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Diversity oriented heterocyclizations of pyruvic acids, aldehydes and 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides: catalytic and temperature control of chemoselectivity

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Abstract Heterocyclization reactions of pyruvic acids, aromatic aldehydes and 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides yielding four different types of final compounds are described. The reactions involving arylidenpyruvic acids lead with high degree of selectivity to either 4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids or 5-[(2-oxo-2,5-dihydrofuran-3-yl)amino]-1*H*-pyrazoles, depending on the catalyst type or temperature regime. The interactions based on arylpyruvic acids can take place under kinetic or thermodynamic control producing 7-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acids or 3-hydroxy-1-(1*H*-pyrazol-5-yl)-1,5-dihydro-2*H*-pyrrol-2-ones, respectively.

Keywords Multicomponent reaction (MCR) · Microwave synthesis · Ultrasonication · Pyruvic acid · 5-Aminopyrazole-4-carboxamide · Selectivity

Introduction

The importance of heterocyclic compounds in medicine and different chemistry disciplines such as organic, bioorganic, combinatorial, and material science can hardly be overstated. It explains the efforts for elaborating new approaches to their synthesis [1,2]. However, although an increasing number of known heterocyclization types have been and continue being developed via multicomponent reactions (MCRs) [3–6], microwave- [7–9] and ultrasonic-assisted synthesis [10–12], reactions in ionic liquids [13,14], critical and supercritical media [15,16], they cover a limited part of chemical space. One of the major problems in the introduction of diversity around heterocyclic systems is quite often the control (or lack of it) of key factors that influence or determine the desired reaction, atom arrangement, electronic- or steric-driven path to output the desired products.

Generally, this problem can be solved with the help of structural factors such as protecting, activating or deactivating groups, or by changing catalytic system, solvent type, temperature, pressure, time or other reaction parameters including activation method. We have recently published methods allowing increasing their selectivity and diversity of final compounds [16–21].

For example, we successfully controlled the outcome of the MCR of 3-substituted 5-aminopyrazoles with cyclic 1,3-diketones and aromatic aldehydes by utilizing specific types of basic catalysts in conjunction with microwave and ultrasonic irradiation allowing precise changing temperature regime [18,19].

This approach allowed not only elaborating high selective procedures for synthesis of two known heterocyclic compounds—6,7,8,9-tetrahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5(4*H*)-ones and 5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8(4*H*)-one (pathway **A** and **B**, Scheme 1), but also discovering a new unusual reaction leading to a novel heterocyclic system—4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9(1*H*)-one (pathway C, Scheme 1).

Changing the temperature also appeared to be a method to control the chemoselectivity of three-component reaction of 5-aminopyrazoles, aldehydes and barbituric acids [21]: application of ultrasonication at room temperature gave

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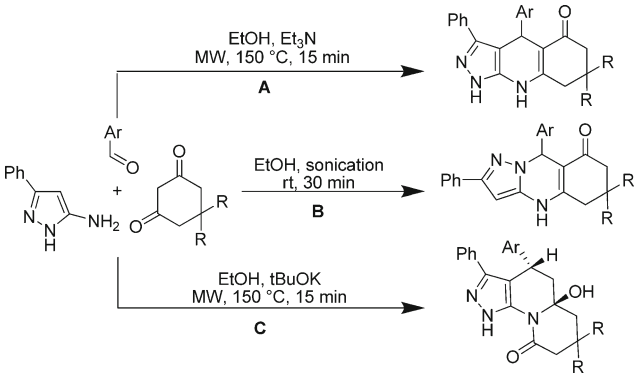


Scheme 1 Control of selectivity of multicomponent reaction of 5-aminopyrazoles, cyclic 1,3-diketones and aldehydes

unexpectedly 1,4,6,7-tetrahydro-1′*H*-spiro[pyrazolo[3,4-*b*] pyridine-5,5′-pyrimidine]-2′,4′,6′(3′H)-trione (pathway D, Scheme 2), while high temperature treatment yielded Hantzsch-type pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5-ones (pathways E and F, Scheme 2).

In the case of heterocyclizations involving pyruvic acids and different aminopyrazoles, the complex approach based on linear and MCRs with the application of special catalytic systems and non-classical activation methods as well as with help of introducing specific substituents gave the opportunity to develop several positional, regio- and chemoselective synthetic procedures to afford diverse classes of heterocyclic compounds [16,20]. As it was shown above for two other examples, temperature was also found to be a key parameter influencing direction of the treatments [20].

In this article, we report our new results in the tuning of selectivity of diversity-oriented heterocyclization reactions between pyruvic acids, aromatic aldehydes and 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides yielding four different types of compounds.

Experimental

General

Melting points of all compounds synthesized were determined with a Kofler melting point apparatus and are uncorrected. The NMR spectra were recorded on a Varian Unity Plus-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) and on a Varian Mercury VX-200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) spectrometers using DMSO-d_6 as the deuterated solvent. The NMR signals are reported in ppm in respect to TMS as internal standard. The MS spectra were recorded on a GC-MS Varian 1200L (ionizing voltage 70 eV) instrument. Elemental analysis was obtained using an EuroVector EA-3000.

Microwave irradiation experiments were performed using the Emrys^{TM} Creator EXP and Emrys^{TM} Initiator synthesizers from Biotage AB (Uppsala, Sweden) possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in sealed microwave process vials using high absorption level settings and IR temperature monitoring. Reaction time reflects irradiation times at the set reaction temperature (fixed hold times).

