Rapid and facile synthesis of spiro[indole-3,3′-[1,2,4]triazol]-2(1*H*)-ones

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Various 4′-aryl-5′-phenyl-2′,4′-dihydrospiro[indole-3,3′-[1,2,4]triazol]-2(1*H*)-ones have been synthesised by reaction of amidrazones with 2-(2-oxoindolin-3-ylidene)malononitrile.

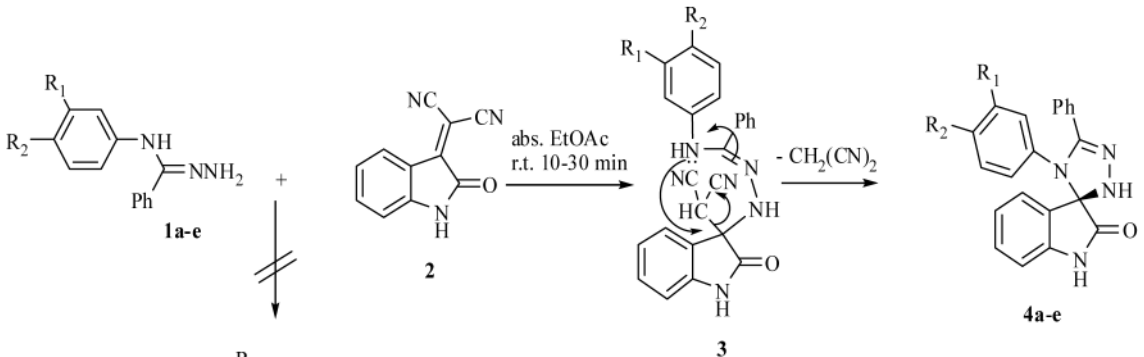
Keywords: amidrazones, 2-(2-oxoindolin-3-ylidene)malononitrile and 4′-aryl-5′-phenyl-2′,4′-dihydrospiro[indole-3,3′-[1,2,4]triazol]-2(1H)-ones

1,2,4-Triazole moieties have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants, sedatives, antianxiety compounds, antimicrobial agents,[1–3] and antimycotics such as voriconazole, fluconazole and intraconazole.[4,5] There are marketed drugs containing the 1,2,4-triazole group which are known to have antimycotic effects *e.g.*, alprazolam[6] and triazolam.[17] Amidrazones are an important class of amidines, since they can be used as synthons for 1,2,4-triazolo compounds and other heterocyclic systems.[7,8] Amidrazones possessing three nitrogen nucleophiles are essential components of molecules exhibiting high biological activities, *e.g.*, lamotrigine and sildenafil (Viagra).[9] Previously investigations described the reactions of amidines and their analogues with π-acceptors and various heterocycles.[10–12] Aly *et al* have recently reviewed the use of hydrazinecarbothioamide, thiocarbohydrazide and other derivatives in the synthesis of heterocycles.[13] Interestingly, a very convenient procedure to synthesise 1,2,4-triazoles in one step has been demonstrated, by a rapid reaction of amidrazones with 2-(1,3-dioxoindan-2-ylidene)malononitrile.[14] Accordingly, we have now investigated the reactions of amidrazones **1a–e** with 2-(2-oxoindolin-3-ylidene)malononitrile (**2**) as electron π-deficient acceptor, aiming to obtain heterocyclic compounds which might have biological activities.

Results and discussion

Scheme 1 outlines the reaction of **1a–e** with **2** in dry ethyl acetate under N_2 atmosphere. The reaction proceeded in a few minutes to yield, after chromatographic purification and recystallization, compounds **4a–e** (66–80%). We chose amidrazones **1a–e** having aryl groups with electron donating and withdrawing substitutents on the benzene ring, in order to examine the effect of electron demand on the course of reaction.

