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Microwave Irradiation Assisted Facile Synthesis of New Imidazole, Pyrazine, and Benzodiazocine Derivatives Using Diaminomaleonitrile

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ABSTRACT: *Utilizing domestic microwave oven reactions of diaminomaleonitrile with various selected reagents, novel heterocycles such as dicyanopyrazine, 4,5-dicyanoimidazole as well as dicyanobenzodiazocine derivatives were prepared.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:365–368, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20212

INTRODUCTION

Microwave irradiation has been recently demonstrated its utility as an energy source to dramatically improve yields and/or reaction conditions, especially in the field of heterocyclic synthesis [1a–g]. To the best of our knowledge, synthesis of heterocyclic compounds by the reaction of diaminomaleonitrile (DAMN) with either acid chloride derivatives, diketones, or dialdehydes have not yet been investigated. As an extension to our work concerning the synthesis of heterocyclic compounds using facile simple methods [2], we investigated the use of microwaves as an energy source in the synthesis of different heteroaromatic compounds. Diaminomaleonitrile (DAMN) serves as a convenient base model for the synthesis of a large number of novel heterocyclic compounds [3–9]. It can serve also as a synthetic precursor for a number of biologically active compounds that are known to be insecticides [10a,b], pesticides [11], fungicides, bactericides and anticancer [12], antagonists [13], and dyes [14–19].

A recent contribution from our laboratory described the reactivity of compound **1** toward a number of acid chlorides **4a–f** and some selected carbonyl compounds such as phthaloylchloride (**6**), acenaphthenequinone (**7**), phthalaldehyde (**8**), and 4-chloro-3-oxo-butyric acid ethyl ester (**9**) in order to synthesize a number of novel heterocycles with the expectation that they might exhibit biological activity.

RESULTS AND DISCUSSION

Although the chemistry of diaminomaleonitrile has been investigated, there is no indication for the use of the microwave assistance for studying it. Herein we undertook to examine the chemistry of diaminomaleonitrile toward reagents under investigation using the domestic microwave technique.

It was known that on reacting compound **1** with trifluoroacetic acid (**2**), cyanotrifluoromethylimidazolecarboxamide (**3**) was obtained [20] as shown in Fig. 1.

Therefore, on reacting the target compound **1** with the acid chlorides **4a–f** in the presence of a catalytic amount of triethylamine, the reaction took place in few minutes to produce 4-cyano-2-substituted-1*H*-imidazole-5-carboxamide **5a–f**, in 80–88% yield (Scheme 1).

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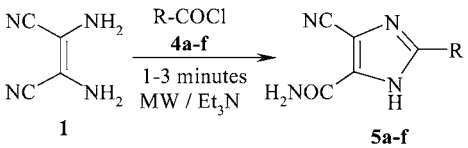


4 and 5	R	Yield
a	CH_3-	88
b	C_6H_5-	86
c	C_6H_4-CH_3-*p*	82
d	C_6H_4-Cl-*p*	81
e	1-naphthyl-	85
f	2-naphthyl-	80

SCHEME 1 Synthesis of novel imidazole derivatives (**5a–f**).

