A Convenient Synthesis of Heterocyclic *N*-Substituted Sulfoximides

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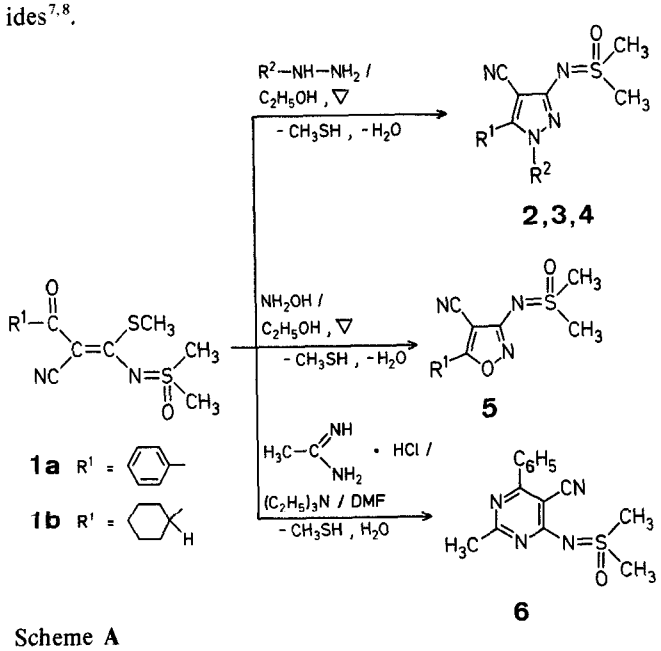
In the course of our work aimed at exploring synthetic potentials of sulfoximides, we reported the reaction of *S,S*-dimethylsulfoximide with acyl(sulfonyl)-cyanoketene *S,S*-acetals in the preceding paper[1].

A general route to *N*-substituted sulfoximides is provided by the trapping of nitrenes, generated by photolytic, thermolytic, and α-elimination reactions from appropriate precursors, with sulfoxides[2,3,4]. The heterocyclic *N*-substituted sulfoximides are prepared by the thermal decomposition of azides in dimethyl sulfoxide[5,6] or by the trapping of nitrenes by sulfoxides[7,8].



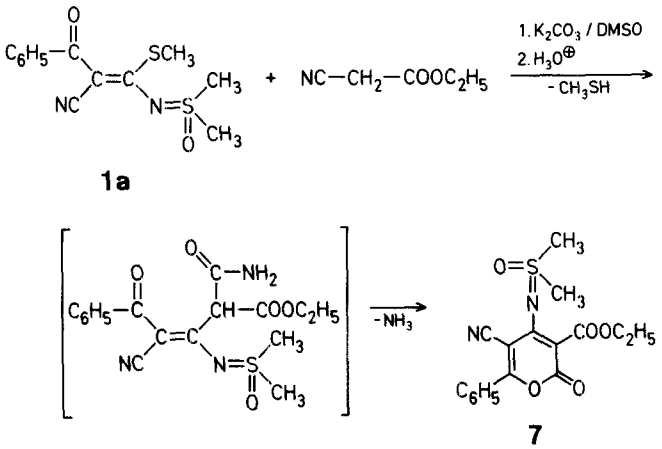
Scheme A

Continuing our studies on polarized ketene *S,N*-acetals[9], we report here a facile condensation of acyl-cyanoketene *S,N*-acetals **1**[1], as a useful synthetic three carbon fragment, with suitable nucleophiles to yield the corresponding heterocyclic *N*-substituted sulfoximides **2, 3,** and **4.** Only a few representative nucleophiles have been selected to test the generality of the method.

When an equimolar mixture of **1a** and a hydrazine was refluxed in ethanol, the 4-cyano-3-(*S,S*-dimethylsulfoximido)-5-phenylpyrazoles **2–4** are formed. The cyclization goes exclusively over the carbonyl group leaving the nitrile group intact. The compounds **1** cyclize with hydroxylamine under the same conditions forming isoxazoles **5.**

The compounds **1** also readily undergo heterocyclization with other bifunctional reactants. Thus, treatment of equimolar quantities of **1a** and acetamidine hydrochloride in the presence of triethylamine in dimethylformamide at room temperature gives the pyrimidine **6** in 21% yield.

The reaction of **1a** with ethyl cyanoacetate in the presence of potassium carbonate in methanol proceeds by nucleophilic substitution of the methylthio group followed by partial hydrolysis of the nitrile group to the amide. The intermediate amide cyclizes with elimination of ammonia to give 5-cyano-3-ethoxycarbonyl-4-(*S,S*-dimethylsulfoximido)-6-phenyl-2-pyrone **(7),** identified by ^{1}H-N.M.R. and mass spectra.



Scheme B

In summary, we have developed a useful method for the synthesis of heterocyclic *N*-substituted sulfoximides.

4-Cyano-3-(*S,S*-dimethylsulfoximido)-5-phenylpyrazoles 2–4; General Procedure:
Hydrazine hydrate, phenylhydrazine or *p*-nitrophenylhydrazine (0.005 mol) is added to a solution of 2-benzoyl-3-methylthio-3-(*S,S*-dimethylsulfoximido)-acrylonitrile (**1a**; 1.47 g, 0.005 mol) in ethanol (15 ml). After refluxing for 2 h, the mixture is cooled, the precipitated solid is collected, and recrystallized from ethanol.

