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Cascade cyclization of 1,2-diamino-4-phenylimidazole with aromatic aldehydes and Meldrum's acid

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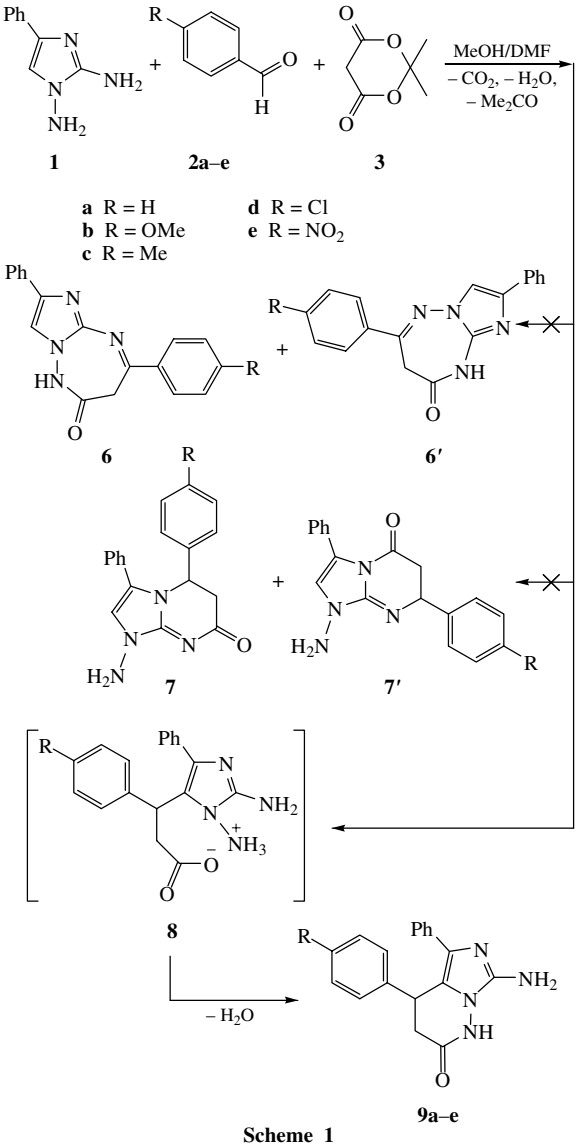
The three-component condensation of 1,2-diamino-4-phenylimidazole with aromatic aldehydes and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) led to 7-amino-4-aryl-5-phenyl-3,4-dihydroimidazo[1,5-*b*]pyridazin-2(1*H*)-ones.

Four nonequivalent nucleophilic centres in 1,2-diamino-4-phenylimidazole are responsible for various reactions with β-bielectrophilic carbonyl reagents, their synthetic precursors or equivalents and for the use of this compound in the synthesis of fused heterocyclic systems. Originally, vicinal di- and triaminoazoles containing the N-amino group in reaction with enones were regarded only as 1,4-binucleophiles yielding azolotriazepine derivatives.[1,2] The reactions of 1,2-di- and 1,2,3-triaminoazoles with α,β-unsaturated ketones, as well as with their bromo and dibromo derivatives or β-aroylacrylic acids, give fused pyridazine[3–5] and pyrimidine[6–9] systems rather than triazepine ones because the amino groups of these azoles are less nucleophilic than their endocyclic reactive sites. The goal of this work was to elucidate the pathways of reactions of 1,2-diamino-4-phenylimidazole **1** with aromatic aldehydes **2a–e** and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) **3** under different reaction conditions.



Scheme 1

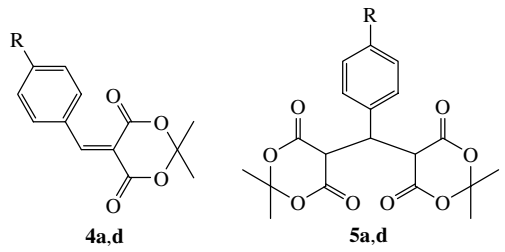
We found that the three-component condensation of equimolar amounts of amine **1**, *para*-substituted benzaldehydes **2a–e** and Meldrum's acid **3** in methanol† or DMF‡ gives imidazo[5,1-*b*]pyridazin-2-one derivatives **9a–e** (Scheme 1). Arylmethylene derivatives **4** and Michael adducts **5** are also possible intermediates in these reactions. Compounds **4a**,**d** and **5a**,**d** were also investigated in the reaction with aminoimidazole **1**.§ In all cases, only imidazo[5,1-*b*]pyridazin-2-ones **9a**,**d** were obtained (Scheme 2). Isomeric compounds **6**, **6′** and **7**, **7′** (Scheme 1) were not detected. For the elucidation of the causes of modest imidazopyridazinones **9a–e** yields on the example

