6-Methyl-5-(2-propynyl)-2-thio-4(1*H*,3*H*)-pyrimidinone (7). Compound 1 (25.10 g, 0.15 mol) was dissolved in 150 mL of MeOH with thiourea (11.64 g, excess) and K_2CO_3 (19.72 g, excess). The reaction was stirred under reflux for 24 h and neutralized with concentrated HCl followed by cooling in the freezer. The solid was filtered and rinsed with 250-mL ice-cold 25% H_2O–MeOH. The fine white powder was dissolved in hot *i*-PrOH and precipitated small thin needles on cooling (15.69 g, 58%). The crystals melted from 258 to 260 °C, and TLC showed one spot at R_f = 0.77 in 10% MeOH–ether: ^{1}H NMR (Me_2SO-d_6) δ 2.10 ()s, 3, CH_3-C(6)), 2.63 (t, J = 2.4 Hz, 1, $CH_2C{\equiv}CH$), 3.11 (d, J = 2.4 Hz, 2, $CH_2C{\equiv}CH$), 12.25 (bs, 2, NHCSNH). ^{13}C NMR (Me_2SO-d_6) δ 13.27, 15.90, 70.51, 80.99, 110.25, 149.93, 160.51, and 174.31. Anal. Calcd for $C_8H_8N_2OS$: C, 53.32; H, 4.47; N, 15.54. Found: C, 53.30; H, 4.60; N, 15.74.

6-Methyl-5-(2-propynyl)-2,4(1*H*,3*H*)-pyrimidinedione (8). The thiopyrimidine 7 (15.69 g, 87 mmol) was added to a solution of $ClCH_2COOH$ (26.5 g, excess) in 50 mL of EtOH and 250 mL of H_2O, and the suspension was refluxed for 7 h at which time the clear, light yellow solution showed no starting material and only one UV (254 nm) active component by TLC (10% MeOH–ether) at R_f = 0.52. The reaction was cooled slowly, and filtration and thorough rinsing with ice-cold EtOH to remove the mephitic odor of thioacetic acid yielded a good crop of small, colorless needles. The crystals were dissolved in hot *i*-PrOH and recrystallized with slow cooling to give 11.85 g (83%) of fine, white needles which melted from 268 to 270 °C dec: ^{1}H NMR (Me_2SO-d_6) δ 2.05 (s, 3, CH_3-C(6)), 2.60 (t, J = 2.4 Hz, 1, $CH_2C{\equiv}CH$), 3.10 (d, J = 2.4 Hz, 2, $CH_2C{\equiv}CH$), 10.62 (s, 1, NH), 10.97 (s, 2, NH); ^{13}C NMR (Me_2SO-d_6) δ 13.22, 16.14, 70.17, 82.01, 104.74, 149.79, 150.76, and 163.63. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.28; H, 5.05; N, 17.05.

2,4-Dichloro-6-methyl-5-(2-propynyl)pyrimidine (9). The dioxopyrimidine 8 (12.07 g, 74 mmol) was stirred into a solution of 100 mL of $POCl_3$ and 0.5 mL of DMF. The mixture was refluxed for 5 h and turned dark black by this time. All excess $POCl_3$ was distilled off, and the thick, black tar was dissolved in ether and poured into 100 mL of ice water. Next, the mixture was separated, the aqueous layer was extracted with ether (2 × 200 mL), and the organic phases were combined, extracted with brine (100 mL), and dried over anhydrous Na_2SO_4. The ether was removed, and the black tar was dissolved in hot *n*-hexane and rinsed over a small column of silica gel (220–400 mesh) to remove color and polar impurities. The eluant was concentrated, and cooling yielded 12.38 g (84%) of broad, white plates which melted from 71.5 to 72.5 °C: ^{1}H NMR ($CDCl_3$) δ 2.11 (t, J = 2.7 Hz, 1, $CH_2C{\equiv}CH$), 2.74 (s, 3, CH_3-C(6)), 3.72 (d, J = 2.7 Hz, 2, $CH_2C{\equiv}CH$); ^{13}C NMR ($CDCl_3$) δ 18.74, 22.49, 75.69, 77.25, 125.90, 157.84, 161.35, 170.66. GC–MS: The gas chromatogram was run on a 6-ft OV-17 column with temperature programming from 150 to 250 °C at 16 °C/min. One peak was observed with a retention time of 5.2 min. MS: m/e 204.1 (M + 4, 11.5), 202.2 (M + 2, 64.5), 200.2 (M^+, 100), 165.1 (M - Cl). Anal. Calcd for $C_8H_6N_2Cl_2$: C, 47.49; H, 3.01; N, 13.93; Cl, 35.27. Found: C, 47.61; H, 3.00; N, 13.97; Cl, 34.96.

2,4-Dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine (10). The 2,4-dichloropyrimidine 9 (3.70 g, 18 mmol) was dissolved in a solution of $B_{10}H_{14}$ (2.51 g, 21 mmol), dry CH_3CN (2.0 mL), and 150 mL of dry toluene, and the reaction was gently refluxed for 20 h at which time TLC (20% ether–petroleum ether) showed no more starting material. The reaction was cooled and rinsed over a small column of silica gel (220–400 mesh) to remove polar, colored impurities. The eluant was concentrated and redissolved in a minimum of hot *n*-hexane by dripping in ethyl acetate until all oil had dispersed. Cooling gave light yellow needles which were recrystallized from the same solvent system to yield 4.28 g (74.5%) of white, threadlike needles which melted from 152 to 154 °C: ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3, CH_3-C(6)), 3.74 (bm, 3, $C_2B_{10}H_{11}CH_2$-C(5) and H-C(2) of carborane). The peak at 3.74 δ had a slightly downfield shoulder which was attributed to the proton on the 2-carbon of the *o*-carborane ring system: ^{13}C NMR ($CDCl_3$) δ 23.47, 36.14, 61.11, 71.69, 125.42, 159.06, 163.11, and 171.98. GC–MS: The gas chromatogram was run on a 6-ft OV-17 column with temperature programming from 200 to 260 °C at 16 °C/min. One broad peak was observed at 11.8 min. MS: $B_{10}C_8H_{16}Cl_2N_2$ m/e 318.3 (M^+), 283.3 (318.3 = Cl), 175.1 (318.3 - $C_2B_{10}H_{11}$). Anal. Calcd for $B_{10}C_8H_{16}Cl_2N_2$: C, 30.10; H, 5.06; N, 8.78; Cl, 22.21; B, 33.86. Found: C, 29.85; H, 5.08; N, 8.61; Cl, 22.43; B, 33.64. IR (KBr, cm^{-1}) 3060 m (C–H stretch of *o*-carborane), 2610 vs (B–H).