4-Cyano-3-(*S,S*-dimethylsulfoximido)-isoxazoles 5; General Procedure:
Potassium carbonate (2.1 g, 0.015 mol) and hydroxylamine hydrochloride (0.7 g, 0.01 mol) are added to a solution of 2-benzoyl-3-methylthio-3-(*S,S*-dimethylsulfoximido)-acrylonitrile (**1a**; 1.47 g, 0.005 mol) in dimethyl sulfoxide (15 ml). After stirring for 2 days at room temperature, the mixture is poured into ice/water (200 ml) and cautiously acidified with dilute hydrochloric acid. The precipitate formed is recrystallized from ethanol.

5-Cyano-2-methyl-6-(*S,S*-dimethylsulfoximido)-4-phenylpyrimidine (6):
To a solution of 2-benzoyl-3-methylthio-3-(*S,S*-dimethylsulfoximido)-acrylonitrile (**1a**; 1.47 g, 0.005 mol) in absolute dimethylformamide

Table. 3-(*S,S*-Dimethylsulfoximido)-pyrazoles **2-4** and 3-(*S,S*-Dimethylsulfoximido)-isoxazoles **5**

Product No.	R^1	R^2	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. m/e (M^+)
2	C_6H_5	H	92	218–220°	$C_{12}H_{14}N_4OS$ (260.3)	3250 (br) 2225	3.67 [s, 6H, $SO(CH_3)_2$]; 7.77 (m, 3 H_{arom}); 8.09 (m, 2 H_{arom}); 13.29 [br. s, 1H, NH][b]	260
3	C_6H_5	C_6H_5	59	234–235°	$C_{18}H_{16}N_4OS$ (336.4)	2230	3.44 [s, 6H, $SO(CH_3)_2$]; 7.31 (m, 10 H_{arom})	336
4	C_6H_5	4-O_2N—C_6H_4	89	231–232.5°	$C_{18}H_{15}N_5O_3S$ (381.4)	2235	3.49 [s, 6H, $SO(CH_3)_2$]; 7.41 (m, 7 H_{arom}); 8.14 (m, 2 H_{arom})	381
5a	C_6H_5	—	54	180–181.5°	$C_{12}H_{11}N_3O_2S$ (261.3)	2240	3.48 [s, 6H, $SO(CH_3)_2$]; 7.58 (m, 3 H_{arom}); 7.92 (m, 2 H_{arom})	261
5b	*c*-C_6H_{11}	—	51	144–146°	$C_{12}H_{17}N_3O_2S$ (267.3)	2240	1.24–2.08 (m, 10H, CH_2); 2.90 (m, 1H, CH); 3.38 [s, 6H, $SO(CH_3)_2$]	267

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.09, N ±0.22, S ±0.26.
[b] Measured in DMSO-d_6.

(15 ml), acetamidine hydrochloride (1.1 g, 0.012 mol) and triethylamine (3.7 ml) are added. The mixture is stirred for 3 days at room temperature and then diluted with water (50 ml) to give the crude pyrimidine **6**, which is crystallized from ethanol; yield: 0.30 g (21%); m.p. 203–205°C.

$C_{14}H_{14}N_4OS$	calc.	C 58.72	H 4.22	N 19.56	S 11.19
(286.4)	found	58.97	4.44	19.67	11.12

I.R. (KBr): ν = 2230 cm^{-1} (CN).

^{1}H-N.M.R. ($CDCl_3$): δ = 2.66 (s, 3H, CH_3); 3.58 [s, 6H, $SO(CH_3)_2$]; 7.46 (m, 3 H_{arom}); 7.92 ppm (m, 2 H_{arom}).

M.S.: m/e = 286 (M^+).

5-Cyano-3-ethoxycarbonyl-4-(*S,S*-dimethylsulfoximido)-6-phenyl-2-pyrone (7):

To a solution of ethyl cyanoacetate (1.13 g, 0.02 mol) in dry dimethyl sulfoxide (15 ml), potassium carbonate (2.08 g, 0.015 mol) and 2-benzoyl-3-methylthio-3-(*S,S*-dimethylsulfoximido)-acrylonitrile (**1a**; 1.47 g, 0.005 mol) are added. After stirring at room temperature for 3 h, the mixture is poured into ice/water (100 ml) and acidified with dilute hydrochloric acid. The precipitate formed is collected by filtration and purified by crystallization from ethanol; yield: 0.36 g (20%); m.p. 131–133°C.

$C_{17}H_{16}N_2O_5S$	calc.	C 56.66	H 4.48	N 7.77
(360.4)	found	56.95	4.52	7.64

I.R. (KBr): ν = 2230 (CN), 1730, 1715 cm^{-1} (CO).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.44 (t, 2H, CH_3); 3.39 [s, 6H, $SO(CH_3)_2$]; 4.32 (q, 2H, OCH_2); 7.54–7.94 ppm (m, 5 H_{arom}).

M.S.: m/e = 360 (M^+).

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