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REACTION OF A FUNCTIONALIZED NITRONE WITH THIOCARBOXYLIC ACIDS. A NEW SYNTHESIS OF 5-ACYLAMINOTHIAZOLES

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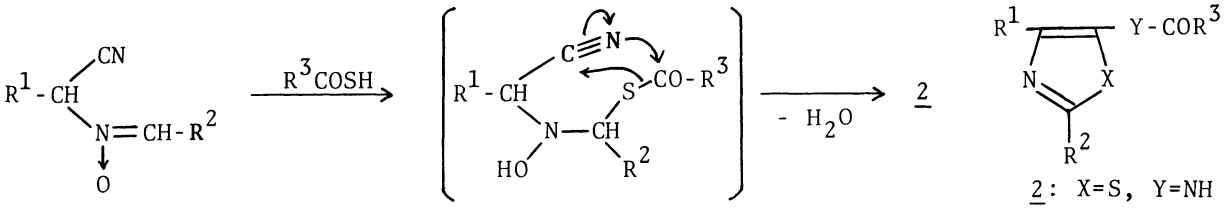
Reaction of N-(1-cyanoalkyl)-α-phenylnitrones with thiocarboxylic acids offers a simple new route to 2-phenyl-4-alkyl-5-acylaminothiazoles.

Thiazoles constitute a group of heterocycles of increasing interest and application in medicinal chemistry, and a great number of synthetic methods of the ring system have been developed.[1] In this communication, we describe a new synthesis of 5-acylaminothiazoles utilizing a functionalized nitrone, N-(1-cyanoalkyl)-α-phenylnitrones (1),[2] and thiocarboxylic acids.

The reaction of N-(1-cyanobutyl)-α-(p-chlorophenyl)nitrone (1d) (4.23 mmol) with thiobenzoic acid (8.5 mmol) was carried out in benzene (12 ml) at room temperature. After 3 days the solid precipitated was filtered and then recrystallized from benzene-hexane. The product was, in contrast with the reaction of 1 with thiols,[3] not an expected 5-benzoylthioimidazole (3) but 2-(p-chlorophenyl)-4-propyl-5-benzoylaminothiazole (2d).[4] From the filtrate another portion of 2d was isolated by column chromatography (SiO_2, successive elution with benzene and benzene/AcOEt: 10/1). The thiazole derivatives (2) obtained under analogous conditions (Method A) are shown in Table 1. Although several efficient procedures for the synthesis of 5-aminothiazoles have been developed,[1,5] no authentic sample of 2 could be obtained by the known methods. Characterization of the structure is, therefore, based on the spectral data,[4] alternative synthesis,[6] and chemical reactivities of 2.[7]

The formation of 2 under conditions of using no solvent (Method B) was rather rapid but the reaction was accompanied by the formation of α-(benzoylamino)thiocarboxamide (4) as a side product. Method B is, however, more convenient than Method A for the reaction of nitrones (1) with a branched alkyl group in R^1 because their reactions in benzene are extremely slow. Although the reaction mechanism is not yet clear, we assume that the reaction proceeds via initial 1,3-addition of thiocarboxylic acid to 1, cyclization of the adduct (5) with concomitant sulfur-to-nitrogen migration of the acyl group, and the loss of water to give 2.



1 5 2

2: X=S, Y=NH

3: X=NH, Y=S

Table 1. 2-Phenyl-4-alkyl-5-acylaminothiazoles (2)

	R^1	R^2	R^3	Method[a]	Time/d	Mp θm/°C	Yield/%[b]
2a	Pr^i	Ph-CH_3(p)	Ph	B	2	168-169	41
2b	Pr^i	Ph	Ph	B	2	180-181	42
2c	Pr^i	Ph-Cl(p)	Ph	A	3 weeks	201-202	48
2d	Pr^n	Ph-Cl(p)	Ph	A	3	178-179	68
				B	15 h		63 (32)[c]
2e	Pr^n	Ph	Ph	B	20 h	139-140	54
2f	Pr^n	Ph-Cl(p)	CH_3	A	3	235-236	40
2g	Et	Ph-Cl(p)	Ph	A	4	183-184	62
				B	20 h		52 (19)[c]
2h	Et	Ph-OCH_3	Ph	A	5	191	58
2i	Me	Ph-Cl(p)	Ph	A	4	235	56
2j	Pr^i	Ph-Cl(m)	Ph	A	3 weeks	189-190	40

a) A: (1)/thioic acid = 0.35 M/0.71 M in benzene at r.t. B: (1)/thioic acid = 1 mmol/3 mmol at 40 °C. b) Isolated yields. c) Yields of the corresponding thioamides, α-(p-chlorobenzoylamino)thiovaleramide (4d) and α-(p-chlorobenzoylamino)thiobutyramide (4g).

References

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2) K. Suda, E. Sekizuka, Y. Wakamatsu, F. Hino, and C. Yijima, Chem. Pharm. Bull., 33, 1297 (1985).
3) M. Masui, K. Suda, M. Yamauchi, and C. Yijima, J. Chem. Soc., Perkin Trans. 1, 1972, 1955.
4) 2d: Found: C, 63.92; H, 4.85; N, 7.75%. Calcd for $C_{19}H_{17}N_2OSCl$: C, 63.95; H, 4.80; N, 7.85%. MS (m/e) 356 (M^+ for ^{35}Cl); UV (EtOH) 225, 329 nm; IR (KBr) 3260 (NH), 1641 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t, CH_3), 1.88 (2H, m, CH_2-CH_2-Me), 2.79 (2H, t, CH_2-Et), 7.25-7.9 (9H, aromatic H), 7.98 (1H, s, NH).
5) A. H. Cook, Sir I. Heilbron, and A. L. Levy, J. Chem. Soc., 1947, 1598; M. Sekiya and Y. Osaki, Chem. Pharm. Bull., 13, 1319 (1965); Y. Tamura, T. Miyamoto, K. Shimooka, and T. Masui, ibid., 19, 119 (1971).
6) Thiation of α-(benzoylamino)valeronitrile by Lawesson's reagent[8] followed by benzoylation can also afford 2e, though in poor yield (7.5%).
7) Desulfurization of 2d with Raney nickel resulted in the decomposition of the aromatic ring system. This indicates that the sulfur atom is a member of the ring system.
8) S. Scheibye, B. S. Pedersen, and S. O. Lawesson, Bull Soc. Chim. Belg., 87, 229 (1978).

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