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Three Synthetic Routes to a Sterically Hindered Tetrazole. A New One-Step Mild Conversion of an Amide into a Tetrazole

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5-[4′-Methyl-1,1′-biphenyl-2-yl]-1*H*-tetrazole (6), which contains a sterically hindered *o*-tetrazole group, was synthesized by three different routes, one of them employing a new tetrazole synthesis. The first involved the reaction of trialkyltin azides with 4′-methyl-1,1′-biphenyl-2-carbonitrile (3). The resultant trimethyltin–tetrazole adduct could be hydrolyzed with acid to yield biphenylyltetrazole 6. The tri-*n*-butyltin–tetrazole adduct, however, was transformed into the corresponding *N*-trityl-protected tetrazole 5 to permit removal of the organic soluble tri-*n*-butyltin byproducts. The trityl group also permits 5 to be brominated at the benzylic position and then alkylated by imidazole derivatives. Subsequent acid hydrolysis of the trityl protecting group of 5 yielded biphenylyltetrazole 6. The second synthesis involved the nitrosation of an *N*-(2-cyanoethyl)-protected biphenylamidrazone 10 using N_2O_4 (g) to yield *N*-(2-cyanoethyl)-protected tetrazole 12. Aqueous base removes the cyanoethyl protecting group to yield biphenylyltetrazole 6. The third method involves the novel transformation of an *N*-(2-cyanoethyl)-substituted amide into the corresponding *N*-(2-cyanoethyl)-protected tetrazole *in one step* using triphenylphosphine, diethyl azodicarboxylate (DEAD), and azidotrimethylsilane. Subsequent base hydrolysis of the cyanoethyl group yielded 6 as before. Examples are also provided of the application of this new reaction to other *N*-(2-cyanoethyl)-protected carboxamides.

DuP 753 (1) is the first nonpeptide angiotensin II receptor antagonist currently in clinical trials for the treatment of hypertension.[2] This molecule is one example of an increasing number of drugs containing a tetrazole

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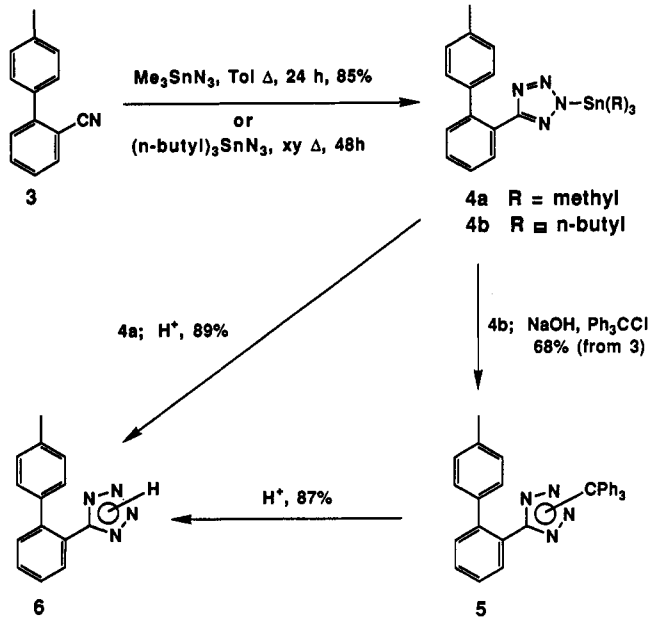
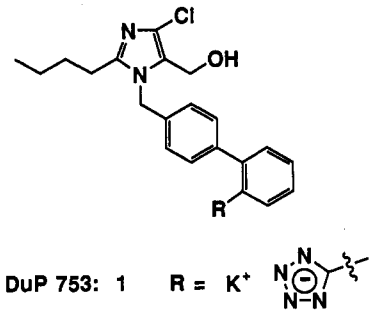
Scheme I



ring that functions as a more metabolically stable isostere for the carboxylic acid group.[3]

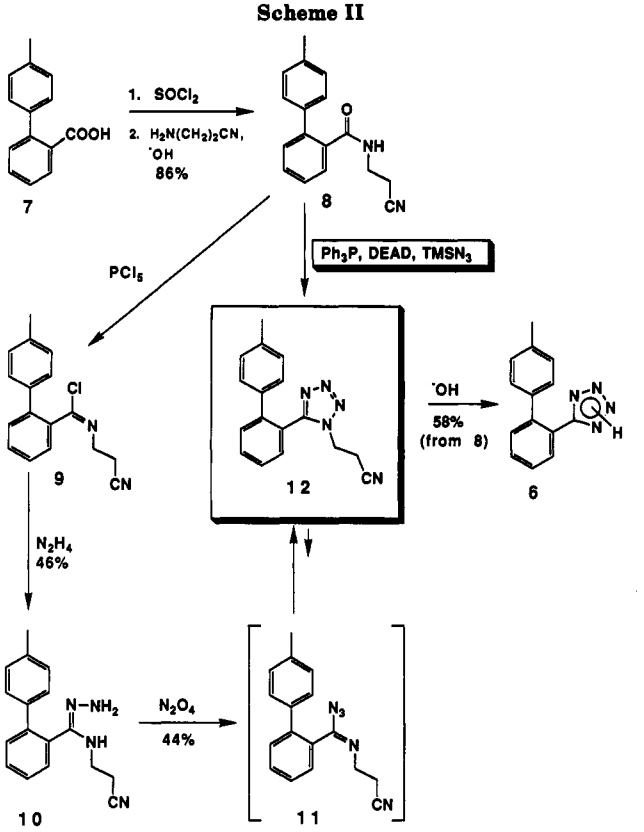


DuP 753: 1 R = K+

2 R = CN

In the original synthesis[2] of 1 using the classical ammonium chloride/sodium azide procedure[4], the tetrazole was formed from the corresponding nitrile 2 in poor yield (33%) and required tedious chromatographic purification. An accelerated rate calorimetry analysis of this reaction showed that at the temperature of tetrazole formation (~115 °C), exothermic decomposition of the product occurs yielding volatile products (N_2, HN_3?) with a rather large heat of decomposition of -66 kcal/mol, thereby making the reaction unsafe. The most likely cause of the poor yield is the sterically hindered nature of the *o*-nitrile group. We have since discovered three synthetic alternatives to the above reaction, one of which is a new and

Scheme II



novel reaction involving the *direct conversion of an amide into a tetrazole in one step*!

