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Phenylbiguanide as Electron Donor in Heterocyclic Synthesis

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ABSTRACT: *Phenylbiguanide reacts with some π-acceptors such as TCNE, TCNQ, CNIND, DCNQ, and CHL-o, to afford imidazole and pyrimidine derivatives.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 15:63–66, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10213

INTRODUCTION

Numerous reports have appeared in the literature, describing the cardiovascular reflexes [1–6], agonists and antagonists [3–9], visceral reflexes [10,11], and physiological [12] activity, as well as industrial [13–17] applications of arylbiguanides. Our long-term interest in chemical reactions induced by charge-transfer complexation forms a part of our systematic efforts to obtain new heterocyclic systems [18–27]. We have turned our attention to phenylbiguanide as electron donor towards some π-acceptors, such as tetracynoethylene (TCNE), 2-dicyanomethyleneindane-1,3-dione (CNIND), 2,3-dicyano-1,4-naphthoquinone (DCNQ), tetracyanoquinodimethane (TCNQ), and 3,4,5,6-tetrachloro-1,2-benzoquinone (CHL-*o*), to synthesize some heterocycles with the expectation that they too might exhibit biological activity.

RESULTS AND DISCUSSION

When 1-phenylbiguanide (**1**) was left to react with TCNE in ethyl acetate, compound **2** was obtained (Scheme 1). The structure of **2** was substantiated by elemental analysis and spectroscopic data. The ^{1}H NMR spectrum disclosed the presence of two broad singlets at $\delta = 8.33$ and 7.92 ppm assignable to two amino groups. The presence of these two groups was further elucidated by IR spectrum, which showed two peaks at $\tilde{\nu} = 3365$ and 3336 cm^{-1}.

However, the imino group that appeared in IR at $\tilde{\nu} = 3322$ cm^{-1} was found in ^{1}H NMR as a broad singlet at $\delta = 7.3$ ppm. Furthermore, there was a peak in IR at $\tilde{\nu} = 2221$ cm^{-1} (characteristic for cyano groups), which was further confirmed by ^{13}C NMR, which gave two peaks at $\delta = 114.91$ and 115.7 ppm. In addition, MS gave strong evidence for the formation of compound **2** by giving a molecular ion peak at $m/z = 278$.

On reacting compound **1** with CNIND, compound **3** was obtained. The ^{1}H NMR spectrum for this compound revealed three different broad singlets at $\delta = 10.2$, 9.8, and 7.2 ppm, characteristic for two —NH— and one —NH$_2$ groups respectively.

The presence of these three groups were further confirmed by IR spectrum, which showed these peaks at 3388–3350 cm^{-1}, in addition to two other peaks at 2221 and 2209 cm^{-1}, characteristic of two different cyano groups. These latter groups appeared in ^{13}C NMR at $\delta = 115.5$ and 114.39 ppm. However, the carbonyl group that existed in IR at $\tilde{\nu} = 1779$ cm^{-1} was found in ^{13}C NMR at $\delta = 179.8$ ppm. The MS of compound **3** revealed a molecular ion peak at $m/z = 367$, which was in accordance with the molecular weight of the compound.

Compound **4** was formed by treatment of **1** with DCNQ. The ^{1}H NMR spectrum showed six protons at $\delta = 9.3$, 8.0, 7.21, and 7.0 ppm, characteristic of the —NH— and —OH groups. These functional groups

