

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.

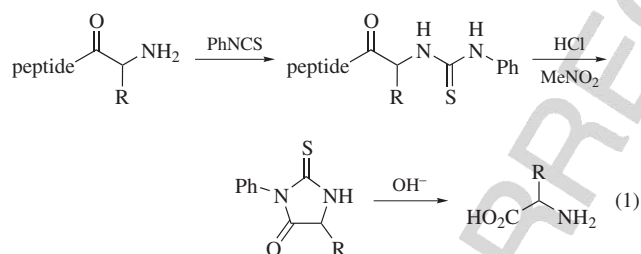
Handling, Storage, and Precautions: use in a fume hood.

Original Commentary

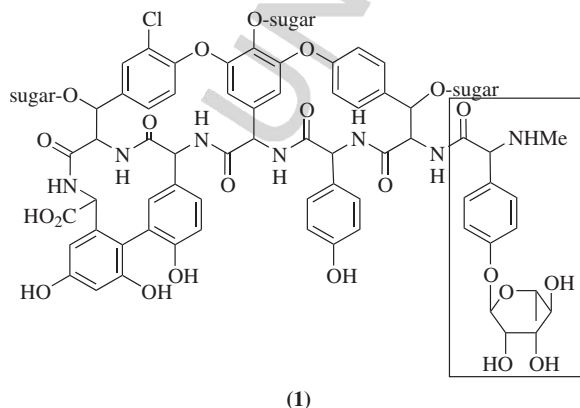
Gary M. Coppola

Sandoz Research Institute, East Hanover, NJ, USA

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).

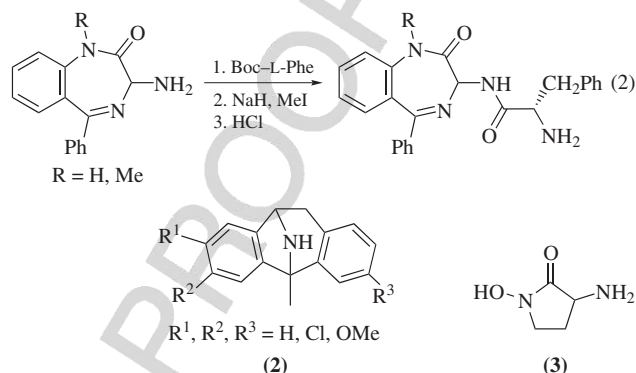


The procedure, which is amenable to complex peptides containing a variety of sensitive functionalities, has been applied to the vancomycin group of antibiotics,²⁻⁴ and was instrumental in the structure elucidation of avoparcin (**1**).^{5,6} In this case, the thiohydantoin of the deoxysugar amino acid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

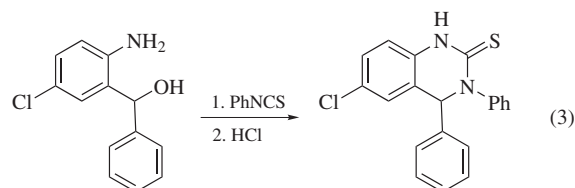


(1)

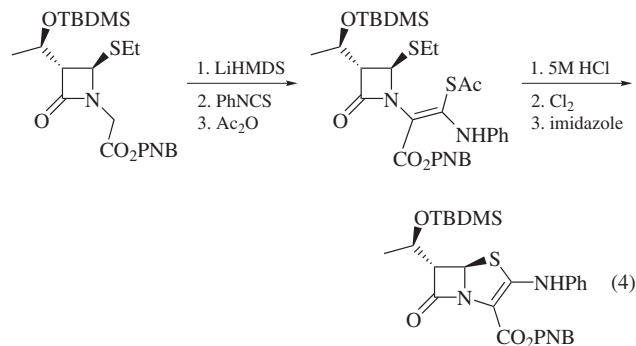
An interesting method for the resolution of amines involves preparing its amide with L-phenylalanine. Chromatographic separation of the corresponding diastereomers followed by an Edman degradation furnishes either pure enantiomer (eq 2).⁷ In this manner, dibenzo[*a,d*]cycloalkenimines (**2**)⁸ and 3-amino-1-hydroxypyrrolidin-2-one (**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

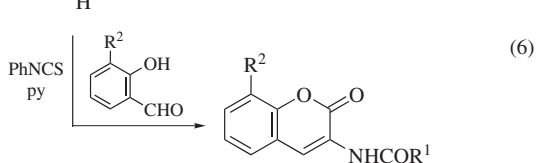
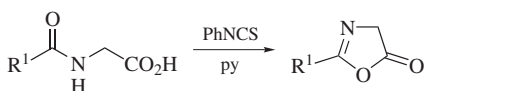
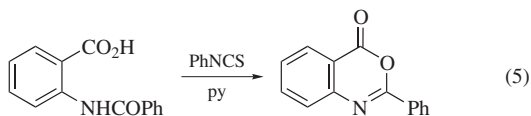


