Tetrahedron 64 (2008) 11041–11049

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Multicomponent cyclocondensation reactions of aminoazoles, arylpyruvic acids and aldehydes with controlled chemoselectivity

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ARTICLE INFO

Article history:
Received 29 July 2008
Received in revised form 9 September 2008
Accepted 25 September 2008
Available online 8 October 2008

Keywords:
Heterocycles
Cyclocondensations
Selective multicomponent reactions
Microwave-assisted organic synthesis
Ultrasonic-promoted reactions
Phenylpyruvic acid
Aminoazoles

ABSTRACT

The multicomponent reactions of 3-amino-1,2,4-triazoles/5-aminotetrazole with phenylpyruvic acids and aromatic aldehydes were studied using conventional thermal heating, ultrasonification and microwave dielectric heating. Two different reaction pathways for these cyclocondensations occurring under either kinetic or thermodynamic control were established depending on the temperature regime and building block selection. In case of aminotriazoles, an unprecedented reaction pathway leading to 5-aryl-7-hydroxy-6-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids was found and discussed.

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1. Introduction

Multicomponent reactions of pyruvic acids with nitrogen containing nucleophiles play an important role in the synthesis of heterocyclic compounds possessing diverse types of physiological activities including antitumour,[1a] antimalarial,[1b,c] antimicrobial,[1d] antifungal,[1e] and analgesic[1f–h] activities. The Döbner reaction, i.e., the three-component condensation of pyruvic acid, aldehydes and aniline derivatives leading to quinoline carboxylic acids, was discovered in the late 19th century[2a,b] and has since been investigated in detail in numerous publications.[1a,3] Initially, it was considered that the Döbner reaction proceeds via arylidenepyruvic acid formation[3a] but later this pathway was refuted and an alternative mechanistic pathway involving the formation of a Schiff base followed by cyclization was proposed.[3c,f,g,]

Multicomponent reactions of arylpyruvic acids leading to heterocyclic compounds have been rarely investigated. It was previously shown that the three-component reaction of phenylpyruvic acid with aldehydes and anilines yields either pyrrolidine-2,3-dione **I** or quinoline-4-carboxylic acid **II** depending on substituents R^1 and R^2 (Scheme 1).[4a,b] In this case no clear relationships between the electronic character of the substituents and the reaction products was established.

A Biginelli-like reaction of arylpyruvic acids with urea and aldehydes in the presence of catalytic amounts of acid to yield dihydropyrimidine carboxylic acids **III** has also been reported in the literature.[4c] Similar pyrimidines were synthesized using a polymer-supported solid-phase procedure.[4d]

Numerous publications deal with arylpyruvic acids as α-keto-acids and describe their transformations with 1,2-diamines yielding quinoxalines or analogous heterocyclic systems.[5] There also is an interesting example of four-component Ugi reactions involving arylpyruvic acids as building-blocks.[5e]

The chemo- and regioselectivity of multicomponent condensations is among the key problems of synthetic organic chemistry.[6] Our previous publications[7] concerning reactions of pyruvic acids with aminoazoles highlighted some of the selectivity issues in this field. The structure of the binucleophile, the electron character of the substituents as well as the reaction conditions significantly influence these multicomponent condensations and several different reaction products can be obtained from similar starting materials.[7a,b] On the other hand, application of non-classical activation methods like microwave and ultrasonic irradiation have appeared as powerful tools for tuning multicomponent condensations.[8]

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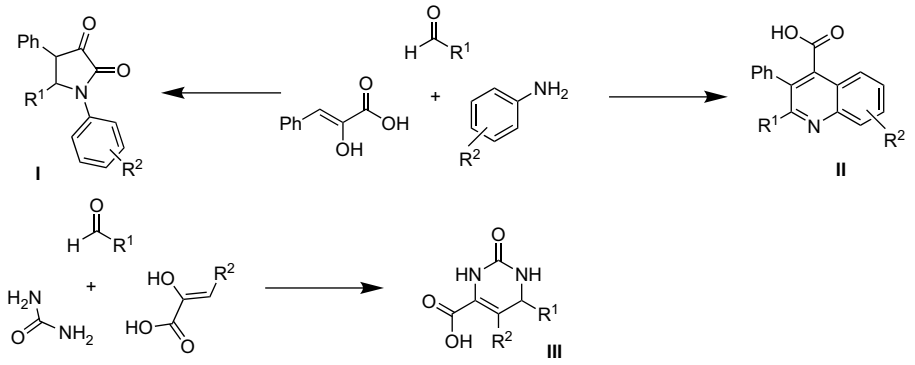
doi:10.1016/j.tet.2008.09.089



Scheme 1.

For example, with the help of low-temperature ultrasonic-promoted and high-temperature microwave-assisted procedures starting from the same building-blocks three different classes of heterocyclic compounds were obtained with good selectivity.[8f,g]

In this article we disclose our results on the tuning of multicomponent condensation reactions of phenylpyruvic acid, aromatic aldehydes and aminoazoles (3-aminotriazoles and 5-aminotetrazole) using both traditional heating and non-classical activation methods—microwave and ultrasonic irradiation.

2. Results and discussion

2.1. Multicomponent reactions of phenylpyruvic acid, aminoazoles and aldehydes

After a series of experiments it was established that the condensation of aminotriazoles **1a**–**d** with phenylpyruvic acid **2** and aromatic aldehydes **3a**–**d** in boiling acetic acid can lead to different products depending on the reaction conditions. 5-Aryl-7-hydroxy-6-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids **4a**–**h** (63–79%) were isolated from the reaction mixture after refluxing (~120 °C) equimolar amounts of aminotriazoles **1a**,**b**, aldehydes **3a**–**d** and phenylpyruvic acid **2** in HOAc for 2–3 min while reaction for 180 min provided 5-aryl-3-hydroxy-4-phenyl-1-(1,2,4-triazol-5-yl)-1,5-dihydro-2*H*-pyrrol-2-ones **5a**–**h** in 56–75% yields (Table 1). Reaction times in between those extremes in most cases led to the formation of both triazolopyrimidines **4** and pyrrolones **5**. It was additionally established that triazolopyrimidinecarboxylic acids **4a**–**h** after refluxing in acetic acid for approximately 3 h were completely converted into pyrrolones **5a**–**h** while heating **4** in NMR tubes in DMSO-d_6 (1 min, 100 °C) led to their decomposition with formation of the starting materials **1**–**3**; after cooling the reverse process occurred, which produced again triazolopyrimidines **4**.

Multicomponent condensations of phenylpyruvic acid **2**, aldehydes **3a**–**d** with 5-aminotetrazole **1c** and 3,5-diamino-1-(4-chlorophenyl)-1,2,4-triazole **1d** in boiling acetic acid did not furnish fused pyrimidines of type **4** but only provided pyrrolones **5i**–**p**.

Work up procedures for compounds **4** and **5** typically consisted of a simple filtration of the crystalline materials after cooling of the reaction mixtures. In the case of pyrrolones **5**, cold ethanol was added before the filtration step for more complete precipitation. No additional purification such as crystallization or column chromatography was required for triazolopyrimidines **4**, while pyrrolones **5** sometimes had to be recrystallized from ethanol.

Our experimental data indicate that in the three-component condensation of phenylpyruvic acid **2**, aminoazoles **1a**,**b** and aromatic aldehydes **3a**–**d** the fused pyrimidines **4** are the kinetically controlled reaction products while pyrrolones **5** may be viewed as the thermodynamically preferred products. In the present study, ultrasonic and microwave irradiations were additionally applied to investigate the formation of 5-aryl-7-hydroxy-6-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids **4** and 5-aryl-3-hydroxy-4-phenyl-1-(1,2,4-triazol-5-yl)-1,5-dihydro-2*H*-pyrrol-2-ones **5**. It was found that treatment of 3-amino-1,2,4-triazoles **1a**,**b**, phenylpyruvic acid and *p*-tolualdehyde **3c** in acetic acid under sonication at room temperature for 30 min yielded exclusively fused triazolopyrimidinecarboxylic acids **4c**,**g**. Longer action of ultrasonic irradiation (up to 3 h) did not change the outcome of the reaction. Using the same procedure for aminoazoles **1c**,**d** was not successful and the starting compounds were isolated unchanged after sonication.