† A mixture of diamine **1** (0.001 mol, 0.17 g), benzaldehyde **2a** (0.001 mol, 0.1 g) and Meldrum's acid **3** (0.001 mol, 0.14 g) in 2 ml of MeOH was refluxed for 2 h. After cooling, the precipitate of imidazopyridazinone **9a** was filtered off and crystallised from propan-2-ol. Compounds **9b–d** were synthesised by a similar method.

‡ A mixture of diamine **1** (0.001 mol, 0.17 g), benzaldehyde **2a** (0.001 mol, 0.1 g), dioxanedione **3** (0.001 mol, 0.14 g) in 0.5 ml of DMF was refluxed for 20 min. After cooling, 2 ml of propan-2-ol was added, then 0.13 g, yield 43%, of compound **9a** was filtered off and crystallised from propan-2-ol. After the separation of a precipitate of **9a** from the filtrate, the solvent was evaporated. The residual dark oil was crystallised from ethanol and 0.04 g (16%) of azomethine **10** [mp 213 °C (decomp.)[11–13]] and 0.02 g (10%) of acetyl derivative **11** [mp 243 °C (decomp.)] were separated.[10]

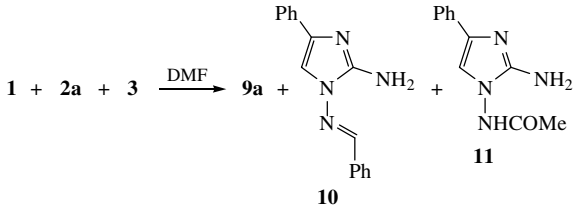
§ A mixture of diamine **1** (0.001 mol, 0.17 g) and benzylidene derivative **4a** (0.001 mol, 0.23 g) in 2 ml of MeOH was refluxed for 2 h. After cooling, 0.17 g (55%) of precipitate **9a** was filtered off and crystallised from propan-2-ol. The presence of azomethine **10** and acetyl derivative **11** in the reaction mixture was checked by TCL on Silufol UV-254 plates with $CHCl_3$–MeOH (9:1) as an eluent. Compound **9d** was synthesised from **1** and **4d** in a similar way in 58% yield.

A mixture of diamine **1** (0.001 mol, 0.17 g) and Michael adduct **5a** (0.001 mol, 0.38 g) in 2 ml of MeOH was refluxed for 2 h. After cooling, 0.16 g (53%) of the precipitate of imidazopyridazinone **9a** was filtered off and crystallised from propan-2-ol. The presence of azomethine **10** and acetyl derivative **11** in the reaction mixture was checked. Compound **9d** was synthesised from **1** and **5d** in a similar way in 51% yield.



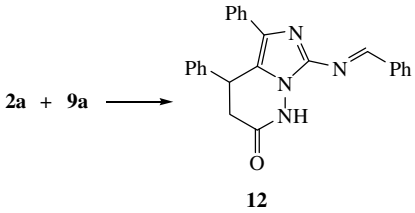
Scheme 2

of the interaction of amine **1** with benzaldehyde **2a** and Meldrum's acid **3** in DMF, it was shown that 2-amino-4-phenyl-1-benzylideneaminoimidazole **10** and 2-amino-1-acetylamino-4-phenylimidazole **11** were present in the reaction mixture with the target product (Scheme 3). These substances occurred in the reaction with amine **1** and compound **4a** or **5a** in methanol, as confirmed by TLC. Probably, acetylaminoimidazole **11** and corresponding azomethines are formed in the condensations as by-products and reduced the yields of target imidazopyridazinones **9**.



