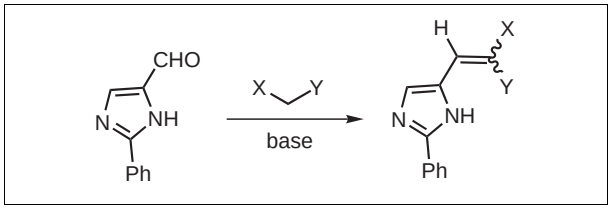
Synthesis and *E*/*Z* Determination of Substituted 2-Phenylimidazoles

Tomáš Szotkowski[a], Filip Bureš[a,*], Oldřich Pytela[a], Jiří Kulhánek[a], Zdeněk Trávníček[b]

[a] Department of Organic Chemistry, University of Pardubice, nám. Čs. Legií 565, Pardubice 53210, Czech Republic, e-mail: Filip.Bures@upce.cz

[b] Department of Inorganic Chemistry, Palacký University, Křížkovského 10, Olomouc 77147, Czech Republic

Received February 23, 2006



Nine new 4-substituted 2-phenylimidazole derivatives have been synthesized by aldol condensation of 2-phenylimidazole-4-carbaldehyde with various active methylene compounds. In case of non-symmetric active methylene compound used, the stereospecific formation of only one *cis-trans* isomer has been observed. The predominant formation of products with bulkier substituents standing opposite on double bond formed by aldol condensation has been proved. *cis-trans* Isomerism of three unsymmetrically substituted products has been determined by ^{1}H coupled ^{13}C NMR experiments. 3-[(2-Phenylimidazol-4-yl)methylene]pentane-2,4-dione has been characterized by single crystal X–ray structural analysis as well. Selected bond lengths and angles have proved the expected large mesomerical stabilisation in the molecule. The hydrogen bond in crystal phase has been observed.

J. Heterocyclic Chem., **43**, 1583 (2006).

Introduction.

The aldol condensation is one of the most common reactions used for carbon–carbon double bond formation. It is based on a condensation between carbonyl compound and an active methylene group compound. The well-known Knoevenagel condensation is basically catalysed by amines or ammonium salts [1-3]. The most reactive methylene compounds are used, such as diethyl malonate, acetylacetone *etc*. Stronger base must be used in case of less reactive methylene compound. In case of non-symmetric methylene compounds the question of *E*/*Z* stereoselectivity of the product arises. There are references of exclusive formation of *E* isomer in aldol condensation of various aldehydes with ethyl cyanoacetate [4,5] and also an example of a *E*/*Z* isomers mixture creation in Knoevenagel condensation of ethyl (trifluoromethylthio)acetate with various aliphatic or aromatic aldehydes has been reported [6].

The five-membered heterocycle imidazole has an interesting reactivity. Imidazole derivatives are also well known for a broad palette of exploitable biological properties [7,8]. Moreover, the imidazole ring has coordination activity, therefore enantiopure imidazole derivatives could be useful in asymmetric catalysis. There are few methods for synthesis of imidazole ring. Recently we have published a method for enantiopure chiral imidazole derivatives formation starting from commercially available amino acids [9]. Another way, which was utilized in this work, has been published before [10]. Herein we report a series of new 2-phenylimidazole derivatives bearing a side chain constructed by aldol condensation reaction and NMR and X–ray studies of structure and *cis-trans* isomerism of unsaturated products. Aldol condensation is studied as the starting step of chiral side chain building.

Results and Discussion.

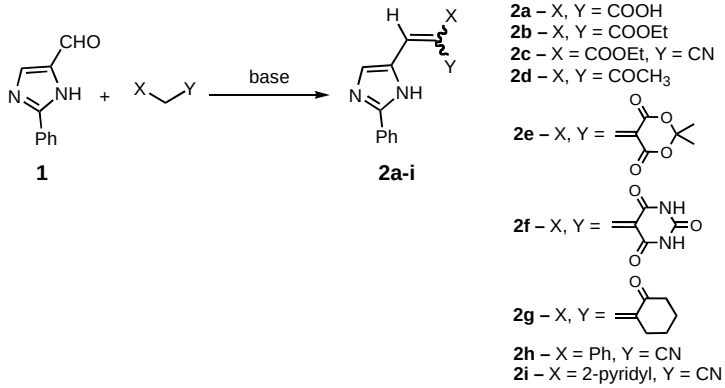
The first group of 2-phenylimidazole derivatives has been prepared starting from 2-phenylimidazole-4-carbaldehyde **1** (Scheme I) by conventional procedure for Knoevenagel condensation [11]. Malonic acid, diethyl malonate, ethyl cyanoacetate, acetylacetone, Meldrum's acid and barbituric acid were used as active methylene compounds and corresponding products **2a–f** (Scheme I) have been obtained. The second group of products **2g–i** (Scheme I) has been gained by condensation with less reactive methylene components (cyclohexanone, benzyl cyanide and 2-pyridylacetonitrile), where the methylene group is activated by presence of only single electron withdrawing group. The use of stronger base such as sodium hydroxide or sodium methoxide instead of piperidinium acetate has been necessary. The reaction sequence is described on Scheme I. Two general methods for aldol condensation have been used (methods A, B). Substances **2a** and **2g** have been prepared by different procedure. The particular method for synthesis and other synthetic details are summarized in Table 1.

