Use of 1-[(Methylthio)thiocarbonylmethyl]pyridinium Iodide as the Starting Material for the Synthesis of 1-Heteroarylmethylpyridinium salts

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Reactions of 1-[(methylthio)thiocarbonylmethyl]pyridinium iodide with hydrazine derivatives and *o*-aminophenols gave 1-heteroarylmethylpyridinium salts derived from 1,3,4-thiadiazole and 1,3-benzazole, under mild conditions.

As the body of knowledge about the reactivity of pyridinium ylides expands, the interest in such compounds as building blocks for the synthesis of heterocycles continuously increases. Most of the work has been carried out with ylides stabilized by simple, electron-attracting groups.[1] Recently, we have been interested in the uses of pyridinium ylides for the preparation of biologically active derivatives, and in relation to this, in the possibility of using an aromatic heterocycle to stabilize the carbanion.

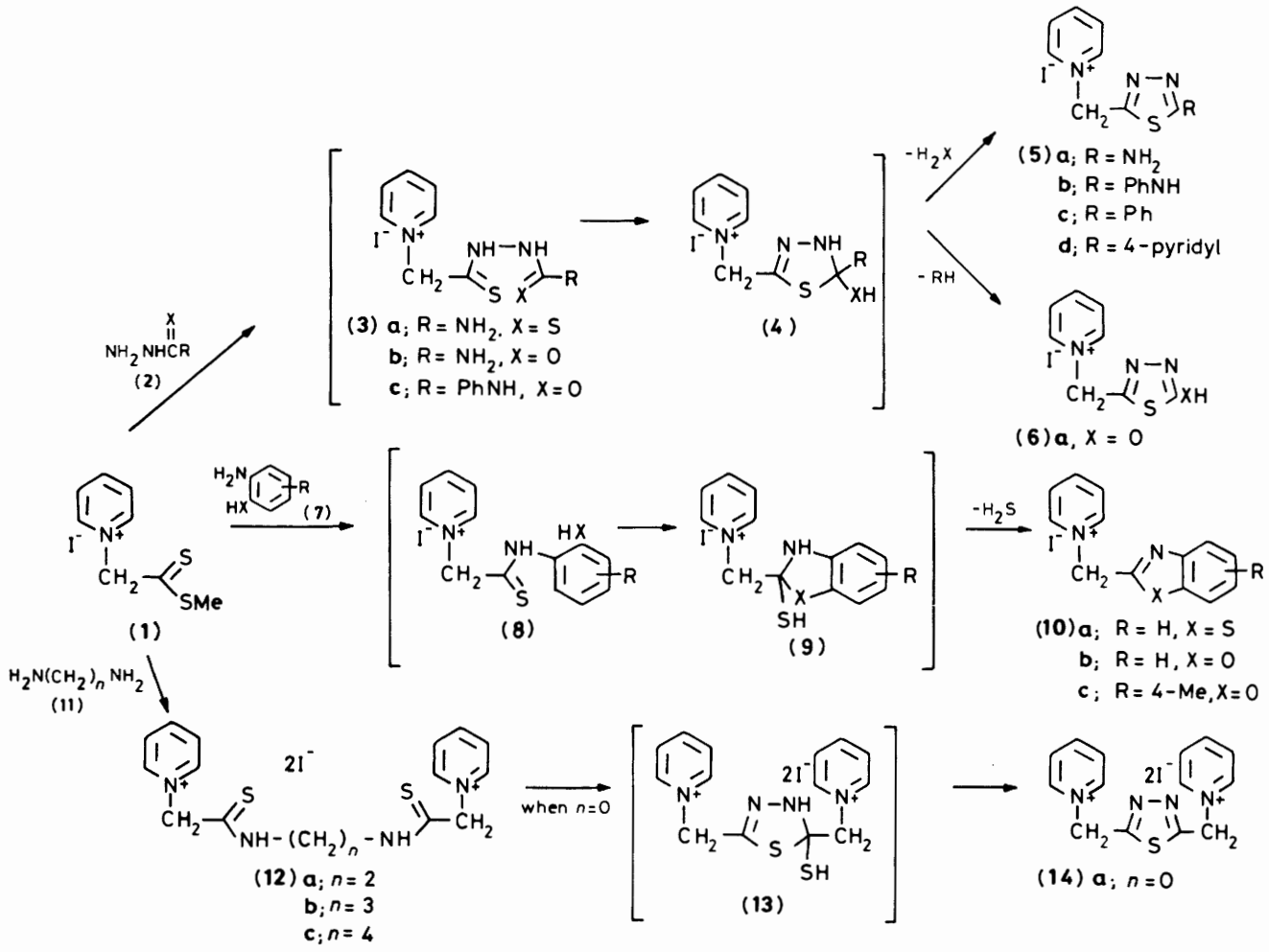
Thus, we treated 1-[(methylthio)thiocarbonylmethyl]pyridinium iodide (**1**),[2] with different dinucleophiles exploiting the reactivity of the dithioester group, in an attempted synthesis of the azoles (**5**), (**6**), and (**10**) (Scheme; the results are given in the Table. In each case, methanol was used as the solvent, usually at reflux temperature.