Scheme 3

The structures of compounds **9a–e** were proved by IR and ^{1}H NMR spectroscopy,¶ and the structures of azomethine **10** and acetyl derivative **11**, by a comparison of physico-chemical and spectral characteristics with published data.[10–13] In the IR spectrum of compounds **9a–e**, the absorption band of the carbonyl group at 1672–1676 cm^{-1} and broad bands of the associated NH and NH_2 groups at 3424–2800 cm^{-1} are characteristic. In the ^{1}H NMR spectrum, beside multiplets of two aromatic nuclei with δ 7.64–7.05 ppm, there are broad singlets of the NH (12.3–12.1 ppm) and NH_2 (5.75–5.63 ppm) groups, which disappeared after exchange for deuterium with CD_3OD, and also signals of the CH_2–CH moiety as a typical ABX system (two doublets and doublet of doublets: J_{AB} 15.2–16.0 Hz, J_{AX} 0 Hz, J_{BX} 6.2–6.0 Hz). According to these experimental data, the structures of triazepinones **6**, **6′** and imidazopyrimidinones **7**, **7′** were rejected. Product **12** was obtained by refluxing compound **9a** with benzaldehyde **2a** (Scheme 4).††



Scheme 4

In its IR spectrum, absorption bands of C=O at 1680 cm^{-1} and associated NH groups at 3060 cm^{-1} were presented. Bands due to the amino group at 3340 and 3440 cm^{-1} were not observed. The ^{1}H NMR spectrum of compound **12** differs from the spectrum of its synthetic precursor **9a** by the presence of a singlet due to the CH proton of the azomethine fragment at δ 9.25 ppm and by the absence of NH_2 group signals. At the same time, the nature of the splitting of the signals for protons of the CH_2–CH moiety as a ABX system (two doublets and doublet of doublets: J_{AB} 15.2 Hz, J_{AX} 0 Hz, J_{BX} 6.2 Hz) preserves. The structure of the compounds as imidazo[5,1-*b*]pyridazin-2-ones was unambiguously proved by X-ray diffraction analysis of azomethine **12**.‡‡ The dihydropyridazine cycle in compound **12** adopts a half-chair conformation. Deviations of the C(2) and C(3) atoms from the mean plane of remaining atoms of the ring are –0.38 and 0.30 Å, respectively. The benzylidenamino fragment and phenyl substituent at the C(5) atom are slightly non-coplanar relatively to the plane of the imidazole cycle [the C(7)–N(4)–C(6)–N(3) and C(4)–C(5)–C(20)–C(21) torsion angles are –16.3(2)° and 18.1(2)°, respectively] in spite of the H(7)···N(3) 2.60 Å and H(25)···N(3) 2.59 Å attractive interactions (the sum of van der Waals radii[14] is 2.67 Å). The phenyl subsituent at the C(3) atom has a pseudoaxial orientation [the C(1)–C(2)–C(3)–C(14) torsion angle is –75.1(2)°] and it is turned almost orthogonally relatively to the C(2)–C(3) bond

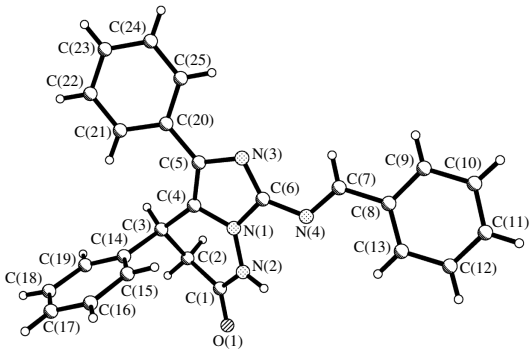


Figure 1 Molecular structure of **12**. Selected bond lengths (Å): O(1)–C(1) 1.227(2), N(1)–C(6) 1.369(2), N(1)–N(2) 1.379(2).

¶ **9a**: yield 52%, mp 292–295 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 12.20 (s, 1H), 7.40–7.05 (m, 10H), 5.63 (s, 2H), 4.72 (d, 1H), 3.07–3.04 (dd, 1H), 2.66–2.58 (d, 1H). IR (KBr, ν/cm^{-1}): 3424–2800, 1676. Found (%): C, 70.94; H, 5.24; N, 18.38. Calc. for $C_{18}H_{16}N_4O$ (%): C, 71.05; H, 5.26; N, 18.42.

9b: yield 50%, mp 290–292 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 12.20 (s, 1H), 7.41–7.11 (m, 9H), 5.57 (s, 2H), 4.63 (d, 1H), 3.71 (s, 3H), 3.01–2.89 (dd, 1H), 2.71–2.64 (d, 1H). IR (KBr, ν/cm^{-1}): 3432–2800, 1676. Found (%): C, 68.20; H, 5.34; N, 16.73. Calc. for $C_{19}H_{18}N_4O_2$ (%): C, 68.26; H, 5.39; N, 16.77.

