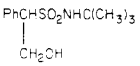
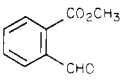
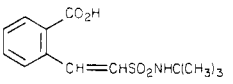
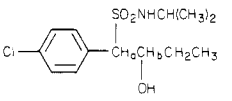
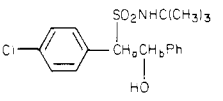
Treatment of methanesulfonamide (**8**) with 2 equiv of *n*-butyllithium (THF, −78 → −30 °C) and addition of methyl iodide gave, after aqueous workup, a rather poor recovery of a crude mixture that proved to consist mostly of unreacted **8** along with *N*,*N*-dimethylmethanesulfonamide (**9**) and a trace of the desired ethanesulfonamide (**10**) (Scheme I). In order to direct alkylation away from the nitrogen atom, the "protected" *N*-*tert*-butyl derivative **11** was prepared.[5] Treatment of **11** with 2 equiv of *n*-butyllithium or LDA (THF, −78 → −30 °C, 45 min) followed by addition of methyl iodide afforded *N*-*tert*-butylethanesulfonamide (**13**) in 73% yield after recrystallization from hexane. No *N*-alkylation was observed and the crude reaction product was contaminated only with a small amount of unreacted **11**. Removal of the *tert*-butyl substituent could be achieved with polyphosphoric acid,[5] trifluoroacetic acid,[6] or *p*-toluenesulfonic acid in refluxing xylenes to give ethanesulfonamide (**10**) (90% yield) in which the amino group is ready for further manipulation.[7]

This reaction has been found to be quite general. A number of substituents are tolerated on the nitrogen atom, and the dianions react efficiently with a variety of electrophiles (Table I). A second substituent on the carbon atom α to the sulfonyl group reduces the ease with which the dilithio species are formed (entries 9, 10, 12, and 13). For example, while the dianion **12** of *N*-*tert*-butylmethanesulfonamide formed below −30 °C, the dianion of *N*-*tert*-butylethanesulfonamide (entry 9) required treat-

(1) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
(2) Dewar, M. J. S. *Adv. Chem. Phys.* **1965**, *8*, 102.
(3) Alkanesulfonamides are traditionally prepared by the reaction of the appropriate sulfonyl chloride and an amine; e.g., see: Huntress, E. H.; Autenrieth, J. S. *J. Am. Chem. Soc.* **1941**, *63*, 3446. This method is, of course, constrained by the availability of both starting materials.
(4) Britcher, S. F.; Cochran, D. W.; Phillips, B. T.; Springer, J. D.; Lumma, W. C., Jr. *J. Org. Chem.* **1983**, *48*, 763.
(5) The *tert*-butyl substituent was chosen primarily for its known ease of removal; a secondary factor was its bulk. No in-depth study was undertaken to ascertain how large a group on nitrogen was required to achieve alkylation on carbon exclusively. For use of the *tert*-butylsulfonamide group in ortho lithiation chemistry, see: Lombardino, J. G. *J. Org. Chem.* **1971**, *36*, 1843.
(6) Catt, J. D.; Matier, W. L. *J. Org. Chem.* **1973**, *38*, 1974.
(7) Mono anions of primary sulfonamides were easily prepared by deprotonation with NaH/THF (0–25 °C) followed by addition of the appropriate electrophile.

0022-3263/84/1949-1700$01.50/0

Table I. Reactions of α,N-Dilithio Sulfonamides, $LiR^1CHSO_2NR^2Li$, with Electrophiles

entry	R^1	R^2	electrophile	product	yield,[a] % (mp, °C)
1	H	$C(CH_3)_3$	CH_3I	$CH_3CH_2SO_2NHC(CH_3)_3$	73 (53-54.5)
2	H	$C(CH_3)_3$	$PhCH_2Br$	$PhCH_2CH_2SO_2NHC(CH_3)_3$	82 (74-76)
3	H	CH_2Ph	$(CH_3)_3SiCl$	$(CH_3)_3SiCH_2SO_2NHCH_2Ph$	57 (79.5-81)[b]
4	H	$C(CH_3)_3$	o-ClC_6H_4CHO		87 (85-88)[b]
5	H	C_6H_{11}			97 (111-112)
6	H	$CH(CH_3)_2$	p-ClC_6H_4CN		63 (117-117.5)
7	H	CH_2Ph	$(CH_3)_2CHCN$		80 (76-78)
8	H	CH_2Ph			91 (138-140)
9	CH_3	$C(CH_3)_3$	$Ph_2C=O$		74 (151-153)
10	Ph	$C(CH_3)_3$	CH_2O		62 (79-81)[b]
11	H	$C(CH_3)_3$		 (trans)	22 (165-167)[c]
12	p-ClC_6H_4	$CH(CH_3)_2$	CH_3CH_2CHO	 (threo/erythro ~ 2:1)	97[d]
13	p-ClC_6H_4	$C(CH_3)_3$	PhCHO	 (ratio of diastereomers ~ 3.6:1)	82[d]