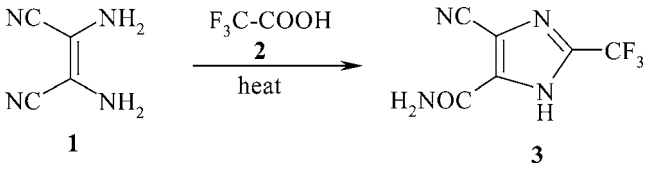


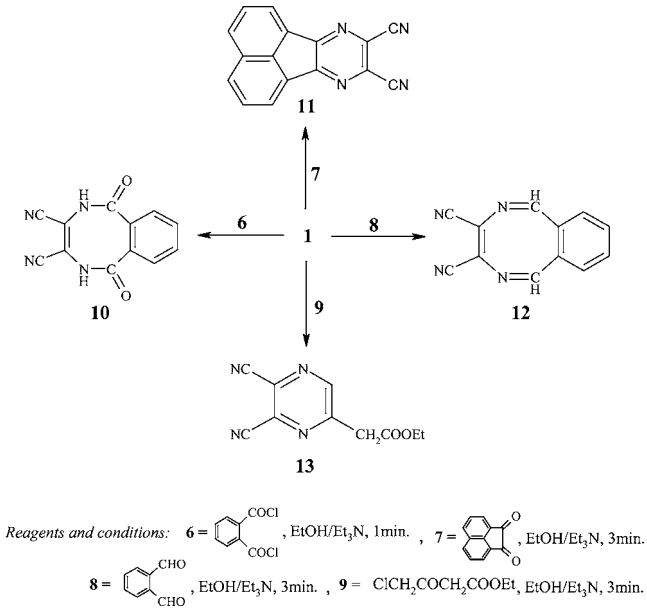
FIGURE 1 Reaction of diaminomaleonitrile (1) with trifluoroacetic acid (**2**).

On the other hand, on reacting diaminomaleonitrile (**1**) with diacid chlorides such as phthaloylchloride (**6**), 1,6-dioxo-1,2,5,6-tetrahydro-2,5-benzodiazocine-3,4-dicarbo-nitrile (**10**) was obtained in 90% yield (Scheme 2). With the aim to explore the chemistry of **1** with ketones such as acenaphthenequinone (**7**), we obtained in a few minutes of microwave irradiation the pyrazine derivative **11** in 80% yield. The classical methods involved the refluxing of DAMN **1** with ketones in the presence of catalyst [21]. These reactions have some limitations such as relatively poor yields, severe reaction conditions, and intractable purification problems.

It was recently discovered that cyclocondensation of di(glyoxalyl)benzene derivatives with DAMN **1** produced bis(2,3-dicyanopyrazine-5-yl)benzene derivatives [22]. Similarly, we found that irradiation of a mixture of compound **1** and phthalaldehyde (**8**) for few minutes in the presence of Et_3N produced 2,5-benzodiazocine-3,4-dicarbonitrile (**12**) in 81% yield.

It was reported that the reaction between 4-chloro-3-oxo-butyric acid ethyl ester (**9**) and aliphatic or aromatic 1,2-aminoalcohols or 1,2-diamines, gave in one pot a six-membered 1,4-heterocyclic system containing the enaminone moiety [23]. Similarly, we found that irradiation of DAMN (**1**) with 4-chloro-3-oxo-butyric acid ethyl ester (**9**) led to the formation of pyrazine derivative **13** in 75% yield (Scheme 2).

In conclusion, the domestic microwave oven reactions of **1** were used to prepare different classes of heterocyclic compounds. The traditional syntheses suffer from multisteps and formation of side products. As an extension to this strategy, we were able



SCHEME 2 Synthesis of pyrazine and benzodiazocine derivatives.

in our laboratory to synthesize variant heterocyclic compounds using the aforementioned domestic microwave oven technique.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and measured on a Bruker AM 400 (400.134 and 100.60 MHz) instrument. The chemical shifts (δ) were measured relative to the internal standard TMS. Coupling constants were expressed in hertz. Elemental analyses were performed by the Microanalysis center at Cairo University, Cairo, Egypt. Mass spectra were performed using a Finnigan MAT 8430 spectrometer at 70 eV. The IR spectra were obtained by Shimadzu 470 spectrometer using KBr pellets. The microwave oven used for this study was a domestic National model (NN-K652, 850 W, 2450 MHz). Diaminomaleonitrile (DAMN), phthalaldehyde and acid chlorides (Fluka), acenaphthenequinone (Sigma) and

4-chloro-3-oxo-butyric acid ethyl ester (Aldrich) were used as received.

General Procedure

A mixture of (0.108 g, 1 mmol) of compound **1** and (1 mmol) of compounds **4a–f, 6–9** in the presence of a catalytic amount of triethylamine as a catalyst was introduced into a microwave oven and heated for 1–3 min in 850 W setting. After cooling to room temperature, the crude product was recrystallized from the proper solvent to give products **5a–f, 10–13** in 75–90% yield.