High-temperature experiments were carried out in a sealed vessel in a monomode microwave reactor, which allowed a precise temperature control. Using microwave heating in acetic acid we observed a significant influence of the reaction temperature and time on the multicomponent process using **1a**, **2** and **3c** as building-blocks. Increasing the reaction temperature from 120 °C to 170 °C

Table 1
Reactions of aminoazoles **1a**–**d** with arylpyruvic acids **2a**–**c** and aldehydes **3a**–**d** (Scheme 2)

Building-blocks					Product	
Aminoazole			Aldehyde			
Compound	X	R^2	Compound	R^1	Compound	Yield[a] (%)
1a	CH	H	**3a**	H	**4a**	79
1a	CH	H	**3b**	Cl	**4b**	76
1a	CH	H	**3c**	CH_3	**4c**	68
1a	CH	H	**3d**	CH_3O	**4d**	65
1b	$CSCH_3$	H	**3a**	H	**4e**	63
1b	$CSCH_3$	H	**3b**	Cl	**4f**	71
1b	$CSCH_3$	H	**3c**	CH_3	**4g**	76
1b	$CSCH_3$	H	**3d**	CH_3O	**4h**	66
1a	CH	H	**3a**	H	**5a**	56
1a	CH	H	**3b**	Cl	**5b**	72
1a	CH	H	**3c**	CH_3	**5c**	60
1a	CH	H	**3d**	CH_3O	**5d**	68
1b	$CSCH_3$	H	**3a**	H	**5e**	70
1b	$CSCH_3$	H	**3b**	Cl	**5f**	75
1b	$CSCH_3$	H	**3c**	CH_3	**5g**	72
1b	$CSCH_3$	H	**3d**	CH_3O	**5h**	71
1c	N	H	**3a**	H	**5i**	60
1c	N	H	**3b**	Cl	**5j**	67
1c	N	H	**3c**	CH_3	**5k**	52
1c	N	H	**3d**	CH_3O	**5l**	64
1d	CNH_2	4-Cl–C_6H_4	**3a**	H	**5m**	59
1d	CNH_2	4-Cl–C_6H_4	**3b**	Cl	**5n**	68
1d	CNH_2	4-Cl–C_6H_4	**3c**	CH_3	**5o**	63
1d	CNH_2	4-Cl–C_6H_4	**3d**	CH_3O	**5p**	62

[a] Isolated yield of pure product (after recrystallization in case of **5e**–**h**,**m**–**p**).

as well as the reaction time led to an increased amount of pyrrolone **5c** at the expense of triazolopyrimidinecarboxylic acid **4c** in the reaction mixture. Specifically, compound **4c** was isolated in 78% yield by three-component condensation of starting materials **1a**, **2** and **3c** in acetic acid applying microwave irradiation at 120 °C for 2 min while after 20 min at the same temperature a mixture containing 70% of **4c** and 30% of **5c** was isolated. The same ratio of two reaction products was observed at 170 °C after 2 min of irradiation. Extending the reaction time to 20 min at 170 °C gave only pyrrolone **5c** in 60% yield. The full rearrangement (NMR control) of triazolopyrimidine **4c** into pyrrolone **5c** at 170 °C in a microwave reactor was achieved in 40 min.

The results presented above confirm our hypothesis about kinetic and thermodynamic control in the three-component processes shown in Scheme 2 and hence allow a simple tuning of chemoselectivity by changing the reaction temperature. Sonication of the starting materials for 30 min at room temperature or heating in acetic acid for 2 min at ~120 °C provides the kinetic triazolopyrimidine products **4a**–**h**, while high-temperature treatment (HOAc, MW, 150 °C, 40 min or refluxing at ~120 °C for 180 min) yielded the thermodynamically preferred pyrrolones **5a**–**h**.

It was additionally established that treatment of Schiff bases **6a**–**c** with phenylpyruvic acid **2** in HOAc under ultrasonic irradiation (room temperature, 30 min) or by thermal heating (2–5 min) also furnished triazolopyrimidines **4** (Scheme 3).

2.2. Structure determination

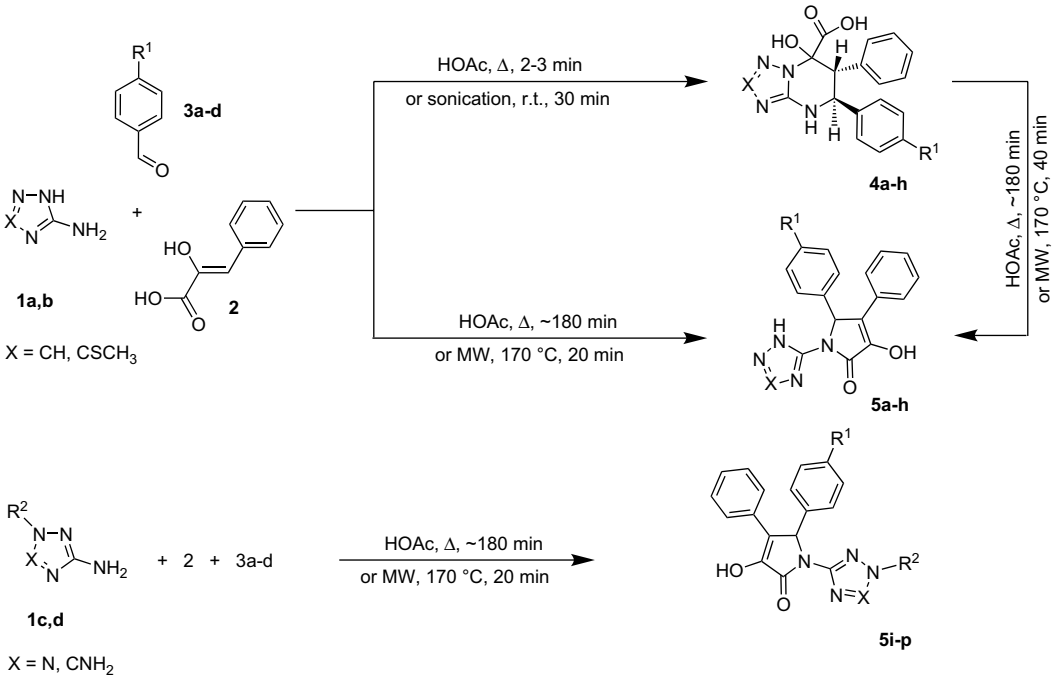
The structures of the heterocyclic compounds synthesized were established by MS-spectrometry, NMR spectral data and an X-ray diffraction study and additionally supported by elemental analysis (for details, see Section 4).

The NMR spectra of heterocycles **4a**–**h** showed duplication of some signals due to the presence of two diastereomeric pairs. ^{1}H NMR spectra of the main stereoisomers of **4a**–**h** contain two doublets for the CH-proton of the pyrimidine ring at 3.67–5.02 ppm with J ~ 11.7–11.9 Hz corresponding to trans-orientation of these protons. In addition a singlet for the CH-group of the triazole ring (compounds **4a**–**d**) at 7.4–7.5 ppm as well as multiplets for the aromatic rings (6.5–7.4 ppm), signals for the NH-group of the pyrimidine ring at ca. 7.8 ppm and signals for the other terminal substituents were observed. For the minor stereoisomers, observed in amounts up to ~5%, practically all signals down-field shifted for 0.2–0.4 ppm while spin–spin coupling constants of tetrahydropyrimidine ring protons are the same (11.7–12.0 Hz) and corresponding to trans-configuration of these stereogenic centres.

