Amidrazones in the Synthesis of 1*H*-1,2,4-Triazoles

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Dedicated to Professor Henning Hopf on the occasion of his 65th birthday

The syntheses of various 2-(4-aryl-2,4-dihydro-3-phenyl-1,2,4-triazol-3-ylidene)indan-1,3-diones are reported. The key to their successful synthesis depends on the reaction of amidrazones **1a**–**f** with 2-(1,3-dioxoindan-2-ylidene)malononitrile (**2**).

Key words: Amidrazones, 2-(1,3-Dioxoindan-2-ylidene)malononitrile, 1*H*-1,2,4-Triazoles

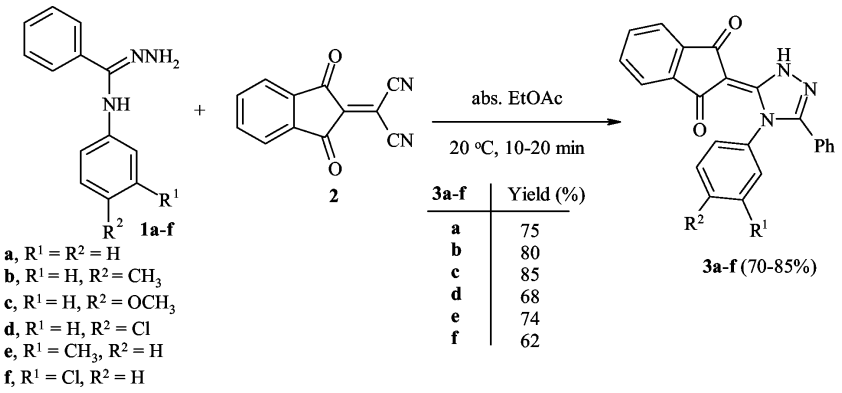
Introduction

The design and synthesis of 1,2,4-triazoles have attracted much attention within the last decades due to their wide applications and their therapeutic importance. For example, triazoles have been used as drugs for certain antiasthmatic [1], antiviral (ribavirin) [2], antifungal (fluconazole) [3], antibacterial [4], and hypnotic (triazolam) drugs [5]. Owing to the broad biological activity of the 1,2,4-triazoles [6 – 12], the ring system represents an attractive target for the elaboration of solid-phase synthesis and the production of combinatorial libraries. 1*H*-1,2,4-Triazoles are proved as electrochemically stable for fuel cell applications and effectively promote proton conductivity of materials under anhydrous conditions [13]. In general, 1*H*-1,2,4-triazoles have wide applications as intermediates for phytosanitary and pharmaceutical products. In addition, some triazoles are used as pesticides, photoconductors, and copying systems. Amidines are used very often in pharmacological and medicinal applications [14 – 18]. Amidrazone derivatives are considered as an important class of amidines and they are used in heterocyclic syntheses [19]. We have recently reported on the synthesis of heterocyclces derived from [2.2]paracyclophanes (heterophanes) during the cycloadditions of alkenyl-[2.2]paracyclophanes with various selected dienophiles [20]. We have also investigated the reactions of amidines and their analogues with π-acceptors [21a] and various heterocycles such as dihydropyridines [21b], acridinones [22, 23], pyrazolidines and pyridazines [23], were obtained. In this publication we undertook to investigate, as the first example, the reactions of amidrazones **1a**–**f** with 2-(1,3-dioxoindan-2-ylidene)malononitrile as electron π-deficient acceptor aiming to obtain heterocyclic compounds, which might have prospective biological activities.

Results and Discussion

Herein, we report a general overall view of the reaction between amidrazones **1a**–**f** [24] with 2-(1,3-dioxoindan-2-ylidene)malononitrile (**2**). Scheme 1 outlines the reaction of **1a**–**f** with **2** in dry ethyl acetate under N_2 atmosphere. The reaction proceeded in a few minutes to yield, after chromatographic purification and recrystallization, compounds **3a**–**f** (62 – 85%). We chose amidrazones **1a**–**f** having aryl groups with electron donating and withdrawing substituents on the benzene ring, in order to examine their reactivity, which might affect the course of reaction.