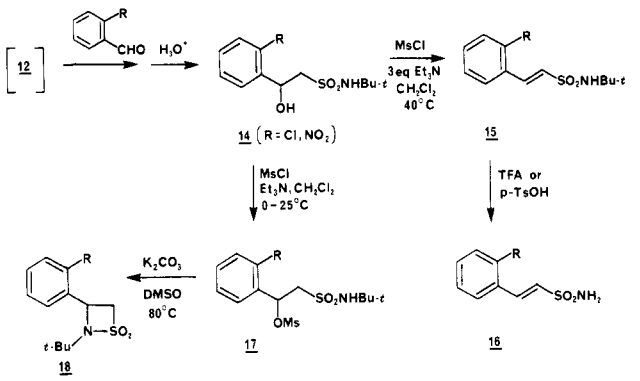
[a] Yields are not optimized and refer to isolated products, which proved homogeneous by TLC and ^1H NMR analyses. Satisfactory spectral (^1H NMR, IR, MS) and physical (elemental analysis, ±0.3%, or high-resolution MS) data were obtained for all new compounds. [b] Purified by flash chromatography (40% EtOAc-hexane). [c] Pure product was isolated by trituration of the crude reaction mixture with Et_2O-hexane (1:1, v/v). This β-styrenesulfonamide presumably arose via lactonization of the initially formed alkoxide followed by elimination. [d] Yield of crude reaction mixture; see ref 11.

ment of **13** with *n*-butyllithium at 0 °C for 1 h.

In contrast to Corey's sulfinanilide dianion **1**, α,N-dilithio sulfonamides add to enolizable ketones in a highly efficient fashion (entry 8). This presumably is a reflection of the diminished basicity of sulfonamide dianions relative to their counterparts of one lower oxidation state.

The adducts from the reaction of these dianions with aryl aldehydes have proven useful as intermediates for the synthesis of β-styrenesulfonamides **15** (and **16**) or 1,2-thiazetidin 1,1-dioxides **18** (Scheme II).[8,9] For example, the mesylate of β-hydroxy sulfonamide **14** was prepared (MsCl, Et_3N, CH_2Cl_2)[10] and could be converted to either of two products. First, by employing 1 equiv of methanesulfonyl chloride and excess triethylamine in refluxing dichloromethane, it was possible to convert alcohol **14** directly to the *trans*-β-styrenesulfonamide **15** (63–97% yields) without isolation of the intermediate methanesulfonate ester **17**. Alternatively, isolation of mesylate **17**

Scheme II



and subsequent exposure to excess potassium carbonate (Me_2SO, 80 °C) resulted in cyclization to give the 1,2-thiazetidin 1,1-dioxide **18** (53–78% yields).

Finally, preliminary studies have revealed a rather modest diastereoselectivity in the reaction of certain dilithio sulfonamides with aldehydes. Addition of propionaldehyde to a THF solution of the dianion of *N*-isopropyl-4-(chlorophenyl)methanesulfonamide (entry 12) at

(8) Culbertson, B. M.; Dietz, S. *J. Chem. Soc. C* **1968**, 992.
(9) For a recent synthesis of 1,2-thiazetidin 1,1-dioxides (β-sultams), see: Koller, W.; Linkies, A.; Rehling, H.; Reuschling, D. *Tetrahedron Lett.* **1983**, *24*, 2131 and references cited therein.
(10) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

−78 °C gave, after aqueous workup, a mixture of diastereomers in a ratio of ca. 2:1 (threo/erythro).[11] When benzaldehyde was added in an identical manner to the dianion of *N-tert*-butyl-4-(chlorophenyl)methanesulfonamide (entry 13), the ratio of diastereomeric β-hydroxy sulfonamides obtained was ca. 3.6:1.