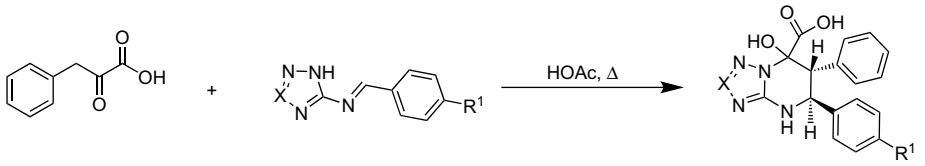
The spectral data obtained for the triazolopyrimidines may correspond to several possible regioisomers **4**, **7**–**9** (Fig. 1). Additional NOE experiments, confirming the spatial closeness of the CH-proton at the aryl substituent with the pyrimidine NH-group, allowed us to exclude structures **7** and **9**. Ultimately, the structures and stereochemistry of triazolopyrimidines **4** were unequivocally established by X-ray diffraction analysis carried out for a single crystal of one diastereomer of compound **4d**, which allowed assignment of the structure as 7-hydroxy-5-(4-methoxyphenyl)-6-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acid (Fig. 2).

The analysis of the bond lengths in the molecule **4d** demonstrates that this compound exists in the crystal phase in zwitterionic form. The C–O bond lengths in the carboxyl group are rather close to each other (C(19)–O(2) 1.233(2) Å, C(19)–O(3) 1.262(2) Å) and are comparable with the mean value[9] of the bond length in the carboxylate anion. This also agrees well with location of hydrogen atoms at the N(1) and N(2) atoms instead of the carboxyl fragment. It can thus be assumed that the negative charge is located within the carboxyl substituent.

The C(1)–N(4) 1.326(2) Å, C(1)–N(2) 1.324(2) Å and C(1)–N(1) 1.328(2) Å bonds of the triazolopyrimidine fragment are equalized and their values are slightly longer than the mean value for a Csp^2=N (1.313 Å) bond and are shorter as compared with the mean value for the Csp^2–N (1.339 Å) bond. Such redistribution of the electron density suggests a description of the structure of the triazolopyrimidine cycle as superposition of the three resonance structures (Fig. 3).



Scheme 2.



2 **6a-c** **4a-c,e-g**

6a-c: **a** R^1 = H, X = CH; **b** R^1 = Cl, X = CH; **c** R^1 = CH_3, X = CH

Scheme 3.

In the crystal phase the zwitter-ionic form is stabilized, probably, by two intermolecular hydrogen bonds: N(1)–H(1N)···O(2)′ (0.5+*x*, 0.5−*y*, 0.5+*z*) H···O 1.97 Å N–H···O 164° and N(2)–H(2N)···O(3)′ (0.5+*x*, 0.5−*y*, 0.5+*z*) H···O 1.68 Å N–H···O 173°.

The tetrahydropyrimidine ring adopts an asymmetric half-chair conformation (the puckering parameters[10] are *S*=0.79, *Θ*=37.3°, *Ψ*=20.3°). Deviations of the C(4) and C(5) atoms from the mean plane of the remaining atoms of the ring are 0.54 Å and −0.27 Å, respectively. This ring conformation leads to an apparent shortened intramolecular contact H(4)···C(1) 2.74 Å (the van der Waals radii sum[11] is 2.87 Å). The hydroxyl group is located in the pseudoaxial position and the carboxyl group is situated in the pseudoequatorial position and it is turned relatively the N(4)–C(3) bond (the C(1)–N(4)–C(3)–O(1), C(1)–N(4)–C(3)–C(19) and N(4)–C(3)–C(19)–O(3) torsion angles are −100.6(2)°, 138.3(2)° and 119.6(2)°, respectively). The geminal substituents form the O(1)–H(1O)···O(3) H···O 1.98 Å O–H···O 131° intramolecular hydrogen bond. The phenyl and methoxyphenyl substituents have an equatorial orientation (the N(4)–C(3)–C(4)–C(13) and C(1)–N(1)–C(5)–C(6) torsion angles are 179.0(2)° and −166.0(2)°, respectively).

The ^{1}H NMR spectra of pyrrolones **5** exhibit, apart from signals for the terminal substituents in appropriate areas and aromatic rings (6.7–8 ppm), sharp singlets for the CH-groups of the pyrrole ring at 6–7 ppm, broad CH (for heterocycles **5a**–**d**) and NH singlets for the triazole ring and signals for hydroxyl group protons at 10.3–11.5 ppm. Broad singlets for the NH_2-group for compounds **5m**–**o** are found at ca. 6.6 ppm. Additionally, for compounds **5m**–**o** a NOE between the NH_2-group and the *ortho*-protons of the aryl substituent is observed that confirms the participation of the amino-group in position 3 of aminoazole **1d** in the reaction. The ^{1}H NMR data observed may correspond to several structures, the most probable are **5**, **10**–**12** (Fig. 4).

The structure of heterocycles of type **5** was assigned on the basis of an X-ray diffraction analysis made for 3-hydroxy-4-phenyl-5-(4-methylphenyl)-1-(1,2,4-triazol-3-yl)-1*H*-pyrrol-2(5*H*)-on **5c** (Fig. 5).

The triazole and dihydropyrrole cycles are turned slightly relative to each other (the C(4)–N(1)–C(5)–N(2) torsion angle is 20.8(6)°), which probably causes the interruption of the conjugation between them. The presence of the bulky substituents at the neighbouring atoms in the dihydropyrrole ring leads to the noticeable repulsion between them (the shortening contacts H(12)···C(2) 2.84 Å, H(15)···C(1) 2.64 Å, H(15)···C(7) 2.77 Å (the van der Waals radii sum is 2.87 Å)). This causes also considerable twisting of the C=C double bond in the partially hydrogenated cycle (the C(1)–C(2)–C(3)–C(4) torsion angle is 9.5(4)°). The tolyl substituent has the pseudoaxial orientation (the C(7)–C(1)–C(2)–C(3) torsion angle is 111.6(4)°) and it is turned relatively the C(1)–C(2) bond (the C(2)–C(1)–C(7)–C(8) torsion angle is 128.4(4)°). The phenyl substituent is coplanar to the endocyclic double bond of the dihydropyrrole ring (the C(3)–C(2)–C(14)–C(19) torsion angle is 1.2(7)°), which is supported partially by the formation of a weak intramolecular hydrogen bond C(19)–H(19)···O(1) H···O 2.31 Å C–H···O 128°.

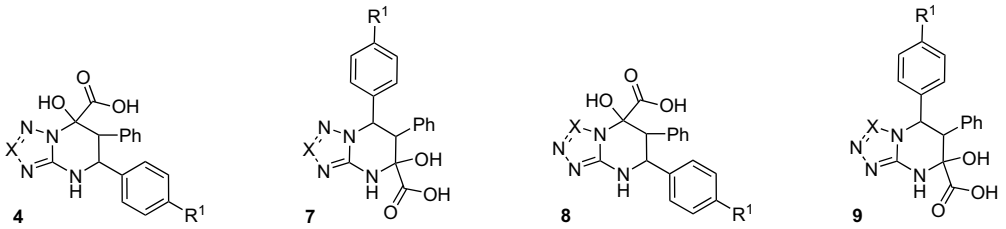
2.3. Mechanistic aspects

In this study, we have disclosed a new direction for the multicomponent condensation of aminotriazoles **1a**,**b**, phenylpyruvic acid **2** and aldehydes **3a**–**d** leading to triazolopyrimidines **4a**–**h**. In general, the three-component reactions have different pathways—the aldehyde can react with the endocyclic NH while the carbonyl group of the CH-acid reacts with the exocyclic NH_2-group (structure 7, Fig. 1).[7a,8h,12] The formation of triazolopyrimidines with such 'classical' orientation of substituents was described in several publications,[13] however, the authors provided no strong arguments for the proposed structures. It should be noted that the direction observed in our case is characteristic for multicomponent processes involving 5-aminopyrazoles.[7b]

The three-component reaction of the starting materials **1**–**3** at low temperatures giving triazolopyrimidines **4** most probably proceeds via the initial formation of azomethines **6** and its subsequent reaction with phenylpyruvic acid and heterocyclization, which is not a synchronous process (pathway 'a', Scheme 4). This pathway was indirectly proven by the treatment of Schiff base **6** with phenylpyruvic acid **2** yielding triazolopyrimidines **4** and by observation of compounds of type **6** in trace amounts in the mother liquor of the multicomponent reaction.