The structures of **3a**–**f** were established on the basis of mass, IR, ^{1}H NMR and ^{13}C NMR spectra as well as elemental analyses. Compounds **3a**–**f** show IR absorptions for NH groups at $\tilde{\nu} = 3280 - 3200$ cm^{-1} and broad bands at $\tilde{\nu} = 1685 - 1680$ cm^{-1} corresponding to the carbonyl groups. Surprisingly, the ^{1}H NMR spectra of compounds **3a**–**f** did not show any resonances due to the NH protons, which is explained by the presence of the triazole-H dione structure of **3a**–**f** in tautomerization with its ketohydroxy form (Fig. 1). The ^{1}H NMR spectra indicated the presence of the hydroxyl proton for **3a**–**f**, which is superimposed by the aromatic protons and appeared between $\delta = 7.70 -$



3a-f	Yield (%)
a	75
b	80
c	85
d	68
e	74
f	62

Scheme 1. Reaction of amidrazones **1a**–**f** with **2**; synthesis of 1*H*-1,2,4-triazoles **3a**–**f**.

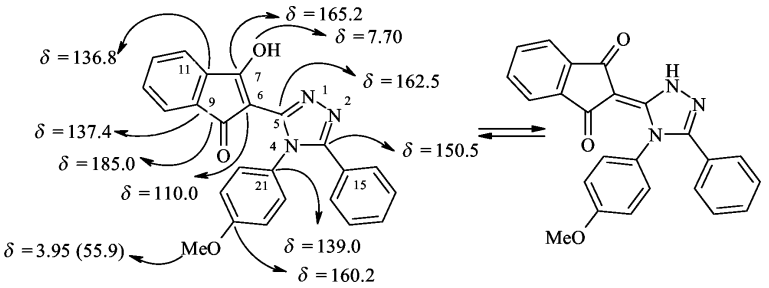


Fig. 1. Tautomerism and some distinctive δ values (^{1}H and ^{13}C NMR) for compound **3c**.

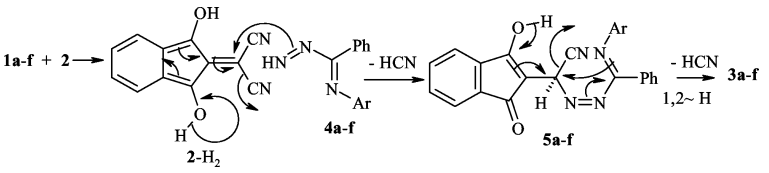


Fig. 2. Proposed mechanism for the formation of 1*H*-1,2,4-triazoles **3a**–**f**.

7.40 (see Experimental Section). The ^{13}C NMR spectra of compounds **3a**–**f** are in accordance with their ^{1}H NMR spectral data. For example, the ^{13}C NMR spectrum of compound **3c** showed only one carbonyl signal which appears at $\delta = 185.0$, whereas the *C*-OH resonates at $\delta = 165.2$. Six distinguished carbon signals resonated in the ^{13}C NMR spectrum of **3c** at $\delta = 55.9$, 110.0, 136.8, 137.4, 150.5 and 162.5, corresponding to O*C*H$_3$, C-6, -8, -9, -3 and -5 (more NMR data are shown in Fig. 1 and the Experimental Section).

It has been reported that the transformation of arylamidrazones into 1,2,4-triazoles occurs *via* the initial formation of azoimines [25]. On the other hand, it is known that the acceptor **2** is considered as oxidizing agent. Therefore, the proposed mechanism for the formation of triazoles **3a**–**f** is thought to involve the initial abstraction of hydrogen atoms from the amidrazone moiety by the acceptor **2** to produce the oxidized **4a**–**f** along with the dihydro-indandione **2**-H$_2$. Subsequently, the hydrazoenamine-NH in **4a**–**f** attacks the vinylic bond in **2**-H$_2$ accompanied by extrusion of HCN from **2**-H$_2$ to form the intermediates **5a**–**f** (Fig. 2). A cyclization process then occurs followed by loss of another molecule of HCN; a [1,2]-H shift finally affords the observed products **3a**–**f** (Fig. 2).

In conclusion, we have now demonstrated a very convenient procedure to synthesize 1,2,4-triazoles in one step including a rapid reaction of amidrazones **1a**–**f** which behave hydrazoenamine-like. Amidrazones **1a**–**f** react with the ylidene **2** *via* an initial addition of the azoimine at the terminal hydrazino-nitrogen, followed by elimination of two molecules of HCN under the reaction conditions to afford the title compounds. Additionally, the variation of the yields of the resulting triazoles **3a**–**f** depended on the type of substituents in the aromatic ring attached to the amino group in **1a**–**f**, *i. e.* the presence of electron donating substituents such as methyl and methoxy groups increased the yields of the obtained triazoles. However and in the case of electron withdrawing groups represented by a chlorine

atom decreased the yield. Moreover, it was also noted that *meta* substitution with either an electron donating or a withdrawing group decreases the yields of the corresponding products as in the case of **3e** and **3f**.