9c: yield 51%, mp > 300 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 12.20 (s, 1H), 7.27–7.39 (dd, 4H), 7.20–7.12 (m, 5H), 5.65 (s, 2H), 4.65 (d, 1H), 3.03–2.92 (dd, 1H), 2.63–2.55 (d, 1H). IR (KBr, ν/cm^{-1}): 3464–2800, 1672. Found (%): C, 71.67; H, 5.70; N, 17.65. Calc. for $C_{19}H_{18}N_4O$ (%): C, 71.70; H, 5.66; N, 17.61.

9d: yield 55%, mp > 300 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 12.10 (s, 1H), 7.41–7.05 (m, 9H), 5.55 (s, 2H), 4.74 (d, 1H), 3.06–2.95 (dd, 1H), 2.67–2.58 (d, 1H). IR (KBr, ν/cm^{-1}): 3464–2800, 1672. Found (%): C, 63.79; H, 4.42; N, 16.50; Cl, 10.47. Calc. for $C_{18}H_{15}N_4ClO$ (%): C, 63.81; H, 4.43; N, 16.54; Cl, 10.49.

9e: yield 60%, mp 204–207 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 12.10 (s, 1H), 8.20–7.49 (dd, 4H), 7.37–7.10 (m, 5H), 5.75 (s, 2H), 4.93 (d, 1H), 3.15–3.04 (dd, 1H), 2.71–2.61 (d, 1H). IR (KBr, ν/cm^{-1}): 3304–2800, 1676, 1352. Found (%): C, 61.85; H, 4.34; N, 20.10. Calc. for $C_{18}H_{15}N_5O_3$ (%): C, 61.89; H, 4.30; N, 20.06.

†† A mixture of imidazopyridazinone **9a** (0.001 mol, 0.3 g) and benzaldehyde **2a** (0.001 mol, 0.1 g) in 2 ml of MeOH was refluxed for 3 h. After cooling, 0.3 g of the precipitate of azomethine **12** was filtered off and crystallised from propan-2-ol. Yield 77%, mp 281–283 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 12.30 (s, 1H), 9.25 (s, 1H), 7.57–7.24 (m, 15H), 4.90 (d, 1H), 3.21–3.18 (dd, 1H), 2.76–2.68 (d, 1H). IR (KBr, ν/cm^{-1}): 3060, 1680. Found (%): C, 76.57; H, 5.14; N, 14.34. Calc. for $C_{25}H_{20}N_4O$ (%): C, 76.53; H, 5.10; N, 14.29.

[the C(2)–C(3)–C(14)–C(15) torsion angle is 98.7(2)°]. In the crystal phase, the molecules of **10** form centrosymmetric dimers due to the intermolecular hydrogen bond N(2)–H(2N)···O(1)′ (–*x*, 1 – *y*, –*z*) H···O 1.94 Å, N–H···O 167°.

Thus, the cascade cyclocondensation of diamino-4-phenylimidazole **1** with aromatic aldehydes **2** and Meldrum's acid **3** is a regioselective process, which exclusively leads to imidazo-[5,1-*b*]pyridazin-2-ones **9**. The direction of the formation of partially hydrogenated pyridazine ring corresponds to the interaction of β-carbon atom in intermediate arylmethylene derivative **4** or Michael adduct **5** with a carbon nucleophilic centre and the carbonyl group with the N-amino group in the diaminoimidazole molecule.

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‡‡ *X-ray diffraction study.* Crystals of **12** are orthorhombic. At 293 K, $a = 9.835(2)$, $b = 20.780(2)$ and $c = 20.987(8)$ Å, $V = 4289(2)$ Å^3, $M_r = 392.45$, $Z = 8$, space group *Pbca*, $d_{calc} = 1.215$ g cm^{-3}, μ(MoKα) = 0.077 mm^{-1}, $F(000) = 1648$. Intensities of 31103 reflections (6245 independent, $R_{int} = 0.060$) were measured on an Xcalibur-3 diffractometer (MoKα radiation, graphite monochromator, CCD detector, ω-scans, $2\theta_{max} = 60°$). The structure was solved by a direct method using the SHELXTL package.[15] Positions of hydrogen atoms were located from electron density difference maps and refined by the 'riding' model with $U_{iso} = 1.2\,U_{eq}$ of carrier non-hydrogen atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation using 6171 reflections was converged to $wR_2 = 0.095$ [$R_1 = 0.039$ for 1618 reflections with $F > 4\sigma(F)$, $S = 0.611$].

CCDC 662071 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

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