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A SIMPLE SYNTHESIS OF AZABICYCLO[1.1.0]BUTANE SULFONES AND SULFOXIDES

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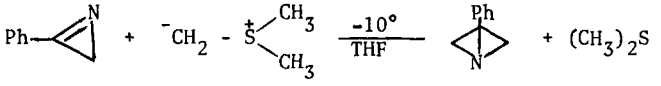
Summary: Azirines react with carbanions derived from α-chloro sulfones and sulfoxides, under mild conditions, to form functionalized azabicyclo[1.1.0]butanes.

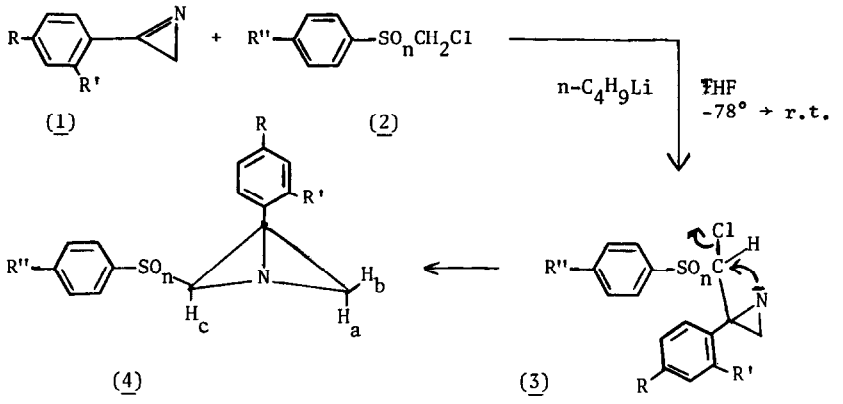
While numerous publications have appeared on the synthesis of bicyclo[1.1.0]butanes, relatively little is known about synthetic approaches to aza analogs of these strained ring compounds. In 1967, Hortmann and Robertson[2] described the synthesis of 3-phenyl-1-azabicyclo-[1.1.0]butane by the reaction of 3-phenyl-2H-azirine with dimethylsulfonium methylide in tetrahydrofuran. The same compound can be prepared, albeit in low yield, by irradiation of



1-azido-2-phenyl-2-propene[3]. Another photochemical approach, that involving expulsion of carbon dioxide from cyclic carbamates, has also been used in the synthesis of 2,2,3-triphenyl and 3-ethyl-2,2-diphenyl substituted azabicyclo[1.1.0]butanes.[4]

The parent member of this class of heterocycles, as well as 3-alkyl derivatives, have been prepared by base induced cyclization of 2-amino-1,3-dibromopropanes.[5] Finally, a recent communication has described the isolation of tri and tetrasubstituted azabicyclo[1.1.0]butanes, containing a vinyl substituent, by reaction of 3-phenyl-2H-azirine with lithiated allyl chloride.[6] We now wish to report a simple and convenient synthesis of sulfur substituted azabicyclo[1.1.0]butanes, i.e. heterocycles containing a sulfone or sulfoxide substituent.

α-Chloro sulfones (2, n=2), either commercially available or readily accessible by literature methods,[7,8] react with n-butyl lithium in tetrahydrofuran and an arylazirine 1, first a -78°C and then at room temperature, to give azabicyclo[1.1.0]butyl sulfones 4, n=2.



The reaction occurs for a variety of 3-aryl-2H-azirines (1) and chloromethyl aryl sulfones, affording 4, n = 2, in 31-93% yields. The reactions are facile, with the exception of chloromethyl p-chlorophenyl sulfone.

This cyclization reaction is also applicable to α-chloro sulfoxides [2, n=1][7,8] as reactants with the bicyclic sulfoxides 4, n=1, being obtained in 73-82% yields. The reactants, reaction times, yields and spectral properties of the products are listed in Table 1.

These reactions likely proceed via nucleophilic addition of the in situ generated lithiated chlorosulfone, or chlorosulfoxide, to the carbon-nitrogen double bond of the azirine affording 3, followed by intramolecular cyclization.

The following general procedure was used: A stirred THF (10 ml) solution of the chloromethyl aryl sulfone or sulfoxide [2, 4.40 mmol] was cooled to -78°C (dry ice-acetone), and 4.4 ml of 1 M n-C_4H_9Li was added dropwise under a nitrogen atmosphere. After 15 minutes, the azirine (1, 4.0 mmol) in THF (10 ml) was added, drop-by-drop, to the reaction mixture (-78°C; N_2 atmosphere). The reaction mixture was then allowed to warm to room temperature, and stirring was continued until the azirine was consumed (followed by thin layer chromatography). Distilled water (10 ml) was added, the layers were separated, and the aqueous phase was extracted with ether. The organic phase was dried ($MgSO_4$), concentrated, and the resulting oil was subjected to flash chromatography (silica gel) using hexane/methylene chloride as the eluant, affording analytically pure 4.

