1-(Benzimidazol-2-yl)-1,2-dioxoalkane arylhydrazones and 2-phenylbenzimidazole as the main products of the reactions of 1,2,3-triketone 2-arylhydrazones with *o*-phenylenediamine

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The reactions of *o*-phenylenediamine with 1,2,3-triketone 2-arylhydrazones containing alkyl substituents result in the predominant formation of 1-(benzimidazol-2-yl)-1,2-dioxoalkane arylhydrazones, whereas phenyl-substituted analogues afford 2-phenylbenzimidazole.

The formation of 1,5-benzodiazepine derivatives under mild conditions is typical of the reactions of 1,3-diketones, including monofluoroalkyl-containing compounds, with *o*-phenylenediamine.[1] More severe reaction conditions, as well as the presence of a second fluoroalkyl substituent in the 1,3-diketone molecule or the acyl group at the 2-position, are favourable for the formation of 2-alkyl(aryl)benzimidazoles.[2–4]

In this work, we studied the interaction of 1,2,3-triketone 2-arylhydrazones **1a**–**h** with *o*-phenylenediamine. We found that compounds **1** do not react with the diamine under conditions of formation of 1,5-benzodiazepines from unsubstituted 1,3-diketones. Under more severe conditions (on boiling in *o*-xylene, toluene with the azeotropic distillation of water or ethanol in the presence of catalytic amounts of acetic and hydrochloric acid), 2-substituted benzimidazoles **2a**–**f** and **3a**,**b** were the main isolated products of these reactions. In this case, the nature of the substituent at the 2-position of the benzimidazole ring depends on the structures of starting 1,2,3-triketone 2-arylhydrazones **1a**–**h**. Thus, compounds **1a**–**f** with alkyl (methyl, butyl, and *tert*-butyl) substituents mainly form 1-(benzimidazol-2-yl)-1,2-dioxoalkane arylhydrazones **2a**–**f**,† whereas phenyl-substituted 1,2,3-triketone 2-arylhydrazones **1g**,**h** give only 2-phenylbenzimidazole **3a**.

It is likely that the initial step in the formation mechanism of the reaction leading to benzimidazoles **2** and **3** are the same. We propose that an amino group of *o*-phenylenediamine attacks the alkyl or aryl substituted carbonyl group of 1,2,3-triketone 2-arylhydrazone **1** to form intermediate diimine **A** (Scheme 1). Next, the free amino group of intermediate **A** adds to the imine containing the R^2 substituent to form 2-substituted benzimidazoline **B**, and not to the carbonyl group containing the R^1 substituent to give alternatively a 1,5-benzodiazepine. It is evident that this direction of addition depends on steric hindrance produced by the bulky arylhydrazone group. Intermediate benzimidazoline **B** has two possibilities for aromatisation: path I by elimination of a saturated hydrocarbon molecule R^2H or path II by elimination of a fluorinated 2-arylhydrazone-substituted ketone. In this case, it is likely that the direction of aromatisation depends on thermodynamic factors.

1,2,3-Triketone 2-arylhydrazones contain alkyl substituents primarily react *via* path I; in this case, 1-(benzimidazol-2-yl)-1,2-dioxoalkane arylhydrazones **2a**–**f** are formed, whereas phenyl-containing analogues reacted *via* path II to result in 2-phenylbenzimidazole **3a**. This was supported by the separation of 2-oxohexanal arylhydrazone **4**† from the reaction mixture of compound **1h** (Scheme 1). It is likely that the reactions of 1,2,3-triketone 2-arylhydrazones with alkyl substituents partially proceed *via* path II. This is evident from the production of 2-methylbenzimidazole **3b** and arylhydrazone **4** in small amounts in the reaction of 1,2,3-triketone 2-arylhydrazone **1e** and from medium yields (68–42%) of benzimidazoles **2a**–**f**. The structures of compounds **3a**,**b** were supported by comparing their identity with authentic samples.[5]

The formation of 2-methyl(phenyl)benzimidazoles **3** *via* path II is typical of the reactions of 1,3-diketones with *o*-phenylenediamine. In the case of monofluoroalkyl-containing 1,3-diketones, it results from the elimination of a ketone containing the most electron-acceptor fluoroalkyl substituent. The production of benzimidazoles **2** *via* path I was unexpected; it was not

† New isolated compounds **2a**–**f**, **4** were characterised by IR (Vaseline oil), ^{19}F NMR (75.0 MHz, C_6F_6) and ^1H NMR (400 and 80 MHz, Me_4Si) spectroscopy and mass spectrometry (EI, 70 eV). Compound **2e** was additionally characterised by ^{13}C NMR spectroscopy (100 MHz, Me_4Si).