4-Cyano-2-methyl-1H-imidazole-5-carboxamide **5a**. Buff *crystals*, (0.13 g, 88%), mp 187–188°C (from $CHCl_3$); $\tilde{\nu}_{max}$ (KBr) = 3350 (NH), 3310–3270 (NH_2) 3100 (Ar-CH), 2900 (Aliph-CH), 2215 (CN), 1660 (CO), 1647 (C=N) cm^{-1}; δ_H ($CDCl_3$): 2.20 (3H, s, CH_3), 10.00 (2H, br, s, NH_2), 11.10 (1H, br, s, NH); δ_C ($CDCl_3$): 19.50 (CH_3), 102.30, 100.90 (2qc, NC—C=C—$CONH_2$), 116.00 (CN), 136.20 (C=N), 167.50 (CO); *m/z*(%) 150 [M^+] (100), 124 (18), 100 (70), 90 (84), 80 (42), 64 (58), 52 (40), 38 (24), 28 (50), 18 (22). Found: C, 47.79; H, 3.89; N, 37.07. $C_6H_6N_4O$ (150.14) requires C, 48.00; H, 4.03; N, 37.32%.

4-Cyano-2-phenyl-1H-imidazole-5-carboxamide **5b**. Colorless *crystals*, (0.18 g 86%), mp 305–308°C (from CH_3OH) (lit. [24] 306°C).

4-Cyano-2-(4-methylphenyl)-1H-imidazole-5-carboxamide **5c**. Brown *crystals*, (0.19 g, 82%), mp 239–240°C (from EtOH); $\tilde{\nu}_{max}$ (KBr) = 3300 (NH), 3285–3210 (NH_2), 3120 (CH), 2214 (CN), 1663 (CO), 1650 (C=N) cm^{-1}; δ_H ($CDCl_3$): 2.50 (3H, s, CH_3), 7.77–7.80 (2H, m, Ar-H), 7.85–7.90 (2H, m, Ar-H), 10.80 (2H, br, s, NH_2), 11.50 (1H, br, s, NH); δ_C ($CDCl_3$): 20.90 (CH_3), 99.76, 91.47 (2qc, NC—C=C—$CONH_2$), 117.20 (CN), 128.90 (2CH, Ar-CH), 129.30 (2CH, Ar-CH), 134.70 (qc, Ar-C), 136.00 (C=N), 140.10 (qc, Ar-C), 167.62 (CO); *m/z* (%) 226 [M^+] (20), 182 (10), 148 (30), 135 (20), 118 (100), 107 (40), 90 (84), 80 (42), 64 (58), 52 (40), 38 (24), 28 (50), 18 (22). Found: C, 63.43; H, 4.30; N, 24.60. $C_{12}H_{10}N_4O$ (226.24) requires C, 63.71; H, 4.46; N, 24.76%.

2-(4-Chlorophenyl)-4-cyano-1H-imidazole-5-carboxamide **5d**. Yellow *crystals*, (0.20 g, 81%), mp 243–246°C (from CH_3OH); $\tilde{\nu}_{max}$ (KBr) = 3350 (NH), 3270–3199 (NH_2), 3130 (CH), 2220 (CN), 1670 (CO), 1650 (C=N) cm^{-1}; δ_H ($CDCl_3$): 7.60–7.67 (2H, m, Ar-H), 7.72–7.83 (2H, m, Ar-H), 10.90 (2H, br, s, NH_2), 11.62 (1H, br, s, NH); δ_C ($CDCl_3$): 112.24, 101.25 (2qc, NC—C=C—$CONH_2$), 117.50 (CN), 129.00 (2CH, Ar-CH), 130.33 (2CH, Ar-CH), 135.34 (qc, Ar-C), 136.13 (qc, Ar-C), 136.29 (C=N), 167.40 (CO); *m/z*(%) 248 (M^{2+}, 30), 246 [M^+] (66), 210 (12), 144 (36), 133 (70), 117 (100), 107 (48), 90 (80), 64 (56), 38 (32), 28 (58), 18 (24). Found: C, 53.29; H, 2.72; Cl, 14.12; N, 22.52. $C_{11}H_7ClN_4O$ (246.66) requires C, 53.57; H, 2.86; Cl, 14.37; N, 22.71%.

