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SYNTHESIS OF THIOAMIDES FROM ALDONITRONES UTILIZING THIOCARBONYL TRANSFER REAGENTS[1]

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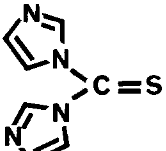
Abstract: The reaction of 1,1'-thiocarbonyldiimidazole and 1,1'-thiocarbonylbis(1,2,4-triazole) with several aldonitrones has been found to afford thioamides in good yield. The effect of solvent polarity and base is discussed.

Heterocyclic thiocarbonyl transfer reagents[2] have in recent years found several important applications in the synthesis of new compounds. For instance, both 1,1'-thiocarbonyldiimidazole (1) and 1,2,4-triazole (2) react with various nucleophiles in a selective fashion, permitting the facile synthesis of unsymmetrically substituted thioureas and related compounds.[3] They also undergo Diels-Alder additions to give cyclic and bicyclic adducts which can be further converted to mercapto esters.[4] The products of these thiocarbonylazoles are crystalline and moisture stable unlike those formed by the parent thiophosgene[5] which tend to be unstable and are required to be stored in the cold. Our current interest in utilizing thiocarbonyl transfer reagents in organic synthesis[3,4] focuses attention on the reaction of thiocarbonyl reagents 1 and 2 with nitrones.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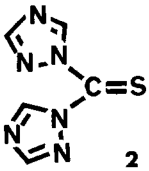
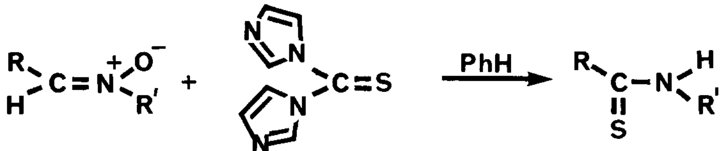

2

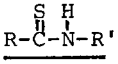
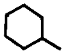
Reaction of C-phenyl-N-methylnitrone[6] (3; R=Ph,R'=Me) with 1,1'-thiocarbonyldiimidazole[2] (1) in refluxing benzene gives rise to a high yield (ca. 75%) of N-methylthiobenzamide (4, R=Ph,R'=Me). The structure of 4 was assigned on the basis of its analysis (Anal. Calc'd. C_8H_9NS) and comparison with an authentic sample.[7] The formation of 4 can be postulated to arise by an initial 1,3-dipolar cycloaddition of the nitrone followed by elimination of 1,1'-carbonyldiimidazole.



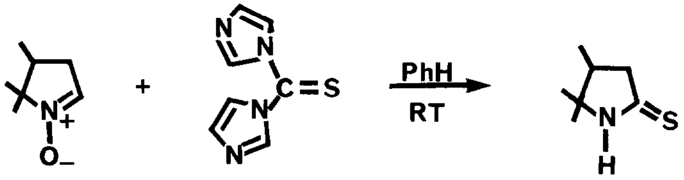
3 1 4

Reaction of the thiocarbonylazole (1) with C-(2-furyl)-N-methyl-(3a), C-cyclohexane-N-methyl- (3c) and C-phenyl-N-benzylnitrone (3d)[8] under similar conditions gave the corresponding thioamides in good yield (TABLE). The structures of the products were unambiguously confirmed by their analytical and spectral data.[9]

TABLE

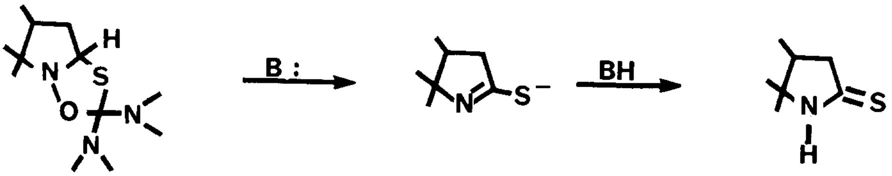
PRODUCT	R	R'	ISOLATED YIELD(%)	 $R-\overset{S}{\overset{\|}{C}}-\overset{H}{\overset{\mid}{N}}-R'$
4a	Ph	Me	75	
4b		Me	68	
4c		Me	67	
4d	Ph	$-CH_2Ph$	70	

Interestingly, it was found that treatment of 4,5,5-trimethyl-Δ'-pyrroline-1-oxide (5)[10] with 1,1'-thiocarbonyldiimidazole (1) in benzene at room temperature gave a high yield of 4,5,5-trimethylpyrrolidine-2-thione (6). This structure was assigned on the basis of its analytical (Anal. Calc'd. $C_7H_{13}NS$) and spectral data.