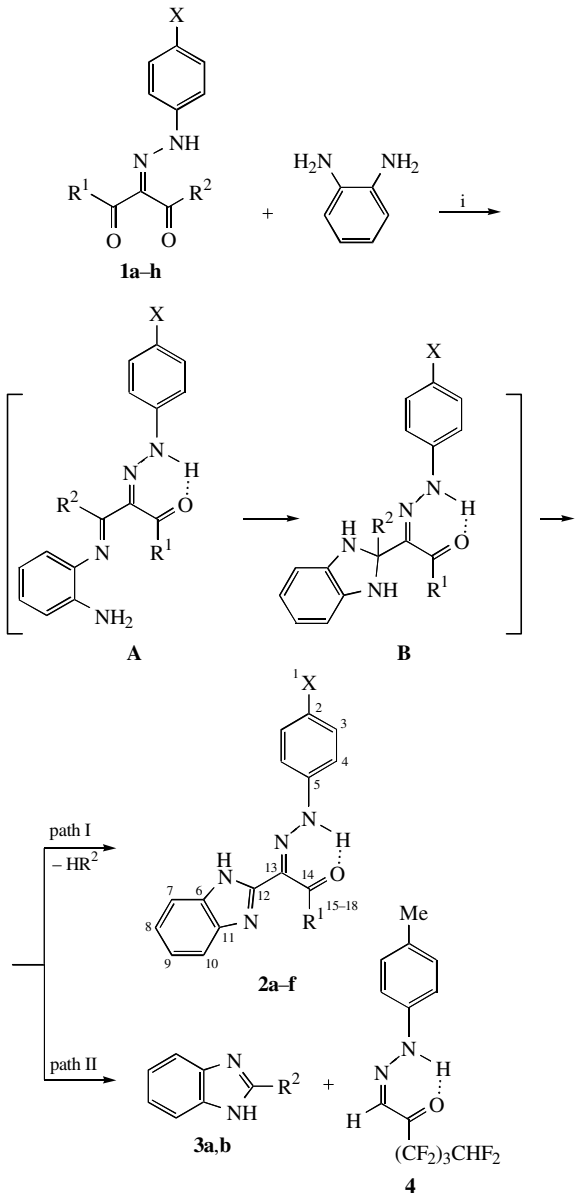
1-(Benzimidazol-2-yl)-1,2-dioxopropane 4-methoxyphenylhydrazone **2a** (general procedure). A mixture of 1,2,3-triketone 2-arylhydrazone **1a** (235 mg, 1 mmol) and *o*-phenylenediamine (108 mg, 1 mmol) was dissolved in *o*-xylene (8 cm^3) [or in toluene, **2e**, or in ethanol in the presence of acetic (0.1 cm^3) and hydrochloric (0.1 cm^3) acids, **2c**]. The reaction mixture was refluxed for 30 h and then concentrated to dryness. After column chromatography on silica gel (100×250 μ) with chloroform as an eluent, 193 mg (65%) of product **2a** was obtained; mp 238–240 °C. ^1H NMR ([$^2H_6$]DMSO/CCl_4) δ: 2.61 (s, 3H, Me), 3.81 (s, 3H, OMe), 6.97–7.73 (2m, 8H, $2C_6H_4$), 12.44, 15.26 (2br. s, 2H, 2NH). IR (ν/cm^{-1}): 3310, 1580 (NH), 1630 (C=O), 1600, 1540, 1500 (C=N, C=C). MS, *m*/*z*: 309 (M^+). Found (%): C, 65.99; H, 5.20; N, 18.05. Calc. for $C_{17}H_{16}N_4O_2$ (%): C, 66.22; H, 5.23; N, 18.17.

1-(Benzimidazol-2-yl)-1,2-dioxo-3,3,4,4-tetrafluorobutane 4-methylphenylhydrazone **2b**: after recrystallisation from benzene, 257 mg (68%) was obtained, mp 201–202 °C. ^1H NMR ([$^2H_6$]DMSO/CCl_4) δ: 2.38 (s, 3H, Me), 6.82 [tt, 1H, $H(CF_2)_2$, $^2J_{H–F}$ 52.5 Hz, $^3J_{H–F}$ 5.7 Hz], 7.26–7.78 (2m, 8H, $2C_6H_4$), 14.20 (br. s, 2H, 2NH). ^{19}F NMR ([$^2H_6$]DMSO/CCl_4) δ: 26.22 (dt, 2F, HCF_2, $^2J_{F–H}$ 52.5 Hz, $^3J_{F–F}$ 8.0 Hz), 43.31 (m, 2F, CF_2). IR (ν/cm^{-1}): 3360, 1590 (NH), 1660 (C=O), 1615, 1550, 1500 (C=N, C=C). Found (%): C, 57.07; H, 3.68; F, 20.23; N, 14.51. Calc. for $C_{18}H_{14}F_4N_4O$ (%): C, 57.15; H, 3.73; F, 20.09; N, 14.81.