Experimental Section

Melting points are uncorrected values. ^{1}H NMR 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 internal standard TMS. 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 are detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried in Assiut Microanalysis Center of Assiut University. Mass spectroscopy was performed with a Finnigan MAT 8430 spectrometer at 70 eV, Institute of Organic Chemistry, TU-Braunschweig, Germany. IR spectra were run on a Shimadzu 470 spectrometer using KBr pellets.

Starting materials: Amidrazones **1a**–**f** were prepared according to reference [24]. 2-(1,3-Dioxoindan-2-ylidene)malononitrile (**2**) was prepared following the procedure mentioned in reference [26].

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

General procedure: A 250 ml two-necked round bottom flask was flame-dried under N_2 atmosphere and then cooled to r. t. To this flask, absolute ethyl acetate (100 ml), a mixture of **1a**–**f** (2 mmol) and **2** (0.41 g, 2 mmol) was added. The mixture was stirred for 10–20 min (the reaction was followed by TLC analysis). The solvent was removed *in vac.* and the residue was separated by preparative plates chromatography (silica gel, toluene : ethyl acetate 5 : 2). The obtained products **3a**–**f** were recrystallized from the stated solvents.

*2-(2,4-Dihydro-3,4-diphenyl-1,2,4-triazol-5-ylidene)indane-1,3-dione (**3a**):* Obtained as yellow needles (0.55 g, 75%); R_f = 0.4 (CH_2Cl_2), m. p. 280 °C (acetone). – IR (KBr): $\tilde{\nu}$ = 3280 (NH), 3010–2970 (Ar-CH), 1680 (CO), 1590 (C=N) cm^{-1}. – UV (CH_3CN): λ_{max} (log ε) = 410 (4.10). – ^{1}H NMR ($CDCl_3$): δ = 7.50–7.38 (m, 13 H, Ar-H, OH), 7.10 (dd, 2 H, J = 8.0, 2.0 Hz). – ^{13}C NMR ($CDCl_3$): δ = 109.80 (*C*-6), 122.40 (Ar-*C*H-18), 125.00 (Ar-*C*), 126.90, 128.00 (2 Ar-*C*H), 128.20, 128.60, 128.80, 130.20 (Ar-*C*H, *C*H-11,-12,-13 and -14), 130.60, 130.80 (2 Ar-*C*H), 132.40 (Ar-*C*H), 136.40 (Ar-*C*-8), 137.00 (Ar-*C*-9), 138.20 (Ar-N-*C*-21), 150.00 (*C*-3), 162.00 (*C*-5), 165.00 (*C*-7-OH), 184.90 (*C*-10). – MS (EI, 70 eV): *m/z* (%) = 366 [M+1] (20), 365 [M$^+$] (100), 364 [M-1] (60), 352 (14), 307 (12), 288 (14), 223 (12), 209 (14), 120 (18), 104 (20). – $C_{23}H_{15}N_3O_2$ (365.39): calcd. C 75.60, H 4.14, H 11.50; found C 75.40, H 4.17, H 11.35.

*2-[2,4-Dihydro-4-(4-methylphenyl)-3-phenyl-1,2,4-triazol-5-ylidene]indane-1,3-dione (**3b**):* Obtained as yellow crystals (0.61 g, 80%); R_f = 0.5 (CH_2Cl_2), m. p. 276–278 °C (EtOH). – IR (KBr): $\tilde{\nu}$ = 3200 (NH), 3050–2900 (Ar-CH), 1682 (CO), 1600 (C=N) cm^{-1}. – UV (CH_3CN): λ_{max} (log ε) = 430 (4.20). – ^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 7.60–7.30 (m, 14 H, Ar-H, OH). – ^{13}C NMR ($CDCl_3$): δ = 32.40 (*C*H$_3$), 109.70 (*C*-6), 122.48 (Ar-*C*H-18), 125.20 (Ar-*C*), 126.92, 128.00 (2 Ar-*C*H), 128.24, 128.64, 128.72, 130.46 (Ar-*C*H, *C*H-11, -12, -13 and -14), 130.80, 131.00 (2 Ar-*C*H), 136.50 (Ar-*C*-8), 136.68 (Ar-*C*-24), 137.40 (Ar-*C*-9), 138.60 (Ar-N-*C*-21), 150.30 (*C*-3), 162.30 (*C*-5), 165.10 (*C*-7-OH), 184.94 (*C*-10). – MS (EI, 70 eV): *m/z* (%) = 380 [M+1] (20), 379 [M$^+$] (14), 378 [M-1] (100), 364 (20), 350 (18), 306 (18), 288 (14), 223 (12), 209 (14), 120 (18), 104 (20). – $C_{24}H_{17}N_3O_2$ (379.42): calcd. C 75.98, H 4.52, H 11.07; found C 75.80, H 4.46, H 11.05.

