

Phenyl Isothiocyanate



[103-72-0] $\text{C}_7\text{H}_5\text{NS}$ (MW 135.20)

InChI = 1S/C7H5NS/c9-6-8-7-4-2-1-3-5-7/h1-5H

InChIKey = QKFJKGMPGYROCL-UHFFFAOYSA-N

(Edman degradation of peptides; synthesis of heterocyclic systems)

Physical Data: bp 221 °C; mp -21 °C; d 1.1288 g cm⁻³.

Solubility: insol H₂O; sol alcohol, ether.

Form Supplied in: liquid; widely available.

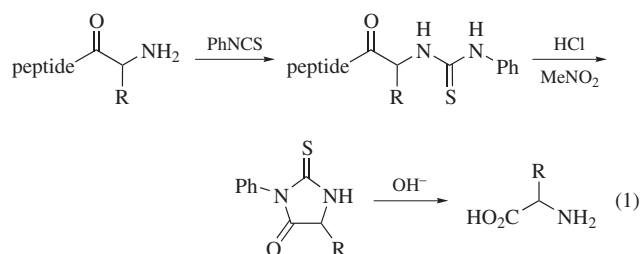
Handling, Storage, and Precautions: use in a fume hood.

Original Commentary

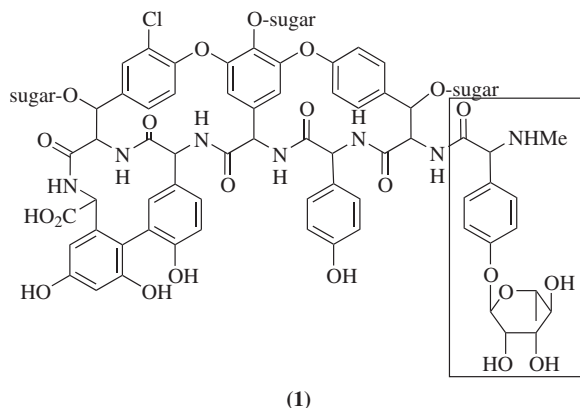
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Edman Degradation. Identification of terminal amino acid residues of peptides can readily be accomplished by an Edman degradation.¹ Treatment of the peptide with phenyl isothiocyanate in pyridine–water (1:1) produces a phenylthiocarbamoyl derivative which, upon exposure to anhydrous **Hydrogen Chloride** in nitromethane, rapidly cleaves to form a 3-phenyl-2-thiohydantoin and a peptide with one less amino acid residue. If needed, the free amino acid can be isolated by hydrolysis of the thiohydantoin with **Barium Hydroxide** (eq 1).

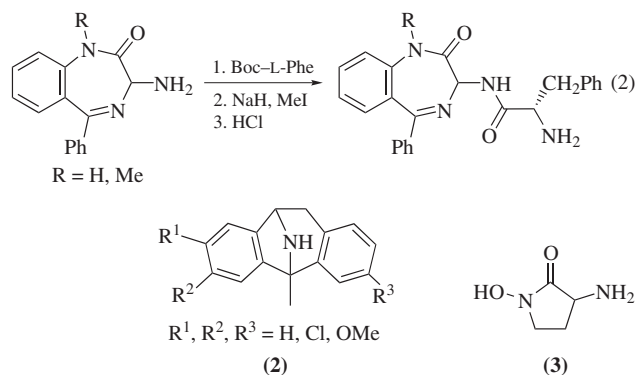


The procedure, which is amenable to complex peptides containing a variety of sensitive functionalities, has been applied to the vancomycin group of antibiotics,²⁻⁴ and was instrumental in the structure elucidation of avoparcin (**1**).^{5,6} In this case, the thiohydantoin of the deoxysugar amino acid fragment forms in the first step without a need for acid-catalyzed cyclization.