5-Aminotetrazole does not form azomethines with aldehydes and therefore the appropriate tetrazolopyrimidines were not isolated.

The high-temperature reaction pathway leading to pyrrolones **5** is also unusual for aminoazoles acting in this reaction as mononucleophiles like anilines.[14] The pathway leading to pyrrolones is not completely clear. The related three-component reaction of anilines, pyruvic acids and aldehydes proceeds through the formation



4 **7** **8** **9**

Figure 1. Possible regioisomers for compounds **4**.

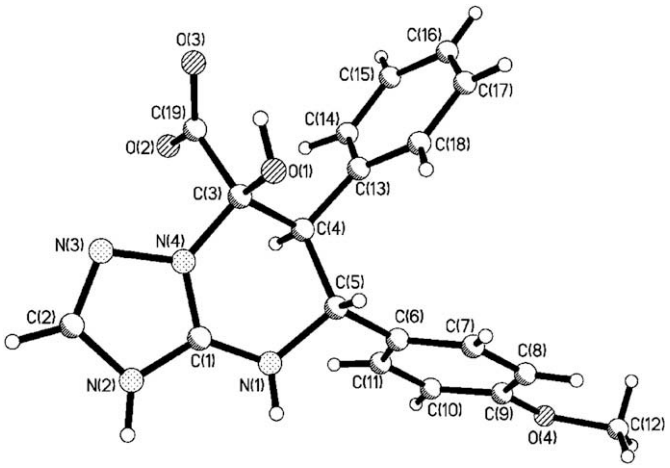


Figure 2. Molecular structure of 7-hydroxy-5-(4-methoxyphenyl)-6-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acid **4d** according to X-ray diffraction data.

of furanone derivatives like **13** (pathway 'b').[15] However, it was established that compounds **13**, synthesized by reaction of phenylpyruvic acid and aldehydes,[16] did not react with aminoazoles **1** and therefore cannot be intermediates in this multicomponent process.

The probable sequence may include formation of aldols **14** at the first stage of the high-temperature three-component reaction, subsequent nucleophilic substitution of the hydroxyl group with aminoazole (intermediate **15**) and ultimately an intramolecular condensation (pathway 'c'). We cannot exclude other mechanisms, for example, via arylidenephenylpyruvic acids **16** formed by water elimination from aldols **15**. However, our attempts to synthesize compound **17** by direct reaction of phenylpyruvic acid and aldehydes under different condition were unsuccessful, which is in good agreement with literature data for the synthesis of similar unsaturated acids.[17]

3. Conclusions

The three-component condensation of 3-amino-1,2,4-triazoles/5-aminotetrazole with phenylpyruvic acid and aromatic aldehydes leads to two distinct and unusual reaction pathways. The kinetically controlled reaction of the starting materials at room temperature proceeds via formation of an azomethine intermediate ultimately providing triazolopyrimidinecarboxylic acids of type **4**. At high temperatures the thermodynamically controlled multicomponent cyclocondensation of the same building-blocks proceeds via a different pathway yielding pyrrolones of type **5**. The use of controlled microwave heating allows the tuning of reaction conditions to access either one of the two isomers in high selectivity.

4. Experimental

4.1. General

Melting points of all compounds synthesized were determined with a Gallenkamp melting point apparatus. The NMR spectra were recorded in DMSO-d_6 at 400 MHz (100 for ^{13}C), 360 MHz (90.5 MHz for ^{13}C) and at 200 MHz (50 MHz for ^{13}C) with a Varian Unity Plus-400, Bruker AMX-360 and Varian Mercury VX-200 spectrometers. The MS spectra were measured on a GC–MS Varian 1200L (ionizing voltage 70 eV) instrument. IR spectra were recorded in KBr pellets with Perkin Elmer Spectrum One FTIR Spectrometer. Elemental analysis was realized on EuroVector EA-3000.

All microwave experiments were performed using the Emrys™ Creator EXP and Emrys™ 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 absorbance level settings and IR temperature monitoring. Reaction time reflect irradiation times at the set reaction temperature (fixed hold times).

Sonication was carried out with help of standard ultrasonic bath producing irradiation at 44.2 kHz in round-bottom flasks equipped with a condenser.

Solvents, aminoazoles **1a**,**c** and aromatic aldehydes were commercially available. Phenylpyruvic acid **2** was synthesized according to the literature procedure.[18] Azomethines **6** were obtained from corresponding aminoazoles and aldehydes.[19] 3-Amino-5-methylthio-1,2,4-triazol **1b** and 3,5-diamino-1-(4-chlorophenyl)-1,2,4-triazole **1d** were synthesized by known methods.[20] 3-Hydroxy-4,5-diphenylfuran-2(5*H*)-one **14** was obtained from phenylpyruvic acid and benzaldehyde.[16]

4.2. General procedure for the synthesis of 5-aryl-7-hydroxy-6-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids 4a–h

Method A. A mixture of 3-amino-1,2,4-triazole **1a**,**b** (2.3 mmol), phenylpyruvic acid **2** (2.3 mmol) and the appropriate aldehyde **3** (2.3 mmol) in 2 mL of acetic acid was refluxed for 2 min in a round-bottom flask equipped with a condenser. After cooling, the precipitate formed was isolated by filtration, washed with ethanol and air dried.

The reaction can be also carried out at room temperature under sonication for 30 min or under microwave irradiation in sealed vessel at 120 °C for 2 min.

Method B. A mixture of phenylpyruvic acid **2** (1.2 mmol) and the appropriate azomethine **6** (1.2 mmol) in 2 mL of acetic acid was refluxed for 2 min in a round-bottom flask equipped with a condenser. After cooling, the precipitate formed was isolated by filtration, washed with ethanol and air dried.

The reaction can be also carried out at room temperature under sonication for 30 min or under microwave irradiation in sealed vessel at 120 °C for 2 min.

*4.2.1. 5,6-Diphenyl-7-hydroxy-4,5,6,7-tetrahydro[1,2,4]triazolo-[1,5-a]pyrimidine-7-carboxylic acid (**4a**)*

Yield 610 mg (79%) of colourless crystals, mp 188–190 °C. IR (KBr): 3114, 2918, 1672. ^{1}H NMR (DMSO-d_6) δ 3.74 (d, J=11.7 Hz, 1H, 6-H), 4.99 (d, J=11.7 Hz, 1H, 5-H), 6.92–7.38 (m, 10H, ArH), 7.43 (s, 1H, 2-H), 7.76 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 53.4, 55.8, 84.1, 127.1, 127.4, 127.6, 127.9, 128.3, 130.5, 134.6, 139.7, 149.1, 153.3, 169.1. MS (EI, 70 eV): m/z (%)=318 (13) [M$^+$−18], 171 (87), 119 (36), 118

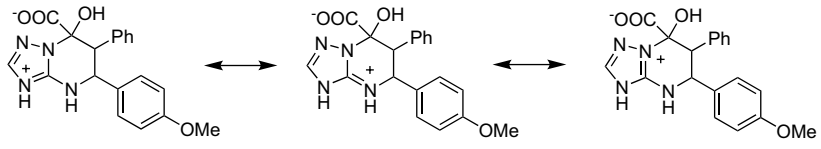


Figure 3. Resonance structures for compound **4d**.

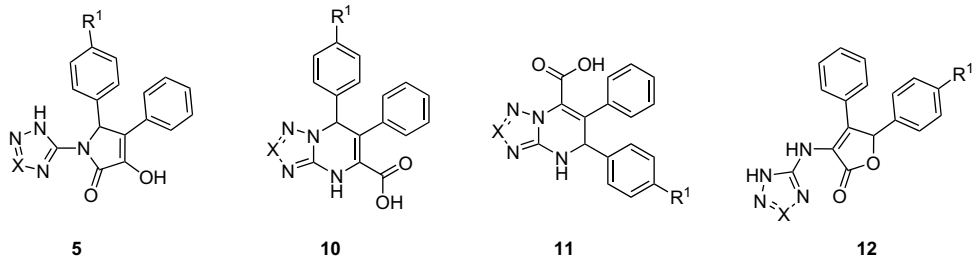


Figure 4. Possible isomers for compounds **5**.