Using biphenylnitrile 3 as a model system, we discovered that both trimethyl- and tri-*n*-butyltin azide react exceptionally well in forming the trialkyltin–tetrazole adducts (Scheme I). For example, 1 equiv of trimethyltin azide[5] is added to a toluene solution of 3. The mixture is refluxed and eventually forms a solution. After the mixture is continuously refluxed, insoluble tin–tetrazole adduct 4a begins to precipitate. When the reaction is finished after 23 h, the product is simply filtered and dried to yield 85% of product 4a. Subsequent acid hydrolysis yields tetrazole 6.

Tri-*n*-butyltin azide is prepared more conveniently in situ since it is an oil.[5] Thus, to a solution of biphenylnitrile 3 in xylene is added 1 equiv each of tri-*n*-butyltin chloride and sodium azide (Scheme I). The mixture is refluxed in xylene for 43 h or toluene for 70 h. The higher temperature and/or longer reaction time are required because of the more bulky character of the tri-*n*-butyltin reagent. The tri-*n*-butyltin–tetrazole adduct 4b is not isolated, but is reacted in the same flask to form the solid trityl-protected tetrazole 5 as discussed in the following text.

To remove the tributyltin moiety, one must transpose the tin group with a trityl protecting group because the tri-*n*-butyltin group when hydrolyzed cannot be satisfactorily removed due to its solubility in organic solvents. This transformation is accomplished by simply adding 1 equiv of sodium hydroxide to 4b followed by trityl chloride to yield in a few hours at room temperature the trityl-protected biphenylyltetrazole 5. One may wash away much of the tri-*n*-butyltin byproducts at this point using solvents such as heptane/water mixtures that solubilize the tri-*n*-butyltin derivatives and not 5.[6] Not only does the trityl

(1) (a) Pharmaceutical Research Division. (b) Chemical Development Division.

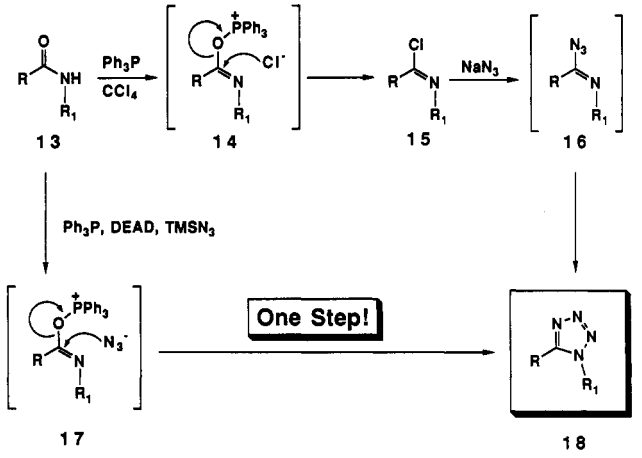
(2) Carini, D. J.; Duncia, J. J. V. Eur. Pat. Appl. 0253310, January 20, 1988.

(3) For a review, see: Singh, H.; Chawla, A.; Kapoor, V.; Paul, D.; Malkorta, R. *Progr. Med. Chem.* **1980**, *17*, 151. Some recent examples include: Fu-Chih, H.; Galemmo, R. A., Jr.; Johnson, W. H., Jr.; Poli, G. B.; Morrissette, M. M.; Mencel, J. J.; Warus, J. D.; Campbell, H. F.; Nuss, G. W.; Carnathan, G. W.; Van Inwegen, R. G. *J. Med. Chem.* **1990**, *33*, 1194. Prous, J. R., Ed. *Drugs Future* **1990**, *15*, 549. Anderson, D. W.; Campbell, M. M.; Malik, M. *Tetrahedron Lett.* **1990**, *31*, 1755. Gapinski, D. M.; Roman, C. R.; Rinkema, L. E.; Fleisch, J. H. *J. Med. Chem.* **1988**, *31*, 172. Bernstein, P. R.; Vacek, E. P. *Synthesis* **1987**, 1133. Yoshida, C.; Tanaka, K.; Hattori, R.; Fukuoka, Y.; Komatsu, M.; Kishimoto, S.; Saikawa, I. *J. Antibiot.* **1986**, *39*, 215.

(4) Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908.

(5) Luitjen, J. G.; Janssen, M. J.; Van Der Kirk, G. J. M. *Recl. Trav. Chim. Pays-Bas* **1963**, *81*, 286.

Scheme III



group in **5** aid in the removal of tin derivatives, but it serves as a tetrazole protecting group as well. Thus, **5**, can be brominated at the benzylic position and alkylated by imidazole derivatives, and finally, the tetrazole can be deprotected to yield **1**.[7] Detritylation of **5** in aqueous acid yields biphenylyltetrazole **6**.

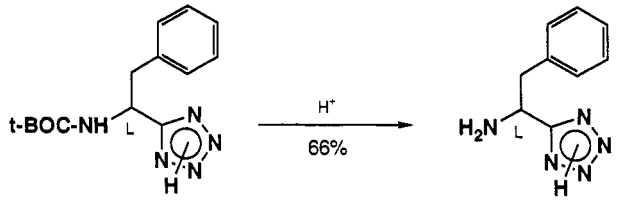
Tetrazoles can be formed from amidrazones through nitrosation.[8] We have found that the recently reported nitrosating reagent dinitrogen tetroxide gas used for the conversion of hydrazines into azides[9] also converts amidrazone **10** into protected tetrazole **12**. (Scheme II). Other nitrosating reagents were not as successful. We have introduced the cyanoethyl protecting group to facilitate conversion of amide **8** into iminoyl chloride **9** by the use of PCl_5. Without the presence of an alkyl protecting group, PCl_5 would convert an unsubstituted amide back to nitrile **3**. The cyanoethyl group is stable to the HCl formed in the synthesis of **9** and to hydrazine in the synthesis of **10**. However, it is labile in aqueous base so that tetrazole **12** can be easily deprotected to form biphenylyltetrazole product **6**.