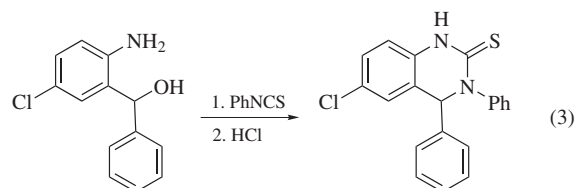


(1)

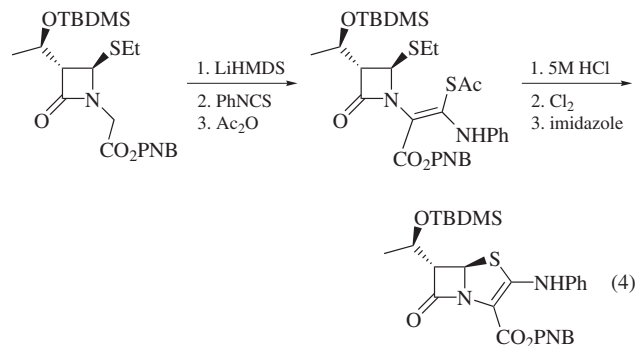
An interesting method for the resolution of amines involves preparing its amide with L-phenylalanine. Chromatographic separation of the corresponding diastereomers followed by an Edman degradation furnishes either pure enantiomer (eq 2).⁷ In this manner, dibenzo[*a,d*]cycloalkenimines (**2**)⁸ and 3-amino-1-hydroxypyrrolidin-2-one (**3**)⁹ have been resolved and evaluated for their *N*-methyl-D-aspartate and glycine antagonist activities, respectively.



Cyclization Reactions. The elements of phenyl isothiocyanate can be incorporated into cyclization motifs to form a variety of heterocyclic systems. For example, treatment of 2-amino-5-chlorobenzhydrol with phenyl isothiocyanate, followed by cyclization of the intermediate thiourea with dilute HCl, produces 6-chloro-3,4-diphenyl-2-thioxo-1,2,3,4-tetrahydroquinazoline in 60% yield (eq 3).¹⁰

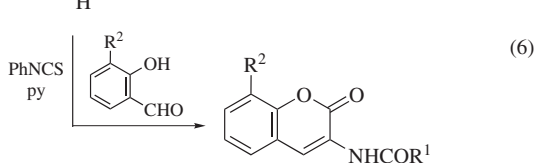
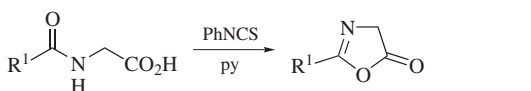
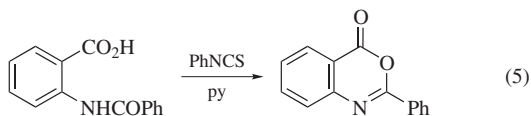


The core of the penem heterocyclic system can readily be assembled using phenyl isothiocyanate to supply the sulfur and one carbon atom for its five-membered ring. Treatment of a suitable azetidinone with **Lithium Hexamethyldisilazide** at -40 °C, followed by phenyl isothiocyanate and acetic anhydride, affords a ketene derivative. Deprotection, chlorinolysis, and hydrolysis produce the 2-phenylaminopenem (eq 4).¹¹



Dehydration Reactions. *N*-Benzoylanthranilic acid, when heated with phenyl isothiocyanate at 160–170 °C in the presence

of *Pyridine* as a catalyst, gives 2-phenyl-3,1-benzoxazin-4-one in 30% yield (eq 5).¹² Analogously, oxazolones are produced by a phenyl isothiocyanate-mediated cyclodehydration of *N*-acylglycines at 160–170 °C.^{13,14} When the reaction is performed in the presence of a salicylaldehyde, 3-*N*-acylaminocoumarins are isolated in yields of 20–68% (eq 6).¹⁵



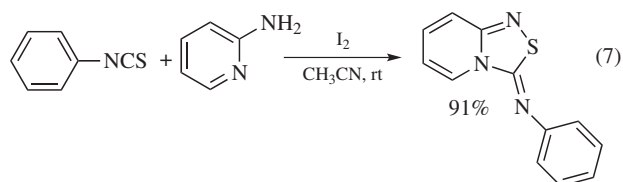
R¹ = Me, Ph, *p*-tolyl
R² = H, OH

Related Reagents. Benzoyl Isothiocyanate; Ethoxycarbonyl Isothiocyanate; Iron(III) Thiocyanate; Mercury(II) Thiocyanate; Methyl Isocyanate; Methyl Isothiocyanate; (*R*)-1-(1-Naphthyl)ethyl Isocyanate; Phenyl Isocyanate; Potassium Thiocyanate; Sodium Thiocyanate.