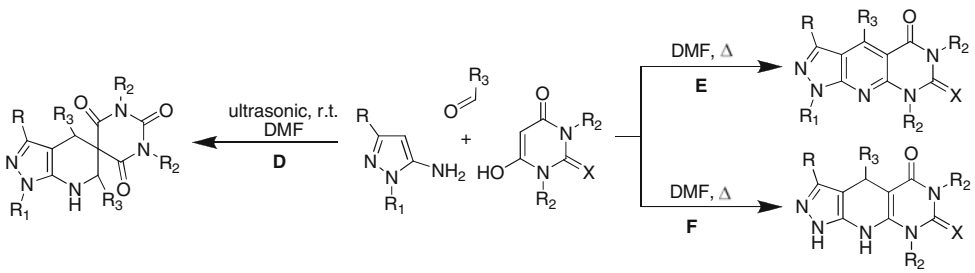
Ultrasonication was carried using a standard ultrasonic bath at 44.2 kHz in round-bottom flasks equipped with a condenser.

Solvents and aromatic aldehydes were commercially available and used without additional purification. Aminopyrazoles **1a–b** were obtained by a known method [22]. Phenylpyruvic acids **2a–d** were synthesized according to literary procedure [23] Azomethines **9a–d** were obtained from corresponding aminoazoles and aldehydes [24,25].

X-ray diffraction data

The crystals of **3g** ($C_{22}H_{20}N_4O_4$) are monoclinic. At 293 K, a = 22.496(6), b = 5.839(2), c = 15.354(3) Å, β = 94.21(2)°, V = 2011.3(9)Å^3, Mr = 404.42, Z = 4, space group P2$_1$/c, d_{calc} = 1.336g/cm^3, μ(MoKα) = 0.094mm^{-1}, F(000) = 848. Intensities of 19376 reflections (3518 independent, R_{int} = 0.097) were measured on the "Xcalibur-3" diffractometer (graphite monochromated MoK$_\alpha$ radiation, CCD detector, ω-scanning, $2\Theta_{max} = 50°$).

The structure was solved by direct method using SHELXTL package [26]. Position of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl and hydroxyl groups and n = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against



Scheme 2 Chemoselectivity of three-component reaction of 5- aminopyrazoles, barbituric acids and aldehydes

F^2 in anisotropic approximation for non-hydrogen atoms using 3439 reflections was converged to $wR_2 = 0.134 (R_1 = 0.058$ for 1460 reflections with $F > 4\sigma(F)$, $S = 0.888$). The final atomic coordinates, and crystallographic data for molecule **3g** have been deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 742205).

Synthesis

General procedure for the synthesis of 7-aryl-3-(arylcarbamoyl)-4,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylic acid (**3**)

Method A: A mixture of 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides **1** (1 mmol) and corresponding arylidenpyruvic acid **2** (1 mmol) in 5 ml of ethanol with addition of catalytic amount of hydrochloric acid was refluxed for 10 min. The mixture was cooled, the resulting precipitate was filtered, washed with ethanol and dried on air.

Method B: A mixture of 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides **1** (1 mmol) and an arylidenpyruvic acid acid **2** (1 mmol) in 5 ml of acetic acid was placed in a 10-mL microwave reaction vessel, the vessel was sealed and the mixture was microwave irradiated under vigorous magnetic stirring at 170°C for 2 min. After cooling the precipitate formed was filtered, washed with ethanol and dried on air.

Melting points and NMR spectra for compounds **3a–e** were identical to the data described previously [16]

7-(4-chlorophenyl)-3-(p-tolylcarbamoyl)-4,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylic acid (**3f**)

M.p. 252 – 254°C, yield (method B) 74%.

^{1}H NMR: $\delta = 2.25$ (s, 3H, CH_3), 5.83 (dd, $J = 4.2$ and 1.8 Hz, 1H, 6-CH), 6.27 (d, $J = 4.2$ Hz, 1H, 7-CH), 8.43 (d, $J = 1.8$ Hz, 1H, 4-NH), 7.03–7.66 (m, 8H, Ar), 8.07 (s, 1H, 2-CH), 9.73 (s, 1H, NH).

^{13}C NMR: 21.1, 59.3, 98.7, 106.4, 121.0, 126.6, 129.4, 129.4, 129.6, 132.9, 133.5, 137.0, 138.8, 140.7, 142.6, 162.4, 163.4.

MS: m/z (%) = 408(4.3) [M^+], 107 (99.9). Anal. Calcd. for $C_{21}H_{17}ClN_4O_3$: C, 61.69; H, 4.19; N, 13.70. Found: C, 64.66; H, 4.22; N, 13.65.

3-(2-methoxyphenylcarbamoyl)-7-p-tolyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylic acid (**3g**)

M.p. 256–258°C, yield (method B) 76%.

^{1}H NMR: $\delta = 2.26$ (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.81 (dd, $J = 4.3$ and 2.0 Hz, 1H, 6-CH), 6.18 (d, $J = 4.3$ Hz, 1H, 7-CH), 8.35 (d, $J = 2.0$ Hz, 1H, 4-NH), 6.84–7.72 (m, 8H, Ar), 8.06 (s, 1H, 2-CH), 9.15 (s, 1H, NH).

^{13}C NMR: 21.2, 56.6, 98.6, 107.2, 112.4, 121.0, 124.7, 125.8, 126.4, 127.4, 127.6, 129.9, 138.1, 138.5, 138.9, 142.6, 151.9, 162.6, 163.4.