The core of the penem heterocyclic system can readily be assembled using phenyl isothiocyanate to supply the sulfur and one carbon atom for its five-membered ring. Treatment of a suitable azetidinone with **Lithium Hexamethyldisilazide** at -40 °C, followed by phenyl isothiocyanate and acetic anhydride, 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



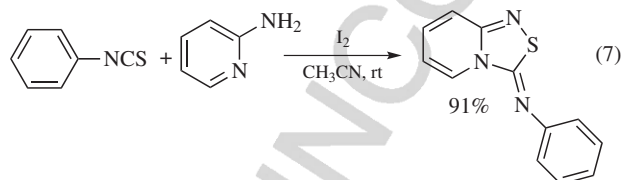
R¹ = Me, Ph, *p*-tolyl
R² = H, OH

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.

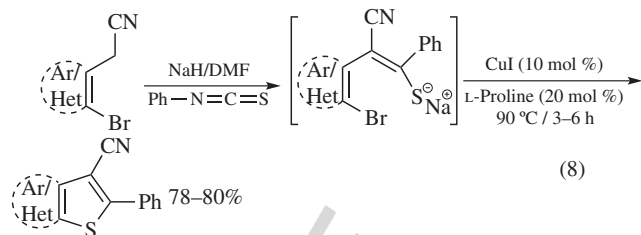
First Update

Nataliya Korol & Mikhaïlo Slivka
Uzhgorod National University, Uzhgorod, Ukraine

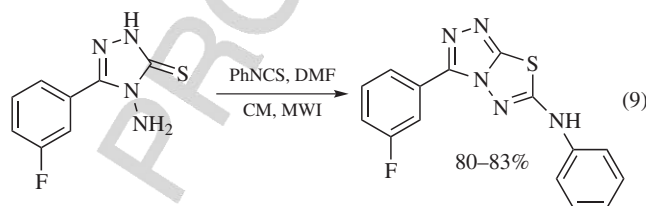
Cyclization Reactions. Phenyl isothiocyanate with 2-aminopyridine in the presence of iodine (0.2 equiv) with no solvent (neat) at room temperature gave the corresponding *N*-fused 1,2,4-thiadiazoles in excellent yields (eq 7).¹⁶



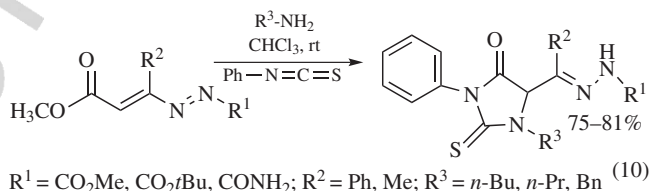
An efficient one-pot synthesis of highly functionalized multisubstituted benzo[*b*]thiophenes and their heterofused analogs, such as thieno[2,3-*b*]thiophenes, indolo[2,3-*b*]thiophenes, and pyrazolo[3,2-*c*]thiophenes, has been reported. The overall strategy involves sequential base-mediated condensation of 2-bromo-*het*(aryl)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



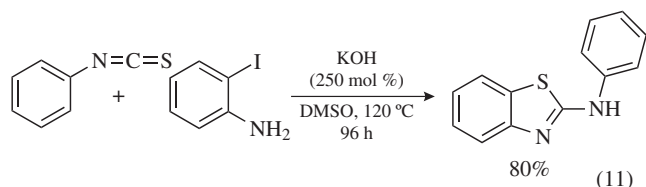
Condensation of a substituted 1,2,4-triazole with phenyl isothiocyanate in dimethylformamide afforded the corresponding 6-(phenylamino)-3-(3-fluorophenyl)-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole both under conventional heating (18–20 h) and MWI (3–4 min) in 80–83% yield (eq 9).¹⁸



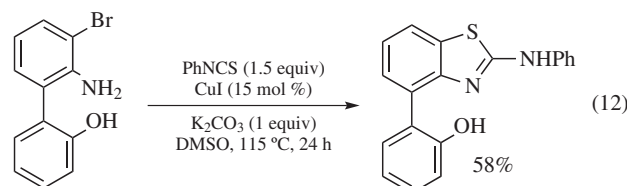
Primary alkylamines were reacted with phenylisothiocyanate in CHCl₃ at room temperature, and subsequently (after the rapid disappearance of the reagents, TLC check), isothiocyanates were added to afford the relevant 2-thiohydantoin derivatives in good to excellent yields (eq 10).¹⁹