4-Cyano-2-(1-naphthyl)-1H-imidazole-5-carboxamide **5e**. Pale brown *crystals*, (0.22 g, 85%), mp 227–228°C (from EtOH); $\tilde{\nu}_{max}$ (KBr) = 3400 (NH), 3300–3200 (NH_2), 3150 (CH), 2220 (CN), 1668 (CO), 1650 (C=N) cm^{-1}; δ_H ($CDCl_3$): 7.05–7.22 (4H, m, Ar-H), 7.28–7.36 (1H, m, Ar-H), 7.41–7.48 (1H, m, Ar-H), 7.50–7.60 (1H, m, Ar-H), 10.84 (2H, br, s, NH_2), 11.46 (1H, br, s, NH); δ_C ($CDCl_3$): 107.47, 87.94 (2qc, NC—C=C—NH_2), 117.11 (CN), 125.80 (2CH, Ar-CH), 126.00 (CH, Ar-CH), 126.40 (CH, Ar-CH), 128.00 (2CH, Ar-CH), 130.30 (CH, Ar-CH), 134.10 (qc, Ar-C), 136.20 (C=N), 136.90 (qc, Ar-C), 133.70 (qc, Ar-C), 167.60 (CO); *m/z*(%) 262 [M^+] (80), 235 (30), 191 (14), 154 (18), 126 (10), 107 (100), 80 (85), 53 (90), 42 (20), 37 (50), 27 (67), 17 (70). Found: C, 68.41; H, 3.67; N, 21.15. $C_{15}H_{10}N_4O$ (262.27) requires C, 68.69; H, 3.84; N, 21.36%.

4-Cyano-2-(2-naphthyl)-1H-imidazole-5-carboxamide **5f**. Brown *crystals*, (0.21 g, 80%), mp 209–211°C (from EtOH); $\tilde{\nu}_{max}$ (KBr) 3350 (NH), 3330–3300 (NH_2), 3120 (CH), 2216 (CN), 1667 (CO), 1650 (C=N) cm^{-1}; δ_H ($CDCl_3$): 7.30 (1H, d, $J = 1.2$ Hz, Ar-H), 7.40–7.44 (1H, dd, $J = 7.5$, 1.2 Hz, Ar-H), 7.50–7.54 (1H, dd, $J = 7.8$, 1.2 Hz, Ar-H), 7.60–7.66 (4H, m, Ar-H); δ_C ($CDCl_3$): 107.40, 87.51 (2qc, NC—C=C—$CONH_2$), 117.20 (CN), 125.80 (2CH, Ar-CH), 126.00 (CH, Ar-CH), 126.40 (CH, Ar-CH), 128.00 (2CH, Ar-CH), 130.30 (CH, Ar-CH), 133.70 (qc, Ar-C), 134.10 (qc, Ar-C), 136.20 (C=N), 136.90 (qc, Ar-C), 167.50 (CO); *m/z*(%) 262 [M^+] (20), 235 (10), 171 (100), 154 (60), 148 (32), 126 (74), 91 (12), 85 (8), 72 (94), 50 (16), 43 (84), 28 (30), 18 (40). Found: C, 68.34; H, 3.60; N, 21.10. $C_{15}H_{10}N_4O$ requires C, 68.69; H, 3.84; N, 21.36%.

1,6-Dioxo-1,2,5,6-tetrahydro-2,5-benzodiazocine-3,4-dicarbonitrile **10**. Yellow *crystals*, (0.21 g, 90%), mp 263–264°C (from CH_3CN); $\tilde{\nu}_{max}$ (KBr) 3350 (NH), 2230, 2220 (CN), 1705 (CO), 1620 (C=C); δ_H ($CDCl_3$): 7.60–7.73 (1H, m, Ar-H), 7.78 (1H, s, Ar-H), 7.91 (1H, d, $J = 1.2$ Hz, Ar-H), 8.00 (1H, d, $J = 7.6$ Hz, Ar-H), 8.95 (2H, br, s, 2NH); δ_C ($CDCl_3$): 102.60 (2qc, NC—C=C—CN), 117.23 (2CN), 127.40 (2CH, Ar-CH), 132.00 (2CH, Ar-CH), 132.30 (2qc, Ar-C), 165.00 (2CO); *m/z*(%) 238 [M^+] (20), 220 [$M^+ - H_2O$] (30),

194 (100), 166 (10), 103 (64), 76 (90), 50 (60), 44 (28), 38 (10), 28 (20). Found C, 60.23; H, 2.40; N, 23.38. $C_{12}H_6N_4O_2$ (238.21) requires C, 60.51; H, 2.54; N, 23.52%.