Iminoyl chloride **15** when reacted with sodium azide forms an iminoyl azide **16** that then tautomerizes to tetrazoles **18** (Scheme III).[10] One way to make iminoyl chlorides is to react a secondary amide with triphenylphosphine in carbon tetrachloride.[11] The mechanism involving the displacement by chlorine anion of an incipient triphenylphosphine oxide molecule is shown by intermediate **14** (Scheme III). It occurred to us that Cl^- could be replaced with N_3^- (intermediate **17**) so that the end result is the conversion of amide **13** into tetrazole **18** *in one step*. Indeed, amide **8** in the presence of triphenylphosphine, diethyl azodicarboxylate (DEAD), and azidotrimethylsilane (an organic solvent soluble source of azide anion) reacts to form tetrazole **12** as shown in Scheme II. Removal of the cyanoethyl protecting group as described previously yields biphenylyltetrazole **6** in 58% overall yield for the two steps.

This new reaction can be applied to other substrates as well, the reactions of which are summarized in Table I. The reaction conditions were not optimized for any of the substrates. Examination of the table reveals that both aliphatic and aromatic amides will react to form tetrazoles. We see that as the steric hindrance around the carboxamide increases, the yields of product tetrazole steadily decrease. For example, in the aliphatic series, least hindered amides **20a** and **20b** give rise to the highest yields of tetrazole products **21a** and **21b**, while **20c** having a neighboring quaternary center reacts poorly (9% yield) to produce **21c**. The low yield of **21f** will be discussed shortly. In the aromatic amide series, the same trend can also be discerned. For example, **20e**, which has two sterically hindering ortho substituents, produces the lowest yield of tetrazole product **21e**, as opposed to products **6** and **21d** that were produced in higher yields due to less steric hindrance.

It is possible to carry out both the tetrazole-forming and the cyanoethyl group deprotection steps consecutively in the same reaction flask. Thus, amide **8** can be converted into tetrazole **6** "in one pot" in an overall yield of 53%, which is slightly less than the yield of 58% where the intermediate cyanoethyl-protected tetrazole **12** (Scheme II) is first isolated and purified. During the workup, the acidity of the tetrazole permits product **6** of the "one-pot reaction" to be soluble in aqueous 1 N sodium hydroxide, while the excess starting materials can be washed out with ether. Subsequent reacidification of the aqueous layer yields tetrazole **6**, circumventing entirely the need for chromatographic purification of intermediate **12**. Unfotunately, in the case of **20f**, some of its tetrazole product **21f** is soluble in ether so that a lower yield resulted when this "one-pot" procedure was employed.

Chirality is preserved in the synthesis of the tetrazole analogue of BOC-L-phenylalanine (**21b**). Deprotection of **21b** yields the tetrazole analogue of L-phenylalanine **22**,[12] which by chiral HPLC is optically pure within limits of detection.[17]



21b **22**

We have presented several methods for synthesizing a sterically hindered tetrazole, one of which involved a newly discovered tetrazole-forming reaction. We hope that these methods might prove to be useful in medicinal chemistry where the tetrazole group is increasingly becoming more important as a carboxylic acid isostere.[3]

Experimental Section

Physical Methods. Melting points (uncorrected) were determined in an open capillary with a Thomas-Hoover melting point apparatus. NMR spectra were determined with an IBM Bruker 200SY (200-MHz) or a Varian VXR300 (300-MHz) spectrometer containing tetramethylsilane as internal standard.

(6) Although elemental analysis works out quite well for the molecular formula, the tin analysis sometimes detects up to a few hundred ppm of tin depending on how well the material was washed to remove the tri-*n*-butyltin residues. Flash chromatography[13] over silica gel reduces the tin levels below 1 ppm.

(7) Carini, D. J.; Wong, P. C. B.; Duncia, J. J. V. Eur. Pat. Appl. 0324377, July 19, 1989, p 191. Carini, D. J.; Duncia, J. V., et al. *J. Med. Chem.*, submitted for publication.

(8) Neilson, D. G.; Roger, R.; Heatlie, J. W. M.; Newlands, L. R. *Chem. Rev.* **1970**, *70*, 163.

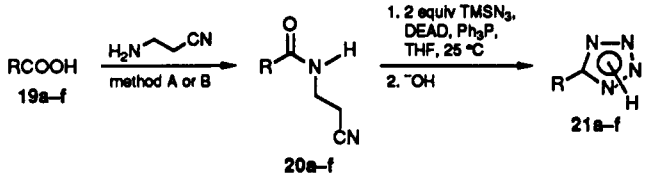
(9) Kim, Y. H.; Kim, K.; Shim, S. B. *Tetrahedron Lett.* **1986**, *27*, 4749.

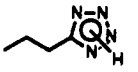
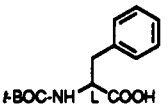
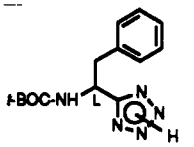
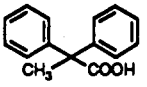
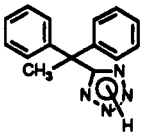
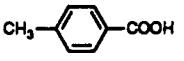
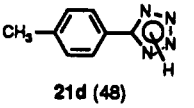
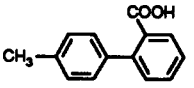
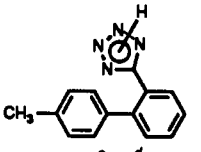
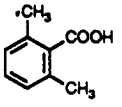
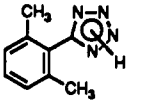
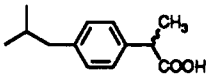
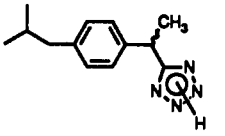
(10) Harvill, E. K.; Herbst, R. M.; Schreiner, E. C.; Roberts, C. W. *J. Org. Chem.* **1950**, *15*, 662.

(11) Appel, R. *Angew. Chem.* **1975**, *14*, 806.

(12) The literature $[\alpha]^{27}_D$ value for tetrazole **22** is +57.5 (c = 0.79 DMF): Morley, J. S. *J. Chem. Soc. (C)* **1969**, 809. Although our sample would dissolve in hot DMF, it would not remain soluble in DMF at lower temperatures to permit an optical rotation determination. Our $[\alpha]^{25}_D$ value is +46.4 (c = 0.74 DMSO).