Table 1 Synthesis of 4

1,R=, R'=	2,R''=, n=	Reaction Time hr	Yield[a] of 4, %	Pertinent Spectral Data: IR, $\nu(SO_n)$[b] cm^{-1}	^{1}H-NMR, δ[c] ppm	MS m/e
H,H	H,2	1	93	1325,1150	1.60(d,1H,H_a,J_{ab}=3Hz),2.54(d,1H,H_b), 2.80(s,1H,H_c),7.10-7.80(m,10H, aromatic)[d]	271 $[M]^+$, 130 $[M-SO_2Ph]^+$
H,H	CH_3,2	3	87	1320,1150	1.60(d,1H,H_a,J_{ab}=3Hz),2.35(s,3H,CH_3), 2.60(d,1H,H_b),2.80(s,1H,H_c),7.10-7.70(m,9H,aromatic).	285 $[M]^+$, 144$[M-SO_2Ph]^+$
H,H	Cl,2	18	64	1325,1150	1.65(d,1H,H_a,J_{ab}=3Hz),2.65(d,1H,H_b) 2.85(s,1H,H_c),7.10-7.90(m,9H, aromatic)	305/307 $[M]^+$
CH_3,H	H,2	1	89	1325,1150	1.52(d,1H,H_a,J_{ab}=3Hz),2.32(s,3H,CH_3), 2.43(d,1H,H_b),2.78(s,1H,H_c),6.90-7.70(m,9H,aromatic)	285 $[M]^+$
CH_3,CH_3	H,2	0.5	54	1325,1150	1.60(d,1H,H_a,J_{ab}=3Hz),2.45(s,3H,CH_3), 2.63(d,1H,H_b),2.65(s,3H,CH_3),2.80 (s,1H,H_c),7.00-7.80(m,8H,aromatic)	299 $[M]^+$ 158$[M-SO_2Ph]^+$
OCH_3,H	H,2	1	46	1320,1150	1.65(d,1H,H_a,J_{ab}=3Hz),2.55(d,1H,H_b), 2.80(s,1H,H_c),3.85(s,3H,OCH_3),7.00-7.70(m,9H,aromatic)	301$[M]^+$, 160$[M-SO_2Ph]^+$
Br,H	H,2	1	31	1325,1150	1.63(d,1H,H_a,J_{ab}=3Hz),2.78(d,1H,H_b), 2.97(s,1H,H_c),7.00-7.80(m,9H, aromatic)	349/351$[M]^+$
H,H	H,1	1	82	1045	1.70(d,1H,H_a,J_{ab}=3Hz),2.72(d,1H,H_b), 2.76(s,1H,H_c),7.10-7.80(m,10H, aromatic).	255 $[M]^+$, 130$[M-SOPh]^+$
H,H	CH_3,1	1	73	1055	1.70(d,1H,H_a,J_{ab}=3Hz),2.20(s,1H,CH_3), 2.46(d,1H,H_b),2.68(s,1H,H_c),6.90-7.50(m,9H,aromatic)	269 $[M]^+$
H,H	Cl,1	1	81	1055	1.48(d,1H,H_a,J_{ab}=3Hz),2.58(d,1H,H_b), 2.70(s,1H,H_c),7.10-7.60(m,9H, aromatic)	289/291 $[M]^+$

[a]Yields are of pure materials. Satisfactory C,H,N analyses were obtained in all cases. [b]Neat. [c]$CDCl_3$ solution. [d] ^{13}C-NMR ($CDCl_3$) δ 36.88 (CH_2), 52.19 ($\underline{C}HSO_2Ph$), 74.34 (Ph$\underline{C}$), 128.45, 128.67, 128.94 (aromatic CH), 134.09 (quat, C of Ph), 137.79 (quat. C of $PhSO_2$).

In conclusion, azabicyclo[1.1.0]butane sulfones and sulfoxides can be easily synthesized from azirines and chloromethyl sulfones and sulfoxides, respectively. Since the sulfoxide or sulfone function, or the hydrogen attached to the sulfur bearing carbon, is known to undergo a variety of transformations in organic chemistry, this route contsitutes a useful entry to these bicyclic heterocycles. Furthermore, solvolysis[9] of 4 may lead to stereochemically defined 2,3-substituted azetidines.

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