

DIPHENYLPHOSPHINODITHIOIC ACID: A REAGENT FOR THE CONVERSION
OF NITRILES TO THIOAMIDES

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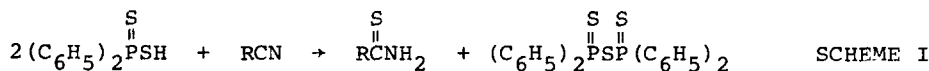
Summary: Diphenylphosphinodithioic acid is a reagent useful for a sequence effecting the hydrolysis of nitriles under mild conditions.

Of all functional groups at the acyl level of oxidation, nitriles are the most resistant to reaction. The poor electrophilicity of the carbon combined with the weak basicity of the nitrogen makes the nitrile group immune to attack under all but the harshest of conditions. Thus, existing procedures for the hydrolysis of nitriles call for either strong acid or strong base, and often require the assistance of elevated temperatures, prolonged reaction times, and potent nucleophiles such as the hydroperoxide anion¹. The instability of other functional groups under such conditions greatly restricts the use of the nitrile group in organic synthesis.

In the course of work with chiral methyl groups, we wished to react the methyl ester of diphenylphosphinodithioic acid (1)



with cyanide anion to produce acetonitrile bearing a chiral methyl group. While the displacement reaction proceeded smoothly, we discovered that the acetonitrile produced reacted further with 1 to produce thioacetamide and diphenylphosphinodithioic acid thioanhydride (2) according to the following scheme (R=CH₃):



While the literature contains a few scattered reports of analogous processes,² this reaction appeared to us to be a hitherto unexplored route for the rapid conversion of nitriles to other functional groups. We report here that 1 reacts with a wide range of nitriles to yield thioamides in high yields under conditions sufficiently mild to preserve intact a wide range of functional groups, including amides, esters, ketones, olefins, and alcohols.

Diphenylphosphinodithioic acid (1) was prepared by the method of Higgins *et al.*³ Crude 1 is a greenish solid that slowly emits H₂S on standing. However, recrystallization from 2-propanol yields white crystals (m.p. 55-56 °C) that are stable at room temperature for months. The following general procedure was suitable for the reaction of most nitriles. The nitrile (1 mmol) and 1 (2 mmol) were added to 15 ml of 2-propanol and heated briefly to 60 °C to completely dissolve the reactants. After standing at 40 °C overnight, the solution was cooled to -10 °C and crystals of 2 (m.p. 118-120 °C, lit.³ 118-121 °C) were removed by filtration. The filtrate was then added to CH₂Cl₂ (50 ml), washed successively with water (50 ml), dilute sodium hydroxide (0.5 M), and saturated sodium bicarbonate, dried (MgSO₄) and evaporated to yield thioamide contaminated with some isopropyl ester (C₆H₅)₂PSOCH(CH₃)₂.

The isopropyl ester could be removed by filtration of a solution of the residue in benzene through a short bed of silica gel. The thioamide was eluted from the silica gel with C₆H₆ : EtOH (1 : 1) and recrystallized (usually from benzene : isooctane). A number of thioamides were prepared by this procedure; the yields are reported in Table I.

TABLE I: Formation of Thioamides from Nitriles According to Scheme I.

R	yield	m.p. ^a	lit.	ref.
CH ₃ CH ₂ -	83% ^b	41 - 43	41 - 43	4
C ₆ H ₅ CH ₂ -	91%	96.5 - 97.5	97 - 98	5
C ₆ H ₅ -	76%	115.5 - 116.5	115 - 116	6
o-Cl (C ₆ H ₄)-	85%	109 - 110		7
p-Cl (C ₆ H ₄)-	83%	122 - 124	124	8
p-NO ₂ (C ₆ H ₄)-	87%	156 - 159	157	9
p-MeO (C ₆ H ₄)-	81%	147.5 - 148.5	148 - 149	10
-(CH ₂) ₄ - ^c	73%	180 - 182	178.5 - 179.5	11

a. corrected b. worked up without aqueous extraction c. 1,4-dicyanobutane

The reaction conditions described above are sufficiently mild to permit the survival of many functional groups. Acetophenone, acetone, benzamide, benzoic acid and a number of alcohols are recovered unchanged under these conditions. Ethyl esters generally undergo 10 - 15 % transesterification with 2-propanol, a side reaction that is avoided by using ethanol as the solvent. Olefins such as cyclohexene, known to react with $\underline{1}$ under harsher conditions,¹² can be recovered unaffected. However, sulfoxides are deoxygenated to sulfides by $\underline{1}$ and terminal acetylenes react under these conditions.

Thioamides themselves are often synthetic targets, and the procedure described here is a logical choice to replace existing methods for their synthesis,¹³ especially when mild conditions are desired. Thioamides can also be readily converted to amines with Raney nickel,¹⁴ and to imidates with alkyl halides,¹⁵ under conditions that leave many other functional groups intact. Furthermore, the S-methyl thioimidate of benzoic acid, prepared in 98% yield from the thioamide using CH_3I , reacted in water to produce methyl thiobenzoate (97%).¹⁷ The thioester was then hydrolyzed in an aqueous acetone solution containing HgCl_2 to produce benzoic acid (98%). Since all of these reactions occurred in minutes at room temperature, the overall sequence hydrolyzed a nitrile to a carboxylic acid under conditions that would normally leave esters and amides intact. Since this transformation is virtually impossible using other synthetic methodology, diphenylphosphinodithioic acid promises to have widespread use as a synthetic reagent.

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