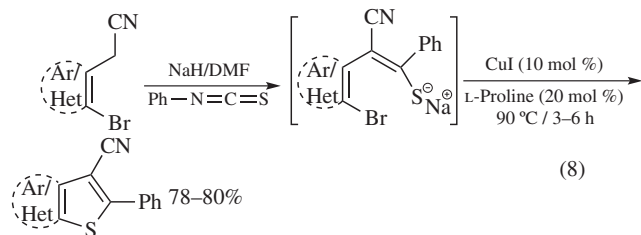
First Update

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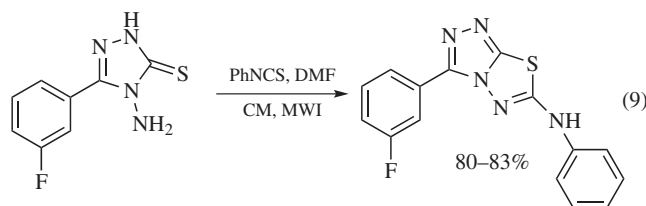
Cyclization Reactions. Phenyl isothiocyanate with 2-aminopyridine in the presence of iodine (0.2 equiv) with no solvent (neat) at room temperature gave the corresponding *N*-fused 1,2,4-thiadiazole in excellent yield (eq 7).¹⁶



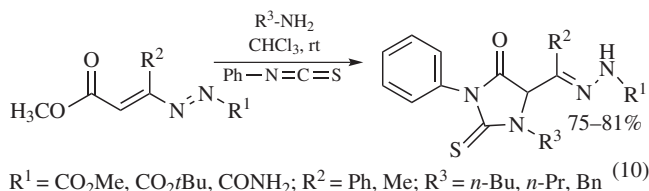
An efficient one-pot synthesis of highly functionalized multisubstituted benzo[*b*]thiophenes and their heterofused analogs, such as thieno[2,3-*b*]thiophenes, indolo[2,3-*b*]thiophenes, and pyrazolo[3,2-*c*]thiophenes, has been reported. The overall strategy involves sequential base-mediated condensation of 2-bromo-*het*-(*het*)acetonitrile precursors with phenyl isothiocyanate followed by intramolecular copper-catalyzed arylthiolation of in situ generated enethiolates, furnishing a broad range of 2-functionalized 3-cyano benzo[*b*]- and heterofused thiophenes in high yield (eq 8).¹⁷



Condensation of a substituted 1,2,4-triazole with phenyl isothiocyanate in dimethylformamide afforded the corresponding 6-(phenylamino)-3-(3-fluorophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole both under conventional heating (18–20 h) and MWI (3–4 min) in 80–83% yield (eq 9).¹⁸

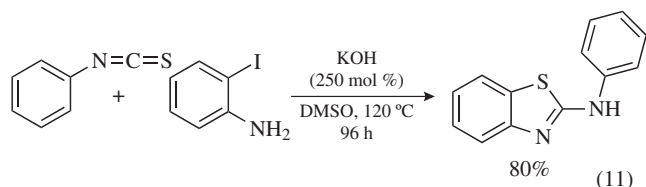


Primary alkylamines were reacted with phenylisothiocyanate in CHCl₃ at room temperature, and subsequently (after the rapid disappearance of the reagents, TLC check), isothiocyanates were added to afford the relevant 2-thiohydantoin derivatives in good to excellent yields (eq 10).¹⁹

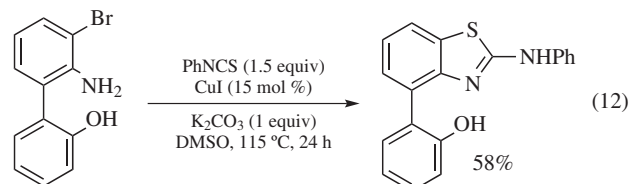


R¹ = CO₂Me, CO₂*t*Bu, CONH₂; R² = Ph, Me; R³ = *n*-Bu, *n*-Pr, Bn

The reaction with equimolar amounts of 2-iodoaniline and phenyl isothiocyanate gave the expected *N*-substituted benzo[*d*]thiazol-2-amine in good yield (eq 11).²⁰

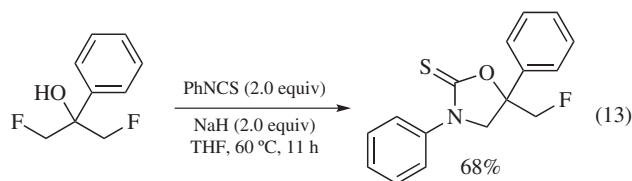


By virtue of their 3-halogen substituents, the 2-amino-2'-hydroxy-1,1'-biaryl products are useful intermediates en route to various unusually substituted heterocycles (eq 12).²¹

