A NOVEL APPROACH TO FUNCTIONALIZATION OF AZINES. OXIRANYL AND THIIRANYL DERIVATIVES OF PYRIDINE, QUINOLINE AND ISOQUINOLINE

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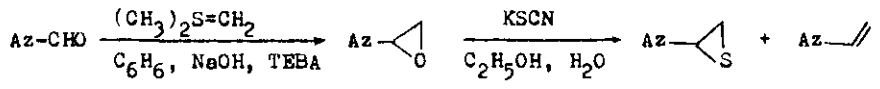
Abstract - Convenient methods for synthesis of the oxiranyl and thiiranyl derivatives of pyridine, quinoline and isoquinoline have been elaborated. Oxiranes have been synthesized from corresponding aldehydes with dimethylsulfonium methylide in anhydrous medium. Exchange of the oxygen atom in the oxirane ring on sulfur with potassium thiocyanate gave thiiranylazines.

Oxiranyl derivatives of aromatic compounds (oxiranylarenes) and their sulphur analogues (thiiranylarenes) could be used as substrates for preparation of many aromatic compounds bearing various substituents. Usefulness of oxiranylarenes in organic synthesis has been extensively reviewed and is of current interest.[1] The chemistry of thiiranylarenes is less developed, nevertheless some reactions useful in synthesis have been reported.[2]
Oxiranylazines remained generally unknown. Only oxiranylpyridines were mentioned in the literature[3,4] but, except for 4-oxiranylpyridine,[4] no spectroscopic and other physicochemical data have been reported. They have been reported as very unstable and reactive liquids. Thiiranylazines remained still unknown.
The aim of our work was to elaborate the general methods for synthesis of oxiranyl and thiiranylazines as the substrates useful in syntheses of the azaaromatic compounds substituted in the side chains.
The main step of the synthesis presented in this paper involves conversion of aldehydes 1 into oxiranes 2. Oxiranes thus obtained were easily converted into thiiranes 3 with are in some cases accompanied by vinyl derivatives 4.



Az = pyridyl	1a-c	2a-c	3a-c	4a-c
Az = quinolyl	1d-j	2d-j	3d-j	4d-j
Az = isoquinolyl	1k,l	2k,l	3k,l	4k,l

Initially, we attempted to synthesize some oxiranylazines by the method of Corey and Chaykowsky[5] but the yields of desired products were low or the method did not work at all. The best results were achieved when the reaction was carried out with dimethylsulfonium methylide generated in situ from trimethylsulfonium chloride in dry benzene with powdered NaOH in the presence of catalytical amounts of

TEBA according to the procedure elaborated recently in our laboratory for the synthesis of unstable oxiranylquinones.[6] The products were isolated without partitioning between water and organic solvent, thus the deleterious effect of water was eliminated. When oxiranes 2a and 2k were synthesized, the reaction was more effective with dimethyloxosulfonium methylide as a reagent. Oxiranes treated with methyl iodide (acetone, room temp., 24 h) gave methiodides except when steric hindrance of the electron pair of the nitrogen atom by the oxirane ring occured (2a,d,j,k,l) or when they easily underwent decomposition (2b,c). In these cases picrates were prepared. The results of the synthesis of oxiranylazines and their characteristics as well as melting points of their derivatives are listed in Table 1, and their ^{1}H NMR spectra are given in Table 3.
For the synthesis of thiiranylazines, potassium thiocyanate was used as a reagent.[7] It must be mentioned that stability of thiiranes 3a,b,d was very low and some of them were accompanied by vinylazines as products of their thermal decomposition and in the cases of 2c and 2f only vinylazines 4c and 4f were isolated. Nevertheless, as shown in Table 2, most thiiranyl derivatives of azines, being under investigation, can be synthesized in the satisfactory yield. ^{1}H NMR data of thiiranylazines and vinylquinolines[8] are given in Table 4.
Starting aldehydes were prepared by oxidation of methylazines with SeO_2.[9] For the synthesis of 5- and 7-formylquinolines, the mixture of corresponding methylquinolines (synthesized from m-toluidine by the Skraup reaction[10] using As_2O_5 as an oxidant) was oxidized with SeO_2 and aldehydes formed were separated chromatographically on silica gel using t-butanol - hexane (1:3) as an eluent.