(69). Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.33; H, 4.73; N, 16.62.

*4.2.2. 5-(4-Chlorophenyl)-7-hydroxy-6-phenyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4b**)*

Yield 650 mg (76%) of colourless crystals, mp 193–195 °C. IR (KBr): 3423, 3147, 2921, 1672, 1649. ^{1}H NMR (DMSO-d_6) δ 3.70 (d, J=11.7 Hz, 1H, 6-H), 5.02 (d, J=11.7 Hz, 1H, 5-H), 6.96–7.37 (m, 9H, ArH), 7.45 (s, 1H, 2-H), 7.85 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 53.3, 55.1, 83.9, 127.2, 127.5, 127.8, 130.2, 130.5, 131.9, 134.3, 138.8, 149.2, 153.2, 168.8. MS (EI, 70 eV): m/z (%)=352 (8%) [M^+−18], 205 (58), 178 (11), 119 (31), 118 (31). Anal. Calcd for $C_{18}H_{15}ClN_4O_3$: C, 58.31; H, 4.08; N, 15.11. Found: C, 58.38; H, 4.06; N, 15.08.

*4.2.3. 7-Hydroxy-6-phenyl-5-p-tolyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4c**)*

Yield 550 mg (68%) of colourless crystals, mp 263–265 °C. IR (KBr): 3379, 3114, 2923, 1672, 1651. ^{1}H NMR (DMSO-d_6) δ 2.13 (s, 3H, CH_3), 3.72 (d, J=11.7 Hz, 1H, 6-H), 4.96 (d, J=11.7 Hz, 1H, 5-H), 6.84–7.25 (m, 9H, ArH), 7.44 (s, 1H, 2-H), 7.73 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 20.5, 53.2, 55.3, 83.9, 127.0, 127.4, 128.1, 128.4, 130.5, 134.6, 136.4, 136.6, 149.2, 153.3, 169.0. MS (EI, 70 eV): m/z (%)=332 (11) [M^+−18], 185 (47), 119 (56), 118 (100). Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.08; H, 5.14; N, 15.96.

*4.2.4. 7-Hydroxy-5-(4-methoxyphenyl)-6-phenyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4d**)*

Yield 550 mg (65%) of colourless crystals, mp 215–216 °C. IR (KBr): 3416, 3034, 2930, 1671. ^{1}H NMR (DMSO-d_6) δ 3.60 (s, 3H, CH_3O), 3.70 (d, J=11.9 Hz, 1H, 6-H), 4.97 (d, J=11.9 Hz, 1H, 5-H), 6.57–7.29 (m, 9H, ArH), 7.44 (s, 1H, 2-H), 7.73 (br s, 1H, NH), 13.35 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 53.3, 54.8, 55.1, 84.1, 113.2, 126.9, 127.4, 129.4, 130.5, 131.5, 134.7, 149.1, 153.3, 158.4, 169.1. MS (EI, 70 eV): m/z (%)=348 (7) [M^+−18], 238 (25), 202 (42), 201 (100). Anal. Calcd for $C_{19}H_{18}N_4O_4$: C, 62.29; H, 4.95; N, 15.29. Found: C, 62.31; H, 4.92; N, 15.26.

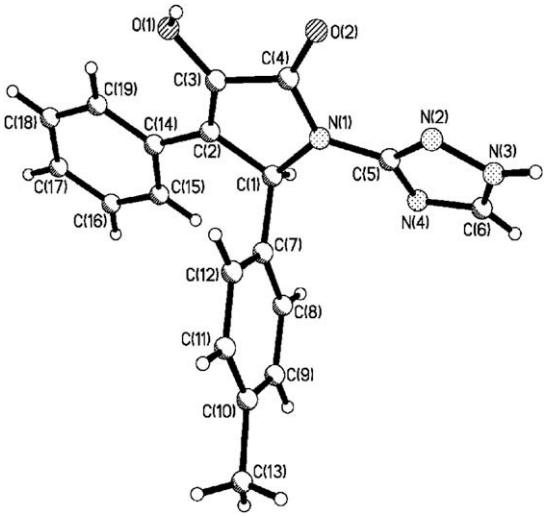


Figure 5. Molecular structure of 3-hydroxy-4-phenyl-5-(4-methylphenyl)-1-(1,2,4-triazol-3-yl)-1*H*-pyrrol-2(5*H*)-on **5c** according to X-ray diffraction data.

*4.2.5. 7-Hydroxy-2-(methylthio)-5,6-diphenyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4e**)*

Yield 550 mg (63%) of colourless crystals, mp 178–180 °C. IR (KBr): 3423, 3033, 2928, 1692. ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H, CH_3), 3.71 (d, J=11.7 Hz, 1H, 6-H), 5.01 (d, J=11.7 Hz, 1H, 5-H), 6.92–7.38 (m, 10H, ArH), 7.94 (br s, 1H, NH), 13.01 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 13.4, 21.0, 53.3, 55.5, 83.9, 127.0, 127.4, 127.5, 127.8, 128.2, 130.4, 134.3, 139.4, 154.2, 157.9, 168.8, 172.0. MS (EI, 70 eV): m/z (%)=364 (11) [M^+−18], 218 (66), 217 (100), 179 (37). Anal. Calcd for $C_{19}H_{18}N_4O_3S$: C, 59.67; H, 4.74; N, 14.65. Found: C, 59.73; H, 4.71; N, 14.62.

*4.2.6. 5-(4-Chlorophenyl)-7-hydroxy-2-(methylthio)-6-phenyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4f**)*

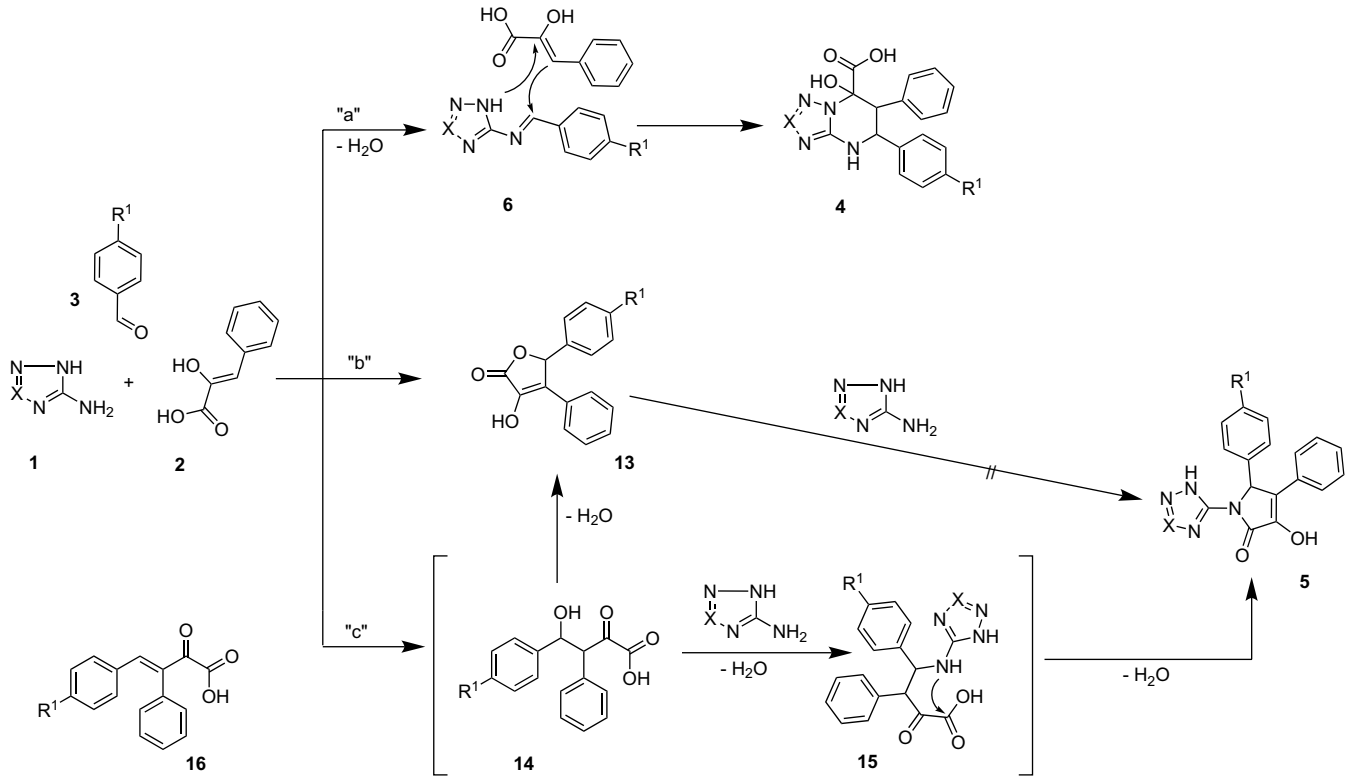
Yield 680 mg (71%) of colourless crystals, mp 191–193 °C. IR (KBr): 3420, 3029, 2931, 1688. ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H, CH_3), 3.70 (d, J=11.7 Hz, 1H, 6-H), 5.02 (d, J=11.7 Hz, 1H, 5-H), 6.96–7.39 (m, 9H, ArH), 7.96 (br s, 1H, NH), 12.78 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 13.4, 53.2, 54.8, 83.9, 127.2, 127.5, 127.8, 130.1, 130.4, 131.9, 134.1, 138.6, 154.0, 157.9, 168.7. MS (EI, 70 eV): m/z (%)=398 (10) [M^+−18], 157 (27). Anal. Calcd for $C_{19}H_{17}ClN_4O_3S$: C, 54.74; H, 4.11; N, 13.44. Found: C, 54.79; H, 4.07; N, 13.39.