*2-[2,4-Dihydro-4-(4-methoxyphenyl)-3-phenyl-1,2,4-triazol-5-ylidene]indane-1,3-dione (**3c**):* Obtained as yellow crystals (0.67 g, 85%); R_f = 0.6 (CH_2Cl_2), m. p. 290–292 °C (EtOH). – IR (KBr): $\tilde{\nu}$ = 3260 (NH), 3030–2980 (Ar-CH), 1682 (CO), 1600 (C=N) cm^{-1}. – UV (CH_3CN): λ_{max} (log ε) = 440 (4.5). – ^{1}H NMR ($CDCl_3$): δ = 3.88 (s, 3 H, OCH_3), 7.70 (dd, 2 H, J = 7.8, 1.9 Hz, H-23,25), 7.60–7.58 (m, 2 H, H-17,19), 7.48–7.28 (m, 10 H, Ar-H, OH). – ^{13}C NMR ($CDCl_3$): δ = 55.90 (O*C*H$_3$), 110.00 (*C*-6), 122.60 (Ar-*C*H-18), 125.20 (Ar-*C*), 127.00, 128.20 (2 Ar-*C*H), 128.30, 128.62, 128.80, 130.44 (Ar-*C*H, *C*H-11, -12, -13 and -14), 130.80, 131.00 (2 Ar-*C*H), 136.80 (Ar-*C*-8), 137.40 (Ar-*C*-9), 139.00 (*C*-21), 150.50 (*C*-3), 160.20 (Ar-*C*-24), 162.50 (*C*-5), 165.20 (*C*-7), 185.00 (*C*-10). – MS (EI, 70 eV): *m/z* (%) = 396 [M+1] (22), 395 [M$^+$] (100), 394 [M-1] (76), 366 (18), 352 (14), 336 (10), 290 (10), 223 (14), 209 (16), 192 (14), 121 (8), 104 (16). – $C_{24}H_{17}N_3O_3$(395.42): calcd. C 72.90, H 4.33, H 10.63; found C 72.80, H 4.27, H 10.65.

*2-[4-(4-Chlorophenyl)-2,4-dihydro-3-phenyl-1,2,4-triazol-5-ylidene]indane-1,3-dione (**3d**):* Obtained as pale yellow crystals (0.54 g, 68%); R_f = 0.3 (CH_2Cl_2), m. p. 287–289 °C (MeOH). – IR (KBr): $\tilde{\nu}$ = 3220 (NH), 3020–2970 (Ar-CH), 1685 (CO), 1590 (C=N) cm^{-1}. – UV (CH_3CN): λ_{max} (log ε) = 420 (3.90). – ^{1}H NMR ($CDCl_3$): δ = 7.54–7.34 (m, 12 H, Ar-H, OH), 7.00 (dd, 2 H, J = 7.8, 2.0 Hz, H-23,25). – ^{13}C NMR ($CDCl_3$): δ = 108.60 (*C*-6), 121.00 (Ar-*C*-24), 122.60 (Ar-*C*-18), 123.90, 124.00 (2 Ar-*C*H), 125.30 (Ar-*C*), 126.70, 127.00 (2 Ar-*C*H), 128.16, 128.20, 128.40, 130.23 (Ar-*C*H, *C*H-11, -12, -13 and -14), 136.40 (*C*-8), 136.80 (*C*-9), 138.20 (Ar-*C*-21), 150.00 (*C*-3), 159.80 (*C*-5), 165.00 (*C*-7), 184.20 (*C*-10). – MS (EI, 70 eV): *m/z* (%) = 401 [M+2] (18), 400 [M+2] (36), 399 [M$^+$] (100), 364 [M-1] (34), 370 (16), 370 (18), 363 (20), 336

(12), 308 (14), 239 (14), 228 (14), 192 (16), 177 (18), 125 (20), 110 (14). – $C_{23}H_{14}ClN_3O_2$ (399.84): calcd. C 69.09, H 3.53, Cl 8.87, H 10.51; found C 69.20, H 3.47, Cl 8.78, H 10.50.