In summary, α,*N*-alkanesulfonamide dianions can be generated under mild conditions and treated with electrophiles to react chemoselectively on the carbon atom. This method permits the preparation of a wide variety of more highly substituted sulfonamides that might otherwise prove difficult to synthesize.

Experimental Section

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 683 grating infrared spectrophotometer; characteristic or strong absorptions are reported in wavenumbers (cm^{-1}) with an accuracy of ±5 cm^{-1}. Proton magnetic resonance (NMR) spectra were recorded at either 90 MHz on a Varian EM-390 or at 200 MHz on a Varian XL-200 instrument. Chemical shifts are reported as δ values in parts per million (ppm) downfield relative to tetramethylsilane (δ = 0.0 ppm). Low-resolution mass spectra (MS) were obtained on a Dupont 21-492 mass spectrometer.

Reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran was distilled under nitrogen from sodium benzophenone ketyl immediately before use. In general, reagent-grade solvents and reagents were used directly or were purified according to standard procedures. Thin-layer chromatography (TLC) was performed on Whatman glass plates precoated with silica gel; visualization was achieved under ultraviolet light or with iodine vapor. Silica gel (230–400 mesh), obtained from the J. T. Baker Chemical Company, was used for flash column chromatographic separations.[12]

Preparation of Alkanesulfonamides. General Procedure. A mechanically stirred solution of the primary amine (approximately 0.5 M) in dry THF under nitrogen is cooled to 0 °C and treated with the appropriate alkanesulfonyl chloride (0.5 equiv) in a dropwise manner. The reaction mixture is allowed to warm to room temperature and is stirred for 2–12 h. Insoluble salts are separated by filtration and the filtrate is concentrated in vacuo. The residue is dissolved in CH_2Cl_2 and the organic layer washed with one portion of 5% aqueous HCl and then several small portions of water. Drying ($MgSO_4$) and evaporation of the organic layer affords the crude alkanesulfonamide, which may be purified by recrystallization from a suitable solvent such as ether or petroleum ether.

The following procedures represent typical conditions for the formation of alkanesulfonamide dianions and their further reactions.

Formation of the Dianion 12 of *N-tert*-Butylmethanesulfonamide (11) and Reaction with Methyl Iodide. Lithium diisopropylamide was generated by the addition of 17.3 mL (27.7 mmol) of 1.6 M *n*-butyllithium in hexane to a solution of 4.30 mL (30.4 mmol) of diisopropylamine in 20 mL dry THF at −78 °C. After being stirred briefly at 0 °C, this solution was recooled to −78 °C and treated with 2.0 g (13 mmol) of *N-tert*-butylmethanesulfonamide in 24 mL of dry THF, added over a period of 10 min. The reaction mixture was allowed to warm −30 °C over a period of 45 min and was then recooled to −78 °C and treated with 1.1 mL (17 mmol) of methyl iodide, added in a fast stream. The solution was stirred at room temperature for approximately 12 h and was cooled to 0 °C and quenched with 5% aqueous HCl. The layers were separated, and the aqueous layer was extracted with three 20-mL portions of ether. The combined organic extracts were back-washed with several small portions of water and were dried over $MgSO_4$. Removal of the solvent in vacuo gave a yellow oil, which crystallized upon standing. Recrystallization from hexane afforded 1.6 g (73%) of *N-tert*-butylethanesulfonamide (**13**) as colorless plates: mp 53–54.5 °C; IR (KBr) 3300, 3000, 2950, 2890, 1315, 1135, 1015 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.35 (t, 3 H, J = 7 Hz), 1.4 (s, 9 H), 3.0 (q, 2 H, J = 7 Hz), 4.7 (br s, 1 H); MS, m/e (relative intensity) 150 (97, $M^+ - 15$), 136 (4, $M^+ - 29$), 86 (12), 58 (100), 57 (55). Anal. Calcd for $C_6H_{15}NO_2S$: C, 43.6; H, 9.2; N, 8.5. Found: C, 43.7; H, 9.1; N, 8.4.

