Diphenyl Cyancarbonimidate and Dichlorodiphenoxymethane as Synthons for the Construction of Heterocyclic Systems of Medicinal Interest

R. Lee Webb*, Drake S. Eggleston, Clifford S. Labaw,
Joseph J. Lewis and K. Wert

Chemistry Department, Smith Kline and French Laboratories 1500 Spring Garden St.,
Philadelphia, PA 19101

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Simple high yield methods for the preparation of heterocyclic *N*-cyanoguanidines (including the anti-ulcer drug cimetidine), substituted triazoles, benzimidazoles and oxadiazoles with anti-histaminic (H2) activity from the title compounds are described.

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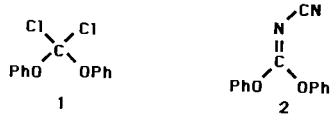
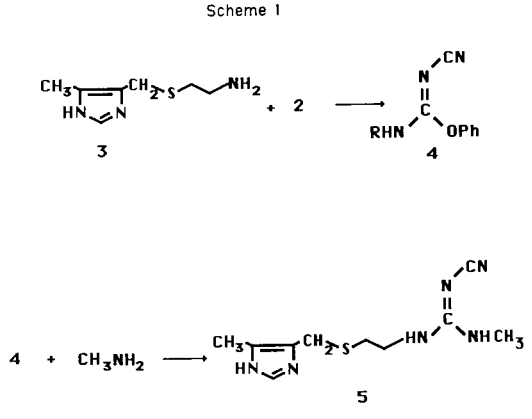
In a previous publication [1] we outlined the large scale synthesis [2] of dichlorodiphenoxymethane **1** and diphenylcyanocarbonimidate **2**.



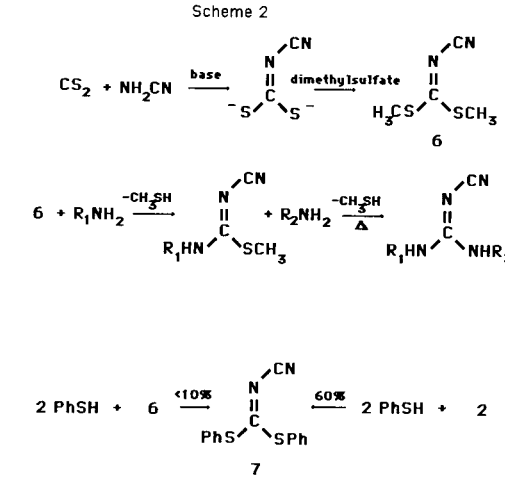
One of our primary goals in undertaking the synthesis of **2** was to provide a simple, low cost, high yield method to prepare *N*-cyanoguanidines which are useful as histamine H2 antagonists. Scheme 1 shows the synthesis of the anti-ulcer drug cimetidine ('Tagamet') **5** from the thioamine **3**. The stepwise displacement of phenol from the phenoxy reagent **2** by amine nucleophiles proceeds rapidly at ambient temperature in a variety of solvents such as alcohols (methanol, ethanol, isopropanol and butanol), ethers (diethylether, tetrahydrofuran) and esters (ethyl acetate, butylacetate). The yields for both steps are in excess of 90%

Scheme 1



in most cases and the reactions are very clean. In addition the phenol formed as a by product during the reaction is highly soluble in these solvents and may be recycled to produce diphenyl carbonate and hence the precursor **1** by treatment with phosphorus pentachloride [1]. The alternate procedure for preparing *N*-cyanoguanidines and a variety of heterocycles utilizes *N*-cyanodithioimidocarbonate **6** [3-9] whose synthesis is shown in Scheme 2. This method generates the malodorous and toxic methyl mercaptan as a by product and the displacement of the second thiomethyl group by amines or other nucleophiles requires more forceful conditions.