MS: m/z (%) = 404 (4.7) [M^+], 123 (99.9). Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.32; H, 5.01; N, 13.81.

General procedure for the synthesis of 5-(5-aryl-2-oxo-2,5-dihydrofuran-3-ylamino)-N-(4-ethoxyphenyl)-1H-pyrazole-4-carboxamide (**4**)

A mixture of 5-amino-*N*-(4-ethoxyphenyl)-1*H*-pyrazol-4-carboxamide **1b** (1 mmol) and an arylidenpyruvic acid **2** (1 mmol) was refluxed in 5 ml of methanol for 30 min. After cooling the precipitate formed was filtered, washed with methanol and dried on air.

5-(5-(4-chlorophenyl)-2-oxo-2,5-dihydrofuran-3-ylamino)-N-(4-ethoxyphenyl)-1H-pyrazole-4-carboxamide (**4a**)

M.p. 246–248°C, yield 75%.

^{1}H NMR: $\delta = 1.3$ (t, 3H, OCH_2CH_3), 3.98 (q, 2H, OCH_2CH_3), 6.24 (d, $J = 2.2$, 1H, 5-CH), 7.0 (d, $J = 2.2$ Hz, 1H, 4-CH), 8.98 (s, 1H, NH), 6.80–7.60 (m, 8H, Ar), 8.42 (s, 1H, CH), 9.76 (s, 1H, NHamide), 12.72 (s, 1H, NHazole).

^{13}C NMR: 15.4, 64.0, 81.4, 102.0, 115.2, 115.3, 120.0, 122.7, 127.7, 129.3, 129.4, 132.3, 133.5, 134.2, 136.6, 140.9, 163.2, 170.4.

MS: m/z (%) = 438 (33.3) [M^+], 394 (52.8), 137 (99.9). Anal. Calcd. for $C_{22}H_{19}ClN_4O_4$: C, 60.21; H, 4.36; N, 12.77. Found: C, 60.18; H, 4.38; N, 12.73.

5-(5-(4-chlorophenyl)-2-oxo-2,5-dihydrofuran-3-ylamino)-N-p-tolyl-1H-pyrazole-4-carboxamide (**4b**)

M.p. 241–243°C, yield 83%.

^{1}H NMR: $\delta = 2.26$ (s, 1H, CH_3), 6.24 (d, $J = 2.0$, 1H, 5-CH), 7.0 (d, $J = 2.0$ Hz, 1H, 4-CH), 8.96 (s, 1H, NH), 7.06–7.62 (m, 8H, Ar), 8.45 (s, 1H, CH), 9.76 (s, 1H, NHamide), 12.74 (s, 1H, NHazole).

^{13}C NMR: 21.1, 81.4, 102.0, 120.1, 121.0, 121.1, 127.7, 129.3, 129.5, 129.7, 133.2, 134.2, 136.6, 136.9, 151.9, 163.3, 170.3.

MS: m/z (%) = 408 (8.4) [M^+], 107 (99.9). Anal. Calcd. for $C_{21}H_{17}ClN_4O_3$: C, 61.69; H, 4.19; N, 13.70. Found: C, 61.65; H, 4.22; N, 13.65.

N-(4-fluorophenyl)-5-(2-oxo-5-p-tolyl-2,5-dihydrofuran-3-ylamino)-1H-pyrazole-4-carboxamide (**4c**)

M.p. 246–248°C, yield 70%.

^{1}H NMR: δ = 2.29 (s, 1H, CH_3), 6.18 (d, J = 2.0, 1H, 5-CH), 6.99 (d, J = 2.0 Hz, 1H, 4-CH), 8.89 (s, 1H, NH), 7.08–7.77 (m, 8H, Ar), 8.44 (s, 1H, CH), 9.90 (s, 1H, NHamide), 12.74 (s, 1H, NHazole).

^{13}C NMR: 21.4, 82.3, 101.8, 115.6, 116.1, 120.6, 122.8, 122.9, 127.4, 127.6, 130.0, 134.5, 135.7, 135.8, 139.1, 163.4, 170.5.

MS: m/z (%) = 392 (1.5) [M^+], 146 (34.4). Anal. Calcd. for $C_{21}H_{17}FN_4O_3$: C, 64.28; H, 4.37; N, 14.28. Found: C, 64.23; H, 4.39; N, 14.26.

5s-(5-(4-chlorophenyl)-2-oxo-2,5-dihydrofuran-3-ylamino)- N-(4-fluorophenyl)-1H-pyrazole-4-carboxamide (**4d**)

M.p. 245–247°C, yield 68%.

^{1}H NMR: δ = 6.24 (d, J = 2.0, 1H, 5-CH), 7.01 (d, J = 2.0 Hz, 1H, 4-CH), 8.91 (s, 1H, NH), 7.07–7.79 (m, 8H, Ar), 8.44 (s, 1H, CH), 10.0 (s, 1H, NHamide), 12.75 (s, 1H, NHazole).

^{13}C NMR: 81.4, 101.9, 115.6, 116.0, 120.1, 122.8, 123.0, 127.8, 129.2, 129.4, 134.2, 135.7, 135.8, 136.6, 163.4, 170.3.

MS: m/z (%) = 412 (4.2) [M^+], 111 (95.3). Anal. Calcd. for $C_{20}H_{14}ClFN_4O_3$: C, 58.19; H, 3.42; N, 13.57. Found: C, 58.15; H, 3.43; N, 13.55.