Table I. Yields for the Conversion of Carboxylic Acids (19) into *N*-(Cyanoethyl)amides (20) and into Tetrazoles (21)



	RCOOH (19)	method A or B[a,b]	% yield 20 (from 19)	RCN_4H (21)[c] (% yield from 19)
19a	$CH_3CH_2CH_2COOH$	A	91	 21a (39)
19b	 (BOC-L-Phe)	B	95	 21b (65)[d]
19c		B	85	 21c (9)
19d		A	74	 21d (48)
7		A	8: 87	 6 (58,[c] 53[d])
19e		A	38	 21e (34)
19f	 (±-ibuprofen)	A	97	 21f (15)[d]

[a] Method A: The carboxylic acid was converted into its acid chloride followed by coupling with the amine in aqueous base. [b] Method B: The carboxylic acid was coupled to the amine with dicyclohexylcarbodiimide. [c] The intermediate *N*-(cyanoethyl)tetrazole was first purified via chromatography before deprotection with aqueous base. [d] The intermediate *N*-(cyanoethyl)tetrazole was not isolated.

Microanalyses were performed by Micro-analysis, Inc., Wilmington, DE, or Quantitative Technologies, Inc., Bound Brook, NJ, and were within 0.4% of the calculated values. Chromatography was done by using the medium-flash method.[13]

5-[4′-Methyl-1,1′-biphenyl-2-yl]-2-(trimethylstannyl)-2*H*-tetrazole (4a). 4′-Methyl-1,1′-biphenyl-2-carbonitrile[2] (3) (13.00 g, 67 mmol, 1 equiv), trimethyltin azide (15.00 g, 73 mmol, 1.1 equiv), and toluene were mixed and refluxed under nitrogen for 23 h. The mixture was cooled, and the precipitated product was filtered, washed with toluene (2 × 20 mL), and dried in vacuo at 40 °C to yield 22.8 g (85%) of a white solid: mp >250 °C; NMR (DMSO-d_6) δ 7.50 (m, 4 H), 7.00 (m, 4 H), 2.20 (s, 3 H), 0.35 (s, 9 H).

5-[4′-Methyl-1,1′-biphenyl-2-yl]-1*H*-tetrazole (6) (via Hydrolysis of 4a). 5-[4′-Methyl-1,1′-biphenyl-2-yl]-2-(trimethylstannyl)-2*H*-tetrazole (4a) (20.4 g, 51.1 mmol) was slurried in a mixture of toluene (150 mL) and THF (8 mL) at room temperature. The mixture was stirred, and anhydrous hydrogen chloride gas was added to give a clear solution followed by precipitation of the product. The mixture was cooled and the product filtered, washed with toluene (1 × 20 mL), and dried in vacuo at 60 °C to yield 9.4 g (78%) of a white solid, mp 146.0–149.0 °C. A second crop was obtained by bubbling additional hydrogen chloride gas into the filtrate: yield 1.34 g (11%); mp 147.0–149.0 °C. The NMR spectrum of this product matches that of the product obtained from the hydrolysis of 12.

5-[4′-Methyl-1,1′-biphenyl-2-yl]-1-(triphenylmethyl)-1*H*-tetrazole (5). 4′-Methyl-1,1′-biphenyl-2-carbonitrile (3) (9.00 g, 47 mmol, 1 equiv), sodium azide (3.00 g, 46 mmol, 1 equiv), tributyltin chloride (16.4 g, 50 mmol, 1.1 equiv), and toluene were heated at 110 °C with mechanical stirring for 70 h. The mixture was diluted with toluene (35 mL) and cooled to room temperature. NaOH (10 N; 5.5 mL, 55 mmol, 1.2 equiv) and triphenylmethyl

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2938.

chloride (13.5 g, 48 mmol, 1 equiv) were added and the resulting mixture stirred for 3 h at room temperature. Water (35 mL) and *n*-heptane (70 mL) were added, and the resulting slurry was cooled in an ice bath for $1^1/_2$ h. The mixture was filtered, and the resultant solids were washed with water (2 × 50 mL) and with a 3:2 v/v mixture of heptane/toluene (50 mL). The solids were dried overnight at 40 °C to yield 18.3 g (82%). This crude product was dissolved in methylene chloride (200 mL) and washed with 0.4 N NaOH (1 × 52 mL). The organic phase was filtered and the solvent removed in vacuo. The resultant solids were reslurried with heptane (100 mL), filtered, and dried in vacuo at 40 °C to yield 15.1 g of a white solid (68% overall yield): mp 161.0–162.0 °C; NMR ($CDCl_3$) δ 8.37 (s, 1 H), 8.10 (d, 1 H, J = 9 Hz), 7.67 (d, 1 H, J = 9 Hz), 7.59–7.14 (m, 20 H), 2.40 (s, 3 H). Anal. ($C_{33}H_{26}N_4$) C, H, N.

5-[4′-Methyl-1,1′-biphenyl-2-yl]-1*H*-tetrazole (6) (via Hydrolysis of 5). 5-[4′-Methyl-1,1′-biphenyl-2-yl]-1-(triphenylmethyl)-1*H*-tetrazole (5 8.63g), trifluoroacetic acid (5.0 mL), water (5.0 mL), and THF (30 mL) were mixed and stirred at room temperature for 2 h. An additional amount of trifluoroacetic acid (20 mL) and water (20 mL) was added, and the contents were stirred for an additional 24 h at room temperature. The reaction was worked up by adding 10 N NaOH until pH = 10, and the mixture was washed with methylene chloride (3 × 50 mL). The aqueous layer was acidified to pH = 3 with 1 N HCl and then extracted with ethyl acetate (3 × 50 mL). The organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo to yield 4.82g of crude product. Recrystallization from *n*-butyl chloride/chloroform yielded 3.18 g (87%) of a white solid, mp 145.0–146.5 °C. The NMR spectrum of this product matches that of the product obtained from the hydrolysis of 12.