Scheme 2

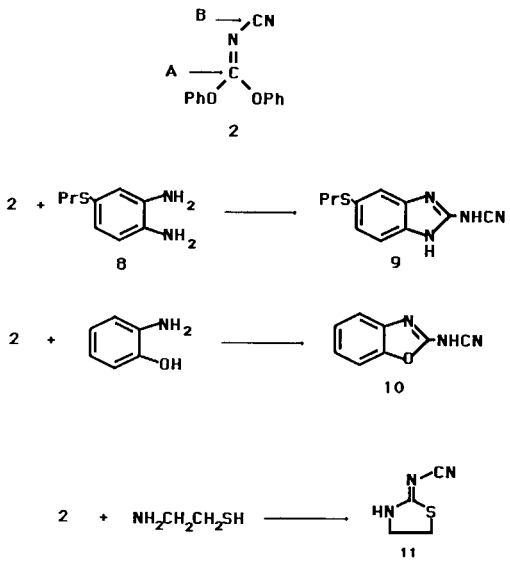


By contrast the use of the phenoxy reagent **2** evolves no gasseous or toxic by-products and the displacement of the second phenoxy group proceeds under milder conditions (often room temperature rather than refluxing 2-propanol).

In the synthesis of other alkyl and arylthio derivatives as exemplified by the dithio analogue **7** higher yields are realized by thiol exchange with the phenoxy reagent **2**.

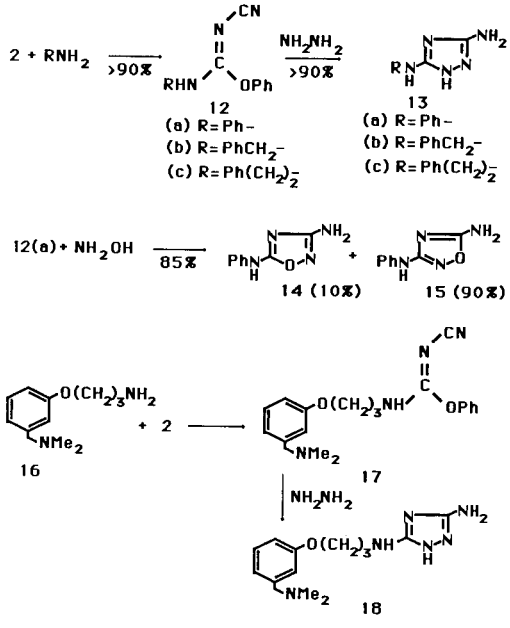
The use of **2** as a synthon for the preparation of *N*-cyanoguanidines thus offers a useful route to these compounds which are often active as histamine H2 receptor antagonists [10]. In addition to the replacement of the phenol moiety at carbon A of **2** by monofunctional nucleophiles, reactions with bifunctional nucleophiles leads to a variety of heterocycles as outlined in Scheme 3.

Scheme 3



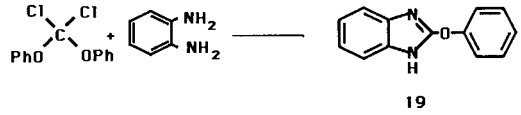
The reaction of a monofunctional nucleophile at carbon atom A of **2** followed by a difunctional nucleophile potentially gives rise to a host of substituted heterocycles. Some of the examples observed to date are shown in Scheme 4.

Scheme 4



Reaction of phenoxy reagent **2** with either aliphatic or aryl amines affords the intermediate isoureas **12** in yields of greater than 90% on stirring in alcohols at room temperature. Conversion to the triazoles **13** takes place on treatment with hydrazine again in high yield. This sequence was used to synthesize the potent H_2 antagonist **18** [11]. Treatment of the isourea **12a** with hydroxylamine affords a mixture of products in a ratio of 90:10. The mixture was separated by recrystallization and the structure of the major component **15** established by X-ray analysis. An ORTEP diagram of **15** is shown as Figure 1. The C3-N2 and C5-N4 bond lengths of 1.311 and 1.314 Å, respectively, clearly establish positions of the double bonds in the oxadiazole ring. These lengths contrast to the C3-N3 bond length of 1.362 Å which is clearly single bond in character. The oxadiazole ring with its primary substituents, and the phenyl ring, are rigorously planar. The dihedral angle between the two planes is 7°. There is intermolecular hydrogen bonding in the crystal with the amino hydrogens but the anilino hydrogen does not appear to be involved in the H-bonding scheme. In addition to the utility of the phenoxy reagent **2** as a synthon, the precursor **1** is itself a useful reagent. Sequence 5 demonstrates the synthesis of the hithertofor unknown 2-phenoxybenzimidazole **19**.

