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Facile Synthesis of 2-Aryl-3-phenyl-5-phenylamino-2,5-dihydro-1,2,4-thiadiazole-5-carbonitriles

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Syntheses of various 2-aryl-3-phenyl-5-phenylamino-2,5-dihydro-1,2,4-thiadiazole-5-carbonitriles are reported. The key to their successful synthesis is represented by the reaction of N-imidoylthioureas with 2-(1,3-dioxoindan-2-ylidene)malononitrile.

Keywords 1,2,4-thiadiazole-5-carbonitriles; 2-(1,3-dioxoindan-2-ylidene)malononitrile; cyano-group transfer; *N*-Imidoylthioureas

INTRODUCTION

The derivatives of 2-amino-3-benzoylthiophene proved capable of enhancing the binding and activity of reference A1 receptor agonists, such as N^6-cyclopentyladenosine (CPA). However, the compounds were found to also act as competitive antagonists at these receptors of PDS81723 (Figure 1) and therefore they became the reference allosteric modulator with the best ratio of enhancement to antagonistic action.[1,2]

Other derivatives of 2-amino-3-benzoylthiophene based on the structure of PDS81723 have been synthesized.[3–6] In previous work,[7] a number of 2,3,5-substituted-1,2,4-thiadiazoles (**II**) were tested as potential allosteric modulators of adenosine receptors.[8] 1,2,4-Thiadiazol-5(2*H*)-imines **III** (Figure 1) became accessible when Barnikow[9] and later Goerdeler[10] proposed a simple method for the preparation of these compounds from imidoyl chlorides. Recently, it has been proven that type **III** substances show high reactivity as sulfhydryl modifying agents rather than acting as allosteric inhibitors.[11] In particular, there are numerous studies on the reaction of imidoyl chlorides with

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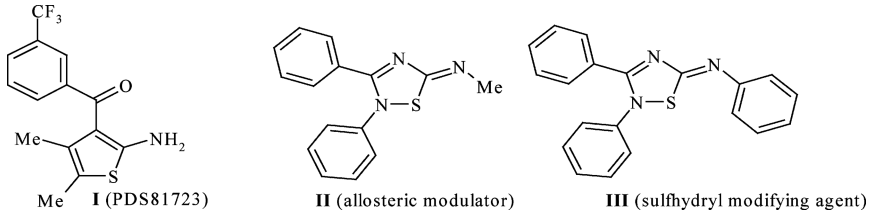
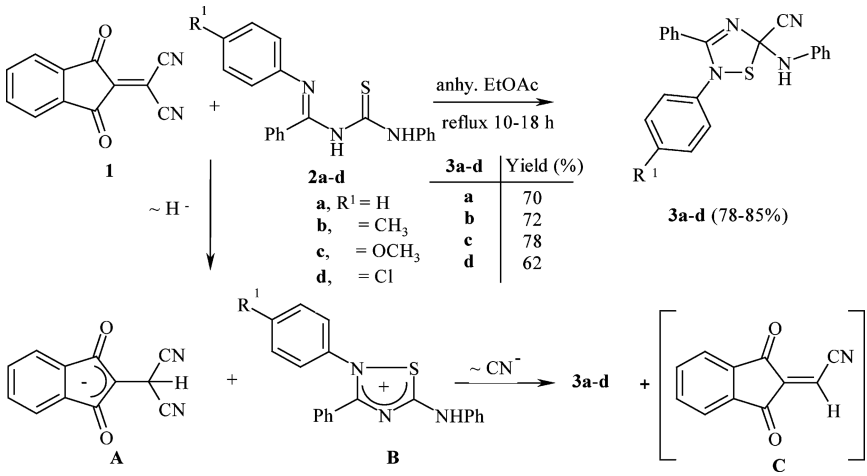