The structure assignment of compounds **4a–e** is well established using traditional spectroscopic tools such as IR, NMR (^{1}H, ^{13}C) and mass spectra, in addition to elemental analyses. Compounds **4a–e** showed IR absorption peaks for NH groups at ν_{max} = 3350–3330 cm^{-1} along with broad bands at ν_{max} = 1680–1695 cm^{-1} corresponding to the carbonyl groups. The mass spectra of compounds **4a–e** showed the molecular peaks, albeit not as the base peaks. For example, **4a** showed a molecular ion peak at *m/z* = 340 (68%), and the elemental analysis confirmed the molecular formula as $C_{21}H_{16}N_4O$. The mass spectra of all compounds **4a–e** contain similar fragments at *m/z* = 91, 113, and 160 (see Fig. 1). The ^{1}H NMR spectrum of **4a** showed the fused phenyl protons at δ_H = 7.90 (t, 2 H, *J* = 7.0 Hz) and 7.85 (d, 2 H, *J* = 7.8 Hz), whilst two NH-protons were observed as broad singlets at δ_H = 6.5 and 8.0. The observed ^{13}C NMR signals of **4a** confirmed the proposed structure of **4a** by the appearance of *spiro*-C at δ_C = 89.0, whilst the C-2 and C=N carbons resonated at δ_C = 168.2 and 156.6 respectively. The chemical shifts (δ_C) of some distinctive carbons of compounds **4a** and **4b** are shown in Fig. 2. The observation of two NH-signals, but no CH-proton or carbon signals, is consistent with structures **4a–e** but excludes the isomeric triazoles **5a–e** (Scheme 1).



1, 3-5	R_1	R_2	Yield of **4** (%)
a	H	H	70
b	H	CH_3	75
c	H	OCH_3	80
d	H	Cl	66
e	CH_3	H	72

Scheme 1 Synthesis of new 4′-aryl-5′-phenyl-2′,4′-dihydrospiro[indole-3,3′-[1,2,4]triazol]-2(1*H*)-ones **4a–e**.

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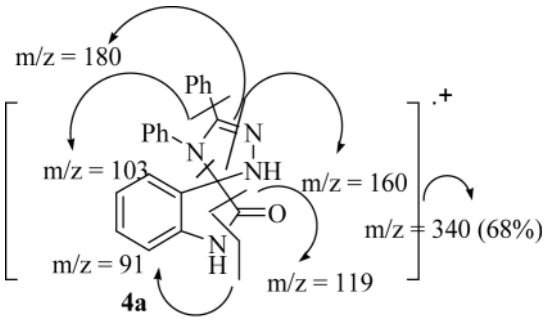

Fig. 1 Mass fragmentation patterns of compound **4a**.

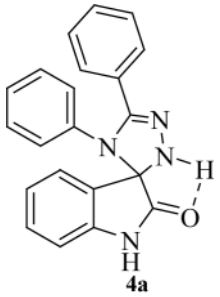

Fig. 3 Hydrogen bond in compound **4a**.

The molecular modelling (MM2)[15] of **4a**, as an example, indicated that the bond distance between the NH proton and the oxygen of the carbonyl group (C-2) is ~1.7 Å enabling them to form a an intramolecular hydrogen bond (Fig. 3). The calculated (ChemNMR) chemical shift of the hydrazine-NH proton is $\delta_H = 4.0$), whereas its experimental value is $\delta_H = 6.50$, in accord with deshielding due to the hydrogen bond just postulated. The angle between the plane N2–C3–N4 of the triazole ring and the plane C2–C3–C3a of the indole is calculated to be 105°.

Mechanistically, the reaction of **2** with **1a–e** is considered to involve addition of the hydrazino-NH_2 of **1** to the ylidene carbon in **2** to produce the intermediate **3** (Scheme 1). Subsequently, elimination of malononitrile, followed by another nucleophilic attack of the imino-NH *via* amidine-like addition to the electrophilic carbon, gives the stable heterocyclic compounds **4a–e** (Scheme 1). The presence of electron donating substituents such as methyl and methoxy *para* to the proximal nitrogen atom in **1a–e** (R_2) increased the yields of products **4a–e,** consistent with nucleophilic attack by this nitrogen.