Formation of the Dianion of *N-tert*-Butylethanesulfonamide (13) and Reaction with Benzophenone. A solution of 4.0 g (24 mmol) of *N-tert*-butylethanesulfonamide in 81 mL of dry THF was cooled to −78 °C and treated with 32 mL (51 mmol) of 1.6 M *n*-butyllithium in hexane in a dropwise manner. The resulting clear yellow solution was allowed to warm to 0 °C (1 h) and was then recooled to −78 °C and treated with a solution of 4.8 g (26 mmol) of benzophenone in 40 mL dry THF, added over a period of about 15 min. During the addition of the benzophenone, the clear solution assumed a brilliant green color that gradually changed to yellow. After being stirred overnight at room temperature, the reaction mixture was cooled to 0 °C and quenched with 100 mL of 5% aqueous HCl. The water layer was extracted with two 50-mL portions of ether and one 50-mL portion of CH_2Cl_2 and was dried ($MgSO_4$) and concentrated in vacuo to yield a white powder. Recrystallization from ether gave 6.2 g (74%) of *N-tert*-butyl-1-methyl-2,2-diphenyl-2-hydroxyethanesulfonamide as a colorless solid: mp 151–153 °C; IR (KBr) 3460, 3320, 2970, 1305, 1130, 1000 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.15 (s, 9 H), 1.55 (d, 3 H, J = 7 Hz), 2.83 (br s, 1 H), 4.27 (q, 1 H, J = 7 Hz), 5.30 (br s, 1 H), 7.20 (br t, 2 H, J = 8 Hz), 7.33 (br t, 4 H, J = 8 Hz), 7.57 (m, 4 H); MS, m/e (relative intensity) 348 (57, M + 1), 331 (66), 330 (100), 274 (79), 184 (38), 183 (94), 105 (94), 77 (61), 58 (79), 57 (60). Anal. Calcd for $C_{19}H_{25}NO_3S$: C, 65.68; H, 7.25; N, 4.03. Found: C, 65.81; H, 7.52; N, 3.92.

Removal of the *tert*-Butyl Group from *N-tert*-Butylethanesulfonamide (13). Trifluoroacetic Acid Method. *N-tert*-Butylethanesulfonamide (2.0 g, 12 mmol) was added to 40 mL of trifluoroacetic acid, and the solution was stirred at room temperature under a drying tube for 24 h. The trifluoroacetic acid was removed in vacuo to leave a yellow oil, which crystallized upon treatment with ether–hexane (1:1, v/v). Filtration and drying afforded 1.2 g (92%) ethanesulfonamide (**10**) as a white powder: mp 57–59 °C (lit.[13] mp 57–58 °C); IR (KBr) 3350, 3260, 2995, 2980, 2950, 1315, 1130, 900, 730 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.42 (t, 3 H, J = 7 Hz), 3.13 (q, 2 H, J = 7 Hz), 4.83 (br s, 2 H); MS, m/e (relative intensity) 110 (35, M + 1), 93 (10), 81 (75), 65 (16), 64 (33), 44 (100).

***trans*-2-Chloro-β-styrenesulfonamide (16, R = Cl).** A solution of 13.3 g (45.6 mmol) of *N-tert*-butyl-2-(*o*-chlorophenyl)-2-hydroxyethanesulfonamide (**14**, R = Cl) and 19.3 mL (138 mmol) triethylamine in 123 mL of CH_2Cl_2 was cooled to 0 °C under a nitrogen atmosphere and treated with 5.3 mL (68 mmol) of methanesulfonyl chloride. The cold bath was removed and the resulting suspension was heated at reflux temperature for 1.5 h. Dichloromethane (100 mL) was added to the cooled solution, and the organic layer was washed with one portion of 5% aqueous HCl and three portions of water. Drying ($MgSO_4$) and evaporation of the organic layer gave 12.1 g (97%) of the β-styrenesulfonamide **15** (R = Cl) as a light orange solid. Analysis by TLC showed a single spot, R_f 0.58 (40% EtOAc–hexane).