1-(Benzimidazol-2-yl)-1,2-dioxo-3,3-difluoropropane 4-methoxyphenylhydrazone **2c**: after recrystallisation from 50% aqueous ethanol, 210 mg (61%) was obtained, mp 220–222 °C. ^1H NMR ([$^2H_6$]DMSO/CCl_4) δ: 3.83 (s, 3H, OMe), 7.22 (t, 1H, HCF_2, $J_{H–F}$ 54.2 Hz), 7.00–7.76 (2m, 8H, $2C_6H_4$), 14.03 (br. s, 2H, 2NH). ^{19}F NMR ([$^2H_6$]DMSO/CCl_4) δ: 35.25 (d, 2F, HCF_2, $J_{F–H}$ 54.2 Hz). IR (ν/cm^{-1}): 3330, 1595 (NH), 1665 (C=O), 1620, 1550, 1510 (C=N, C=C). MS, *m*/*z*: 345 (M^+). Found (%): C, 58.89; H, 4.37; F, 10.93; N, 16.45. Calc. for $C_{17}H_{14}F_2N_4O_2$ (%): C, 59.30; H, 4.10; F, 11.03; N, 16.27.

1-(Benzimidazol-2-yl)-1,2-dioxo-3,3-difluoropropane 4-methylphenylhydrazone **2d**: after recrystallisation from benzene, 164 mg (50%) was obtained, mp 220–221 °C. ^1H NMR ([$^2H_6$]DMSO/CCl_4) δ: 2.37 (s, 3H, Me), 7.22 (t, 1H, HCF_2, $J_{H–F}$ 54.1 Hz), 7.25–7.76 (2m, 8H, $2C_6H_4$), 14.23 (br. s, 2H, 2NH). ^{19}F NMR ([$^2H_6$]DMSO/CCl_4) δ: 35.20 (d, 2F, HCF_2, $J_{F–H}$ 54.1 Hz). IR (ν/cm^{-1}): 3335, 1595 (NH), 1670 (C=O), 1620, 1560, 1510, 1470 (C=N, C=C). Found (%): C, 62.57; H, 4.37; F, 11.93; N, 17.08. Calc. for $C_{17}H_{14}F_2N_4O$ (%): C, 62.19; H, 4.30; F, 11.57; N, 17.06.

1-(Benzimidazol-2-yl)-1,2-dioxo-3,3,4,4,5,5,6,6-octafluorohexane 4-methylphenylhydrazone **2e**: after recrystallisation from benzene, 201 mg (42%) was obtained, mp 221–222 °C. ^1H NMR ([$^2H_6$]DMSO/CCl_4) δ: 2.38 (s, 3H, Me), 6.90 [tt, 1H, $H(CF_2)_4$, $^2J_{H–F}$ 51.0 Hz, $^3J_{H–F}$ 5.6 Hz], 7.27–7.79 (2m, 8H, $2C_6H_4$), 14.24 (br. s, 2H, 2NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 20.80 (C^1), 115.49, 117.29, 121.61, 123.59, 130.15, 135.06, 135.14, 135.85 ($C^{2–11}$), 141.19, 144.31 ($C^{12,13}$), 177.16 (t, C^{14}, $^2J_{C–F}$ 22.6 Hz), 107.84–114.72 ($C^{15–18}$). ^{19}F NMR ([$^2H_6$]DMSO/CCl_4) δ: 24.50 (dm, 2F, HCF_2, $^2J_{F–H}$ 51.0 Hz), 33.76 (m, 2F, CF_2), 40.97 (m, 2F, CF_2), 52.25 (m, 2F, CF_2). IR (ν/cm^{-1}): 3380, 1585 (NH), 1645 (C=O), 1610, 1540, 1500, 1470 (C=N, C=C). Found (%): C, 50.01; H, 2.90; F, 31.67; N, 11.65. Calc. for $C_{20}H_{14}F_8N_4O$ (%): C, 50.22; H, 2.95; F, 31.77; N, 11.71.