Experimental

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 (δ) are given relative to internal standard TMS, and coupling constants *(J)* are 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 are detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried out in the Microanalysis Center of the Institut für Anorganische Chemie, Technische Universität Braunschweig. Mass spectroscopy was performed with a Finnigan Mat 8430 spectrometer at 70 eV, Institute of Organic Chemistry, TU-Braunschweig. Germany. IR spectra were obtained on Shimadzu 470 spectrophotometer using potassium bromide pellets; absorption maxima (ν_{max}) are reported in cm^{-1}.

Amidrazones **1a–e** were prepared according to ref. 7. 2-(2-Oxoindolin-3-ylidene)malononitrile (**2**) was prepared[16] from isatin (Merck).

Reaction of **1a–e** *with 2-(2-oxoindolin-3-ylidene)malononitrile* **(2)**

General procedure

A 250 mL two-necked bottom flask was flame-dried under N_2 atmosphere and then cooled to room temperature. Absolute ethyl acetate (100 mL) containing a mixture of **1a–e** (1 mmol) and **2** (0.195 g 1 mmol) was added to this flask. The reaction mixture was further stirred at room temperature for 10–30 min until the starting materials were consumed (the reaction progress was monitored by TLC analysis). The solvent was removed under vacuum and the residue was separated by PLC (silica gel, toluene: ethyl acetate 5: 1). The obtained products **4a–e** were recrystallised from the stated solvents.

*4′,5′-Diphenyl-2′,4′-dihydrospiro[indole-3,3′-[1,2,4]triazol]-2(1*H*)-one* (**4a**): Colourless crystals (0.24 g, 70%), m.p. (methanol) 160–162 °C. IR: ν_{max} = 3350 (NH), 3090–3010 (ArCH), 1695 (C=O), 1580 (C=C). ^{1}H NMR: δ_H = 8.0 (br, s, 1 H, NH, exchangeable with D_2O), 7.90 (t, 2 H, *J* = 7.0), 7.85 (d, 2 H, *J* = 7.8), 7.56–7.20 (m, 10 H, ArH), 6.50 (br, s, 1 H, NH, exchangeable with D_2O). ^{13}C NMR: δ_C = 168.2 (C=O), 156.6 (C=N), 142.0, 132.0, 131.0, 130.6 (ArC), 128.7, 128.4 (ArCH), 128.2, 127.4 (ArCH-*p*), 127.0, 126.8 (Ar2CH-*o*), 126.2, 126.0 (Ar2CH-*m*), 125.8, 118.6 (ArCH), 89.0 (spiro-C). MS (70 eV, EI): *m/z* = 340 (68), 180 (28), 160 (24), 113 (26), 103 (40), 194 (60), 91 (100), 77 (28). Anal. Calcd for $C_{21}H_{16}N_4O$ (340.381): C, 74.10; H, 4.74; N, 16.46. Found: C, 73.89; H, 4.70; N, 16.38.

*4′-(4″-Methylphenyl)-5′-phenyl-2′,4′-dihydrospiro[indole-3,3′-[1,2,4]triazol]-2(1*H*)-one* (**4b**): Colourless crystals (0.27 g, 75%), m.p. (ethanol) 228–230 °C. IR: ν_{max} = 3330 (NH), 3090–3015 (ArCH), 2980–2870 (aliph.-CH), 1680 (C=O), 1610 (C=N), 1580 (C=C). ^{1}H NMR: δ_H = 8.20 (br, s, 1 H, NH, exchangeable with D_2O), 8.10 (t, 2 H, *J* = 7.0), 7.92 (d, 2 H, *J* = 7.8), 7.66–7.10 (m, 9 H, ArH), 6.30 (br, s, 1 H, NH, exchangeable with D_2O), 2.32 (s, 3 H, CH_3). ^{13}C NMR: δ_C = 168.8 (C=O), 156.6 (C=N), 142.2, 134.2, 132.4, 131.4, 131.2 (ArC), 129.0, 128.6 (ArCH), 128.4 (ArCH-*p*), 128.0, 127.6 (Ar2CH-*o*), 127.2, 127.0 (Ar2CH-*m*), 126.5, 119.0 (ArCH), 89.6 (spiro-C), 22.1 (CH_3-Ar). MS (70 eV, EI): *m/z* (%) = 354 (60), 326 (22), 263 (16), 251 (20), 160 (20), 113 (12), 110 (100), 91 (60), 91 (34), 77 (30).