General procedure for the synthesis of 5-aryl-3-(4-ethoxyphenylcarbamoyl)-7-hydroxy-6-phenyl-4,5,6, 7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**7**)

A mixture of 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides **1** (2.3 mmol), phenylpyruvic acid **6** (2.3 mmol) and corresponding aldehyde **5** (1 mmol) in 4 ml of acetic acid was ultrasonicated at room temperature in a standard ultrasonic bath for 30 min. The precipitate formed was filtered, washed with ethanol and dried on air.

3-(4-ethoxyphenylcarbamoyl)-7-hydroxy-5,6-diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**7a**)

M.p. 208–210°C, yield 72%.

^{1}H NMR: δ = 1.28 (t, 3H, OCH_2CH_3), 3.96 (q, 2H, OCH_2CH_3), 3.87 (d, J = 11.7, 1H, 6-CH), 5.1 (d, J = 11.7 Hz, 1H, 5-CH), 6.75–7.61 (m, 14H, Ar), 7.97 (s, 1H, CH), 6.68 (s, 1H, NHazine), 9.42 (s, 1H, NHamide).

^{13}C NMR: 15.4, 53.6, 55.8, 63.9, 85.4, 96.3, 115.2, 122.3, 127.8, 128.1, 128.5, 128.8, 131.1, 131.2, 133.1, 135.3, 138.4, 140.3, 148.4, 155.1, 162.7, 169.6.

MS: m/z (%) = 334 (5) [M^+ − 164], 257 (26.2). Anal. Calcd. for $C_{28}H_{26}N_4O_5$: C, 67.46; H, 5.26; N, 11.24. Found: C, 67.43; H, 5.29; N, 11.21.

3-(4-ethoxyphenylcarbamoyl)-7-hydroxy-5-(4-methoxyphenyl)-6-phenyl-4,5,6, 7-tetrahydropyrazolo[1,5-a] pyrimidine-7-carboxylic acid (**7b**)

M.p. 203–205°C, yield 83%.

^{1}H NMR: δ = 1.28 (t, 3H, OCH_2CH_3), 3.95 (q, 2H, OCH_2CH_3), 3.63 (s, 3H, OCH_3), 3.88 (d, J = 11.9, 1H, 6-CH), 4.95 (d, J = 11.9 Hz, 1H, 5-CH), 6.60–7.66 (m, 13H, Ar), 7.88 (s, 1H, CH), 6.46 (s, 1H, NHazine), 9.36 (s, 1H, NHamide).

^{13}C NMR: 15.3, 53.5, 55.1, 55.7, 64.0, 85.4, 96.2, 114.4, 115.2, 122.3, 127.7, 128.1, 128.9, 130.0, 131.2, 132.2, 133.1, 135.5, 148.5, 155.1, 159.5, 162.7, 169.6.

MS: m/z (%) = 364 (3) [M^+ − 164], 137 (21.6). Anal. Calcd. for $C_{29}H_{28}N_4O_6$: C, 65.90; H, 5.34; N, 10.60. Found: C, 65.85; H, 5.37; N, 10.57.

5-(4-chlorophenyl)-3-(4-ethoxyphenylcarbamoyl)-7-hydroxy-6-phenyl-4,5,6, 7-tetrahydropyrazolo[1,5-a] pyrimidine-7-carboxylic acid (**7c**)

M.p. 216–218°C, yield 85%.

^{1}H NMR: δ = 1.28 (t, 3H, OCH_2CH_3), 3.95 (q, 2H, OCH_2CH_3), 3.87 (d, = 11.9, 1H, 6-CH), 4.98 (d, J = 11.9 Hz, 1H, 5-CH), 6.73–7.66 (m, 13H, Ar), 7.87 (s, 1H, CH), 6.59 (s, 1H, NHazine), 9.34 (s, 1H, NHamide).

^{13}C NMR: 15.4, 53.6, 55.2, 63.9, 85.3, 96.5, 115.1, 122.3, 127.8, 128.2, 128.7, 130.7, 131.2, 133.0, 133.1, 135.2, 138.4, 139.5, 148.4, 155.1, 162.7, 169.4.

MS: m/z (%) = 368 (30) [M^+ − 164], 138 (19.6). Anal. Calcd. for $C_{28}H_{25}ClN_4O_5$: C, 63.10; H, 4.73; N, 10.51. Found: C, 63.07; H, 4.75; N, 10.53.

3-(4-ethoxyphenylcarbamoyl)-7-hydroxy-6-phenyl-5-p-tolyl-4,5,6, 7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**7d**)

M.p. 260–262°C, yield 78%.

^{1}H NMR: δ = 1.28 (t, 3H, OCH_2CH_3), 3.95 (q, 2H, OCH_2CH_3), 2.15 (s, 3H, CH_3), 3.87 (d, J=11.9, 1H, 6-CH), 5.03 (d, J=11.9 Hz, 1H, 5-CH), 6.73 – 7.62 (m, 13H, Ar), 7.94 (s, 1H, CH), 6.57 (s, 1H, NHazine), 9.41 (s, 1H, NHamide).

^{13}C NMR: 15.3, 21.2, 53.4, 55.4, 64.0, 85.4, 96.2, 115.2, 122.3, 127.7, 128.7, 128.7, 129.5, 131.2, 132.9, 133.1, 134.7, 135.5, 137.8, 148.5, 155.1, 162.8, 169.5.