Acenaphtho[1,2-b]pyrazine-8,9-dicarbonitrile **11**. Yellowish green *crystals*, (0.20 g, 80%), mp 324–327°C (from 1,4-dioxane); $\tilde{\nu}_{max}$ (KBr) 3100 (Ar-CH), 2220, 2215 (CN), 1650 (C=N), 1620 (C=C); δ_H ($CDCl_3$): 6.85–6.90 (2H, m, Ar-H), 7.05–7.16 (2H, m, Ar-H), 7.20–7.30 (2H, m, Ar-H); δ_C ($CDCl_3$): 117.70 (2CN), 125.90 (2CH, Ar-CH), 126.10 (2CH, Ar-CH), 128.15 (2CH, Ar-CH), 128.70 (2qc, Ar-C), 131.11 (2qc, Ar-C), 133.40 (qc, Ar-C), 133.80 (qc, Ar-C), 156.30 (2qc, C=N). *m/z*(%) 254 [M^+] (50), 228 (32), 198 (60), 166 (10), 103 (64), 76 (90), 50 (60), 38 (10), 28 (20). Found C, 75.31; H, 2.21; N, 21.88. $C_{16}H_6N_4$ requires C, 75.59; H, 2.38; N, 22.04%.

2,5-Benzodiazocine-3,4-dicarbonitrile **12**. Yellow *crystals*, (0.17 g, 81%), mp 205–207°C (from EtOH); $\tilde{\nu}_{max}$ (KBr) 3120 (Ar-CH), 2225, 2219 (CN), 1675 (CH=N), 1620 (C=C); δ_H ($CDCl_3$): 7.45–7.60 (2H, m, Ar-H), 7.70–7.86 (2H, m, Ar-H), 8.80 (2H, s, CH=N)); δ_C ($CDCl_3$): 117.17 (2CN), 125.54 (2qc, NC—*C*=*C*—CN), 129.10 (2CH, Ar-CH), 131.13 (2CH, Ar-CH), 137.74 (2qc, Ar-C), 162.90 (2CH, *C*H=N); *m/z*(%) 206 [M^+] (15), 193 (22), 166 (12), 148 (24), 132 (100), 118 (26), 103 (52), 89 (20), 74 (62), 65 (18), 51 (40), 39 (20), 28 (40), 18 (84). Found C, 69.67; H, 2.78; N, 26.93. $C_{12}H_6N_4$ requires C, 69.90; H, 2.93; N, 27.17%.

Ethyl(5,6-dicyanopyrazin-2-yl)acetate **13**. Yellowish white *crystals*, (0.16 g, 75%), mp 195–197°C (from $CHCl_3$); $\tilde{\nu}_{max}$ (KBr) 3120 (Ar-CH), 2990 (aliph. CH), 2212, 2209 (CN), 1728 (CO), 1650 (C=N), 1627 (C=C); δ_H ($CDCl_3$):1.25 (3H, t, $J = 7.0$ Hz, CH_2—*CH*$_3$), 3.93 (2H, s, *C*H_2—CO) 4.09–4.15 (2H, q, $J = 7.0$ Hz, *CH*$_2$—CH_3), 8.10 (1H, s, Ar-H); δ_C ($CDCl_3$): 14.06 (CH_2—*C*H_3), 42.90 (*C*H_2CO), 61.50 (*C*H_2—CH_3), 117.86 (2CN), 131.16 (qc, Ar-C), 133.30 (qc, Ar-C), 148.14 (CH, Ar-CH), 162.90 (qc, Ar-C), 171.79 (CO); *m/z*(%) 216 [M^+] (75), 187 (100), 171 (41), 166 (12), 148 (24), 132 (14), 118 (36), 103 (50), 89 (28), 77 (62), 65 (18), 51 (40), 30 (20). Found C, 55.29; H, 3.60; N, 25.72. $C_{10}H_8N_4O_2$ requires C, 55.56; H, 3.73; N, 25.91%.

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