(11) The ratio of diastereomers was determined both by ^1H NMR (200 MHz) and HPLC analyses of the crude reaction mixtures. In addition to the β-hydroxy sulfonamide isomers, approximately 10% of unreacted starting material was detected along with another, less polar, side product which was not identified. The stereochemical assignments were based largely on the coupling constant, J_{ab}, following the precedent of Hauser et al.; (*J. Org. Chem.* **1965**, *30*, 2035) and House et al. (*J. Am. Chem. Soc.* **1973**, *95*, 3310). The ^1H NMR data ($CDCl_3$, 200 MHz) for entry **12** are as follows: major (threo) isomer δ 0.88 (3 H, t, J = 8 Hz), 1.09 (3 H, d, J = 8 Hz), 1.14 (3 H, d, J = 8 Hz), 1.28 (2 H, m), 3.42 (1 H, m), 3.61 (1 H, d, J = 2 Hz, −OH), 4.02 (1 H, d, J = 9 Hz, H_a), 4.25 (1 H, d, J = 7 Hz, −NH), 4.40 (1 H, d t d, J = 2, 8, 9 Hz, H_b), 7.22–7.40 (4 H, m); minor (erythro) isomer δ 0.92 (3 H, t, J = 8 Hz), 1.16 (3 H, d, J = 8 Hz), 1.23 (3 H, d, J = 8 Hz), 1.30 (2 H, m), 3.18 (1 H, d, J = 2 Hz, −OH), 3.43 (1 H, m), 4.03 (1 H, d, J = 6 Hz, H_a), 4.25 (1 H, d, J = 7 Hz, −NH), 4.50 (1 H, unresolved multiplet, H_b), 7.2–7.5 (4 H, m). The pure threo isomer (R_f 0.26, 20% EtOAc–hexane) was isolated by flash chromatography and recrystallized from ether to give colorless needles, mp 122–124 °C. Pure erythro isomer (R_f 0.29) was not isolated. The stereochemical assignments for entry 13 are somewhat more tentative as J_{ab} was virtually the same, 10 Hz, for both diastereomers.

(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(13) Hunter, W. H.; Sorenson, B. E. *J. Am. Chem. Soc.* **1932**, *54*, 3364.

Recrystallization from ether afforded 10.5 g of the pure product as a colorless solid: mp 85–88 °C; IR (KBr) 3480, 3250, 2980, 1320, 1290, 1140, 1015 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.4 (s, 9 H), 4.85 (br s, 1 H), 6.9 (d, 1 H, J = 15 Hz), 7.3–7.7 (m, 4 H), 7.95 (d, 1 H, J = 15 Hz).

A mixture of **15** (R = Cl) (1.5 g, 5.5 mmol) and 300 mg of *p*-toluenesulfonic acid monohydrate in 18 mL of xylenes was heated at reflux temperature for 4 h. As the reaction solution cooled to room temperature, a precipitate formed. This solid was filtered, washed with hexane, and dried. The yield of pure **16** was 1.1 g (96%) as a colorless solid: mp 125–127 °C (lit.[8] mp 124.5–126.5 °C); IR (KBr) 3320, 3240, 1620, 1330, 1140 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6, 90 MHz) δ 7.2 (d, 1 H, J = 15 Hz), 7.3–7.6 (m, 3 H), 7.75 (m, 1 H), 7.8 (d, 1 H, J = 15 Hz).

2-*tert*-Butyl-3-(*o*-nitrophenyl)-1,2-thiazetidine 1,1-Dioxide (18, R = NO_2). A solution of 1.5 g (5.1 mmol) of *N*-*tert*-butyl-2-(*o*-nitrophenyl)-2-hydroxyethanesulfonamide (**14**, R = NO_2) (prepared by the addition of dianion **12** to *o*-nitrobenzaldehyde) and 1.40 mL (10.0 mmol) of triethylamine in 10 mL of CH_2Cl_2 was cooled to 0 °C under a nitrogen atmosphere and treated with 0.60 mL (7.8 mmol) of methanesulfonyl chloride. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 5 h. Dichloromethane (50 mL) was added and the organic layer was washed with two portions of 5% aqueous HCl and three portions of water. Drying ($MgSO_4$) and evaporation of the CH_2Cl_2 layer afforded a yellow oil from which 1.6 g (82%) of pure methanesulfonate ester **17** (R = NO_2), mp 136–138 °C dec, crystallized upon addition of ether; NMR ($CDCl_3/Me_2SO$-d_6, 90 MHz) δ 1.35 (s, 9 H), 3.2 (s, 3 H), 3.7 (m, 2 H), 6.6 (br t, 1 H, J = 6 Hz), 6.8 (br s, 1 H), 7.6–8.2 (m, 4 H).