MS: m/z (%) = 348 (19.5) [M^+ − 164], 212 (12.2), 137 (44.7). Anal. Calcd. for $C_{29}H_{28}N_4O_5$: C, 67.96; H, 5.51; N, 10.93. Found: C, 67.92; H, 5.54; N, 10.90.

General procedure for the synthesis of N-(4-ethoxyphenyl)-5-(2-(4-aryl-4-hydroxy-5-oxo-3-phenyl-2,5-dihydro-1H-pyrrol-1-yl)-1H-pyrazole-4-carboxamide (**8**)

A mixture of 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides **1** (2.3 mmol), phenylpyruvic acid **6** (2.3 mmol) and corresponding aldehyde **5** (1 mmol) in 3 ml of acetic acid was placed in a 10-mL microwave reaction vessel. The vessel was sealed and the mixture was microwave irradiated under vigorous magnetic stirring at 170°C for 20 min. After cooling, 5 ml of ethanol was added to the reaction mixture and the precipitate formed was filtered, washed with ethanol and dried on air.

N-(4-ethoxyphenyl)-5-(3-hydroxy-2-oxo-4,5-diphenyl-2,5-dihydro-1H-pyrrol-1-yl)-1H-pyrazole-4-carboxamide (**8a**)

M.p. 281–283°C, yield 75%.

^{1}H NMR: δ = 1.29 (t, 3H, OCH_2CH_3), 3.97 (q, 2H, OCH_2CH_3), 6.15 (s, 1H, 5-CH), 6.77–7.69 (m, 14H, Ar), 8.21 (s, 1H, CHazole), 9.66 (s, 1H, NHamide), 10.59 (bs, 1H, NHazole), 13.01 (s, 1H, NHazole).

^{13}C NMR: 15.3, 61.9, 64.0, 113.1, 115.2, 121.8, 122.3, 123.7, 127.8, 128.0, 128.6, 128.8, 128.9, 131.7, 132.6, 132.9, 137.7, 137.8, 143.8, 155.4, 160.6, 166.6.

MS: m/z (%) = 480 (2.7) [M^+], 179 (99.9), 137 (65.9). Anal. Calcd. for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.97; H, 5.07; N, 11.64.

N-(4-ethoxyphenyl)-5-(3-hydroxy-5-(4-methoxyphenyl)-2-oxo-4-phenyl-2,5-dihydro-1H-pyrrol-1-yl)-1H-pyrazole-4-carboxamide (**8b**)

M.p. 275–277°C, yield 79%.

^{1}H NMR: δ = 1.29 (t, 3H, OCH_2CH_3), 3.97 (q, 2H, OCH_2CH_3), 3.61 (s, 3H, OCH_3), 6.11 (s, 1H, 5-CH), 6.57–7.74 (m, 13H, Ar), 8.21 (s, 1H, CHazole), 9.65 (s, 1H, NHamide), 10.53 (bs, 1H, NHazole), 13.01 (s, 1H, NHazole). ^{13}C NMR: 15.3, 55.7, 63.7, 64.1, 114.5, 115.4, 122.3, 123.9, 124.0, 127.8, 128.0, 128.1, 128.8, 128.9, 129.5, 130.0, 132.7, 132.9, 143.7, 155.5, 159.7, 160.6, 166.6.

MS: m/z (%) = 510 (1.7) [M^+], 165 (17.9), 137 (57.9). Anal. Calcd. for $C_{29}H_{26}N_4O_5$: C, 68.22; H, 5.13; N, 10.97. Found: C, 68.20; H, 5.16; N, 10.94.

5-(2-(4-chlorophenyl)-4-hydroxy-5-oxo-3-phenyl-2,5-dihydro-1H-pyrrol-1-yl)-N-(4-ethoxyphenyl)-1H-pyrazole-4-carboxamide (**8c**)

M.p. 283–285°C, yield 82%.

^{1}H NMR: δ = 1.29 (t, 3H, OCH_2CH_3), 3.97 (q, 2H, OCH_2CH_3), 6.18 (s, 1H, 5-CH), 6.71 – 7.72 (m, 13H, Ar), 8.21 (s, 1H, CHazole), 9.68 (s, 1H, NHamide), 10.65 (bs, 1H, NHazole), 13.02 (s, 1H, NHazole). ^{13}C NMR: 15.4, 63.0, 63.8, 112.7, 115.0, 122.2, 123.2, 127.9, 128.9, 130.1, 130.8, 131.5, 131.7, 132.4, 133.2, 134.1, 137.0, 144.1, 144.2, 155.2, 160.7, 166.4.

MS: m/z (%) = 514 (2.5) [M^+], 213 (12.9), 193 (12.9). Anal. Calcd. for $C_{28}H_{23}ClN_4O_4$: C, 64.61; H, 4.5; N, 10.88. Found: C, 64.58; H, 4.52; N, 10.84.

N-(4-ethoxyphenyl)-5-(3-hydroxy-2-oxo-4-phenyl-5-p-tolyl-2,5-dihydro-1H-pyrrol-1-yl)-1H-pyrazole-4-carboxamide (**8d**)

M.p. 276–278°C, yield 77%.

^{1}H NMR: δ = 1.29 (t, 3H, OCH_2CH_3), 3.97 (q, 2H, OCH_2CH_3), 2.13 (s, 3H, CH_3), 6.13 (s, 1H, 5-CH), 6.75–7.73 (m, 13H, Ar), 8.21 (s, 1H, CHazole), 9.67 (s, 1H, NHamide), 10.51 (bs, 1H, NHazole), 13.0 (s, 1H, NHazole).

