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A General Synthetic Method for the Formation of Substituted 5-Aminotetrazoles from Thioureas: A Strategy for Diversity Amplification

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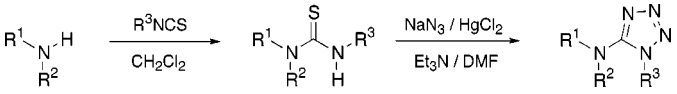
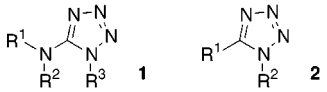
ABSTRACT



A general method for the synthesis of 5-aminotetrazoles is outlined using the mercury(II)-promoted attack of azide anion on a thiourea. The reaction proceeds through a guanyl azide intermediate, which undergoes electrocyclization to the tetrazole. The method is high yielding and provides access to mono-, di-, and trisubstituted 5-aminotetrazoles, targets of potential interest for combinatorial library development.

Combinatorial chemistry is now an indispensable technique in the pharmaceutical and agrochemical industries.[1] The ability to synthesize and test compounds in a high-throughput manner offers many advantages, but new synthetic methods are required to meet the demands of creating highly diverse compound libraries.[2] Diversity is usually created through the combination of a scaffold synthesis and the functionalization of pendant reactive groups such as amines, alcohols, thiols, carboxylic acids, etc. An example of a widely used functionalization procedure is the formation of thioureas through the coupling of amines with isothiocyanates. The resultant thiourea functionality may be present in the target structure, but can also be used for further synthetic transformations such as guanidine formation. As part of an interest in such "diversity amplifying" (DA) reactions, we have initiated a project on the synthesis of 5-aminotetrazoles **1** and their use in peptidomimetic structures. We envisaged that thioureas could serve as versatile intermediates for the synthesis of highly substituted 5-aminotetrazoles **1**, in a transformation which can be viewed as both a functionalization and a scaffold synthesis reaction.



1 **2**

There is considerable interest in the medicinal and biological applications of tetrazoles **2**,[3] particularly those containing a ring N−H (**2**, $R^2 = H$), as they are isosteric with carboxylic acids. The comparable acidity and increased metabolic stability of tetrazoles **2** ($R^2 = H$) has resulted in their use in a variety of pharmacologically active compounds.[3,4] 1,5-Disubstituted tetrazoles **2** have also been incorporated into biologically active peptides such as bradykinin[5] and de-

(1) Dolle, R. E.; Nelson, K. H., Jr. *J. Comb. Chem.* **1999**, *1*, 235−282.
(2) Weber, L. *Curr. Opin. Chem Biol.* **2000**, *4*, 295−302.
(3) For reviews of tetrazole chemistry see: (a) Moderhack, D. *J. Prakt. Chem.* **1998**, *340*, 687−709. (b) Butler, R. N. *Comprehensive Heterocyclic Chem. II*; Katrinsky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: New York, 1996; Vol. 4; pp 621−678. (c) Wittenberger, S. J. *Org. Prep. Proced. Int.* **1994**, *26*, 499−531. (d) Butler, R. N. *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: New York, 1984; Vol 5; pp 791−838.
(4) For a few recent examples, see (a) White, A. D.; Creswell, M. W.; Chucholowski, A. W.; Blankley, C. J.; Wilson, M. W.; Bousley, R. F.; Essenburg, A. D.; Hamelehle, K. L.; Krause, B. R.; Stanfield, R. L.; Dominick, M. A.; Neub, M. *J. Med. Chem.* **1996**, *39*, 4382−4395. (b) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 6391−6394.
(5) Zabrocki, J.; Dunbar, J. B.; Marshall, K. W.; Toth, M. V.; Marshall, G. R. *J. Org. Chem.* **1992**, *57*, 202−209.