***N*-(2-Cyanoethyl)-4′-methyl-1,1′-biphenyl-2-carboxamide (8).** 4′-Methyl-1,1′-biphenyl-2-carboxylic acid[2] (7) (50.00 g, 236 mmol, 1 equiv), thionyl chloride (87.5 mL, 1.2 mol, 5.1 equiv), and chloroform (500 mL) were mixed and refluxed for 4 h. The solvent was removed in vacuo and the residue evaporated twice from toluene with the rotary evaporator to remove traces of thionyl chloride. The acid chloride thus obtained was dissolved in THF (250 mL) and dripped in five equal portions alternating with five equal portions of 1.000 N NaOH (236 mL) into a solution of 2-aminopropionitrile fumarate (30.25 g, 236 mmol, 1 equiv) in 1.000 N NaOH (236 mL) at 0 °C. After 12 h at room temperature, water (250 mL) was added and the contents were extracted with ethyl acetate (3 × 500 mL). The organic layers were collected and dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was recrystallized from methylcyclohexane to yield 53.50 g (86%) of a white solid: mp 102.0–103.5 °C; NMR ($CDCl_3$) δ 7.68 (d, 1 H, J = 7 Hz), 7.56–7.19 (m, 7 H), 5.65 (b m, 1 H), 3.43 (dt, 2 H, J = 7, 7 Hz), 2.39 (t, 2 H, J = 7 Hz). Anal. ($C_{17}H_{16}N_2O$) C, H, N.

***N*-(2-Cyanoethyl)-4′-methyl-1,1′-biphenyl-2-carboximidic Acid Hydrazide (10).** *N*-(2-Cyanoethyl)-4′-methyl-1,1′-biphenyl-2-carboxamide (8 35.5 g, 126.7 mmol, 1 equiv) and phosphorous pentachloride (29.01 g, 139.3 mmol, 1.1 equiv) were mixed and gently heated under aspirator vacuum with a heat gun to maintain a slow but constant evolution of gas. After gas evolution had stopped (15–30 min), the resultant oil was dissolved in 300 mL of dioxane and hydrazine was slowly added thereto (20.09 mL, 633.7 mmol, 5 equiv). The resultant biphasic mixture was stirred overnight at room temperature. The solvent was removed in vacuo and the residue partitioned between water and ethyl acetate. The organic layers were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to yield an orange glass. Slurrying this glass in 1:1 hexane/ethyl acetate yielded 16.14 g (46%) of a light pink solid: mp 146.5–147.0 °C; NMR ($CDCl_3$) δ 7.60–7.16 (m, 10 H), 6.15 (m, 1 H), 2.98 (dt, 2 H, J = 7, 7 Hz), 2.40 (s, 3 H), 1.93 (t, 2 H, J = 7 Hz). Anal. ($C_{17}H_{18}N_4$) C, H, N.

5-[4′-Methyl-1,1′-biphenyl-2-yl]-1*H*-tetrazole-1-propanenitrile (12). *N*-(2-Cyanoethyl)-4′-methyl-1,1′-biphenyl-2-carboximidic acid hydrazide (10; 2.00 g, 7.2 mmol, 1 equiv) was slurried in acetonitrile (40 mL) and to this mixture was added a solution of 0.73 M dinitrogen tetroxide gas in carbon tetrachloride (19.6 mL, 14.4 mmol, 2 equiv) at room temperature. The entire contents eventually formed a solution. After 24 h, the solvent was removed in vacuo to yield an orange solid. This solid was dissolved in *n*-butyl chloride and the insoluble matter filtered. The filtrate was evaporated to yield 1.44 g of an orange oil that was flash chromatographed in 1:1 hexane/ethyl acetate to yield 1.10 g of a light yellow oil that eventually solidified. Recrystallization from hexane/*n*-butyl chloride yielded 910 mg (44%) of a pale yellow crystalline powder: mp 90.0–92.0 °C; NMR ($CDCl_3$) δ 7.76–7.50 (m, 4 H), 7.17 (d, 2 H, J = 10 Hz), 7.04 (d, 2 H, J = 10 Hz), 3.80 (t, 2 H, J = 7 Hz), 2.37 (s, 3 H), 2.24 (t, 2 H, J = 7 Hz). Anal. ($C_{17}H_{15}N_5$) C, H, N.

5-[4′-Methyl-1,1′-biphenyl-2-yl]-1*H*-tetrazole-1-propanenitrile (12) (Synthesized from Amide 8). *N*-(2-Cyanoethyl)-4′-methyl-1,1′-biphenyl-2-carboxamide (8 1.00 g, 3.8 mmol, 1 equiv), triphenylphosphine (0.99 g, 3.8 mmol, 1 equiv), diethyl azodicarboxylate (0.60 mL, 3.8 mmol, 1 equiv), trimethylsilyl azide (0.50 mL, 3.8 mmol, 1 equiv), and THF were mixed and stirred at room temperature under N_2. After 24 h, another 1 equiv of each of the above reagents was added and the mixture was stirred for another 24 h. The mixture was cooled to 0 °C, and an excess of a 5.5% aqueous solution of ammonium cerium(IV) nitrate (300 mL, 15 mmol, 4 equiv) was slowly added (**caution**: N_2 evolution!). THF was then also added (100 mL) to dissolve the precipitated organic matter. The mixture was then checked for azide ion by use of the ferric chloride procedure[14] and IR and was found negative. The aqueous mixture was extracted with methylene chloride (3 × 250 mL). The organic layers were combined and dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was flash chromatographed in 75:25 hexane/ethyl acetate over silica gel to yield 1.68 g of a light yellow oil. NMR shows the presence of product, possibly a cyanoethyl isomer of the product and 1,2-dicarbethoxyhydrazine. This product was taken to the next step without further purification.

5-[4′-Methyl-1,1′-biphenyl-2-yl]-1*H*-tetrazole (6) (via Hydrolysis of 12). 5-[4′-Methyl-1,1′-biphenyl-2-yl]-1*H*-tetrazole-1-propanenitrile (12; from the previous step) (1.68 g, 3.8 mmol, 1 equiv), 1.000 N NaOH (37.5 mL, 3.8 mmol, 1 equiv), and THF (20 mL) were mixed and stirred at room temperature for 1 h under N_2. Methanol (25 mL) was added to aid in dissolution, and the mixture was stirred for another 72 h. The mixture was acidified with 1 N HCl to pH = 3–4 and extracted with ethyl acetate (1 × 100 mL). The organic layer was separated and washed with 1 N HCl (2 × 50 mL) and with brine (1 × 50 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to yield 850 mg (95% from 8) of a white solid. Recrystallization from *n*-butyl chloride yielded 516 mg (58% from 8) of a white solid: mp 145.5–146.5 °C; NMR (DMSO-d_6) δ 16.30 (m, 1 H), 7.73–7.52 (m, 4 H), 7.14 (d, 2 H, J = 9 Hz), 6.97 (d, 2 H, J = 9 Hz), 2.28 (s, 3 H). Anal. ($C_{14}H_{12}N_4$) C, H, N.