^{13}C NMR: 14.6, 20.6, 62.7, 63.0, 112.0, 114.2, 121.3, 122.7, 127.0, 127.2, 128.0, 128.1, 128.8, 130.9, 131.9, 132.1, 134.0, 137.0, 143.0, 143.5, 154.4, 159.9, 165.7.

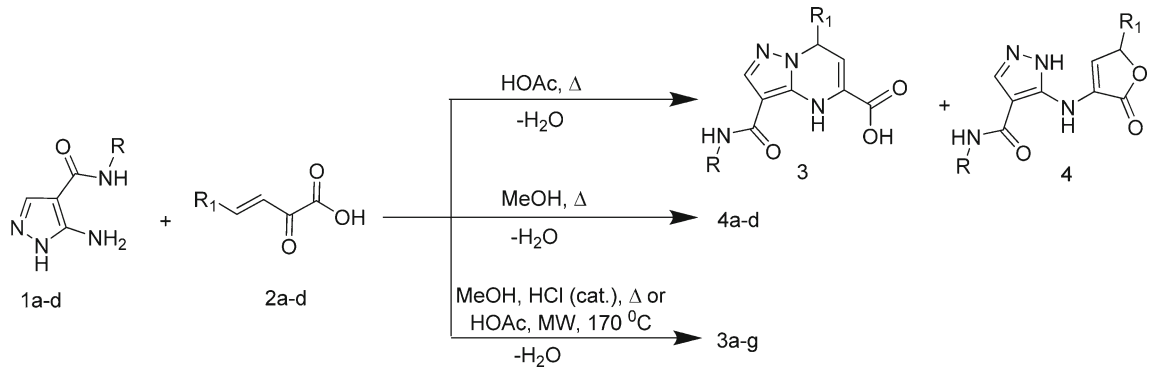
MS: m/z (%) = 494 (7.3) [M^+], 357 (38.6), 137 (44.4). Anal. Calcd. for $C_{29}H_{26}N_4O_4$: C, 70.43; H, 5.3; N, 11.3. Found: C, 70.39; H, 5.5; N, 11.29.

Results and discussion

In our earlier publication [16], it was reported that in the case of 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides both two-component reactions with arylidenpyruvic acids and MCRs involving pyruvic acid and aldehydes in boiling acetic acid yielded 7-aryl-3-(arylcarbamoyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids. However, this study shows a more complicated character of the two-component treatment leading often to a mixture of pyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids **3** and furanyl-5-aminopyrazoles **4**. In order to develop synthetic methodologies to selectively produce heterocyclic compounds **3** and **4**, we studied the effect of several reactions parameters such as solvent, catalyst and heating types.

We established that the conventional heating of equimolar mixtures of starting materials **1** and **2** for 5 min in boiling DMF yielded solely furanones **4** in very low yields (ca. 30%). A significant yield improvement was obtained when primary alcohols were used as solvents (e.g., methanol, ethanol, 1-butanol) producing selectively heterocycles **4a–d** in 70–83% yields (Scheme 3, Table 1). It is important to point out that not only methanol provided the best yields, but also that the final yields were independent of the reaction temperature.

The addition of catalytic HCl had a profound effect in this reaction. Thus, contrary to the above observation where **4** was selectively made, with hydrochloric acid compounds **3**



Scheme 3 Reaction of 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides with arylidenpyruvic acids

Table 1 Synthesis of 4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids **3** and 2,5-dihydrofuran-3-ylamino-1*H*-pyrazoles **4**

Aminopyrazol	R	Acid	R_1	Product	Yield[a]
1a	C_6H_5	**2b**	4-$CH_3OC_6H_4$	**3a**	72[b]
1b	4-$C_2H_5OC_6H_4$	**2a**	C_6H_5	**3b**	70[b]
1b	4-$C_2H_5OC_6H_4$	**2c**	4-ClC_6H_4	**3c**	78[b]
1b	4-$C_2H_5OC_6H_4$	**2b**	4-$CH_3OC_6H_4$	**3d**	68[b]
1b	4-$C_2H_5OC_6H_4$	**2d**	4-$CH_3C_6H_4$	**3e**	70[b]
1b	4-$CH_3C_6H_4$	**2c**	4-ClC_6H_4	**3f**	74[b]
1d	2-$CH_3OC_6H_4$	**2d**	4-$CH_3C_6H_4$	**3g**	76[b]
1b	4-$C_2H_5OC_6H_4$	**2c**	4-ClC_6H_4	**4a**	75[c]
1b	4-$CH_3C_6H_4$	**2c**	4-ClC_6H_4	**4b**	83[c]
1c	4-FC_6H_4	**2d**	4-$CH_3C_6H_4$	**4c**	70[c]
1c	4-FC_6H_4	**2c**	4-ClC_6H_4	**4d**	68[c]

[a] Isolated yield, [b] HOAc, MW, 170°C, [c] MeOH, Δ

were selectively produced in approx. 70% yield (Scheme 3). Since a major drawback of using catalytic HCl with alcohols was the esterification of **3** (up to 10%—for ethanol; up to 30%—for methanol and 1-butanol), we searched for the alternate reactions conditions. Finally, after a thorough investigation, we determined that the temperature also sufficiently influenced the reaction and the best outcome was achieved when using acetic acid under microwave irradiation (2 min at 170°C) producing **3a**–**g** in 68–78% yields and excellent purity (Scheme 3; Table 1).