1a–h **A** **B** **2a–f** **3a**,**b** **4**

1 **a** $R^1 = R^2 = Me$, X = OMe
b $R^1 = CF_2CHF_2$, R^2 = Bu, X = Me
c $R^1 = CHF_2$, $R^2 = Bu^t$, X = OMe
d $R^1 = CHF_2$, R^2 = X = Me
e $R^1 = (CF_2)_3CHF_2$, R^2 = X = Me
f $R^1 = (CF_2)_3CF_3$, R^2 = X = Me
g $R^1 = CF_3$, R^2 = Ph, X = Me
h $R^1 = (CF_2)_3CHF_2$, R^2 = Ph, X = Me

2 **a** R^1 = Me, X = OMe
b $R^1 = CF_2CHF_2$, X = Me
c $R^1 = CHF_2$, X = OMe
d $R^1 = CHF_2$, X = Me
e $R^1 = (CF_2)_3CHF_2$, X = Me
f $R^1 = (CF_2)_3CF_3$, X = Me

3 **a** R^2 = Ph
b R^2 = Me

Scheme 1 *Reagents and conditions*: i, *o*-xylene (toluene, ethanol, H^+), T_b, 30 h.

observed previously in the reactions of 1,3-diketones and their derivatives with *o*-phenylenediamine.

However, Elderfield and MaCarthy[6] reported on the formation of 2-alkyl(aryl)benzimidazoles in the reactions of ketones with *o*-phenylenediamine as a result of aromatisation of intermediate 2-disubstituted benzimidazolines by the elimination of a saturated hydrocarbon. In a number of cases, they isolated and characterised benzimidazolines and detected gas evolution.

The cleavage of 1,2,3-triketone 2-arylhydrazones in the reaction with *o*-phenylenediamine is unexpected because only 'acid' cleavage[7] was previously known for the reactions of 1,3-diketones, including 2-mono- and -disubstituted compounds, with alkaline and basic reagents.

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1-(Benzimidazol-2-yl)-1,2-dioxo-3,3,4,4,5,5,6,6,6-nonafluorohexane 4-methylphenylhydrazone **2f**: after recrystallisation from benzene, 233 mg (47%) was obtained, mp 222–224 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.36 (s, 3H, Me), 7.34–7.84 (2m, 8H, $2C_6H_4$), 14.10 (br. s, 2H, 2NH). IR (ν/cm^{-1}): 3380, 1590 (NH), 1655 (C=O), 1620, 1550, 1470 (C=N, C=C). Found (%): C, 48.69; H, 2.55; F, 34.18; N, 11.56. Calc. for $C_{20}H_{13}F_9N_4O$ (%): C, 48.40; H, 2.64; F, 34.45; N, 11.29.

2-Phenylbenzimidazole **3a**: after recrystallisation from 30% aqueous alcohol, 132 mg (68%) from compound **1g** or 118 mg (61%) from compound **1h** was obtained, mp 289–290 °C, *cf*. ref. 5.

2-Methylbenzimidazole **3b**: after recrystallisation from water, 15 mg (12%) was obtained, mp 174–175 °C, *cf*. ref. 5.

2-Oxo-3,3,4,4,5,5,6,6-octafluorohexanal 4-methylphenylhydrazone **4**: after column chromatography on silica gel (100×250 μ) with chloroform as an eluent, 163 mg (45%) from compound **1h** or 33 mg (9%) from compound **1e** was obtained, mp 72–74 °C. ^{1}H NMR ([$^2H_6$]DMSO/CCl_4) δ: 2.31 (s, 3H, Me), 6.83 [tt, 1H, $H(CF_2)_4$, $^2J_{H–F}$ 50.5 Hz, $^3J_{H–F}$ 5.6 Hz], 7.14 (m, 4H, C_6H_4), 7.54 (s, 1H, =CH), 12.13 [br. s, 1H, NH(OH)]. ^{19}F NMR ([$^2H_6$]DMSO/CCl_4) δ: 24.16 (dm, 2F, HCF_2, $^2J_{F–H}$ 50.5 Hz), 33.29 (m, 2F, CF_2), 39.24 (m, 2F, CF_2), 46.37 (m, 2F, CF_2). IR (ν/cm^{-1}): 3220, 3190, 3130, 3050, 1590 (NH, OH), 1650, 1640 (sh, C=O), 1530, 1500, 1470 (C=C). Found (%): C, 42.89; H, 2.57; F, 41.55; N, 7.44. Calc. for $C_{13}H_{10}F_8N_2O$ (%): C, 43.11; H, 2.78; F, 41.96; N, 7.73.