*4.2.7. 7-Hydroxy-2-(methylthio)-6-phenyl-5-p-tolyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4g**)*

Yield 690 mg (76%) of colourless crystals, mp 195–197 °C. IR (KBr): 3370, 3029, 2926, 1678. ^{1}H NMR (DMSO-d_6) δ 2.13 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.69 (d, J=11.7 Hz, 1H, 6-H), 4.96 (d, J=11.7 Hz, 1H, 5-H), 6.79–7.36 (m, 9H, ArH), 7.86 (br s, 1H, NH), 13.48 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 13.4, 20.5, 53.2, 55.1, 83.9, 127.0, 127.4, 128.1, 128.4, 130.4, 134.5, 136.4, 136.5, 154.1, 157.9, 168.8. MS (EI, 70 eV): m/z (%)=378 (5) [M^+−18], 164 (30), 119 (98), 118 (100). Anal. Calcd for $C_{20}H_{20}N_4O_3S$: C, 60.59; H, 5.08; N, 14.13. Found: C, 60.63; H, 5.06; N, 14.11.

*4.2.8. 7-Hydroxy-5-(4-methoxyphenyl)-2-(methylthio)-6-phenyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4h**)*

Yield 630 mg (66%) of colourless crystals, mp 185–187 °C. IR (KBr): 3410, 2923, 1675. ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3H, CH_3), 3.61 (s, 3H, CH_3O), 3.69 (d, J=11.9 Hz, 1H, 6-H), 4.94 (d, J=11.9 Hz, 1H, 5-H), 6.59–7.27 (m, 9H, ArH), 7.82 (br s, 1H, NH), 13.46 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 13.97, 53.85, 55.38, 55.41, 84.50, 113.75, 127.51, 127.93, 129.86, 130.99, 131.89, 135.13, 154.72, 158.37,



Scheme 4.

158.96, 169.35. MS (EI, 70 eV): *m*/*z* (%)=394 (19) [M^+-18], 248 (60), 247 (36), 164 (42), 118 (100). Anal. Calcd for $C_{20}H_{20}N_4O_4S$: C, 58.24; H, 4.89; N, 13.58. Found: C, 58.28; H, 4.92; N, 13.61.

4.3. General procedure for the synthesis of 5-aryl-3-hydroxy-4-phenyl-1-azolyl-1,5-dihydro-2*H*-pyrrol-2-ones 5a–p

Method A. A mixture of 3-amino-1,2,4-triazole **1a**,**b** (2.3 mmol), phenylpyruvic acid **2** (2.3 mmol) and the appropriate aldehyde **3** (2.3 mmol) in 3 mL of acetic acid was refluxed for 3 h in a round-bottom flask equipped with a condenser. After cooling, the reaction mixture was allowed to stand overnight, then 6 mL of ethanol was added and the formed precipitate was isolated by filtration, washed with ethanol and air dried. In case of compounds **5e**–**h**,**m**–**p**, the crude reaction products were recrystallized from ethanol.

Method B. A mixture of 3-amino-1,2,4-triazole **1a**,**b** (2.3 mmol), phenylpyruvic acid **2** (2.3 mmol) and the appropriate aldehyde **3** (2.3 mmol) in 2 mL of acetic acid was microwave irradiated in 10 mL sealed vial with vigorous stirring at 170 °C for 20 min. After cooling the reaction mixture was allowed to stand overnight, then 6 mL of ethanol was added and the formed precipitate isolated by filtration, washed with ethanol and air dried. In case of compounds **5e**–**h**,**m**–**p** the crude reaction products were recrystallized from ethanol.

*4.3.1. 3-Hydroxy-4,5-diphenyl-1-(2H-1,2,4-triazol-3-yl)-1H-pyrrol-2(5H)-one (**5a**)*

Yield 420 mg (56%) of colourless crystals, mp 274–276 °C. IR (KBr): 3231, 2925, 1698. ^{1}H NMR (DMSO-d_6) δ 6.23 (s, 1H, 5-H), 6.64–7.95 (m, 10H, ArH), 8.09 (s, 1H, CHtriaz), 10.71 (br s, 1H, OH), 13.79 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 61.4, 126.9, 127.1, 127.3, 127.4, 127.5, 127.6, 130.9, 136.7, 141.9, 164.3. MS (EI, 70 eV): *m*/*z* (%)=318 (35) [M^+], 208 (23), 178 (35), 111 (100). Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.6. Found: C, 67.95; H, 4.41; N, 17.56.

*4.3.2. 5-(4-Chlorophenyl)-3-hydroxy-4-phenyl-1-(2H-1,2,4-triazol-3-yl)-1H-pyrrol-2(5H)-one (**5b**)*

Yield 580 mg (72%) of colourless crystals, mp 269–272 °C. IR (KBr): 3203, 2923, 1702. ^{1}H NMR (DMSO-d_6) δ 6.28 (s, 1H, 5-H), 6.76–7.85 (m, 9H, ArH), 8.21 (s, 1H, CHtriaz), 10.88 (br s, 1H, OH), 13.79 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 55.5, 60.5, 123.4, 126.9, 127.5, 127.6, 128.8, 129.2, 130.8, 132.1, 135.9, 142.2, 144.9, 164.2. MS (EI, 70 eV): *m*/*z* (%)=352 (28) [M^+], 178 (48), 111 (100). Anal. Calcd for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.28; H, 3.67; N, 15.85.

*4.3.3. 3-Hydroxy-4-phenyl-5-p-tolyl-1-(2H-1,2,4-triazol-3-yl)-1H-pyrrol-2(5H)-one (**5c**)*

Yield 460 mg (60%) of colourless crystals, mp 292–294 °C. IR (KBr): 3209, 2923, 1700. ^{1}H NMR (DMSO-d_6) δ 2.13 (s, 3H, CH_3), 6.20 (s, 1H, 5-H), 6.72–7.93 (m, 9H, ArH), 8.35 (s, 1H, CHtriaz), 10.72 (br s, 1H, OH), 13.73 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 19.8, 61.1, 122.9, 124.0, 126.9, 127.1, 127.3, 127.6, 128.3, 131.1, 133.7, 136.8, 141.9, 164.4. MS (EI, 70 eV): *m*/*z* (%)=332 (32) [M^+], 222 (100). Anal. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.69; H, 4.82; N, 16.84.