Sequence 5



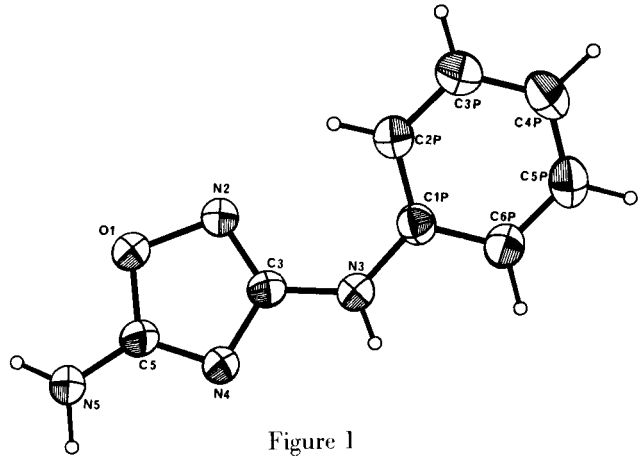


Figure 1

EXPERIMENTAL

Melting points were determined using a Hoover capillary apparatus and are uncorrected. The nmr spectra were recorded on Varian EM 360 and FT 80A instruments. Infrared spectra were run on a Perkin Elmer 137 spectrophotometer. Mass spectra were obtained using Hitachi-Perkin Elmer RMV-GE (ei) and Finnigan 3300 (ci) spectrometers.

1,1-Dichloro-1,1-diphenoxymethane **1** and *N*-cyanodiphenoxyimidocarboante **2** were prepared as outlined in reference [1] as was 2-cyanoaminobenzoxazole **10**.

Table 1

Bond Distances in Angstroms

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	N2	1.452(1)	C1P	C6P	1.390(2)
O1	C5	1.342(1)	C2P	C3P	1.383(2)
N2	C3	1.314(2)	C2P	NC2P	0.934(15)
N3	C1P	1.401(1)	C3P	C4P	1.377(2)
N3	C3	1.362(2)	C3P	HC3P	0.97(2)
N3	HN3	0.84(2)	C4P	C5P	1.372(2)
N4	C3	1.367(2)	C4P	HC4P	0.97(2)
N4	C5	1.311(1)	C5P	C6P	1.381(2)
N5	C5	1.320(1)	C5P	HC5P	0.98(2)
N5	H1N5	0.97(2)	C6P	HC6P	0.998(15)
N5	H2N5	0.87(2)	H1N5	H2N5	1.56(2)
C1P	C2P	1.387(2)			

Numbers in parentheses are estimated standard deviations in the least significant digits.

N-[2[[(5-Methyl-1-*H*-imidazol-4-yl)methyl]thio]ethyl]-*N'*-cyano-*O*-phenylisourea **4**.

To a solution of **3** (180 g, 0.74 mole) [10] in 500 ml of distilled water was added 117 g (0.85 mole) of potassium carbonate in small portions to avoid excessive foaming. The solution was filtered and charged into a 2 liter three necked flask containing 500 ml of ethyl acetate and equipped with a mechanical stirrer. *N*-Cyanodiphenoxyimidocarbonate **2** (172 g, 0.74 mole) was then added with stirring to the two phase system. The mixture was stirred for 4 hours, cooled to 5°. filtered and washed with 200 ml of cold 50:50 ethyl acetate:acetone and dried to yield **4** (215 g, 92%), mp 137-138°; ir (nujol): 2200 cm^{-1} (C≡N), 1637 cm^{-1} (C=N); ^{1}H nmr (DMSO-d_6): δ 2.09 (3H, s), 2.4-3.6 (4H, m), 3.7 (2H, s), 7.0-7.6 (6H, m).