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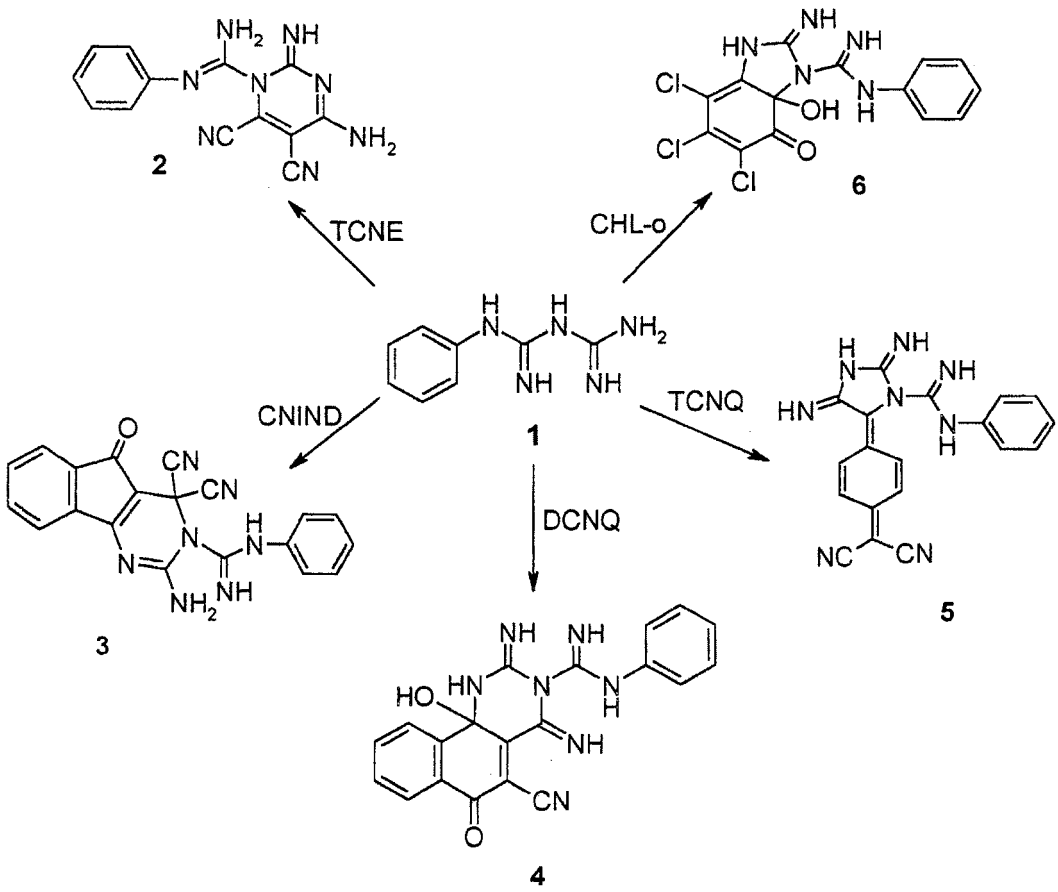

SCHEME 1

can be detected in the IR spectrum at $\tilde{\nu} = 3405$ and 3330–3280 cm^{-1}. In addition, the IR spectrum showed two peaks at 2190 and 1711 cm^{-1}, which was assigned to the cyano and the carbonyl groups, respectively. These two groups were further confirmed by ^{13}C NMR spectrum as two peaks at $\delta =$ 117.0 and 187.0 ppm, related to the cyano and carbonyl groups, respectively. Furthermore, the molecular ion peak was accounted for by MS at $m/z = 385$, which corresponds to the molecular weight of the compound.

Treatment of **1** with TCNQ led to the formation of compound **5**. Its ^{1}H NMR spectrum showed five broad singlets in the range 9.1–7.5 ppm, assigned to the exchangeable protons (NH). The presence of these protons were further confirmed by IR spectrum, which disclosed the presence of these groups at 3320–3290 cm^{-1}. Moreover, the cyano groups that were present in the IR spectrum at $\tilde{\nu} = 2210$ and 2195 cm^{-1} appeared in the ^{13}C NMR spectrum at $\delta = 117.2$ ppm. The MS showed a peak at $m/z = 354$, which is in accordance with the molecular weight of the compound.

On the other hand, compound **6** was obtained by treatment of compound **1** with CHL-*o*. This compound gave five exchangeable protons in the ^{1}H NMR spectrum at $\delta = 8.9$, 8.1, and 6.9 ppm. The presence of these protons was further detected by IR spectrum, which showed a peak at $\tilde{\nu} = 3410$ cm^{-1}, characteristic of the OH group, and a peak at $\tilde{\nu} = 3305$ cm^{-1}, related to the NH group. However, the carbonyl group that was found in IR at $\tilde{\nu} = 1710$ cm^{-1} was detected in ^{13}C NMR spectrum at $\delta = 196$ ppm. The structure of compound **6** was further supported by MS, which showed molecular ion peaks at $m/z =$ 385, 383, 381, and 379, assigned to the ions M^{+6}, M^{+4}, M^{+2}, and M^{+}, respectively.