This mesylate (1.1 g, 2.9 mmol) was added to a well-stirred suspension of 1.2 g (8.7 mmol) of anhydrous K_2CO_3 in 14 mL of dry Me_2SO. The mixture was warmed to 80 °C under a nitrogen atmosphere for approximately 1 h, allowed to cool, and then poured into 25 mL of water, causing an immediate precipitate. This solid was collected by filtration, washed well with water and ether, and dried to give 440 mg (53%) of the 1,2-thiazetidin 1,1-dioxide **18** (R = NO_2) as a white powder: mp 179–181 °C; IR (KBr) 2490, 1525, 1350, 1300, 1190, 1140 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 9 H), 3.80 (dd, 1 H, J = 2, 12 Hz), 4.69 (dd, 1 H, J = 4, 12 Hz), 5.05 (dd, 1 H, J = 2,4 Hz), 7.50 (br t, 1 H, J = 3 Hz), 7.73 (br t, 1 H, J = 3 Hz), 7.95 (br d, 1 H, J = 3 Hz), 8.23 (br d, 1 H, J = 3 Hz); MS, m/e (relative intensity) 285 (14, M + 1), 269 (38, M^+ – 15), 212 (14), 148 (27), 146 (53), 91 (15), 77 (54), 58 (100), 57 (80), 56 (45); exact mass calcd for $C_{12}H_{16}N_2O_4S$ 284.0831, found 284.0873.

Acknowledgment. I express my appreciation to Mr. Thomas P. Boyle for technical assistance and to Dr. Paul K. Tseng for performing HPLC analyses.

Registry No. **10**, 1520-70-3; **13**, 89556-99-0; **14** (R = Cl), 89557-00-6; **14** (R = NO_2), 89557-01-7; **15** (R = Cl), 89557-02-8; **16** (R = Cl), 89557-03-9; **17** (R = NO_2), 89557-04-0; **18** (R = NO_2), 89557-05-1; $CH_3SO_2NHC(CH_3)_3$, 2512-23-4; $CH_3SO_2NHCH_2Ph$, 3989-45-5; $CH_3SO_2NH(c\text{-}C_6H_{11})$, 19299-40-2; $PhCH_2SO_2NHC(CH_3)_3$, 51270-35-0; $p\text{-}ClC_6H_4CH_2SO_2NHCH(CH_3)_2$, 85952-21-2; $PhCH_2Br$, 100-39-0; $(CH_3)_3SiCl$, 75-77-4; $o\text{-}ClC_6H_4CHO$, 89-98-5; CH_3I, 74-88-4; $p\text{-}ClC_6H_4CN$, 623-03-0; $(CH_3)_2CHCN$, 78-82-0; $Ph_2C{=}O$, 119-61-9; CH_2O, 50-00-0; $PhCH_2CH_2SO_2NHC(CH_3)_3$, 89557-07-3; $(CH_3)_3SiCH_2SO_2NHCH_2Ph$, 89557-08-4; $(2\text{-}C_4H_3S)CHO$, 98-03-3; $(2\text{-}C_4H_3S)CH(OH)CH_2SO_2NH(c\text{-}C_6H_{11})$, 89557-09-5; $p\text{-}ClC_6H_4COCH_2SO_2NHCH(CH_3)_2$, 89557-10-8; $(CH_3)_2CHCOCH_2SO_2NHCH_2Ph$, 89557-11-9; $PhCH(CH_2OH)SO_2NHC(CH_3)_3$, 89557-12-0; *trans*-$2\text{-}HO_2CC_6H_4CH{=}CHSO_2NHC(CH_3)_3$, 89557-13-1; $4\text{-}ClC_6H_4CH[SO_2NHCH(CH_3)_2]CH(OH)CH_2CH_3$ (isomer 1), 89557-14-2; $4\text{-}ClC_6H_4CH[SO_2NHCH(CH_3)_2]CH(OH)CH_2CH_3$ (isomer 2), 89557-15-3; $4\text{-}ClC_6H_4CH[SO_2NHC(CH_3)_3]CHPhOH$ (isomer 1), 89557-16-4; $4\text{-}ClC_6H_4CH[SO_2NHC(CH_3)_3]CHPhOH$ (isomer 2), 89557-17-5; $Ph_2C(OH)CH(CH_3)SO_2NHC(CH_3)_3$, 89557-06-2; $o\text{-}O_2NC_6H_4CHO$, 552-89-6; $o\text{-}OHCC_6H_4CO_2CH_3$, 4122-56-9; CH_3CH_2CHO, 123-38-6; PhCHO, 100-52-7; $CH_3SO_2NHCH(CH_3)_2$, 23705-43-3; lithium diisopropylamide, 4111-54-0; butyllithium, 109-72-8; cyclohexanone, 108-94-1; *N*-benzyl-1-hydroxycyclohexanemethanesulfonamide, 89557-18-6.