Anal. Calcd. for $C_{15}H_{17}N_5OS$: C, 57.12; H, 5.43; N, 22.20; M$^+$, 315. Found: C, 56.86; H, 5.28; N, 22.23; M$^+$, 315.

N-Cyano-*N'*-methyl-*N''*-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl]-guanidine **5** (cimetidine).

The isourea **4** (240 g, 0.76 mole) was suspended in a solution of 1200 ml of 2-propanol and 600 ml of ethyl acetate containing 118 g (3.8 moles) of monomethylamine. The reaction mixture was stirred overnight, the precipitate filtered, washed with 200 ml ethyl acetate and dried to yield **5** (174 g, 80%), mp 141-143°, lit 141-143 [3,10].

Diphenyl-*N*-cyanodithioimidocarbonate **7**.

Thiophenol (3.8 ml, 38 mmoles) and triethylamine (5.3 ml, 38 mmoles) were dissolved in nitrogen saturated chloroform (180 ml). *N*-cyanodiphenoxyimidocarbonate **2** (4.42 g, 18.6 mmoles) was added in small portions. The solution was stirred overnight at room temperature under nitrogen. After washing with 2 × 200 ml of water the chloroform was evaporated yielding 3.0 g (60%) of a white crystalline mass of **7**, mp 118-119°; ir: 2165 cm^{-1} (C≡N); ^{1}H-nmr (DMSO-d_6): δ 7.1-7.6 (m, aromatics).

Anal. Calcd. for $C_{14}H_{10}N_2S_2$: C, 62.19; H, 3.73; N, 10.36; S, 23.72; M$^+$, 270. Found: C, 61.84; H, 3.77; N, 10.34; S, 23.61.

5-Propylthio-2-cyanoaminobenzimidazole **9**.

A mixture of **2** (2.4 g, 0.01 mole) and 4-propylthio-*o*-phenylenediamine (1.9 g, 0.01 mole) was refluxed in methanol for 6 hours, evaporated and recrystallized from 2-propanol to give 1.74 g (75%) of **9**, mp 220° dec; ir: 2190 cm^{-1} (C≡N); ^{1}H nmr (DMSO-d_6): δ 1.12 (3H, t, J = 7 Hz), 1.8 (2H, m), 3.03 (2H, t, J = 7 Hz), 7.60 (2H, m), 7.71 (1H, s).

Anal. Calcd. for $C_{11}H_{12}N_4S$: C, 56.87; H, 5.21; N, 24.12; S, 13.80; M$^+$, 232. Found: C, 56.65; H, 5.40; N, 24.09; S, 13.88; M$^+$ 232.

2-Cyanoaminothiazolidine **11**.

Sodium hydroxide (0.4 g, 0.01 mole) was dissolved in 10 ml of water containing 1.14 g, 0.01 mole of cysteamine hydrochloride and added with stirring to a suspension of **2** (2.38 g, 0.01 mole) in 20 ml of methanol. The mixture was heated to reflux, cooled, evaporated and the residue recrystallized from aqueous ethanol to yield 1.0 g, of **11**, mp 156-157°, lit 156° [12]. This material was identical in all respects with an authentic sample provided by Dr. H. Graboys of Smith Kline Chemicals.

N-Phenyl-*N'*-cyano-*O*-phenylisourea **12a** was prepared as described in reference [1].

N-Benzyl-*N'*-cyano-*O*-phenylisourea **12b**.

Reaction of 10.70 g, 0.10 mole of benzylamine with 23.8 g (0.10 mole) of **2** under conditions identical to those described above [1] afforded 22.98 g (91%) of **12b**, mp 137-138°; ir: 2200 cm^{-1}; ^{1}H nmr: δ 4.15 (2H, s), 7.0-7.5 (10H, m).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72; M$^+$ 251. Found: C, 71.67; H, 5.33; N, 16.94; M$^+$, 251.

N-2-Phenylethylamino-*N'*-cyano-*O*-phenylisourea **12c**.