EXPERIMENTAL

Synthesis of oxiranylazines. A solution of aldehyde (10 mM), trimethylsulfonium chloride (1.35 g, 12 mM), powdered sodium hydroxide (2.0 g, 50 mM) and TEBA (0.05 g) in dry benzene (40 ml) was placed in the glass-stopered flask and stirred magnetically at room temp. for suitable time (Table 1). The reaction mixture was filtered through Celite and the solvent was evaporated in vacuo. The residue was purified on the column packed with silica gel using chloroform - - ethyl acetate (1:1) as an eluent. The crystalline products were recrystallized from hexane. In the case of 2j, chromatography was omitted and the crude product was recrystallized from hexane.
2-Oxiranylpyridine 2a and 1-oxiranylisoquinoline 2f were also synthesized in other way. To the vigorously stirred dimethyloxosulfonium methylide, prepared according to lit.[5] from $(CH_3)_3SOCl$ (1.29 g, 10 mM), the solution of 2-formylpyridine (0.86 g, 8 mM) in dry THF (10 ml) was added dropwise during 15 min. The reaction mixture was diluted with ethyl ether (60 ml) and worked up as described above.
Synthesis of thiiranylazines. To a solution of oxiranylazine (5 mM) in ethanol (15 ml), a solution of potassium thiocyanate (0.58 g, 6 mM) in water (5 ml), was added and the reaction mixture was allowed to stand at room temp. for suitable time (Table 2) with occasional stirring. The reaction mixture was diluted with ethyl ether (70 ml) and washed twice with saturated aq. NaCl. A small amount of active carbon was added to the organic layer which was allowed to

stand over anhydrous K_2CO_3. Then solid was filtered off and the solvent was evaporated from filtrate in vacuo to give crude product which was separated or purified on the column packed with silica gel using chloroform - ethyl acetate (1:1) as an eluent.

Table 1. Oxiranylpyridines, -quinolines and -isoquinolines

Compound	Position of substituent	Reaction time, h	Yield %	m.p. °C	(IR CCl_4) [a,b] cm^{-1}	Derivative [c] m.p. °C
2a	2	1	3	oil	827, 1153, 1240	picr. 110-112
		3 [d]	17			
2b	3	5	25	oil	820, 1128, 1252	picr. 105-106
2c	4	24	15	oil	828, 1150, 1415	picr. 132-134 (lit.[4] 130-135)
2d	2	45 [e]	28	oil	860, 1117, 1240	picr. 133
2e	3	8	38	30-31	850, 1130, 1250	meth. 145
2f	4	22	57	42	855, 1142, 1238	meth. 119
2g	5	22	73	25-26	850, 1146, 1235	meth. 126
2h	6	18	61	16-19	847, 1163, 1250	meth. 138
2i	7	30	50	35-36	840, 1147, 1249	meth. 136
2j	8	20	65	59	830, 1170, 1241	picr. 77-78
2k	1	20	5	36-37	828, 1128, 1240	picr. 126-128
		0.5 [d]	21			
2l	3	5	33	25	845, 1123, 1240	picr. 128-131

[a] Adsorption bands characteristic of the oxirane ring.[4] [b] The IR spectra compound 2a-d were measured in film. [c] Picrate - picr., methiodide - meth. [d] $(CH_3)_2SO{=}CH_2$ as a reagent. [e] No TEBA was added.

Table 2. Reaction of oxiranylazines with potassium isothiocyanate

Substrate	Reaction time h	Products: Thiiranylazine Nr	Yield %	m.p. °C	Vinylazine Nr	Yield %	Substrate	Reaction time h	Products: Thiiranylazine Nr	Yield %	m.p. °C	Vinylazine Nr	Yield %
2a	95	3a	32	oil [a]	4a	0	2g	48	3g	42	46-47	4g	0
2b	20	3b	51	oil [a]	4b	0	2h	40	3h	54	64-66	4h	0
2c	46	3c	0	-	4c	5	2i	30	3i	39	49-51	4i	0
2d	45	3d	7	oil [a]	4d	11	2j	40	3j	40	18-20	4j	0
2e	43	3e	36	72	4e	0	2k	72	3k	34	52-54	4k	0
2f	48	3f	0	-	4f	26	2l	70	3l	46	50-52	4l	0

[a] Easily decomposing at room temp.