FIGURE 1 Structural variety with allosteric modulator activity

isocyanates, isothiocyanates, and carbodiimides.[12–15] Some time ago, we investigated the reactions of amidine analogues with π-acceptors and the synthesis of various heterocycles such as dihydropyridines,[16] acridinones,[17,18] pyrazolidines, and pyridazines.[18] Recently, we have reported a very convenient procedure to synthesize 1,2,4-triazoles in one step involving a rapid reaction of amidrazones with 2-(1,3-dioxoindan-2-ylidene)malononitrile (**1**).[19] Compound **1** can react by net cyanation and most likely by initial hydride abstraction and subsequent transfer of a cyanide ion.[20] Additionally, compound **1** shows electron-transfer mediated rearrangement process during its reaction with isoindolines, which leads to the formation of 2-cyano-1,4-naphthoquinon-1-yl.[20] Moreover **1** is well-known for its oxidizing activity along with its basic character.[21] In addition, compound **1** has an exocyclic π-deficient double bond, which indicates its ability to undergo [2 + 3] cycloaddition reactions.[22] The most interesting aspect of imidoyl chlorides is their ability to act as precursors of nitrilum ylides and therefore to take part as 1,3-dipoles in [3+2] cycloadditions.[12–15] Kihara et al.[23] described the reaction of diethyl diazenedicarboxylate with amidinothioureas, imidoylthioureas and thioacylamidines, which yielded the corresponding thiadiazoles by oxidative cyclic S-N bond formation. From the above findings, it is valuable to investigate the behavior of the target acceptor announcing by compound **1** during its reaction with *N*-imidoylthioureas.

RESULTS AND DISCUSSION

Scheme 1 shows the reaction of **2a–d**[11] with **1** in anhydrous ethyl acetate. The reaction proceeded in a few hours to yield after chromatographic purification the 1,2,4-thidiazoles **3a–d** (62–78%). We have chosen the *N*-imidoylthioureas **2a–d** having aryl groups with electron donating and withdrawing substituents at the benzene ring, in order to examine their reactivity, which might affect the course of the reaction. The structure of **3a–d** was established on the basis of mass, IR, ^{1}H NMR, and ^{13}C NMR spectra as well as elemental analyses. The products **3a–d**



SCHEME 1 Reactions of **1** with *N*-imidoylthioureas **2a–d**.

showed spectral data similes to those reported for 2-aryl-3-phenyl-5-phenylamino-2,5-dihydro-1,2,4-thiadiazoles.[11,15] The main differences found were the following: 1) the IR spectra indicated the presence of nitrile groups at $\nu = 2220$–2212 cm^{-1}; 2) the ^{13}C NMR spectra showed the appearance of a signal in a range typical for a quaternary carbon atom (C-5) at $\delta = 95.5$–96.2; and 3) the ^{1}H NMR spectra of **3a–d** showed the protons of the phenyl ring at the nitrogen atom in position-2 to be the most deshielded. For example, in the case of **3c**, the aforesaid distinguished phenyl protons resonated as two doublets of doublets at $\delta =$ 8.00 and 7.70 ($J = 8.2$, 1.2 Hz). Moreover, the NH protons appeared superimposed on the aromatic protons (see the Experimental Section). The ^{13}C NMR spectra of compounds **3a–d** further support their identity. Thus the ^{13}C NMR spectrum of compound **3c** shows a signal for the cyano group at $\delta = 113.4$, whereas C-3 ot the azomrthine moiety resonates at $\delta = 155.0$.

Calculations of the bond lengths of imidoylthioureas indicated that there is a shortening of the distance between the nitrogen and the sulfur atom, which might be caused by the difference in electronegativity.[15] Since compound **1** can act as an oxidizing, as well as a cyano-transferring reagent,[20,21,24] the proposed mechanism for the formation of thiadiazoles **3a–d** might involve the initial oxidation of the *N*-imidoylthioureas **2a–d** by the acceptor **1**. Oxidation process is accompanied by a formal hydride transfer process generating species **A** and **B** (Scheme 1). The intermediate **B** picks up a cyanide anion from **A** to form product **3**. Although the cyanation process according to that

pathway appears reasonable, we could not isolate the expected compound **C** (Scheme 1). The yields of the 1,2,4-thiadiazoles **3a**–**d** depend on the type of substituents at the aromatic ring attached to the amino group in **1a**–**d**. The presence of electron donating substituents such as methyl and methoxy groups increases the yield of the product, while in the case of electron withdrawing groups like chlorine the yield decreases. In conclusion, scope and limitations of this process have not been explored yet.