Using reaction conditions identical to those described above, 23.8 g (0.1 mole) of **2** and 12.1 g (0.1 mole) of phenethylamine in 250 ml of 2-propanol afforded 24.1 g (91%) of **12c** mp 133-134°; ir: 2200 cm^{-1}; ^{1}H nmr: δ 2.68-2.88 (2H, m), 3.10-3.33 (2H, m), 7.0-7.5 (5H, m).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84; M$^+$ 265. Found: C, 72.45; H, 5.53; N, 15.60; M$^+$, 265.

3-Amino-5-aminophenyl-1,2,4-triazole **13a** was prepared as described in reference [1]. In a similar manner **12b**, 5.02 g (0.02 mole) afforded 3.44 g (91%) of 3-amino-5-benzylamino-1,2,4-triazole **13b**, mp 150-151°; ^{1}H-nmr (DMSO-d_6): δ 4.22 (2H, d), 5.3 (2H, s, broad), 6.1 (1H, s broad), 7.15-7.45 (5H, m), 10.7 (1H, s broad).

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.14; H, 5.86; N, 37.01; M$^+$, 189. Found: C, 57.36; H, 6.01; N, 36.82; M$^+$, 189.

Analogously 5.3 g (0.02 mole) of **12c** gave 3.74 g (92%) of **13c**, mp 118-119°; ^{1}H nmr (DMSO-d_6): δ 2.68-2.88 (2H, m), 3.10-3.33 (2H, m), 7.0-7.5 (10H, m).

Anal. Calcd. for $C_{10}H_{13}N_5$: C, 59.10; H, 6.45; N, 34.46; M$^+$, 203. Found: C, 58.93; H, 6.67; N, 34.55; M$^+$, 203.

5-Amino-3-aminophenyl-1,2,4-oxadiazole **15**.

Compound **12a**, 9.48 g (0.04 mole) was dissolved in 150 ml of methanol and an aqueous solution of hydroxylamine [prepared by dissolving 2.78 g (0.04 mole) of hydroxylamine hydrochloride in 10 ml of water containing 3.2 ml of 50% w/v sodium hydroxide (0.04 mole)] added with stirring. After stirring overnight at room temperature, the mixture was evaporated and taken up in water. The white precipitate was filtered, washed with water and cold 2-propanol and dried to yield 5.99 g (85%) of a white powder mp 159-161°; ir (potassium bromide): 1580, 1565 (C=C, C=N), no nitrile stretch observed.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80; M$^+$, 176. Found: C, 54.47; H, 4.65; N, 32.00; M$^+$, 176.

High pressure liquid chromatography on a Waters micro-bondipack C18 column using acetonitrile:water mobile phase showed two peaks in the ratio 90:10. The ^{13}C nmr spectroscopy showed the presence of small additional aromatic carbon resonances. Recrystallization from 2-propanol several times or formation of the hydrochloride salt from ethanolic hydrogen chloride followed by recrystallization from 2-propanol (mp 176-178°) and regeneration of the free base afforded pure **15**, mp 163-164°; ^{13}C nmr (DMSO-d_6): with off resonance decoupling, δ 117.1, 129.0, 120.6 (2° aromatic carbons), 140.8, 165.5, 169.8 (3° aromatic carbons). Hplc showed a single peak.

X-Ray Analysis of **15**.

A crystal of approximate dimensions 0.30 × 0.35 × 0.35 mm, grown by slow evaporation from acetone/ethyl acetate solution, was mounted on a glass fiber with epoxy for data collection. Preliminary analysis and data collection were performed on an Enraf-Nonius CAD4 diffractometer equipped with graphite monochromated MoKα radiation (λMoKα =