*4.3.4. 3-Hydroxy-5-(4-methoxyphenyl)-4-phenyl-1-(2H-1,2,4-triazol-3-yl)-1H-pyrrol-2(5H)-one (**5d**)*

Yield 550 mg (68%) of colourless crystals, mp 259–264 °C. IR (KBr): 3209, 2931, 1694. ^{1}H NMR (DMSO-d_6) δ 3.61 (s, 3H, CH_3O), 6.19 (s, 1H, 5-H), 6.61–7.79 (m, 9H, ArH), 8.32 (s, 1H, CHtriaz), 10.72 (br s, 1H, OH), 13.77 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 54.8, 56.0, 109.2, 114.2, 126.5, 126.9, 127.6, 128.7, 128.8, 130.6, 131.1, 134.4, 141.4, 158.4, 163.1. MS (EI, 70 eV): *m*/*z* (%)=348 (44) [M^+], 238 (84), 165

(34), 111 (100). Anal. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.49; H, 4.62; N, 16.05.

4.3.5. 3-Hydroxy-1-(5-(methylthio)-2H-1,2,4-triazol-3-yl)-4,5-diphenyl-1H-pyrrol-2(5H)-one (**5e**)

Yield 590 mg (70%) of colourless crystals, mp 209–210 °C. IR (KBr): 3303, 2929, 1698, 1569. ^{1}H NMR (DMSO-d_6) δ 2.45 (s, 3H, CH_3), 6.25 (s, 1H, 5-H), 7.02–7.82 (m, 10H, ArH), 11.04 (br s, 1H, OH), 13.64 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 13.6, 60.7, 127.3, 127.5, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.9, 129.2, 131.2, 136.9, 171.9. MS (EI, 70 eV): m/z (%)=364 (48) [M^+], 178 (33), 157 (100). Anal. Calcd for $C_{19}H_{16}N_4O_2S$: C, 62.62; H, 4.43; N, 15.37. Found: C, 62.66; H, 4.41; N, 15.34.

4.3.6. 5-(4-Chlorophenyl)-3-hydroxy-1-(5-(methylthio)-2H-1,2,4-triazol-3-yl)-4-phenyl-1H-pyrrol-2(5H)-one (**5f**)

Yield 690 mg (75%) of colourless crystals, mp 214–217 °C. IR (KBr): 3370, 2923, 1698, 1577. ^{1}H NMR (DMSO-d_6) δ 2.46 (s, 3H, CH_3), 6.28 (s, 1H, 5-H), 7.01–7.90 (m, 9H, ArH), 11.20 (br s, 1H, OH), 13.40 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 13.6, 59.8, 127.5, 127.9, 128.3, 128.4, 130.0, 130.8, 132.6, 136.0, 141.9, 147.2, 157.5, 164.8, 172.0. MS (EI, 70 eV): m/z (%)=398 (59) [M^+], 213 (17), 178 (19), 157 (100). Anal. Calcd for $C_{19}H_{16}ClN_4O_2S$: C, 57.21; H, 3.79; N, 14.05. Found: C, 57.25; H, 3.75; N, 14.03.

4.3.7. 3-Hydroxy-1-(5-(methylthio)-2H-1,2,4-triazol-3-yl)-4-phenyl-5-p-tolyl-1H-pyrrol-2(5H)-one (**5g**)

Yield 630 mg (72%) of colourless crystals, mp 194–196 °C. IR (KBr): 3313, 2925, 1683, 1572. ^{1}H NMR (DMSO-d_6) δ 2.15 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.19 (s, 1H, 5-H), 6.92–7.74 (m, 9H, ArH), 11.51 (br s, 1H, OH), 12.62 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 13.4, 19.8, 60.8, 126.8, 126.9, 127.0, 127.3, 127.4, 127.6, 128.1, 128.7, 130.8, 133.3, 136.8, 141.5, 164.2. MS (EI, 70 eV): m/z (%)=378 (27) [M^+], 157 (100). Anal. Calcd for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N, 14.80. Found: C, 63.49; H, 4.75; N, 14.79.

4.3.8. 3-Hydroxy-5-(4-methoxyphenyl)-1-(5-(methylthio)-2H-1,2,4-triazol-3-yl)-4-phenyl-1H-pyrrol-2(5H)-one (**5h**)

Yield 640 mg (71%) of colourless crystals, mp 247–249 °C. IR (KBr): 3225, 2923, 1687, 1563. ^{1}H NMR (DMSO-d_6) δ 2.47 (s, 3H, CH_3), 3.63 (s, 3H, CH_3O), 6.20 (s, 1H, 5-H), 6.69–7.79 (m, 9H, ArH), 10.79 (br s, 1H, OH), 13.65 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 13.6, 54.9, 60.2, 113.6, 125.2, 127.6, 128.2, 128.7, 128.9, 129.3, 131.1, 141.7, 147.2, 157.5, 158.9, 164.9. MS (EI, 70 eV): m/z (%)=394 (48) [M^+], 157 (100). Anal. Calcd for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.94; H, 4.57; N, 14.16.

4.3.9. 3-Hydroxy-4,5-diphenyl-1-(1H-tetrazol-5-yl)-1H-pyrrol-2(5H)-one (**5i**)

Yield 440 mg (60%) of colourless crystals, mp 224–226 °C. IR (KBr): 3315, 2918, 1709, 1609. ^{1}H NMR (DMSO-d_6) δ 6.82 (s, 1H, 5-H), 6.92–7.48 (m, 10H, ArH), 10.68 (br s, 1H, OH), 13.69 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 62.6, 114.4, 125.8, 126.7, 126.8, 127.1, 127.7, 128.1, 128.5, 135.1, 137.9, 149.1, 162.8. MS (EI, 70 eV): m/z (%)=319 (27) [M^+], 246 (100), 242 (80), 220 (81), 208 (49). Anal. Calcd for $C_{17}H_{13}N_5O_2$: C, 63.94; H, 4.10; N, 21.93. Found: C, 63.97; H, 4.12; N, 21.91.

4.3.10. 5-(4-Chlorophenyl)-3-hydroxy-4-phenyl-1-(1H-tetrazol-5-yl)-1H-pyrrol-2(5H)-one (**5j**)

Yield 540 mg (67%) of colourless crystals, mp 217–219 °C. IR (KBr): 3309, 2923, 2851, 1741, 1606. ^{1}H NMR (DMSO-d_6) δ 6.88 (s, 1H, 5-H), 6.96–7.42 (m, 9H, ArH), 10.72 (br s, 1H, OH), 13.49 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 61.9, 113.8, 126.1, 126.9, 127.2, 128.1, 128.5, 128.7, 133.0, 135.1, 136.9, 149.1, 162.7. MS (EI, 70 eV): m/z (%)=353 (38) [M^+], 324 (50), 281 (57), 280 (84), 242 (45). Anal. Calcd for $C_{17}H_{12}ClN_5O_2$: C, 57.72; H, 3.42; N, 19.80. Found: C, 57.68; H, 3.45; N, 19.77.

4.3.11. 3-Hydroxy-4-phenyl-1-(1H-tetrazol-5-yl)-5-p-tolyl-1H-pyrrol-2(5H)-one (**5k**)

Yield 400 mg (52%) of colourless crystals, mp 233–235 °C. IR (KBr): 3480, 2923, 2532, 1959, 1713, 1602. ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 3H, CH_3), 6.76 (s, 1H, 5-H), 6.84–7.51 (m, 9H, ArH), 10.63 (br s, 1H, OH), 13.35 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 20.6, 62.3, 114.7, 126.1, 127.4, 127.5, 127.9, 128.8, 129.3, 135.7, 135.8, 138.1, 149.3, 163.8. MS (EI, 70 eV): m/z (%)=333 (29) [M^+], 304 (51), 260 (65), 242 (100). Anal. Calcd for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.89; H, 4.51; N, 21.03.