We also explored the influence the temperature regime on MCR of phenylpyruvic acid **6** and aromatic aldehydes **5** with 5-aminopyrazoles **1** as it was earlier observed for similar reactions involving 3-amino-1,2,4-triazole [20]. In this study, ultrasonication and microwave irradiation were used as the powerful tool to investigate selectivity of this treatment.

We found that ultrasonication for 30 min of equimolar mixture of **1b** with aromatic aldehydes **5a**–**d** and phenylpyruvic acid **6** in acetic acid at room temperature yielded pyrimidine-7-carboxylic acids **7a**–**d** (Scheme 4, Table 2) and that longer reaction times did not have an impact in the reaction yields.

High temperature experiments in acetic acid were performed in a sealed vessel using monomode microwave reactor allowing precise temperature and time control. Using microwave heating, we established that direction of multicomponent treatment of **1b**, **5a**–**d**, and **6** strongly depended on the reaction temperature: its increasing from ca. 120 °C (the boiling point of acetic acid) to 170 °C led to an increased amount of **8a**–**d** at the expense of carboxylic acids **7a**–**d**. The reaction duration also impacted the treatment. Thus, under microwave irradiation at 120 °C compounds **7a**–**d** were isolated from the reaction mixture after 2 min of heating while after 20 min at the same temperature we observed their mixtures with **8a**–**d**. Pure pyrrolones **8a**–**d** were synthesized in 75–82% yields by the reaction in acetic acid under microwave heating (170°C for 20 min) or by conventional refluxing the starting materials for 180 min in the same solvent (Scheme 4, Table 2).

We also established that tetrahydropyrimidines **7a**–**d** decomposed into starting materials under smooth heating (up to 50° C) in acetic acid or DMSO-d_6 (NMR control), while their heating at higher temperature led to rearrangement into pyrrolones **8**. Full conversion was achieved by heating of **7a**–

Scheme 4 Three-component reaction of 5-amino-*N*-(4-ethoxyphenyl)-1*H*-pyrazole-4-carboxamide with phenylpyruvic acid and aldehydes

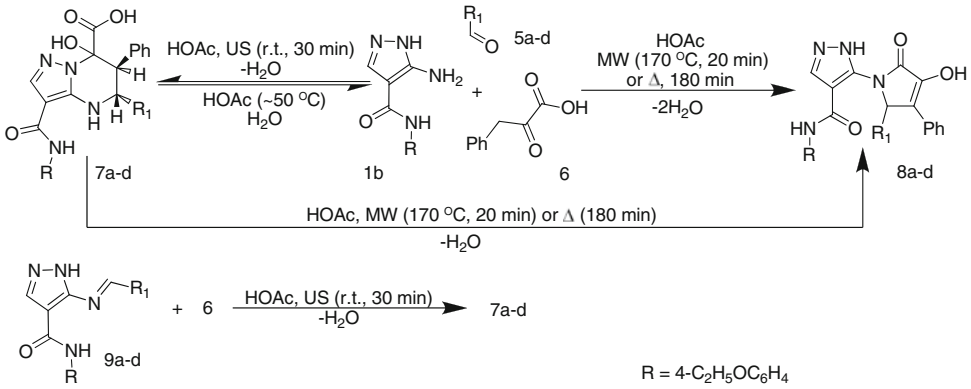


Table 2 Synthesis of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acids **7** and pyrazol-5-yl-1,5-dihydro-2*H*-pyrrol-2-ones **8**

Compound	R_1	Yield (%)[a]
7a	C_6H_5	72[b], 68[d]
7b	$4\text{-}CH_3OC_6H_4$	83[b], 80[d]
7c	$4\text{-}ClC_6H_4$	85[b], 76[d]
7d	$4\text{-}CH_3C_6H_4$	78[b], 71[d]
8a	C_6H_5	75[c], 72[e]
8b	$4\text{-}CH_3OC_6H_4$	79[c], 76[e]
8c	$4\text{-}ClC_6H_4$	82[c], 80[e]
8d	$4\text{-}CH_3C_6H_4$	77[c], 68[e]

[a] Isolated yield, [b] under ultrasonication, [c] under MW irradiation, [d] reaction of imide under ultrasonication, [e] rearrangement of **7a–d** under MW irradiation

d in acetic acid in a microwave reactor at 170°C for 20 min or by refluxing for 180 min (Scheme 4, Table 2).

In addition, compounds **7a–d** were obtained via preliminary synthesis of imides **9a–d** and their further treatment with phenylpyruvic acid **6** in acetic acid under ultrasonic irradiation at room temperature for 30 min or by conventional refluxing for 3–5 min.

Thus, the direction of three-component treatments of phenylpyruvic acid and aromatic aldehydes with 5-amino-*N*-phenyl-1*H*-pyrazole-4-carboxamide depends on the reaction temperature and can be controlled kinetically or thermodynamically producing two different heterocyclic systems—4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acids and pyrazol-5-yl-1,5-dihydro-2*H*-pyrrol-2-ones, respectively.

The structures of the heterocyclic compounds synthesized were established with help of MS-spectrometry, 1D and 2D NMR spectral data, X-ray diffraction study, and additionally supported by elemental analysis (see "Experimental" section).

The ^{1}H NMR spectra of compounds **3a-g** contain doublet of doublets for the 6-CH protons at ca. 5.8 ppm (J = 4.1 and 1.8 Hz), doublet for 7-CH at 6.2. ppm (J = 4.2 Hz), singlet for CH of pyrazole ring near 8 ppm, doublet of pyrimidine NH at 8.4 ppm (J = 1.8 Hz), signal of carboxamide NH at 9.7 ppm and signals of aromatic rings and other functional groups. In addition, NOESY spectra showed correlation peaks between CH-groups in positions 6 and 7 while pyrimidine NH exhibited no correlations with these protons.