0.71073 Å). A total of 2748 reflections, ($2\theta \leq 60°$; +h +k ±l) were scanned in an ω-θ mode. Of these 1456 unique observations with $I \geq 3\sigma(I)$ were used in the subsequent refinement. Data were corrected for Lorentz-polarization effects but not for absorption. Symmetry equivalent reflections were averaged. The structure was solved by direct methods and refined by full matrix least squares (on F) with the function $\Sigma w(|Fo|-|Fc|)^2$ minimized. All hydrogen positions were located from a difference Fourier map and were refined with isotropic temperature factors. With anisotropic librational parameters for non hydrogen atoms there were 151 variables in the final refinement cycles, including an extinction coefficient which refined to $1.91(1) \times 10^{-6}$. The refinement converged to values of standard crystallographic residuals of R = 0.039 and Rw = 0.0482 (max $\Delta/\sigma = 0.06$). The "goodness of fit" was 1.535. A final difference Fourier map was featureless. Crystal Data: Monoclinic, $P2_1/_n$, a = 7.682(2), b = 9.252(3), c = 12.188(9)Å, $\beta = 104.64°$, Z = 4, Dc = 1.393, Dm = 1.39(1)gcm^{-3}, T = 298K.

N'-Cyano-*N*-[3-[3-[(dimethylamino)methyl]phenoxy]propyl]-*O*-phenylisourea **17**.

To a stirred suspension of **2** (2.3 g, 9.6 mmoles) in 40 ml of ether was added 2.0 g, 9.6 mmoles of 3-(3-aminopropoxy)-*N,N*-dimethylbenzenemethanamine [11] and the mixture stirred 1 hour at room temperature. The white precipitate was filtered and washed with ether to yield after drying 3.1 g (92%) of **17** mp 99-100°; nmr (DMSO-d_6): δ 2.19 (6H, s, $N(CH_3)_2$), 3.15-3.70 (4H, m, CH_2CH_2), 3.38 (2H, s, CH_2NMe_2), 3.89-4.14 (2H, m, OCH_2), 6.62-7.51 (9H, m, aromatics).

Anal. Calcd. for $C_{20}H_{24}N_4O_2$: C, 68.18; H, 6.86; N, 15.90; M^+, 352. Found: C, 68.35; H, 7.01; N, 15.77; M^+, 352.

1-Methyl-N^6-[3-[3-[(dimethylamino)methyl]phenoxy]propyl]-1*H*-1,2,4-triazole-3,5-diamine **18**.

To a suspension of 1.0 g (2.8 mmoles) of **17** in ether was added 0.313 g (2.8 mmoles) of *N*-methylhydrazine and the mixture stirred 1 hour then refluxed 1 hour. The ether was removed and the yellow oil chromatographed on silica using chloroform/methaol as eluent. Recrystallization from petroleum ether/ether yielded after drying 610 mg (72%) of **18** mp 95-97°; lit mp 95-96.5° [11].

2-Phenoxybenzimidazole **19**.

A solution of 1,1-dichloro-1,1-diphenoxymethane **1**, 26.9 g (0.1 mole) in 50 ml of ethyl acetate was added dropwise to a stirred mixture of *o*-phenylenediamine (10.8 g, 0.1 mole) and sodium carbonate (5.3 g, 0.05 mole) in 100 ml of ethyl acetate and stirred at room temperature for 5 hours. The precipitate was filtered, washed with 50 ml of ethyl acetate, dried and slurried in 100 ml of water. The white solid was filtered and dried to afford 11.0 g of **19**, mp 220-222° dec; ir (nujol): 1635 cm^{-1} (C=C), 1585 cm^{-1} (C=N); ^{1}H nmr (DMSO-d_6): δ 6.95-7.68 (aromatics).

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32; M^+, 210. Found: C, 74.00; H, 4.96; N, 13.19; M^+ 210.

Acknowledgement.

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REFERENCES AND NOTES

[1] R. Lee Webb and Clifford S. Labaw, *J. Heterocyclic Chem.*, **19**, 1205 (1982).

[2] The preparation of **1** and **2** has now been routinely carried out on 100 gallon scale in our pilot plant equipment.

[3] U. S. Patent 3,950,333.

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[9] R. Lee Webb and Clifford S. Labaw, unpublished observations.

[10] See for example, G. J. Durant et. al., *J. Med. Chem.*, **20**, 901 (1977); D. E. Bays and R. Stables, *Annual Reports in Medicinal Chemistry*, **18**, Chapter 10, 89 (1983).

[11] GB 2,023,133 Patent to Glaxo.

[12] German Patent 2,205,745 to Thomae GmbH.