EXPERIMENTAL

Melting points obtained were uncorrected. IR spectra were obtained on Nicolet 320 FT-IR, using KBr pellets. ^{1}H and ^{13}C NMR were run at 400 and 100 MHz respectively using a Bruker AM 400 spectrometer with TMS as internal standard. Mass spectra were run at 70 eV electron impact mode, using

a Finnigan MAT 8430 spectrometer. For preparative layer chromatography (plc), glass plates (20 × 48 cm^2) were covered with a slurry of silica gel (Merck PF_{254}) and air-dried, using the solvents listed for development. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were performed by the Microanalytical Unit at Cairo University, Cairo, Egypt.

Starting Materials

1-Phenylbiguanide (**1**) and TCNE (both from Aldrich) was recrystallized from chlorobenzene and sublimed. CHL-*o* (Aldrich) was used without purification. TCNQ was from Fluka and CNIND was prepared according to Chatterjee [28]. DCNQ was prepared from DCHNQ (Merck) according to Bundi [29].

General Procedure

A mixture of **1** (0.177 g, 1 mmol) in 20 ml absolute ethyl acetate and the π-acceptor (1 mmol) in 25 ml of absolute ethyl acetate was stirred at room temperature for 24 h. The reaction was monitored by TLC till the consumption of the starting materials. The solvent was concentrated under reduced pressure and the residue was subjected to chromatographic plates, using dichloromethane as eluent. The products were separated and then recrystallized from appropriate solvents.

*4-Amino-5,6-dicyano-2-imino-N-phenyl-2H-pyrimidine-1-carboxamidine (**2**).* Colorless crystals from EtOH. mp 140–141°C. Yield = 90 mg, 32%. IR: $\tilde{\nu}_{max}$ (KBr)/(cm^{-1}) 3365, 3336 (NH_2), 3222 (NH), 2221 (CN), 1644 (C=N). ^{1}H NMR (DMSO-d_6) $\delta = 8.33$ (2H, br-s, NH_2), 7.92 (2H, br-s, NH_2), 7.54–7.46 (2H, m, Ph), 7.45–7.37 (3H, m, Ph), 7.30 (1H, br-s, NH). ^{13}C NMR (DMSO-d_6) $\delta = 164.41$ (C=N), 163.38 (C=N), 162.99 (C=N), 132.36 (qc), 130.19 (qc), 129.26 (CH), 128.8 (CH), 128.5 (qc), 128.1 (CH), 127.3 (CH), 127.05 (CH), 115.72 (CN), 114.91 (CN). MS (70 eV) *m/z* (%) 278 (M^+, 85), 250 (10), 237 (20), 210 (12), 186 (10), 161 (15), 144 (20), 118 (34), 93 (42), 77 (26). $C_{13}H_{10}N_8$ (278.28): Calcd C, 56.11; H, 3.62; N, 40.27; Found C, 55.90; H, 3.39; N, 40.10%.

*2-Amino-4,4-dicyano-5-oxo-N-phenyl-4,5-dihydroindeno[1,2-d]pyrimidine-3-carboxamidine (**3**).* Yellow crystals from EtOH. mp > 300°C. Yield = 110 mg, 30%. IR: $\tilde{\nu}_{max}$ (KBr)/(cm^{-1}) 3388–3350 (NH and NH_2), 2221, 2209 (CN), 1779 (CO), 1643 (C=N). ^{1}H NMR (DMSO-d_6) $\delta = 10.2$ (1H, br-s, NH), 9.8 (1H, br-s, NH), 7.9–7.7 (4H, m, Ar-H), 7.42–7.30 (5H, m, Ph), 7.2 (2H, br-s, NH_2). ^{13}C NMR (DMSO-d_6) $\delta = 179.8$ (CO), 167.8 (C=N), 167.3 (C=N), 159.2 (qc), 143.4 (qc), 135.7 (2CH), 131.8 (2CH), 129.3 (CH), 126.7 (2qc), 125.79 (qc), 125.03 (2CH), 123.37 (2CH), 115.5 (qc), 114.39 (qc), 95.96 (qc). MS (70 eV) *m/z* (%) 367 (M^+, 60), 342 (20), 322 (16), 290 (18), 221 (26), 202 (8), 179 (12), 147 (10), 130 (14), 118 (42), 104 (26), 93 (100), 77 (22). $C_{20}H_{13}N_7O$ (367.37): Calcd C, 65.39; H, 3.57; N, 26.69; Found C, 65.17; H, 3.41; N, 26.48%.