The first group of reactions was performed with the hydrazine derivatives (**2**). The reaction of compound (**1**) with thiosemicarbazide at room temperature produced, after 17 h, compound (**3a**) in 72% yield, which could not be purified because crystallization in methanol gave mixtures of (**3a**) and (**5a**) containing increasing percentages of the latter. Crude compound (**3a**), heated to 105 °C for 1 min, was converted into (**5a**) in 94% yield. Compounds (**5a**) and (**3b**), however, were directly prepared after reflux of compound (**1**) with the corresponding thiosemicarbazide for 5 h. 1-Phenylthiosemicarbazide did not produce any cyclized product after 7 h of

Table. Pyridinium salts derived from compound (**1**)[a]

Salt	Reaction time (h)	Yield (%)	M.p. (° C)	Found (%) (Required) C	H	N	^{1}H N.m.r. data[b] 2-, 6-H	3-, 5-H	4-H	CH_2	Others	$J_{2,3}$	$J_{3,4}$
(**3a**)	17[c]	72[d]											
(**5a**)	5	45	225—227[e]	30.0 (30.0)	3.1 (2.8)	17.6 (17.5)	9.16 (d)	8.22 (t)	8.69 (t)	6.18 (s)	7.44 (br s, 2 H, NH_2)	5.5	7.7
(**5b**)	5	99	211—214	42.4 (42.4)	3.3 (3.3)	14.0 (14.1)	9.20 (d)	8.22 (t)	8.69 (t)	6.26 (s)	10.49 (br s, 1 H, NH), 6.97—7.63 (m, 5 H)	5.5	7.8
(**3b**)	5	34	164—165[e]	28.3 (28.4)	3.3 (3.3)	16.7 (16.6)	9.01 (d)	8.21 (t)	8.70 (t)	5.76 (s)	6.50 (br s, 3 H, $NHCONH_2$), 9.25 (s, 1 H, CSNH)	6.0	7.5
(**3c**)	7	91	169—181	40.7 (40.6)	3.9 (3.7)	13.8 (13.5)	9.05 (d)	8.23 (t)	8.70 (t)	5.86 (s)	7.20 (br s, 1 H, NNHCO), 7.42 (s, 5 H), 9.25 (s, 1 H, CSNH), 9.60 (s, 1 H, CONHPh)	6.0	7.5
(**6a**)	22	58	223—225[e]	30.0 (29.9)	2.5 (2.5)	13.1 (13.1)	9.23 (d)	8.28 (t)	8.76 (t)	6.13 (s)	13.07 (s, 1 H, OH)	5.0	7.5
(**5c**)	6	51	193—195[e]	43.9 (44.1)	3.2 (3.2)	11.2 (11.0)	9.37 (d)	8.33 (t)	8.80 (t)	6.64 (s)	7.58 (br s, 3 H), 7.95 (br s, 2 H)	5.7	7.5
(**5d**)	2	75	225—227	39.0 (39.0)	3.4 (3.3)	14.4 (14.0)	9.0 (d)	8.19 (t)	8.67 (t)	5.80 (s)	9.81 (d, 2 H), 8.79 (d, 2 H)	5.9	7.6
(**10a**)	7	46	179—180	44.4 (44.1)	3.1 (3.1)	7.8 (7.9)	9.31 (d)	8.35 (t)	8.77 (t)	6.56 (s)	7.43—7.54 (m, 2 H), 7.86—7.98 (m, 1 H), 8.14—8.22 (m, 1 H)	5.5	7.0
(**10b**)	7	66	191—193[e]	46.1 (46.2)	3.3 (3.3)	8.0 (8.3)	9.28 (d)	8.31 (t)	8.78 (t)	6.42 (s)	7.65—7.60 (m, 2 H), 7.72—7.84 (m, 2 H)	5.5	7.6
(**10c**)	7	81	179—180	47.7 (47.7)	3.8 (3.7)	7.9 (8.0)	9.30 (d)	8.35 (t)	8.75 (t)	6.42 (s)	2.40 (s, 3 H, Me_3) 7.20—7.80 (m, 3 H)	6.0	8.0
(**14a**)	5	89	213—215[e]	32.3 (32.1)	2.9 (2.7)	11.0 (10.7)	9.21 (d)	8.23 (t)	8.70 (t)	6.49 (s)		5.5	7.7
(**12a**)	2	66	243—245	32.2 (32.8)	3.6 (3.4)	9.5 (9.5)	8.93 (d)	8.18 (t)	8.67 (t)	5.68 (s)	3.88 (s, 4 H, 10.85 (br s, 2 H, NH)	5.5	7.7
(**12b**)	7	7	197—198	33.8 (34.0)	3.8 (3.7)	9.4 (9.3)	8.93 (d)	8.17 (t)	8.66 (t)	5.68 (s)	2.63 (br t, 2 H), 3.56—3.69 (m, 4 H), 10.70 (2 H, OH)	5.5	7.7
(**12c**)	7	51	222—223[e]	35.6 (35.6)	4.1 (3.9)	9.2 (9.1)	8.92 (d)	8.16 (t)	8.65 (t)	5.65 (s)	1.72 (m, 4 H,), 10.69 (br s, 2 H, NH)	5.5	8.0