Cyclization Reactions of Hydrazones Induced by Isocyanates. Syntheses of 1,3,4-Thiadiazoline and 1,2,4-Triazoline Derivatives

Yoshinori Nakayama and Yuzuru Sanemitsu*

Pesticide Division, Takarazuka Research Institute, Sumitomo Chemical Co. Ltd., Takarazuka, Hyogo 665, Japan

Received October 24, 1983

Cyclization reactions of various hydrazones (**1**, **6**, **10**, and **13**) were found to be induced by isocyanates under mild conditions and to afford 1,3,4-thiadiazolines **3** and **11** and 1,2,4-triazolines **9**, **14**, and **18** in excellent yields. The cyclization reactions via inter- and intramolecular double additions were studied by ^1H and ^{13}C NMR spectroscopy. The syntheses of 4-(methoxycarbonyl)-Δ^2-1,2,4-triazolines **14** and **18** and derived fused heterocycles such as 1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1,3(2*H*)-diones **16** and 2,3-dihydro-3-thioxo-1*H*,5*H*-[1,2,4]-triazolo[1,2-*a*][1,2,4]triazol-1-ones **19** and **20** were achieved in high yields. The bicyclic structures of **16**, **19**, and **20** were confirmed by a single-crystal X-ray structure determination of **16a**.

The cycloaddition reactions of carbon–nitrogen double-bond systems with isocyanates are of great use for the syntheses of heterocyclic compounds.[1] In spite of considerable nucleophilicity of hydrazones, their cycloadditions to isocyanates have been studied only in a few limited cases.[2] The utility of hydrazones[3–7] as synthons for various heterocycles prompted us to investigate the behavior of hydrazones toward isocyanates. We found a new type of cyclization reactions of hydrazones **1**, **6**, **10**, and **13** induced by isocyanates. These reactions are characterized as a kind of inter- and intramolecular double additions. Thus, hydrazone derivatives reacted with iso-

(1) Ulrich, H. "Cycloaddition Reactions of Heterocumulenes", Organic Chemistry, A Series of Monographs; Blomquist, A. T., Ed.; Academic Press: New York and London, 1967; Vol. 9, pp 122–220.

(2) (a) Schildknecht, H.; Hatzmann, G. *Liebigs Ann. Chem.* **1969**, *724*, 226. (b) Arai, I. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2215. (c) Tsuge, O.; kanemasa, S. *Ibid.* **1974**, *47*, 2676. (d) Yamamoto, I.; Mamba, A.; Gotoh, H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2243. (e) Toro, V. D.; Gozzo, F.; Lorusso, S.; Garavaglia, C. Ger. Offen. 2921307, 1979; *Chem. Abstr.* **1980**, *92*, 128933*y*.

(3) (a) Heugebaert, F. C.; Willems, J. F. *Tetrahedron* **1966**, *22*, 913. (b) Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1970**, *24*, 179.

(4) Jones, D. H.; Slack, R.; Squires, S.; Wooldridge, K. R. H. *J. Med. Chem.* **1965**, *8*, 676.

(5) West, P. R.; Warkentin, J. *J. Org. Chem.* **1969**, *34*, 3233.

(6) Mayer, K. H.; Lauerer, D. *Liebigs Ann. Chem.* **1970**, *731*, 142.

(7) (a) Kubota, S.; Fujikane, K.; Uda, M.; Yoshida, T. *Heterocycles* **1976**, *4*, 1909. (b) Kubota, S.; Ueda, Y.; Fujikane, K.; Toyooka, K.; Shibuya, M. *J. Org. Chem.* **1980**, *45*, 1473.

0022-3263/84/1949-1703$01.50/0