5-[4′-Methyl-1,1′-biphenyl-2-yl]-1*H*-tetrazole (6) (Synthesized from Amide 8 in One Pot). *N*-(2-Cyanoethyl)-4′-methyl-1,1′-biphenyl-2-carboxamide (8; 1.33 g, 5.0 mmol, 1 equiv), triphenylphosphine (2.64 g, 10.1 mmol, 2 equiv), diethylazodicarboxylate (1.58 mL, 10.1 mmol, 2 equiv), trimethylsilyl azide (1.34 mL, 10.1 mmol, 2 equiv), and THF (50 mL) were mixed and stirred at room temperature under N_2. After 24 h, the solvent and excess trimethylsilyl azide were cautiously removed in vacuo behind a shield. The organic residue was checked for the presence of azide by use of the ferric chloride procedure[14] and IR and was found to be negative. The residue was dissolved in THF, and 1.000 N sodium hydroxide (5.03 mL, 5.0 mmol, 1 equiv) was added with stirring at room temperature. After 24 h, the reaction was incomplete so that another 1 equiv of sodium hydroxide was added. After 1 h, the reaction was complete and the organic solvent was removed in vacuo. The aqueous phase was diluted with water (25 mL) and 1 N sodium hydroxide (10 mL), and this aqueous mixture was extracted with ethyl ether (3 × 25 mL). Methanol (10 mL) was added to the aqueous layer, and the aqueous mixture was acidified to pH = 2 with concd HCl. Solids precipitated, and these were filtered and dried under high vacuum to yield 935 mg (53%) of tetrazole 6, which was identical with the batch obtained previously via the isolation of intermediate 12.

***N*-(Cyanoethyl)-2,2-diphenylpropanamide (20c).** 2,2-Diphenylpropanoic acid (4.65 g, 20.5 mmol, 1 equiv), (2-cyanoethyl)amine (1.44 g, 20.5 mmol, 1 equiv), *N*-hydroxybenzotriazole (2.78 g, 20.5 mmol, 1 equiv), dicyclohexylcarbodiimide (4.66 g,

(14) Feigl, F. *Rec. Trav. Chim. Pays-Bas* **1939**, *58*, 477.

20.5 mmol, 1 equiv), and DMF (50 mL) were mixed and stirred at 0 °C. After 48 h at 0 °C, the DMF was removed in vacuo and the residue flash chromatographed in 9:1 pentane/ethyl acetate to yield 4.84 g (85%) of a white solid: mp 106.5–107.0 °C; NMR ($CDCl_3$) δ 7.45–7.20 (m, 10 H), 5.94 (m, 1 H), 3.47 (t of d, 2 H, J = 7, 7 Hz), 2.62 (t, 2 H, J = 7 Hz), 2.00 (s, 3 H). Anal. ($C_{18}H_{18}N_2O$) C, H, N.

The following compounds were prepared by the procedures used in the synthesis of 8 (method A in Table I).

***N*-(2-Cyanoethyl)butanamide (20a)**: mp 72.5–74.0 °C; NMR (DMSO-d_6) δ 8.17 (s, 1 H), 3.27 (dt, 2 H, J = 7, 7 Hz), 2.63 (t, 2 H, J = 7 Hz), 2.07 (t, 2 H, J = 7 Hz), 1.52 (tq, 2 H, J = 7, 7 Hz), 0.85 (t, 3 H, J = 7 Hz). Anal. ($C_7H_{12}N_2O$) C, H, N.

***N*-(2-Cyanoethyl)-4-methylbenzamide (20d)**: mp 108.0–108.5 °C; NMR (DMSO-d_6) δ 8.78 (t, 1 H, J = 7 Hz), 7.77 (d, 2 H, J = 8 Hz), 7.29 (d, 2 H, J = 8 Hz), 3.49 (dt, 2 H, J = 7, 7 Hz), 2.78 (t, 2 H, J = 7 Hz), 2.36 (s, 3 H). Anal. ($C_{11}H_{12}N_2O$) C, H, N.

***N*-(2-Cyanoethyl)-2,6-dimethylbenzamide (20e)**: mp 148.5–149.5 °C; NMR (DMSO-d_6) δ 8.66 (m, 1 H); 7.16 (t, 1 H, J = 7 Hz), 7.04 (d, 2 H, J = 7 Hz), 3.46 (dt, 2 H, J = 7, 7 Hz), 2.77 (t, 2 H, J = 7 Hz); 2.23 (s, 6 H). Anal. ($C_{12}H_{14}N_2O$) C, H, N.

***N*-(2-Cyanoethyl)-2-[4-(2-methylpropyl)phenyl]propanamide (20f)**: wax; NMR (DMSO-d_6) δ 8.30 (m, 1 H), 7.21 (d, 2 H, J = 8 Hz), 7.06 (d, 2 H, J = 8 Hz), 3.58 (m, 1 H), 3.50–3.10 (m, 2 H), 2.61 (t, 2 H, J = 7 Hz), 2.40 (d, 2 H, J = 7 Hz), 1.95–1.70 (m, 1 H), 1.33 (d, 3 H, J = 7 Hz), 0.86 (d, 6 H, J = 7 Hz). Anal. ($C_{16}H_{22}N_2O$) C, H, N.

The following compound was prepared by procedures used in the preparation of **20c** (method B in Table I).

(*S*)-[2-[(2-Cyanoethyl)amino]-2-oxo-1-(phenylmethyl)-ethyl]carbamic acid, 1,1-dimethylethyl ester (20b): mp 83.5–85.5 °C; NMR (DMSO-d_6) δ 8.31 (t, 1 H, J = 7 Hz), 7.40–7.00 (m, 5 H), 6.96 (d, 1 H, J = 8 Hz), 4.13 (m, 1 H), 3.50–3.15 (m, 2 H), 2.96 (dd, 1 H, J = 7, 7 Hz), 3.00–2.67 (m, 1 H), 2.60 (t, 2 H, J = 7 Hz), 1.40–1.10 (m, 9 H). Anal. ($C_{17}H_{23}N_3O_3$) C, H, N.