[a] Isolated pure products obtained in refluxing methanol, except when stated, and crystallized from EtOH–H_2O. [b] Taken on a Varian FT80A instrument, with $(CD_3)_2SO$, as solvent, and Me_4Si as internal reference; chemical shifts in p.p.m. and coupling constants in Hz. [c] At room temperature. [d] Crude product, not isolated as it spontaneously cyclized into (**5b**) [e] With decomposition.



Scheme. Reactions of 1-[(methylthio)thiocarbonylmethyl]pyridinium iodide (**1**) with different nucleophiles

reflux, compound (**1**) being recovered in 82% yield. Reaction of compound (**1**) with semicarbazides produced open-chain products (**3b**) and (**3c**) after 5 and 7 h of reflux in methanol, but refluxing compound (**1**) with semicarbazide (**2**; R=H) for over 22 h produced the hydroxy-1,3,4-thiadiazole (**6a**) in 58% yield.

The reaction of compound (**1**) with the hydrazides (**2**; X=O, R=aryl) again produced the thiadiazoles (**5c**) and (**5d**) in 51 and 75% yield, respectively; the reaction with aminoguanidine hydrogen carbonate (**2**; $X=NH_2^+$, $R=NH_2$) produced tars even at 0 °C, with no traces of the aminotriazole.

The mechanism of the thiadiazole ring closure can be represented as shown in the Scheme, the initially formed diacylhydrazine (**3**) giving, *via* the cyclic form (**4**), compound (**5a—d**) or (**6a**), depending on the leaving group RH($R=NH_2$, NHPh, Ph, 4-pyridyl or XH_2 (X=S, O). The process is related to the well known cyclization of dithioacylhydrazines with loss of hydrogen sulphide.[3]

The reaction of compound (**1**) with aromatic 1,4-dinucleophiles such as *o*-aminophenols produced the benzoxazoles (**10b**) and (**10c**) after reflux for 7 h, in 66% and 81% yield respectively; 2-aminothiophenol yielded the benzothiazole (**10a**) in 46% yield. The process, however, depends on the nucleophilicity of the amino group involved, as the reactions with 2-amino-5-nitrophenol, and 2-amino-3-hydroxypyridine yielded unchanged compound (**1**) in more than 80% yield, after reflux for 7 h. Thus (**1**) → (**8**) → (**9**) → (**10**) (Scheme) can be included in the general synthetic approach to 1,3-benzazoles *via* a 1,2-disubstituted benzene and carboxylic acid derivatives.[4].

Attempts to produce cyclic amidines with aliphatic diamines[5] were unsuccessful, yielding the thioamides (**12a—c**) in 66.7, and 51% yields respectively. With the hydrazine (**11**; $n = 0$), the resulting compound (**12a**) undergoes cyclization spontaneously to produce an aromatic system (**14a**) [Scheme: *cf.* (**1**) → (**3**) → (**4**) → (**5**)].

Analytical and ^1H n.m.r. data from the pyridinium salts obtained are presented in the Table. The i.r. spectra were in accordance with the proposed structures and did not give any additional information.

Conclusion

The results obtained show that 1-[(methylthio)thiocarbonylmethyl]pyridinium iodide (**1**) is a valuable starting material for the preparation of 1-heteroarylmethylpyridinium salts, derived from 1,3,4-thiadiazoles and from 1,3-benzazoles in good yields and under mild conditions.

Experimental

M.p.s were determined in capillary tubes, with a Büchi-Tottoli apparatus, and are uncorrected. Spectra were recorded with a Perkin-Elmer 1310 i.r. grating spectrophotometer, and a Varian FT-80A (80 MHz) n.m.r. spectrometer.

General Procedure.—Compound (**1**) (5 mmol) and the corresponding nucleophile (5 mmol) were suspended in methanol (20 ml). When the nucleophile was used as the hydrochloride [as in (**3b**), (**6a**), (**12a**), (**12c**), (**14a**)] an equimolar amount of pyridine was added. The reaction mixture was then refluxed for the time indicated in the Table, or in the case of (**1**), stirred at room temperature. On cooling, a solid precipitated from the solution and was filtered off. In the case of (**3c**), (**10a—c**), and (**12b**) the final product was isolated by concentrating the solution and triturating the residue with drops of ethanol. Finally, the product was crystallized from ethanol–water.

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