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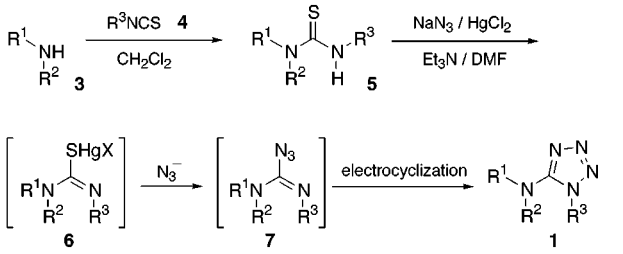
aminooxytocin,[6] acting as *cis*-amide bond mimics.[7] Our interest is in the utility of highly substituted 5-aminotetrazoles **1**, which are less common targets. Although there a variety of procedures for the synthesis of **2**,[3] currently the only method for the direct construction of trisubstituted 5-aminotetrazoles **1**, with potentially general applicability, requires a three-step procedure involving diazotization under relatively harsh conditions.[8,9] Disubstituted 5-aminotetrazoles **1** ($R^1/R^2 \neq H$, $R^3 = H$) can be similarly accessed, or can be generated through the addition of hydrazoic acid to cyanamides at high temperatures.[10] Disubstituted 5-aminotetrazoles **1** ($R^1/R^3 \neq H$, $R^2 = H$) are typically prepared from aminoguanidines through the diazotization method,[11] or from the reaction of carbodiimides with sodium azide or hydrazoic acid.[12] A modification of the latter method involving tandem acylation has led to a synthesis of trisubstituted 5-aminotetrazoles **1** (R^1/R^3 = aryl, R^2 = benzoyl).[13] Generally, however, selective alkylation of aminotetrazoles is not possible because of competitive formation of 1- and 2-alkylated-5-aminotetrazoles.[4a]

There is clearly a need for a general method for the synthesis of 5-aminotetrazoles **1** of any substitution pattern, using readily available starting materials, which can be efficiently coupled under mild conditions. We envisaged that such a method would allow us to use the 5-aminotetrazole moiety as a scaffold for combinatorial elaboration. By analogy with the mercury(II)-promoted guanadinylation of di-Boc-protected thioureas with primary or secondary amines, developed by Kim and Qian,[14] we reasoned that the use of sodium azide as a nucleophile would allow for the synthesis of 5-aminotetrazoles **1**. Thus, displacement by sodium azide of a mercury(II)-activated thiourea would generate an intermediate guanyl azide **7**, which upon electrocyclization would render the 5-aminotetrazole **1** (Scheme 1). It is known

Scheme 1



that the imino nitrogen must have sufficient electron density for electrocyclization to occur.[3d] Thioureas **5** serve as ideal intermediates, as they are easily accessible from the reaction of amines **3** with isothiocyanates **4**. The wide range of commercially available amines and aryl, alkyl, and acyl isothiocyanates make this approach all the more appealing.

Phenyl-*n*-propylthiourea was chosen as a test substrate for the synthesis of a disubstituted 5-aminotetrazole and was prepared from the reaction of *n*-propylamine with phenyl isothiocyanate. Reaction with mercury(II) chloride, sodium azide, and triethylamine in DMF[15] at room temperature furnished exclusively the 1-phenyl 5-propylaminotetrazole in quantitative yield (Table 1, entry 1).[16] The regioselectivity

Table 1. Formation of Mono- and Disubstituted 5-aminotetrazoles **1** via Thioureas **5**[a]

entry	R^1	R^2	R^3	yield of **5** [%]	yield of **1** [%]
1	Pr	H	Ph	99	99
2	Pr	H	Bn	99	89[b]
3	Pr	H	Bz	63	0
4	$MeOOC(CH_2)_3$	H	COOEt	96	0
5	H	H	Ph	72	76

[a] For experimental conditions, see ref 16. [b] 1:1 Mixture of regioisomeric tetrazoles obtained.

of the electrocyclization step is in accordance with earlier results, leading to the product having the tetrazole and phenyl rings conjugated.[12a] Benzyl-*n*-propylthiourea was subjected

(6) Lebl, M.; Slaninova, J.; Johnson, R. L. *Int. J. Pept. Protein Res.* **1990**, *33*, 16.