5 1 6

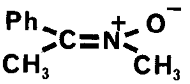
The solvent polarity was shown not to have an appreciable effect as reaction with benzene, chlorobenzene or ethylacetate all gave the product in similar yield. The presence of a trace amount of pyridine in the reaction mixture reduced the reaction time to 5 hr from 8 hr with no significant change in isolated yield. The base is thought to assist in the likely elimination step (Eq. 1).



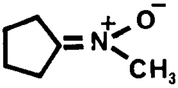
Eq.1

Treatment of 1,1'-thiocarbonylbis-1,2,4-triazole (2)[3] with C-phenyl-N-methylnitrone (3a), C-(2-furan)-N-methylnitrone (3b) and C-phenyl-N-benzylnitrone (3d) in benzene at room temperature also gave the corresponding thioamides in good yield (62%, 58%, and 60% respectively). A similar mechanism is invoked for these reactions.

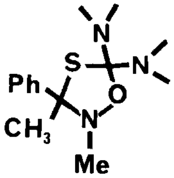
We also studied the reaction of the thiocarbonylazole (1) with several ketonitrones. Treatment of 1,1'-thiocarbonyldiimidazole with either C-methyl-C-phenyl-N-methylnitrone (7a)[6] or N-methylcyclopentanone oxime (7b)[11] in refluxing benzene gave no thioamide with only starting material being recovered even after 3 days. It is possible that some cycloadduct 8 is formed but there is no hydrogen on the ketonitrone carbon so the elimination step cannot take place as suggested for aldonitrones in Equation 1. The possibility that thioamide formation is light induced[12] in this case was dismissed when 6 was formed in a dark reaction.



7a



7b



8

Examples of cycloaddition reactions between nitrones and thiocarbonyl compounds are rare[12,13]. Cyclic aldonitrones are reported to be converted to the related thiolactams by refluxing in carbon disulphide[14]. However, non-cyclic nitrones do not give the thioamides but rather are isomerized by this method. We found that reaction of C-phenyl-N-methylnitrone (3a) with thiophosgene at room temperature in benzene gave N-methylbenzamide only. This demonstrates an interesting contrast with the related thiocarbonylazoles. Aldonitrones are known to rearrange to the isomeric amides by treatment with a variety of acidic reagents such as phosgene, SO_2, PCl_3 and acetyl chloride.[15]

Further reactions involving the use of other thiocarbonylazole systems and nitrones is currently under investigation and will be reported at a later date.

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6. Nitrones 1a, b, c and 6a were all easily prepared in high yield (ca. 98%) from the corresponding aldehyde or ketone with N-methylhydroxylamine hydrochloride in the presence of sodium acetate in ethanol at RT. All gave satisfactory physical and spectral data.
7. Prepared from N-methylbenzamide by treatment with phosphorus pentsulphide by the method of R.F. Meltzer, A.D. Lewis and J.A. King, J. Am. Chem. Soc., 77, 4062 (1955).
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9. 4a; mp 79-80°C (Lit.[16] 79-80°C), NMR (60 MHz, $CDCl_3$) 8.20(bs, 1H), 7.8-7.2(m,5H), 3.15(d,3H,J=5 Hz); MS,m/e 151(M+), 136, 121 and 77; Anal Calc'd for C_8H_9NS:C,63.54;H,6.00;N, 9.26. Found: C,63.48;H,6.01;N,9.26. 4b; mp 70-71°C (Lit.[7] 71-71.5°C), NMR(60 MHz,$CDCl_3$) 8.2(bs,1H),7.35(m,2H),6.42(m,1H),3.30(d,3H,J=5 Hz); MS, m/e 141(M+), 124, 111 and 100; Anal. Calc'd. for C_6H_7NOS:C,51.04;H,5.00;N,9.92. Found: C,51.00;H,4.93;N;9.84. 4c; mp 64-65°C, NMR(60 MHz,$CDCl_3$) 7.8(bs,1H), 3.22(d,3H,J=5 Hz), 2.3-1.0(m,11H); MS,m/e 157(M+), 142, 124 and 102; Anal. Calc'd. for $C_8H_{15}NS$:C,61.09;H,9.61;N,8.90. Found:C,60.93;H,9.65;N,8.75. 4d; mp 82-83°C (Lit.[17] 82-83°C), NMR(60 MHz,$CDCl_3$) 7.8-7.0(m,11H),4.96(d,2H,J=5 Hz) MS,m/e 227(M+), 211, 195, 165 and 91; Anal. Calc'd. for $C_{14}H_{13}NS$:C,73.97;H,5.76;N,6.16. Found: C,74.02;H,5.70;N,6.11.
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