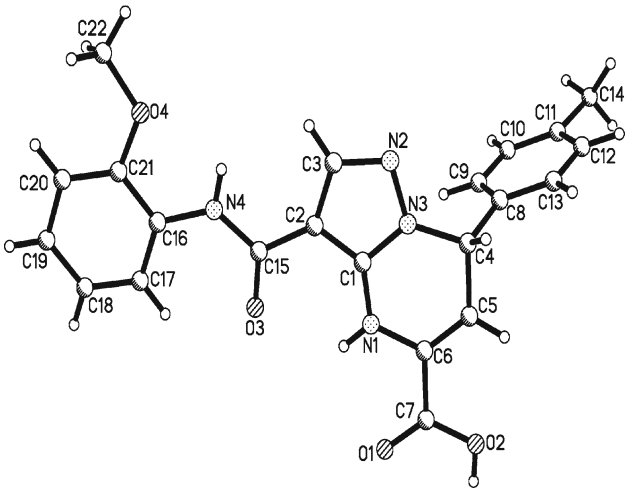


Fig. 1 Molecular structure of compound **3g** (X-ray diffraction data)

Ultimately, the structure of heterocycles **3** were established by X-ray diffraction analysis carried out for a single crystal of compound **3g**, which allowed assignment of the structure 3-(2-methoxyphenylcarbamoyl)-7-(4-methylphenyl)-4,7-dihydropyrazolo [1,5-a]pyrimidine-5-carboxylic acid (Fig. 1).

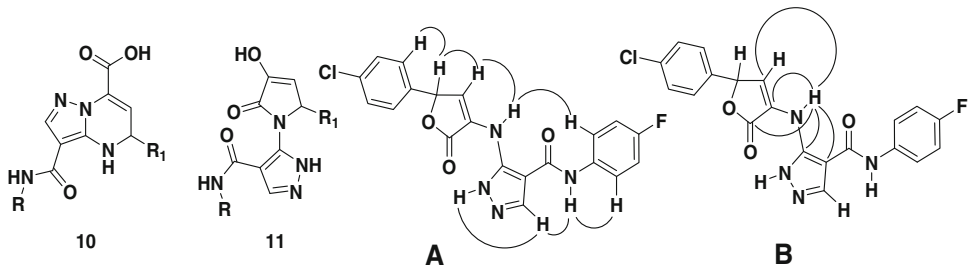


Fig. 2 Alternative structures and the most informative correlations in ROESY (**a**) and HMBC (**b**) for compound **4d**

The structures of compounds **4a–d** were established with help of ^{1}H and ^{13}C NMR spectral data as well as by 2D NMR methods. Application of ^{1}H NMR in combination with ^{13}C NMR, COSY and HSQC allowed assignment of protons and carbons in compounds **4a–d**, while ROESY and HMBC (Fig. 2) allowed rejecting alternative structures **10**, **11** and proving the structure of 2,5-dihydrofuran-3-ylamino-1*H*-pyrazoles for heterocycles **4a–d**.

^{1}H NMR spectra of heterocycles **7a–d** exhibit two doublets of pyrimidine CH protons at 3.9 and 5.1 ppm with the coupling constants 11.7–11.9 Hz showing their *trans*-orientation, singlets of pyrimidine NH, pyrazole CH, and amide NH at 6.6, 7.8 and 9.4 ppm, respectively, multiplets of aromatic protons at 6.60–7.66 ppm, as well as peaks for other functional groups at the appropriate positions. Signal of hydroxylic group is appeared only for sodium salts of acids **7** at 6.1–6.4 ppm. In addition, NOE experiments show special contiguity of methine proton in position 5 with pyrazole NH, 6-CH and *ortho*-protons of R_1 substituent. On the other hand, 6-CH exhibits NOE with *ortho*-protons of phenyl substituent and with 5-CH. All these spectral data correspond to the suggested structure of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acids **7**. However, it should be noted that the MS spectra of the compounds **7a–d** contained no signal of molecular ion while only peaks of fragments corresponding to the appropriate azomethine and phenylpyruvic acid (*m/z* 164) were found.

^{1}H NMR spectra of heterocyclic compounds **8a–d** exhibit singlets of pyrazole CH at 8.2 ppm and pyrrolone methine protone at 6.1 ppm, signals of carboxamide and pyrazole NH at 9.7 and 13.0 ppm, OH groups at 10.6 ppm and signals of aromatic rings and other functional groups. COSY and NOESY spectra do not contain correlation peaks between methine proton and NH or OH groups, though NOESY experiments show effect between CH and *ortho*-protons of aldehyde and phenylpyruvic acid aryl rings.

Conclusions

In summary, direction of reactions of 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides with arylidenpyruvic acids or with phenylpyuruvic acids and aldehydes can be easily controlled with help of catalyst type and temperature regime producing with high degree of selectivity four different heterocyclic systems. Four preparative efficient procedures for the synthesis of 4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids, 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acids, (2,5-dihydrofuran-3-yl)amino-1*H*-pyrazoles and pyrazol-5-yl-1,5-dihydro-2*H*-pyrrol-2-ones were developed and tested. The new synthetic approaches favor diversity of heterocyclic compounds based on pyruvic acids and aminopyrazoles reactions.

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