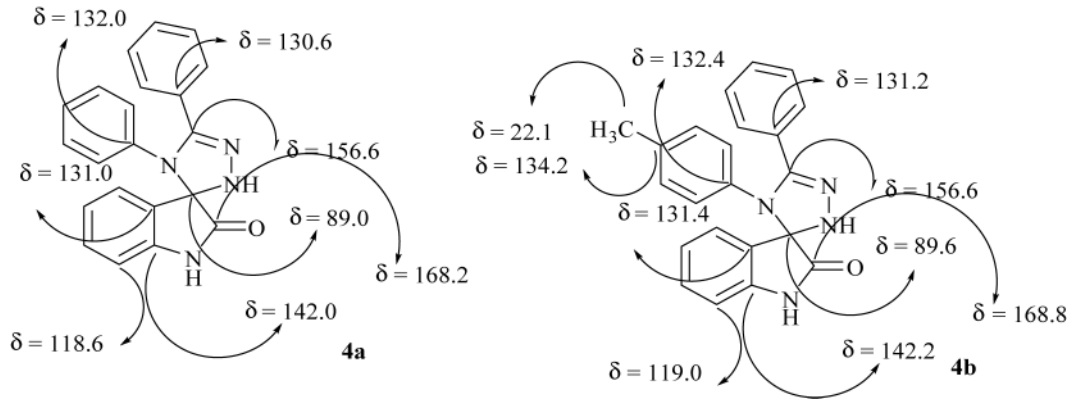

Fig. 2 Assignment carbon signals and their δ values of compounds **4a** and **4b**.

Anal. Calcd for $C_{22}H_{18}N_4O$ (354.407): C, 74.56; H, 5.12; N, 15.81. Found C, 74.40; H, 5.10; N, 15.70.

*4′-(4″-Methoxyphenyl)-5′-phenyl-2′,4′-dihydrospiro[indole-3,3′-[1,2,4]triazol]-2(1*H*)-one* (**4c**): Colourless crystals (0.3 g, 80%), m.p. (methanol) 190 °C. IR: ν_{max} = 3338 (NH), 3087–3010 (ArCH), 2987–2860 (aliph.-CH), 1680 (C=O), 1610 (C=N), 1586 (C=C). ^{1}H NMR: δ_H = 8.30 (br, s, 1 H, NH, exchangeable with D_2O), 8.10 (d, 2 H, *J* = 7.8), 7.80 (d, 2 H, *J* = 7.8), 7.70–7.12 (m, 7 H, ArH), 6.90 (m, 2 H, ArH), 6.40 (br, s, 1 H, NH, exchangeable with D_2O), 3.90 (s, 3 H, OCH_3). ^{13}C NMR: δ_C = 169.2 (C=O), 158.0 (C=N), 156.0, 134.4, 132.0, 131.2, 131.0 ArC), 129.2, 128.8 (ArCH), 128.2 (ArCH-*p*), 127.4 (Ar2CH-*o*), 127.0, 126.8 (Ar2CH-*m*), 122.0 (Ar2CH-*o*), 126.5, 119.0 (ArCH), 90.0 (spiro-C), 51.0 (CH_3–Ar). MS (70 eV, EI): *m/z* = 370 (56), 342 (22), 327 (22), 249 (30), 210 (77), 160 (24), 113 (28), 110 (100), 91 (22), 77 (20). Anal. Calcd for $C_{22}H_{18}N_4O_2$ (370.407): C, 71.34; H, 4.90; N, 15.13. Found: C, 71.30; H, 4.80; N, 15.08.