Table 3. ^{1}H NMR spectra of oxiranylazines

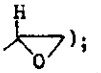
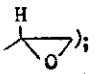
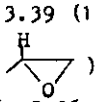
Comp. No	^{1}H NMR 100MHz (CCl_4), δ(ppm)
2a	2.99 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.33 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 4.18 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.37 (1H, dd, J=8 Hz and 1 Hz, 3-H); 7.42 (1H, dd, J=8 Hz and 1 Hz, 5-H); 7.75 - 7.94 (1H, m, 4-H); 8.70 - 8.76 (1H, m, 6-H).
2b	2.96 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.35 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 4.05 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.44 (1H, dd, J=8 Hz and 4 Hz, 5-H); 7.70 (1H, dd, J=6 Hz and 2 Hz, 4-H); 8.70 - 8.78 (2H, m, 2 and 6-H).
2c	2.92 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.36 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 4.00 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.37 (2H, dd, J=4.5 Hz and 1.5 Hz, 3 and 5-H); 8.74 (2H, dd, J=4.5 Hz and 1.5 Hz, 2 and 6-H).
2d	3.08 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.34 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 4.38 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.52 (1H, d, J=8 Hz, 3-H); 7.62 - 8.00 (3H, m, 5,6 and 7-H); 8.28 (1H, d, J=8 Hz, 4-H); 8.20 - 8.34 (1H, m, 8-H).
2e	3.03 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.39 (1H, dd, J=6Hz and 4 Hz, $-CH_2-$); 4.16 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.55 - 7.98 (3H, m, 5,6 and 7-H); 8.13 (1H, d, J=2 Hz, 4-H); 8.26 - 8.36 (1H, m, 8-H); 8.99 (1H, d, J=2 Hz, 2-H).
2f	2.88 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.45 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 4.57 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.48 (1H, d, J=5 Hz, 3-H); 7.62 - 7.98 (2H, m, 6 and 7-H); 8.16 - 8.28 (2H, m, 5 and 8-H); 9.03 (1H, d, J=5 Hz, 2-H).
2g	2.93 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.40 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 4.35 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.56 (1H, dd, J=8 Hz and 4 Hz, 3-H); 7.66 - 7.92 (2H, m, 6 and 7-H); 8.23 (1H, dd, J=8 Hz and 2 Hz, 4-H); 8.60 (1H, dd, J=8 Hz and 2 Hz, 8-H); 9.08 (1H, dd, J=4 Hz and 2 Hz, 2-H).
2h	2.98 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.36 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 4.15 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.54 (1H, dd, J=8 Hz and 4 Hz, 3-H); 7.73 (1H, dd, J=8 Hz and 2 Hz, 7-H); 7.78 (1H, d, J=2 Hz, 5-H); 8.24 (1H, dd, J=8 Hz and 2 Hz, 4-H); 8.28 (1H, d, J=8 Hz, 8-H); 9.05 (1H, dd, J=4 Hz and 2 Hz, 2-H).
2i	3.01 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.37 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 4.19 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.49 (1H, dd, J=8 Hz and

Table 3 (continued)

2i	2 Hz, 3-H); 7.53 (1H, d, J=8 Hz, 5-H); 7.99 (1H, d, J=8 Hz, 6-H); 8.18 - 8.30 (2H, m, 4 and 8-H); 9.05 (1H, dd, J=4 Hz and 2 Hz, 2-H).
2j	2.89 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 3.52 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 5.22 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.62 (1H, dd, J=8 Hz and 4 Hz, 3-H); 7.70 - 7.96 (3H, m, 5, 6 and 7-H); 8.33 (1H, dd, J=8 Hz and 2 Hz, 4-H); 9.11 (1H, dd, J=4 Hz and 2 Hz, 2-H).
2k	3.33 (1H, dd, J=6 Hz and 4 Hz, $-CH_2-$); 3.60 (1H, dd, J=6 Hz and 2.5 Hz, $-CH_2-$); 4.63 (1H, dd, J=4 Hz and 2.5 Hz, ); 7.68 - 8.04 (4H, m, 4, 5, 6 and 7-H); 8.60-8.72 (2H, m, 3 and 8-H).
2l	3.13 (1H, dd, J=6 Hz and 2 Hz, $-CH_2-$); 3.37 (1H dd, J=6 Hz and 4 Hz, $-CH_2-$); 4.30 (1H dd, J=4 Hz and 2 Hz,  ; 7.70 - 8.20 (5H, m, 4, 5, 6, 7 and 8-H); 9.36 (1H, s, 1-H).