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

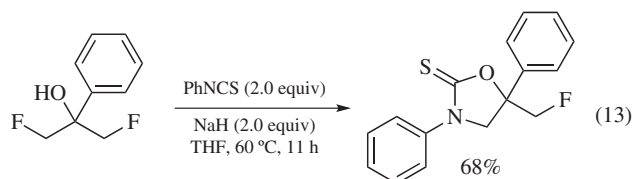


By virtue of their 3-halogen substituents, the 2-amino-2'-hydroxy-1,1'-biaryl products are useful intermediates en route to various unusually substituted heterocycles (eq 12).²¹

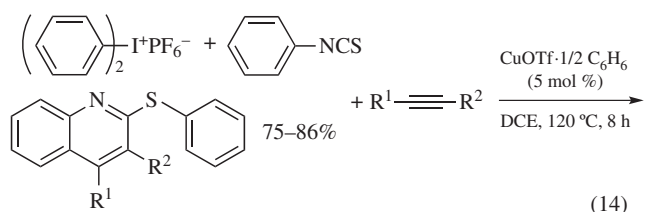


Tandem carbamoylation/cyclization was investigated. Phenyl isothiocyanate reacted with 2-aryl-1,3-difluoro-propan-2-ol under

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

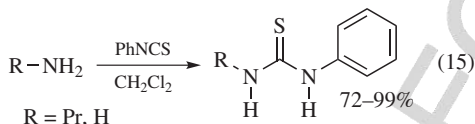


CuOTf-catalyzed substituent-controlled cascade [2 + 2 + 2] and [4 + 2] annulation reactions of heterocumulenes, alkynes, and diaryliodonium salts were achieved. Various quinoline derivatives could be obtained in good yields with excellent selectivity. This methodology provided a novel pathway to activate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



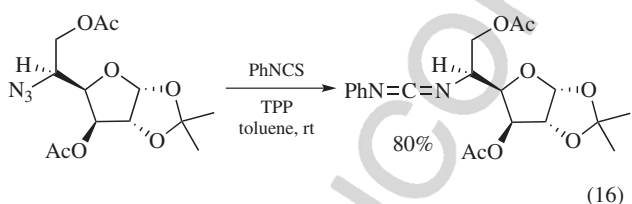
$R^1 = \text{Ph}, 4\text{-OMe-C}_6\text{H}_4$; $R^2 = \text{Ph}, 4\text{-OMe-C}_6\text{H}_4, n\text{-Bu}$

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

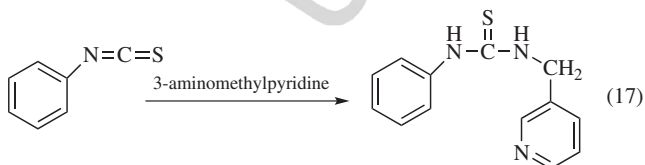


$R = \text{Pr}, \text{H}$

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

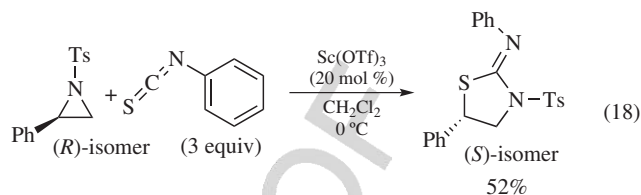


Phenyl isothiocyanate readily reacts with 3-aminomethylpyridine to give *N*-aryl-*N*-(3-pyridylmethyl)thiourea in nearly quantitative yield (eq 17).²⁶

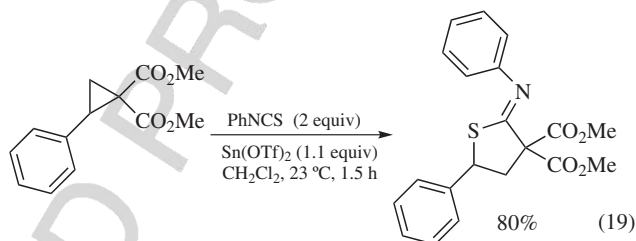


Cycloaddition Reactions. Reaction of (*R*)-2-phenyl-*N*-tosylaziridine with phenyl isothiocyanate in the presence of a