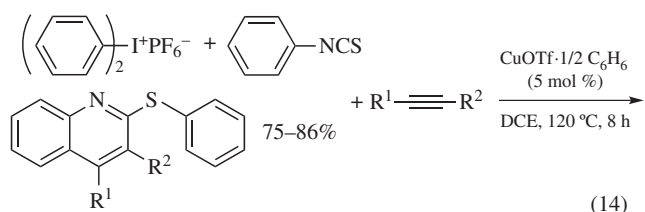


Tandem carbamoylation/cyclization was investigated. Phenyl isothiocyanate reacted with 2-aryl-1,3-difluoro-propan-2-ol under

the optimized conditions to furnish the cyclized product in 68% (eq 13).²²

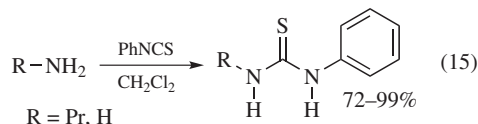


CuOTf-catalyzed substituent-controlled cascade [2 + 2 + 2] and [4 + 2] annulation reactions of heterocumulenes, alkynes, and diaryliodonium salts were achieved. Various quinoline derivatives could be obtained in good yields with excellent selectivity. This methodology provided a novel pathway to activate heterocumulenes via a highly reactive cationic intermediate. The reaction process was well elucidated by density functional theory calculations (eq 14).²³



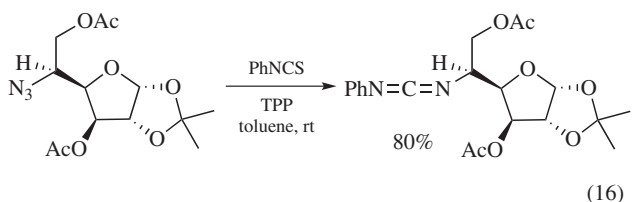
R¹ = Ph, 4-OMe-C₆H₄; R² = Ph, 4-OMe-C₆H₄, *n*-Bu

Addition Reactions. Thioureas are easily accessible from the reaction of amines with phenyl isothiocyanate (eq 15).²⁴

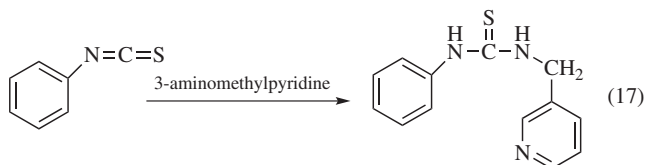


R = Pr, H

Tandem Staudinger-aza-Wittig-type condensation of the 5-azido-5-deoxysugar with phenyl isothiocyanate proceeded smoothly in toluene at room temperature to afford the phenyl-carbodiimide derivative in 80% yield (eq 16).²⁵

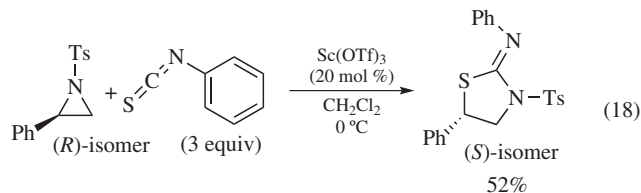


Phenyl isothiocyanate readily reacts with 3-aminomethylpyridine to give *N*-aryl-*N*-(3-pyridylmethyl)thiourea in nearly quantitative yield (eq 17).²⁶

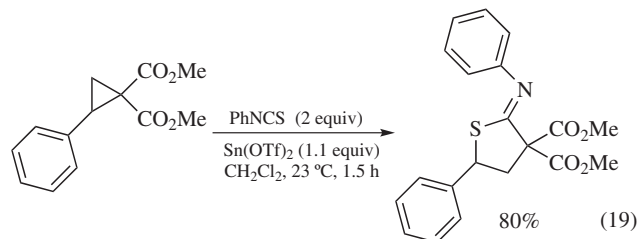


Cycloaddition Reactions. Reaction of (*R*)-2-phenyl-*N*-tosylaziridine with phenyl isothiocyanate in the presence of a

catalytic amount of scandium(III) triflate in dichloromethane at 0 °C proceeded sluggishly affording iminothiazolidine as a single regioisomer in moderate yield and poor enantiomeric excess (34% ee) (eq 18).²⁷



Thioimidates with electron-rich aryl substituents were obtained with short reaction times. Reactions leading to products with *ortho* or electron-withdrawing arene substituents were slower (eq 19).²⁸



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