EXPERIMENTAL

All melting points were recorded on a Gallenkamp apparatus. ^{1}H and ^{13}C NMR spectra (Bruker AM 400, ^{1}H: 400.13 MHz, ^{13}C: 100.6 MHz) were obtained from $CDCl_3$ solutions; the chemical shifts are given relative to TMS. Coupling constants are given in Hz. For preparative thin layer chromatography (PLC), glass plates (20 × 48 cm) 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 carried out with an Elemental analyzer Model 2400 Perkin-Elmer at Cairo Microanalysis lab in Cairo University. Mass spectrometry was performed with a Finnigan MAT 8430 spectrometer at 70 eV in the Institute of Organic Chemistry, TU-Braunschweig, Germany. IR spectra were run on a Shimadzu 470 spectrometer using KBr pellets.

Starting Materials

N-Imidoylthioureas **2a**–**d** were prepared according to Göblyös et al.[11] The acceptor **1** was prepared following the procedure mentioned in Chaterjee.[25]

Reaction of 2a–d with 2-(1,3-dioxoindan-2-ylidene) malononitrile (1)

In a 250 mL two-necked round bottom flask a mixture of **2a**–**d** (2 mmol) and **1** (0.42 g, 2 mmol) dissolved in absolute ethyl acetate (100 mL) was gently refluxed for 10–18 h. The reaction was followed by TLC analysis. The solvent was removed in vacuo and the residue was separated by preparative plate chromatography (silica gel, toluene : ethyl acetate 5:1). Compounds **3a**–**d** were recrystallized from the solvents given below.

2,3-Diphenyl-5-phenylamino-2,5-dihydro-1,2,4-thiadiazole-5-carbonitrile (3a)

Yellow needles (0.50 g, 70 %); $R_f = 0.3$ (CH_2Cl_2), m.p. 240°C (EtOH). ^{1}H NMR ($CDCl_3$): $\delta = 7.70$ (dd, $J = 8.0$, 1.2 Hz, 2H, *ortho*-H), 7.60–7.30 (m, 9H, arom-H, NH), 7.24–7.10 (m, 5H, arom-H). ^{13}C NMR ($CDCl_3$): δ = 95.5 (*C*−5), 112.6 (CN), 124.6, 125.8, 126.4, 127.6, 128.0, 128.4, 128.9, 130.0, 132.0, 134.0, 138.9, 142.4, 153.6 (*C*−3). IR, ν_{max} (cm^{-1}): 3270 (NH), 3040–2990 (arom-CH), 2212 (CN), 1596 (C=N). UV, λ_{max} (CH_3CN, nm, lg ε): 414 (4.0). MS (EI, 70 eV): *m/z* (%) = 357 ([M+1], 18), 356 ([M^+], 70), 298 (54), 264 (20), 252 (12), 180 (76), 104 (16), 77 (100), 51 (34). $C_{21}H_{16}N_4S$ (356.49): found C, 70.80; H, 4.46; N, 15.85; S, 9.04 %. Calcd. C, 70.76; H, 4.52; N, 15.72; S, 9.00%.

2-(4′-Methylphenyl)-3-phenyl-5-phenylamino-2,5-dihydro-1,2,4-thiadiazole-5-carbonitrile (3b)

Yellow crystals (0.52 g, 72%); $R_f = 0.5$ (CH_2Cl_2), m.p. 260°C (EtOH). ^{1}H NMR($CDCl_3$): δ = 7.80 (dd, J = 8.2, 1.2 Hz, 2H, *ortho*-H), 7.60–7.30 (m, 13H, arom-H, NH), 2.34 (s, 3H, CH_3).^{13}C NMR($CDCl_3$): δ = 32.8 (CH_3), 95.8 (C-5), 113.9 (CN), 125.2, 126.2, 127.2, 128.4, 128.8, 130.0, 132.8, 134.0, 134.6, 136.6, 138.9, 142.8, 154.8 (*C*−3). IR, ν_{max} (cm^{-1}): 3260 (NH), 3090-3010 (arom-CH), 2970–2862 (aliph-CH), 2216 (CN),1600 (C=N). UV, λ_{max} (CH_3CN, nm, lg ε): 430 (4.18). MS (EI, 70 eV): *m/z* (%) = 371 ([M + 1], 26) 370 ([M^+], 64), 354 (10), 312 (58), 310 (30), 278 (20), 266 (10), 219 (12), 208 (20), 194 (54), 183 (18), 180 (8), 146 (76), 104 (100), 91 (46), 76 (82), 65 (28), 50 (42). $C_{22}H_{18}N_4S$ (370.48): found C, 71.50; H, 4.85; N, 15.10; S, 8.60 %. Calcd. C, 71.33; H, 4.90, N, 15.12; S, 8.65 %.