The following compounds were prepared by the method described for making tetrazole 6 from amide 8 via the chromatographic purification of intermediate 12.

5-*n*-Propyl-1*H*-tetrazole (21a):[15] wax; NMR (DMSO-d_6) δ 2.86 (t, 2 H, J = 7 Hz), 1.71 (tq, 2 H, J = 7, 7 Hz), 0.91 (t, 3 H, J = 7 Hz). Anal. ($C_4H_8N_4$) C, H, N.

(*S*)-[2-Phenyl-1-(1*H*-tetrazol-5-yl)ethyl]carbamic acid, 1,1-dimethylethyl ester (21b): mp 140.0–144.0 °C; NMR (DMSO-d_6) δ 7.61 (d, 1 H, J = 8 Hz), 7.35–7.10 (m, 5 H), 5.06 (dd, 1 H, J = 7, 7 Hz), 3.40–3.00 (m, 2 H), 1.40–1.00 (m, 9H); $[\alpha]^{25}_D$ (c = 1.02, MeOH) = −15.9 ± 0.8°. Anal. ($C_{14}H_{19}N_5O_2$) C, H, N.

5-[1,1-Diphenylethyl]-1*H*-tetrazole (21c): mp 131.5–134.0 °C; NMR ($CDCl_3$) δ 7.40–7.20 (m, 6 H), 7.20–7.00 (m, 4 H), 2.27 (s, 3 H). Anal. ($C_{15}H_{14}N_4$) C, H, N.

5-[4-Methylphenyl]-1*H*-tetrazole (21d): mp 249.0–250.5 °C; NMR (DMSO-d_6) δ 7.93 (d, 2 H, J = 8 Hz), 7.41 (d, 2 H, J = 8 Hz), 2.40 (s, 3 H). Anal. ($C_8H_8N_4$) C, H, N.

5-[2,6-Dimethylphenyl]-1*H*-tetrazole (21e): mp 168.0–169.5 °C; NMR (DMSO-d_6) δ 7.38 (t, 1 H, J = 8 Hz), 7.23 (d, 2 H, J = 8 Hz), 2.02 (s, 6 H). Anal. ($C_9H_{10}N_4$) C, H, N.

The following compound was made by the same procedure described for making tetrazole 6 from amide 8 in one pot without the isolation of intermediate 12.

(*R,S*)-5-[1-[4-(2-Methylpropyl)phenyl]ethyl]-1*H*-tetrazole (21f):[16] mp 101.0–102.0 °C; NMR (DMSO-d_6) δ 7.30–7.00 (m, 4 H), 4.50 (q, 1 H, J = 7 Hz), 2.38 (d, 2 H, J = 7 Hz), 1.79 (m, 1 H), 1.66 (d, 3 H, J = 7 Hz), 0.86 (d, 6 H, J = 7 Hz). Anal. ($C_{13}H_{18}N_4$) C, H, N.

(*S*)-5-(1-Amino-2-phenylethyl)-1*H*-tetrazole (22). (*S*)-2-phenyl-1-(1*H*-tetrazol-5-yl)ethylcarbamic acid, 1,1-dimethylethyl ester (21b) (500 mg, 1.7 mmol, 1 equiv), 4 N HCl (2.16 mL, 8.6 mmol, 5 equiv), and THF were mixed and stirred at room temperature. After 4 h, another 5 equiv of 4 N HCl was added. After 20 h, the THF was removed in vacuo, water (10 mL) was added, and the pH of the aqueous mixture was adjusted to 4–5 with 10 N NaOH. Solids precipitated. These were filtered and dried under high vacuum to yield 218 mg (66%) of a white powder: mp 273.5–277.0 °C (slow decomposition); NMR (DMSO-d_6) δ 7.30–7.00 (m, 5 H), 4.66 (dd, 1 H, J = 7, 7 Hz), 3.34 (dd, 1 H, J = 7, 7 Hz), 3.16 (dd, 1 H, J = 7, 7 Hz); $[\alpha]^{27}_D$ (c = 0.74, DMSO) = +46.4 ± 1.1°. Anal. ($C_9H_{11}N_5$) C, H, N.

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(15) Borg-Warner Corp., Brit. Pat. GB1163355, September 4, 1969.

(16) Valenti, P.; Rampa, A.; Fabbri, G.; Giusti, P.; Cima, L. *Acta Pharm. Weinheim* **1983**, *316*, 752. Reported mp 90–91 °C.

(17) Both the L enantiomer and the D,L-mixture of 22 were synthesized. Chiral resolution of D,L-22 was achieved on a Crownpak CR column at 40 °C at pH = 3 in 10% ethanol and 90% aqueous perchloric acid. Elution of L-22 under identical conditions showed the presence of only one enantiomer, thereby signifying that the sample is at least 98% the L-isomer.

Formation of Imidazopyridines by the Phase Transfer Catalyzed Reaction of α-(Aminomethyl)pyridines with $CHCl_3$ and Alkaline Hydroxide

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The reaction of chloroform with 2-(aminomethyl)pyridine (1) under basic phase-transfer catalysis affords the highly fluorescent imidazo[1,5-*a*]pyridine (2) in 25% isolated yield. Despite the formation of considerable tarry residue, GC–MS indicates that the volatile fraction of the reaction is simple and consists of 2 and two minor components identified as *N*-(2-pyridylmethyl)formamide (6) and (2-pyridylmethyl)isonitrile (7). The basic phase transfer catalyzed reaction of chloroform with a series of α-(aminomethyl)azanaphthalenes was found to be general and yield the corresponding annulated imidazo derivatives in comparable yields. Despite product yields in the 25% range, GC of the reaction mixtures indicates that the volatile fractions generally consist of residual starting aminomethyl compound, the imidazo product, and a minor amount of the (α-azanaphthylmethyl)formamide. However, 3-(aminomethyl)isoquinoline (18) failed to provide any of the expected imidazo[1,5-*b*]isoquinoline (19). The failure to detect 19 was investigated.

Groundwater contaminated with $CHCl_3$ has become an important public health issue, and considerable effort is being directed toward development of low-cost, on-site analytical methods for monitoring contamination levels. We sought to apply remote fiber fluorometry to groundwater analysis by development of a method capable of

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