*4′-(4″-Chlorophenyl)-5′-phenyl-2′,4′-dihydrospiro[indole-3,3′-[1,2,4]triazol]-2(1*H*)-one* (**4d**): Pale yellow crystals (0.3 g, 66%), m.p. (ethyl acetate) 220 °C. IR: ν_{max} = 3334 (NH), 3098–3040 (ArCH), 1682 (C=O), 1612 (C=N), 1580 (C=C). ^{1}H NMR: δ_H = 8.40 (br, s, 1 H, NH, exchangeable with D_2O), 7.40–6.80 (m, 13 H, ArH), 6.10 ((br, s, 1 H, NH, exchangeable with D_2O). ^{13}C NMR: δ_C = 168.8 (C=O), 156.2 (C=N), 132.0, 131.8, 130.2, 130.0 (ArC), 128.5, 128.2 (ArCH), 128.0 (ArCH-*p*), 126.8, 126.6 (Ar2CH-*o*), 126.2 (Ar2CH-*m*), 125.4 (Ar2CH–Cl), 122.0 (ArC), 125.6, 118.6 (ArCH), 89.2 (spiro-C). MS (70 eV, EI): *m/z* = 376 [M+2] (38), 374 (100), 330 (22), 271 (16), 214 (30), 160 (32), 91 (80), 114 (28), 113 (32), 77 (24). Anal. Calcd for $C_{21}H_{15}N_4ClO$ (374.83): C, 67.29; H, 4.04; N, 14.95. Found. C, 67.12; H, 4.00; N, 15.00.

*4′-(3″-Methylphenyl)-5′-phenyl-2′,4′-dihydrospiro[indole-3,3′-[1,2,4]triazol]-2(1*H*)-one* (**4e**): Colourless crystals (0.26 g, 72%), m.p. (ethanol) 200 °C. IR: ν_{max} = 3334 (NH), 3092–3020 (ArCH), 2960–2860 (aliph.-CH), 1684 (C=O), 1612 (C=N), 1586 (C=C). ^{1}H NMR: δ_H = 8.10 (br, s, 1 H, NH, exchangeable with D_2O), 8.00 (t, 2 H, *J* = 7.4), 7.90 (d, 2 H, *J* = 7.6), 7.70–6.96 (m, 9 H, ArH), 6.20 (br, s, 1 H, NH, exchangeable with D_2O), 2.30 (s, 3 H, CH_3). ^{13}C NMR: δ_C = 169.0 (C=O), 156.5 (C=N), 142.0, 134.0, 132.2, 131.6, 131.4 (ArC), 129.0, 128.8 (ArCH), 128.6 (ArCH-*p*), 128.2, 127.6 (Ar2CH-*o*), 127.4, 127.2 (Ar2CH-*m*), 126.3, 119.2 (ArCH), 89.2 (spiro-C), 22.4 (CH_3-Ar). MS (70 eV, EI): *m/z* (%) = 354 (56), 326 (20), 263 (14), 251 (24), 160 (24), 113 (22), 110 (100), 91 (46), 91 (30), 77 (28). Anal. Calcd for $C_{22}H_{18}N_4O$ (354.407): C, 74.56; H, 5.12; N, 15.81. Found C, 74.44; H, 5.08; N, 15.68.

Professor Ashraf A. Aly thanks the DAAD foundation for the scholarship that enabled him to carry out NMR spectra analysis in the Institute of Organic Chemistry, TU-Braunschweig University, Germany.

Received 25 January 2010; accepted 11 March 2010
Paper100979 doi: 10.3184/030823410X12698845637794
Published online: 28 April 2010

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