*2-[2,4-Dihydro-4-(3-methylphenyl)-3-phenyl-1,2,4-triazol-5-ylidene]indane-1,3-dione (**3e**):* Obtained as pale yellow crystals (0.56 g, 74%); $R_f = 0.4$ (CH_2Cl_2), m. p. 268 °C (EtOH). – IR (KBr): $\tilde{\nu} = 3240$ (NH), 3030 – 2940 (Ar-CH), 1680 (CO), 1594 (C=N) cm^{-1}. – UV (CH_3CN): λ_{max} (log ε) = 435 (4.25). – ^{1}H NMR ($CDCl_3$): $\delta = 2.36$ (s, 3 H, CH_3), 7.62 (dd, 1 H, $J = 1.8$ Hz, H-22), 7.54 – 7.28 (m, 13 H, Ar-H, OH). – ^{13}C NMR ($CDCl_3$): $\delta =$ 32.60 (*C*H$_3$), 109.72 (*C*-6), 122.50 (Ar-*C*H), 125.10 (Ar-*C*), 126.92, 127.20, 128.00, 128.20 (Ar-*C*H), 128.28, 128.62, 128.80, 132.00 (Ar-*C*H, *C*H-11, -12, -13 and -14), 130.84, 131.20 (Ar-*C*H), 136.54 (*C*-8), 136.62 (*C*-23), 137.20 (*C*-9), 138.10 (Ar-N-*C*-21), 150.10 (*C*-3), 162.20 (*C*-5), 165.00 (*C*-7), 184.80 (*C*-10). – MS (EI, 70 eV): *m/z* (%) = 380 [M+1] (18), 379 [M^+] (16), 378 [M-1] (100), 364 (18), 350 (22), 306 (24), 288 (16), 222 (16), 208 (12), 120 (16), 104 (18). – $C_{24}H_{17}N_3O_2$ (379.42): calcd. C 75.98, H 4.52, H 11.07; found C 75.86, H 4.52, H 11.00.

*2-[4-(3-Chlorophenyl)-2,4-dihydro-3-phenyl-1,2,4-triazol-5-ylidene]indane-1,3-dione (**3f**):* Obtained as pale yellow crystals (0.45 g, 62%); $R_f = 0.2$ (CH_2Cl_2), m. p. 246 – 248 °C (EtOH). – IR (KBr): $\tilde{\nu} = 3200$ (NH), 3025 – 2965 (Ar-CH), 1685 (CO), 1592 (C=N) cm^{-1}. – UV (CH_3CN): λ_{max} (log ε) = 410 (3.80). – ^{1}H NMR ($CDCl_3$): $\delta = 7.60$ – 7.38 (m, 13 H, Ar-H, OH), 7.50 (dd, 1 H, $J = 1.8$ Hz, H-22). – ^{13}C NMR ($CDCl_3$): $\delta = 108.90$ (*C*-6), 122.00 (Ar-*C*H-22), 124.00, 124.20 (2 Ar-*C*H), 125.00 (Ar-*C*), 126.00 (Ar-*C*-23), 126.30, 126.38, 127.00, 127.40, (Ar-*C*H), 128.00, 128.40, 128.60, 130.40 (Ar-*C*H, *C*H-11, -12, -13 and -14), 136.20 (*C*-8), 136.44 (*C*-9), 137.00 (Ar-*C*-21), 148.90 (*C*-3), 158.60 (*C*-5), 165.10 (*C*-7), 184.40 (*C*-10). – MS (EI, 70 eV): *m/z* (%) = 401 [M+2] (20), 400 [M+2] (38), 399 [M^+] (100), 364 [M-1] (36), 371 (14), 370 (16), 364 (12), 336 (8), 308 (8), 239 (12), 228 (14), 192 (14), 177 (14), 125 (16), 111 (18). – $C_{23}H_{14}ClN_3O_2$ (399.84): calcd. C 69.09, H 3.53, Cl 8.87, H 10.51; found C 69.00, H 3.50, Cl 8.78, H 10.45.

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