Table 4. ^{1}H NMR spectra of thiiranylazines and vinylquinolines

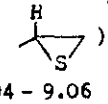
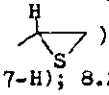
Comp. No	^{1}H NMR 100MHz (CCl_4), δ (ppm)
3a	3.04 (1H, dd, J=6.5 Hz and 1 Hz, $-CH_2-$); 3.19 (1H, dd, J=5.5 Hz and 1 Hz, $-CH_2-$); 4.19 (1H, dd, J=6.5 Hz and 5.5 Hz, ); 7.26 - 7.52 (2H, m, 3-H and 5-H); 7.70 - 7.90 (1H, m, 4-H); 8.64 - 8.74 (1H, m, 6-H).
3b	2.95 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 3.24 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 4.20 (1H, t, J=6 Hz, ); 7.56 (1H, dd, J=8 Hz and 4.5 Hz, 5-H); 7.94 (1H, dt, J=8 Hz and 2 Hz, 4-H); 8.82 (1H, dd, J=4.5 Hz and 2 Hz 6-H); 8.92 (1H, d, J=2 Hz, 2-H).
3d	3.12 - 3.30 (2H, m, $-CH_2-$); 4.42 (1H, t, J=6 Hz, ); 7.45 (1H, d, J=8 Hz, 3-H); 7.66 - 7.99 (3H, m, 5, 6 and 7-H); 8.23 (1H, d, J=8 Hz, 4-H); 8.16 - 8.32 (1H, m, 8-H).
3e	2.90 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 3.10 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 4.16 (1H, t, J=6 Hz, ); 7.60 - 7.93 (3H, m, 5, 6 and 7-H); 8.07 (1H, d, J=2 Hz, 4-H); 8.13 - 8.33 (1H, m, 8-H); 8.94 (1H, d, J=2 Hz, 2-H
3g	3.12 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 3.34 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 4.76 (1H, t, J=6 Hz, ); 7.76 - 8.06 (3H, m, 3, 6 and 7-H); 8.34 - 8.45 (1H, m, 4-H); 8.94 - 9.06 (1H, m, 8-H); 9.26 - 9.34 (1H, m, 2-H).
3h	3.02 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 3.24 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 4.33 (1H, t, J=6 Hz, ); 7.59 (1H, dd, J=8 Hz and 4 Hz, 3-H); 7.80 (1H, dd, J=9 Hz and 2 Hz, 7-H); 8.02 (1H, d, J=2 Hz, 5-H); 8.28 - 8.40

Table 4 (continued)

3h	(2H, m, 4 and 8-H); 9.17 (1H, dd, J=4 Hz and 2 Hz, 2-H).
3i	2.95 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 3.16 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 4.28 (1H, t, J=6Hz, ); 7.44 - 7.62 (2H, m, 3 and 5-H); 7.88 (1H, d, J=8 Hz, 6-H); 8.18 - 8.34 (2H, m, 4 and 8-H); 9.04 - 9.12 (1H, m, 2-H
3j	2.80 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 3.13 (1H, dd, J=6 Hz and 1.5 Hz, $-CH_2-$); 5.45 (1H, t, J=6 Hz, ); 7.68 (1H, dd, J=8 Hz and 4 Hz, 3-H); 7.68 - 7.90 (3H, m, 5, 6 and 7-H); 8.27 (1H, dd, J=8 Hz and 2 Hz, 4-H); 9.11 (1H, dd, J=4 Hz and 2 Hz, 2-H).
3k	3.09 (1H, d, J=6 Hz, $-CH_2-$); 4.01 (1H, d, J=5.5 Hz, $-CH_2-$); 4.76 (1H, dd, J=6 Hz and 5.5 Hz, ); 7.70 - 8.10 (4H, m, 4, 5, 6 and 7-H); 8.57 - 8.72 (2H, m, 3 and 8-H).
3l	3.09 (1H, d, J=6.5 Hz, $-CH_2-$); 3.40 (1H, d, J=5.5 Hz, $-CH_2-$); 4.34 (1H, dd, J=6.5 Hz and 5.5 Hz, ); 7.71 - 8.20 (5H, m, 4, 5, 6, 7 and 8-H); 9.35 (1H, s, 1-H).
4d	5.80 (1H, dd, J=12 Hz and 2 Hz, $=CH_2$); 6.47 (1H, dd, J=18 Hz and 2 Hz, $=CH_2$); 7.20 (1H, dd, J=18 Hz and 12 Hz, $-CH=$); 7.60 - 7.96 (4H, m, 3, 5, 6 and 7-H); 8.19 (1H, d, J=8 Hz, 4-H); 8.14 - 8.34 (1H, m, 8-H).
4f	5.86 (1H, dd, J=11 Hz and 2 Hz, $=CH_2$); 6.14 (1H, dd, J=18 Hz and 2 Hz, $=CH_2$ 7.45 - 8.00 (4H, m, $-CH=$, 3, 6 and 7-H); 8.22 - 8.42 (2H, m, 5 and 8-H); 9.06 (1H, d, J=5 Hz, 2-H).

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