(7) (a) Satoh, Y.; De Lombaert, S.; Marcopulos, N.; Moliterni, J.; Moskal, M.; Tan, J.; Wallace, E. *Tetrahedron Lett.* **1998**, *39*, 3367−3370. (b) Beusen, D. D.; Zabrocki, J.; Slomczynska, U.; Head, R. D.; Kao, J. L. F.; Marshall, G. R. *Biopolymers* **1995**, *36*, 181−200. (c) Boteju, L. W.; Hruby, V. J.; *Tetrahedron Lett.* **1993**, *34*, 1757−1760. (d) Zabrocki, J.; Smith, G. D.; Dunbar, J. B.; Iijima, H.; Marshall, G. R. *J. Am. Chem. Soc.* **1988**, *110*, 5875−5880.

(8) A trisubstituted thiourea is first *S*-methylated, converted to the aminoguanidine (hydrazine hydrate in ethanol at reflux), and then converted to the tetrazole using concentrated $HCl/NaNO_2$. See Atherton, F. R.; Lambert, R. W. *Tetrahedron* **1983**, *39*, 2599−2608.

(9) For other less general methods utilizing harsh conditions, see (a) Imhof, R.; Ladner, D. W.; Muchowski, J. M. *J. Org. Chem.* **1977**, *42*, 3709−3713. (b) Boyd, G. V.; Cobb, J.; Lindley, P. F.; Mitchell, J. C.; Nicolaou, G. A. *J. Chem. Soc., Chem. Commun.* **1987**, 99−101. (c) Gupton, J. T.; Idoux, J. P.; Baker, G.; Colon, C.; Crews, A. D.; Jurss, C. D.; Rampi, R. C. *J. Org. Chem.* **1983**, *48*, 2933−2936.

(10) (a) Garbrecht, W. L.; Herbst, R. M. *J. Org. Chem.* **1953**, *18*, 1003−1010. (b) Castro, J. L.; Ball, R. G.; Broughton, H. B.; Russell, M. G. N.; Rathbone, D.; Watt, A. P.; Baker, R.; Chapman, K. L.; Fletcher, A. E.; Patel, S.; Smith, A. J.; Marshall, G. R.; Ryecroft, W.; Matassa, V. G. *J. Med. Chem.* **1996**, *39*, 842−849.

(11) Kurzer, F.; Godfrey, L. E. A. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 459−476.

(12) (a) Svetlik, J.; Hrusovsky, I.; Martvon, A. *Coll. Czech. Chem. Commun.* **1979**, *44*, 2982−2986. (b) Habich, D. *Synthesis* **1992**, 358−360.

(13) Ding, Y.-X.; Weber, W. P. *Synthesis* **1987**, 823−824.

(14) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677−7680. The scope of this reaction has been expanded by Levallet, C.; Lerpiniere, J.; Ko, Y. S. *Tetrahedron* **1997**, *53*, 5291−5304.

(15) Kadaba, P. K. *J. Org. Chem.* **1976**, *41*, 1073−1075.

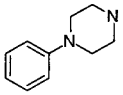
(16) **Representative procedure for the preparation of tetrazoles (1) via thioureas (5).** A solution of amine **3** (6.0 mmol, 1.0 equiv) in 15 mL of dry CH_2Cl_2 was treated dropwise with isothiocyanate **4** (6.0 mmol, 1.0 equiv). The resulting solution was stirred at room temperature for 16 h and then diluted with H_2O (50 mL) and extracted with 3 × 15 mL of CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by recrystallization (CH_2Cl_2:hexanes) or column chromatography through silica gel to give thiourea **5**. To a suspension of **5** (1.25 mmol, 1.0 equiv), sodium azide (244 mg, 3.75 mmol, 3.0 equiv), and mercuric chloride (373 mg, 1.38 mmol, 1.1 equiv) in 5 mL of dry DMF was added triethylamine (503 μL, 3.75 mmol, 3.0 equiv). The resulting suspension was stirred for 3 h at room temperature or until TLC indicated complete consumption of starting material. The suspension was filtered through a pad of Celite, washing with CH_2Cl_2. The filtrate was diluted with water and extracted with 3 × 15 mL of CH_2Cl_2, the combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give tetrazole **1**.