2-(4′-Methoxyphenyl)-3-phenyl-5-phenylamino-2,5-dihydro-1,2,4-thiadiazole-5-carbonitrile (3c)

Yellow crystals (0.60 g, 78%); $R_f = 0.6$ (CH_2Cl_2), m.p. 290°C (EtOAc). ^{1}H NMR($CDCl_3$): $\delta = 8.00$ (dd, $J = 8.0$, 1.2 Hz, 2H, arom-H), 7.73 (dd, $J = 8.2$, 1.2 Hz, 2H, arom-H), 7.60–7.20 (m, 11H, arom-H, NH), 3.95 (s, 3H, OCH_3). ^{13}C NMR($CDCl_3$): $\delta = 50.9$ (OCH_3), 96.2 (*C*−5), 113.4 (*C*N), 125.6, 126.8, 127.6, 128.2, 128.6, 130.2, 132.6, 133.2, 134.8, 140.0, 142.4, 146.0, 155.0 (*C*−3). IR, ν_{max} (cm^{-1}): 3250 (NH), 3090-3020 (arom-CH), 2980–2850 (aliph-CH), 2220 (CN), 1610 (C=N). UV, λ_{max} (CH_3CN, nm, lg ε): 440 (4.24). MS (EI, 70 eV): *m/z* (%) = 387 ([M + 1], 22), 386 ([M^+], 60), 355 (28), 316 (50), 268 (24), 208 (30), 194 (56), 160 (28), 146 (70), 106 (100), 91 (62), 76 (80), 50 (32). $C_{22}H_{18}N_4OS$ (386.48): found C, 68.46; H, 4.60; N, 14.48; S, 8.26%. Calcd. C, 68.37; H, 4.69; N, 14.50; S, 8.30%.

2-(4′-Chlorophenyl)-3-phenyl-5-phenylamino-2,5-dihydro-1,2,4-thiadiazole-5-carbonitrile (3d)

Yellow crystals (0.48 g, 62%); $R_f = 0.3$ (CH_2Cl_2), m.p. 267°C (MaOH). ^{1}H NMR ($CDCl_3$): $\delta = 7.64$–7.40 (m, 13H, arom-H, NH), 7.30 (dd, $J =$ 8.2, 1.4 Hz, 2H, arom-H). ^{13}C NMR ($CDCl_3$): $\delta = 96.0$ ($C-5$), 112.6 (CN), 125.9, 125.0, 126.4, 126.9, 127.8, 128.0, 128.4, 128.8, 129.0, 134.0, 138.0, 139.0, 152.8 ($C-3$). IR, ν_{max} (cm^{-1}): 3256 (NH), 3020-2970 (arom-CH), 2218 (CN), 1596 (C=N). UV, λ_{max} (CH_3CN, nm, lg ε): 420 (3.90). MS (EI, 70 eV): m/z (%) = 392 ([M + 2], 20), 390 ([M^+], 100), 389 ([M − 1], 32), 370 (16), 370 (18), 363 (20), 336 (12), 308 (14), 239 (16), 228 (14), 192 (16), 177 (18), 125 (20), 110 (14), 77 (20), 44 (60). $C_{21}H_{15}ClN_4S$(390.89): found C, 64.40; H, 3.82; Cl, 9.00; N, 14.30; S, 8.16%. Calcd. C, 64.53; H, 3.87; Cl, 9.07; N, 14.33; S, 8.20%.

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