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



Thioimides 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



- (a) Edman, P., *Acta Chem. Scand.* **1950**, 283. (b) Fieser & Fieser **1967**, I, 844; **1969**, 2, 323.
- Booth, P. M.; Stone, D. J. M.; Williams, D. H., *J. Chem. Soc., Chem. Commun.* **1987**, 1694.
- Nagarajan, R.; Schabel, A. A., *J. Chem. Soc., Chem. Commun.* **1988**, 1306.
- Booth, P. M.; Williams, D. H., *J. Chem. Soc., Perkin Trans. 1* **1989**, 2335.
- Hlavka, J. J.; Bitha, P.; Boothe, J. H.; Morton, G., *Tetrahedron Lett.* **1974**, 175.
- McGahren, W. J.; Martin, J. H.; Morton, G. O.; Hargreaves, R. T.; Leese, R. A.; Lovell, F. M.; Ellestad, G. A.; O'Brien, E.; Holker, J. S. E., *J. Am. Chem. Soc.* **1980**, 102, 1671.
- Rittle, K. E.; Evans, B. E.; Bock, M. G.; DiPardo, R. M.; Whitter, W. L.; Homnick, C. F.; Veber, D. F.; Freidinger, R. M., *Tetrahedron Lett.* **1987**, 28, 521.
- Thompson, W. J.; Anderson, P. S.; Britcher, S. F.; Lyle, T. A.; Thies, J. E.; Magill, C. A.; Varga, S. L.; Schwering, J. E.; Lyle, P. A.; Christy, M. E.; Evans, B. E.; Colton, C. D.; Holloway, M. K.; Springer, J. P.; Hirshfield, J. M.; Ball, R. G.; Amato, J. S.; Larsen, R. D.; Wong, E. H. F.; Kemp, J. A.; Tricklebank, M. D.; Singh, L.; Oles, R.; Priestly, T.; Marshall, G. R.; Knight, A. R.; Middlemiss, D. N.; Woodruff, G. N.; Iversen, L. L., *J. Med. Chem.* **1990**, 33, 789.
- Williams, B. J.; Leeson, P. D.; Hannah, G.; Baker, R., *J. Chem. Soc., Chem. Commun.* **1989**, 1740.
- Richter, P.; Oertel, F., *Pharmazie* **1990**, 45, 721.
- Barker, A. J.; Teall, M. R., *Tetrahedron Lett.* **1987**, 28, 2283.
- Ashare, R.; Mukerjee, A. K., *Indian J. Chem., Sect. B* **1986**, 25, 1180.
- Ashare, R.; Ram, R. N.; Mukerjee, A. K., *Indian J. Chem., Sect. B* **1984**, 23, 759.
- Jain, A.; Mukerjee, A. K., *Heterocycles* **1987**, 26, 1521.
- Jain, A.; Mukerjee, A. K., *J. Prakt. Chem.* **1989**, 331, 493.
- Tumula, N.; Jatangi, N.; Palakodety, R. K.; Balasubramanian, S.; Nakka, M., *J. Org. Chem.* **2017**, 82, 5310.

17. Acharya, A.; Kumar, V.; Saraiah, B.; Ila, H., *J. Org. Chem.* **2015**, *80*, 2884.
18. Aouad, M. R.; Al-Saedi, A. M.; Ali, A. A.; Rezki, N.; Messali, M., *Org. Prep. Proced. Int.* **2016**, *48*, 355.
19. Attanasi, O. A.; Bartoccini, S.; Favi, G.; Giorgi, G.; Perrulli, F. R., *J. Org. Chem.*, **2012**, *77*, 1161.
20. Cano, R.; Ramon, D. J.; Yus, M., *J. Org. Chem.* **2011**, *76*, 654.
21. Gao, H.; Ess, D. H.; Yousufuddin, M.; Kürti, L., *J. Am. Chem. Soc.* **2013**, *135*, 7086.
22. Haufe, G.; Suzuki, S.; Yasui, H.; Terada, C.; Kitayama, T.; Shiri, M.; Shibata, N., *Angew. Chem., Int. Ed.* **2012**, *49*, 12441.
23. Chi, Y.; Yan, H.; Zhang, W.-X.; Xi, Z., *Org. Lett.* **2017**, *19*, 2694.
24. Batey R. A.; Powell, D. A., *Org. Lett.* **2000**, *2*, 3237.
25. Aguilar, M.; Diaz-Pere, P.; Garcia-Moreno, M. I.; Mellet, C. O.; Femandez, J. M. G., *J. Org. Chem.* **2008**, *73*, 1995.
26. Cui, D.; Li, Z.; Liu, R.; Song, G.; Qian, X., *Org. Prep. Proc. Int.* **2003**, *35*, 223.
27. Bhattacharyya, A.; Kavitha, C.V.; Ghorai, M. K., *J. Org. Chem.* **2016**, *81*, 6433.
28. Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A.; Stoltz, B. M., *Org. Lett.* **2012**, *14*, 5314.

UNCORRECTED PROOF