to the above conditions to give a 1:1 mixture of tetrazole isomers, resulting from competitive cyclization of the guanyl azide (Table 1, entry 2). More electron-deficient thioureas failed to give the desired tetrazoles (Table 1, entries 3 and 4). Both of these substrates reacted with mercury but failed to convert to the tetrazole, and no other intermediates or products were detected. The method can also be used for the synthesis of monosubstituted 5-aminotetrazoles from the terminal phenylthiourea (Table 1, entry 5). By contrast, terminal arylthioureas and amines do not react in Hg(II)-promoted guanadinylation reactions.[14]

Of greater significance is the synthesis of trisubstituted 5-aminotetrazoles **1** (Table 2), products which are not accessible through the conventional reaction of sodium azide or hydrazoic acid with carbodiimides. Thus, the thiourea obtained from pyrrolidine and benzyl isothiocyanate reacted with mercury(II) chloride and sodium azide to give the corresponding 5-aminotetrazole in 89% yield (Table 2, entry 1), the structure of which was unambiguously confirmed by X-ray crystallography (Figure 1).[17] Other pyrrolidine-derived thioureas gave similarly high yields of the tetrazole substrates (Table 2, entries 2−4). For the allyl isothiocyanate derived thiourea, lower yields were obtained, presumably because of competitive reaction of mercury(II) with the terminal alkene (Table 2, entry 3).[18] Other *N*,*N*,*N*′-trisubstituted thioureas also gave 5-aminotetrazoles in good to excellent yields (Table 2, entries 5−9). Notably the more electron-deficient pyrrolidinone substituent could also be used, albeit with somewhat lower efficiency. All of the above reactions were complete within 3 h or less at room temperature. Tetrazole formation was not possible from *N*,*N*-disubstituted thioureas or *N*,*N*-disubstituted *N*′-acylthioureas,[19] where the imino lone pair on the guanyl azide lacks sufficient electron density to cyclize.

A preliminary screen revealed that other mercury(II) salts also promote the reaction with trisubstituted thioureas, including $HgBr_2$, HgI_2, and $Hg(OAc)_2$. However, reaction did not occur with red HgO, Zn(II), Cu(I), or Cu(II) salts or in the absence of mercury(II) salts. The reaction can also be conducted in the absence of triethylamine, although at a significantly slower rate, requiring 3 h for 30% conversion and 16 h for 50%, as determined by ^{1}H NMR. Since the electrocyclization of guanyl azides is known to be inhibited under acidic conditions, the role of the triethylamine is presumably to neutralize the HCl produced during the formation of **6**.[3b]

Table 2. Formation of Trisubstituted 5-aminotetrazoles **1** via Thioureas **5**[a]

Entry	R^1R^2N	R^3	Yield **5** [%]	Yield **1** [%]
1		Bn	92	89
2		Ph	99	92
3		allyl	89	52
4		Chx	93	83
5		Bn	92[b]	54[c]
6		Bn	41	87
7		Bn	72	80
8	Et_2N	Bn	94	78
9		Bn	97	66

[a] For experimental conditions, see ref 16. [b] This thiourea was prepared by deprotonation of 2-pyrrolidinone with NaH, followed by reaction with BnNCS. [c] Recovered thiourea (26%) was also obtained.

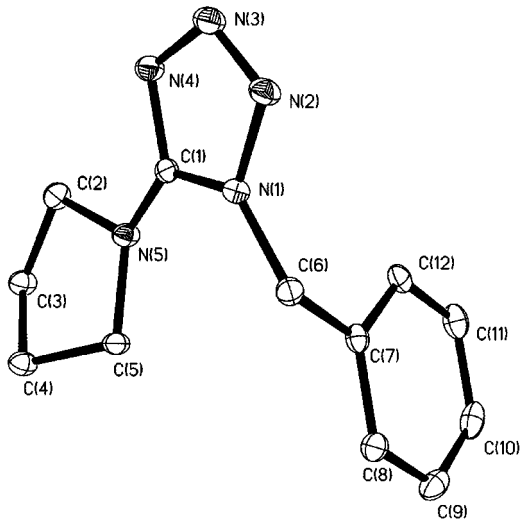


Figure 1. ORTEP drawing of 1-benzyl-5-pyrrolidin-1-yl-1*H*-tetrazole (from Table 2, entry 1) with 30% thermal ellipsoids.