*5-Cyano-10b-hydroxy-2,4-diimino-6-oxo-N-phenyl-1,4,6,10b-tetrahydro-2H-benzo[h]quinazoline-3-carboxamidine (**4**).* Orange crystals from EtOH. mp > 360°C. Yield = 100 mg, 26%. IR: $\tilde{\nu}_{max}$ (KBr)/(cm^{-1}) 3405 (OH), 3330–3280 (NH), 2190 (CN), 1711 (CO), 1645 (C=N). ^{1}H NMR (DMSO-d_6) $\delta = 9.3$ (1H, br-s, NH), 8.0 (3H, br-s, 3NH), 7.8–7.71 (4H, m, Ar-H), 7.5–7.39 (5H, m, Ph), 7.21 (1H, br-s, NH), 7.0 (1H, br-s, OH). ^{13}C NMR (DMSO-d_6) $\delta = 187.0$ (CO), 163.7 (C=N), 162.8 (2C=N), 156.4 (qc), 143.1 (qc), 137.2 (qc), 133.0 (2CH), 129.3 (2CH), 128.7 (2CH), 125.7 (CH), 117.0 (CN), 116.9 (2CH), 112.6 (qc), 75.8 (qc). MS (70 eV) *m/z* (%) 385 (M^+, 50), 335 (30), 292 (28), 278 (22), 255 (56), 191 (18), 166 (22), 148 (100), 127 (24), 96 (42), 70 (60). $C_{20}H_{15}N_7O_2$ (385.39): Calcd C, 62.33; H, 3.92; N, 25.44; Found C, 62.12; H, 3.80; N, 25.26%.

*5-(4′-Dichloromethylene-cyclohexa-2′,5′-dienylidine)-2,4-diimino-N-phenyl-imidazolidine-1-carboxamidine (**5**).* Yellow crystals from EtOH. mp 320–322°C. Yield 75 mg, 21%. IR: $\tilde{\nu}_{max}$ (KBr)/(cm^{-1}) 3320 (NH), 2210, 2195 (CN), 1635 (C=N). ^{1}H NMR (DMSO-d_6) $\delta = 9.1$ (1H, br-s, NH), 8.3 (2H, br-s, 2NH), 8.01 (2H, d, $J = 7.91$ Hz, Ar-H), 7.93 (d, 2H, $J = 7.90$ Hz, Ar-H), 7.9 (br-s, 1H, NH), 7.5 (br-s, 1H, NH), 7.2–6.96 (5H, m, Ph). ^{13}C NMR (DMSO-d_6) $\delta = 163.7$, 162.8, 160.3 (C=N), 143.5 (qc), 133.3 (2qc), 129.7 (3CH), 128.9 (3CH), 121.8 (qc), 117.2 (2CN), 116.8 (CH), 112.3 (2CH), 90.5 (qc). MS (70 eV) *m/z* (%) 354 (M^+, 40), 346 (22), 306 (16), 255 (10), 166 (20), 148 (100), 126 (20), 96 (14), 70 (24). $C_{19}H_{14}N_8$ (354.38): Calcd C, 64.40; H, 3.98; N, 31.62; Found C, 64.25; H, 3.89; N, 31.46.

*4,5,6-Trichloro-7a-hydroxy-2-imino-7-oxo-N-phenyl-2,3,7,7a-tetrahydrobenzo-imidazole-1-carboxamidine (**6**).* Brown crystals from EtOH. mp 198–200°C. Yield 89 mg, 23%. IR: $\tilde{\nu}_{max}$ (KBr)/(cm^{-1}) 3410 (OH), 3305 (NH), 1710 (CO), 1640 (C=N). ^{1}H NMR (DMSO-d_6) $\delta = 8.9$ (1H, br-s, NH), 8.1 (3H, br-s, 3NH), 6.9 (1H, br-s, OH), 7.5–7.1 (5H, m, Ph). ^{13}C NMR (DMSO-d_6) $\delta = 196$ (CO), 164.5, 163.6

(C=N), 145, 143.5, 133, 131, 130.7, 129.9, 128.3, 121.7, 119.6, 106.2 (Ar-C), 96.1 (C-OH). MS (70 eV) *m/z* (%) 385 (M^{+6}, 8), 383 (M^{+4}, 11), 381 (M^{+2}, 10), 379 (M^{+}, 20), 283 (22), 255 (30), 195 (20), 151 (20), 128 (18), 95 (50), 77 (36). $C_{14}H_{10}Cl_3N_5O$ (386.63): Calcd C, 43.49; H, 2.61; Cl, 27.51; N, 18.11; Found C, 43.23; H, 2.53; Cl, 27.32; N, 17.94.

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