4.3.12. 3-Hydroxy-5-(4-methoxyphenyl)-4-phenyl-1-(1H-tetrazol-5-yl)-1H-pyrrol-2(5H)-one (**5l**)

Yield 510 mg (64%) of colourless crystals, mp 232–234 °C. IR (KBr): 3276, 2839, 2517, 1885, 1693. ^{1}H NMR (DMSO-d_6) δ 3.66 (s, 3H, CH_3O), 6.75 (s, 1H, 5-H), 6.78–7.31 (m, 9H, ArH), 10.64 (br s, 1H, OH), 13.62 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 55.1, 62.1, 114.1, 114.9, 126.1, 127.4, 127.9, 128.8, 128.9, 130.7, 135.9, 149.3, 159.3, 163.8. MS (EI, 70 eV): m/z (%)=349 (47) [M^+], 320 (41), 288 (54), 276 (100). Anal. Calcd for $C_{18}H_{15}N_5O_3$: C, 61.89; H, 4.33; N, 20.05. Found: C, 61.86; H, 4.31; N, 20.01.

4.3.13. 1-(5-Amino-1-(4-chlorophenyl)-1H-1,2,4-triazol-3-yl)-3-hydroxy-4,5-diphenyl-1H-pyrrol-2(5H)-one (**5m**)

Yield 600 mg (59%) of yellowish crystals, mp 274–276 °C. IR (KBr): 3197, 1698, 1619. ^{1}H NMR (DMSO-d_6) δ 6.12 (s, 1H, 5-H), 6.63 (br s, 2H, NH_2), 7.03–7.77 (m, 14H, ArH), 10.36 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 61.0, 122.7, 124.0, 127.3, 127.4, 128.0, 128.1, 128.2, 128.3, 129.3, 130.9, 131.4, 135.7, 137.6, 142.8, 152.6, 154.1, 164.2. MS (EI, 70 eV): m/z (%)=443 (52) [M^+], 238 (41), 236 (100). Anal. Calcd for $C_{24}H_{18}ClN_5O_2$: C, 64.94; H, 4.09; N, 15.78. Found: C, 64.99; H, 4.05; N, 15.74.

4.3.14. 1-(5-Amino-1-(4-chlorophenyl)-1H-1,2,4-triazol-3-yl)-5-(4-chlorophenyl)-3-hydroxy-4-phenyl-1H-pyrrol-2(5H)-one (**5n**)

Yield 750 mg (68%) of yellowish crystals, mp 294–296 °C. IR (KBr): 3183, 2923, 1715, 1639. ^{1}H NMR (DMSO-d_6) δ 6.16 (s, 1H, 5-H), 6.64 (br s, 2H, NH_2), 7.09–7.74 (m, 13H, ArH), 11.16 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 60.1, 122.4, 124.1, 127.3, 127.4, 128.2, 128.3, 129.3, 129.9, 131.0, 131.2, 132.4, 135.7, 136.7, 142.9, 152.5, 154.1, 164.1. MS (EI, 70 eV): m/z (%)=477 (39) [M^+], 236 (100). Anal. Calcd for $C_{24}H_{17}Cl_2N_5O_2$: C, 60.26; H, 3.58; N, 14.64. Found: C, 60.29; H, 3.55; N, 14.61.

4.3.15. 1-(5-Amino-1-(4-chlorophenyl)-1H-1,2,4-triazol-3-yl)-3-hydroxy-4-phenyl-5-p-tolyl-1H-pyrrol-2(5H)-one (**5o**)

Yield 660 mg (63%) of yellowish crystals, mp 279–281 °C. IR (KBr): 3208, 2923, 1697. ^{1}H NMR (DMSO-d_6) δ 2.16 (s, 3H, CH_3), 6.08 (s, 1H, 5-H), 6.62 (br s, 2H, NH_2), 6.93–7.74 (m, 13H, ArH), 10.60 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 20.6, 60.7, 122.7, 124.0, 127.2, 127.4, 127.9, 128.1, 128.9, 129.3, 130.9, 131.5, 134.5, 135.7, 137.2, 142.7, 152.6, 154.1, 164.2. MS (EI, 70 eV): m/z (%)=457 (48) [M^+], 238 (27), 236 (100). Anal. Calcd for $C_{25}H_{20}ClN_5O_2$: C, 65.57; H, 4.40; N, 15.29. Found: C, 65.59; H, 4.37; N, 15.26.

4.3.16. 1-(5-Amino-1-(4-chlorophenyl)-1H-1,2,4-triazol-3-yl)-3-hydroxy-5-(4-methoxyphenyl)-4-phenyl-1H-pyrrol-2(5H)-one (**5p**)

Yield 670 mg (62%) of yellowish crystals, mp 272–273 °C. IR (KBr): 3290, 2925, 1705. ^{1}H NMR (DMSO-d_6) δ 3.63 (s, 3H, CH_3O), 6.05 (s, 1H, 5-H), 6.62 (br s, 2H, NH_2), 6.71–7.73 (m, 13H, ArH), 10.20 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 54.8, 60.5, 113.6, 122.6, 124.0, 127.2, 127.4, 128.1, 129.1, 129.2, 129.3, 130.9, 131.5, 135.7, 142.7, 152.4, 154.1, 158.7, 164.1 MS (EI, 70 eV): m/z (%)=473 (100) [M^+], 443 (36), 236 (63). Anal. Calcd for $C_{25}H_{20}ClN_5O_3$: C, 63.36; H, 4.25; N, 14.78. Found: C, 63.39; H, 4.22; N, 14.76.

4.4. X-ray diffraction data

The colourless crystals of **4d** ($C_{19}H_{18}N_4O_4$) are monoclinic. At 293 K a=13.243(1), b=10.953(5), c=13.447(1) Å, β=116.54(1)°, V=1745.1(9) Å^3, M_r=366.37, Z=4, space group $P2_1/n$, d_{calcd}=1.395 g/cm^3, μ(Mo Kα)=0.100 mm^{-1}, F(000)=768. Intensities of 9437 reflections (3033 independent, R_{int}=0.050) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scanning, $2\Theta_{max}$=50°). The structure was solved by direct method using SHELXTL package.[21] 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 group and n=1.2 for other hydrogen atoms). The hydrogen atoms participating in the formation of the hydrogen bonds were refined in isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 2996 reflections was converged to wR_2=0.060 (R_1=0.035 for 1323 reflections with $F>4\sigma(F)$, S=0.679). The final atomic coordinates, and crystallographic data for molecule **6** have been deposited to with 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 695198.

The colourless crystals of **5c** ($C_{19}H_{16}N_4O_2$) are monoclinic. At 293 K a=16.493(1), b=7.212(1), c=16.497(1) Å, β=119.37(1)°, V=1710.0(2) Å^3, M_r=332.36, Z=4, space group $P2_1/c$, d_{calcd}=1.291 g/cm^3, μ(Mo Kα)=0.087 mm^{-1}, F(000)=696. Intensities of 4979 reflections (2952 independent, R_{int}=0.070) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scanning, $2\Theta_{max}$=50°). The structure was solved by direct method using SHELXTL package.[21] 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 group and n=1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation using 2910 reflections was converged to wR_2=0.195 (R_1=0.085 for 1995 reflections with $F>4\sigma(F)$, S=1.072). The final atomic coordinates, and crystallographic data for molecule **6** have been deposited to with 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 695199.

Acknowledgements

The present work was supported by an INTAS grant (V.A.C., Nr. 04-83-2844) and DAAD Euler scholarship (Y.I.S.). We thank Biotage AG for the use of the Emrys Creator and Emrys Initiator microwave reactors. We also thank Dr. Vladimir Musatov for recording some ^{1}H NMR spectra, Dr. Dmytro S. Sofronov for recording IR spectra and Ms. Irina Knyazeva for measuring MS spectra.

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