(17) Crystal data for 1-benzyl-5-pyrrolidin-1-yl-1*H*-tetrazole (Table 2, entry 1): $C_{12}H_{15}N_5$; FW = 229.29, orthorhombic, space group *Pna*2$_1$ [no. 33], block cut from colorless needles, a = 8.1926(3) Å, b = 12.2982(4) Å, c = 11.3204(5) Å, V = 1140.58(8) Å^3, Z = 4, D_{calcd} = 1.335 Mg/m^3, μ(Mo Kα) = 0.86 cm^{-1}, Nonius Kappa-CCD diffractometer, λ = 0.71073 Å, ϕ scans and ω scans with κ offsets, $2\theta_{max}$ = 60.16°, 3122 reflections (unique), *R1* = 0.00493, *wR2* = 0.1094, GOF = 1.006.

(18) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985.

(19) For the reaction of *N*-(pyrrolidine-1-carbothioyl)benzamide, we may have obtained a bis-thiomercury(II) complex. See Richter, R.; Seiler, J.; Beyer, L.; Lindqvist, O.; Andersen, L. *Z. Anorg. Allg. Chem.* **1985**, *522*, 171−183.

The mercury-promoted dehydration of thioureas to give carbodiimides is well-known,[20] and for *N*,*N*′-disubstituted thioureas, carbodiimide intermediacy is likely (i.e., reaction occurs through coordination of Hg(II) to give **6** followed by an elimination−addition mechanism). Ko and co-workers have observed these intermediates in the mercury-promoted guanadinylation reaction,[14] and reagents such as EDCI[21] or Mukaiyama's reagent[22] which are known to react with thioureas to give carbodiimides, have also been explored in the context of guanadinylations. The mechanism of 5-aminotetrazole formation from trisubstituted thioureas is not as clear. Although carbodiimidium compounds are known,[23] they are difficult to synthesize requiring long reaction times and high temperatures. As powerful electrophiles they readily react with even sterically hindered alcohols.[21] However, when sodium azide is replaced with an amine as the nucleophile, the corresponding guanidine is not obtained.[14,24] Thus, it is unlikely that a reactive carbodiimidium moiety is an intermediate, since reaction with weaker nucleophiles would be expected to occur. Furthermore, such an intermediate would be severely destabilized for substrates bearing electron-withdrawing groups, yet the reaction works even when R^2 is an acyl or aromatic group (Table 2, entries 5 and 7). The most likely mechanism therefore involves Hg(II) coordination to give **6**, followed by attack of azide anion to give **7**, via an addition−elimination pathway, a mechanism that will only operate with strong sterically unencumbered nucleophiles such as azide anion. A similar mechanism has been proposed in the reaction of thioamides with mercury carboxylates to give imides.[25]

In conclusion, we have developed a new method for the mild and efficient preparation of mono-, di-, and tri substituted 5-aminotetrazoles from amines, isothiocyanates, and azide anion. Further examination of the scope and mechanism of the reaction and the identification of mercury free conditions which are amenable to the generation of combinatorial libraries of 5-aminotetrazole-containing peptidomimetics is currently underway in our laboratories.

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Supporting Information Available: X-ray crystallographic data for 1-benzyl-5-pyrrolidin-1-yl-1*H*-tetrazole and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For a review of carbodiimides, see (a) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589−636. (b) Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233−284.

(21) (a) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933−5936. (b) Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D. *J. Org. Chem.* **2000**, *65*, 1566−1568.

(22) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540−1542.

(23) (a) Scheffold, R.; Saladin, E. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 229−231. (b) Hartke, K.; Rossbach, F.; Radau, M. *Justus Liebigs Ann. Chem.* **1972**, *762*, 167−177.

(24) We have confirmed the results of Ko and co-workers (ref 14) in the reaction of thiourea **5** (Table 2, entry 1) with benzylamine in the presence of $HgCl_2$, which did not give any guanidine product, even after heating to 60 °C for 24 h.

(25) Avalos, M.; Babiano, R.; Cintas, P.; Duran, C. J.; Higes, F. J.; Jimenez, J. L.; Lopez, I.; Palacios, J. C. *Tetrahedron* **1997**, *53*, 14463−14480.