The molecular structure of **2d** is depicted in Fig. 1, while selected bond lengths and angles are given in Table 2. Molecules are linked by N(3)–H(3a)…O(15)^{i} hydrogen

Table 1
Synthetic Methods, Reaction Times and Yields for Synthesis of **2a-i** (Scheme I)

Product	Methylene compound	Synthetic method	Reaction time [h]	Yield [%]
2a	Malonic acid	see Experimental	2	78
2b	Diethyl malonate	A	18	96
2c	Ethyl cyanoacetate	A	3	52
2d	Acetyl acetone	A	18	63
2e	Meldrum's acid	A	4	92
2f	Barbituric acid	A	3	95
2g	Cyclohexanone	see Experimental	18	64
2h	Benzyl cyanide	B	24	62
2i	2-Pyridylacetonitrile	B	3	95

Scheme I



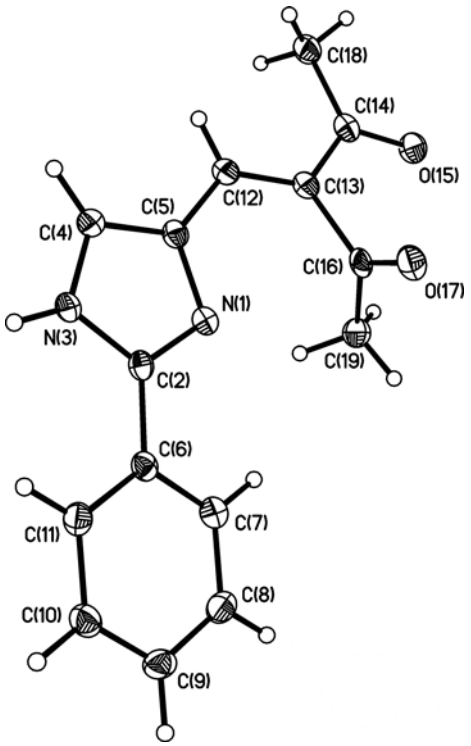


Figure 1. The molecular structure of the compound **2d** (Table 1), including the atom-numbering scheme. Thermal ellipsoids are drawn at the level of 50% probability.

bonds [symmetry code: (i) x+1, y, z] to form infinite chain along *X*-axis (Fig. 2). The N(3)…O(15)^{i} distance is 2.866(2) Å, the N(3)–H(3a)–O(15)^{i} angle is 177.5°. The molecule contains nearly planar benzene and imidazole ring systems (as expected) with the maximal displacement 0.0025(2) Å for benzene and 0.0062(2) Å for imidazole, respectively. The dihedral angle between the planes is 10.32(1)°. Interatomic

Table 2
Selected Bond Lengths and Angles for **2d**, for Atom-numbering Scheme see Fig. 1

Bond	Length [Å]	Bonds	Angle [°]
N(1)–C(2)	1.319(2)	C(2)–N(1)–C(5)	106.01(11)
N(1)–C(5)	1.382(2)	N(1)–C(2)–N(3)	110.88(11)
C(2)–N(3)	1.373(2)	N(1)–C(2)–C(6)	123.48(11)
C(2)–C(6)	1.471(2)	N(3)–C(2)–C(6)	125.61(11)
N(3)–C(4)	1.366(2)	C(4)–N(3)–C(2)	107.56(11)
C(4)–C(5)	1.378(2)	N(3)–C(4)–C(5)	105.89(12)
C(5)–C(12)	1.444(2)	C(4)–C(5)–N(1)	109.65(12)
C(6)–C(7)	1.397(2)	C(4)–C(5)–C(12)	128.93(13)
C(6)-C(11)	1.400(2)	N(1)–C(5)–C(12)	121.41(12)
C(7)-C(8)	1.386(2)	C(13)–C(12)–C(5)	124.77(13)
C(8)-C(9)	1.391(2)	C(12)–C(13)–C(14)	123.31(13)
C(9)-C(10)	1.391(2)	C(12)–C(13)–C(16)	123.05(12)
C(10)-C(11)	1.391(2)	C(14)–C(13)–C(16)	113.62(11)
C(12)–C(13)	1.353(2)	O(15)–C(14)–C(13)	118.39(13)
C(13)–C(14)	1.472(2)	O(15)–C(14)–C(18)	120.27(12)
C(13)–C(16)	1.521(2)	C(13)–C(14)–C(18)	121.33(11)
C(14)–O(15)	1.237(2)	O(17)–C(16)–C(19)	122.63(13)
C(16)–O(17)	1.217(2)	O(17)–C(16)–C(13)	119.56(13)
		C(19)–C(16)–C(13)	117.73(11)

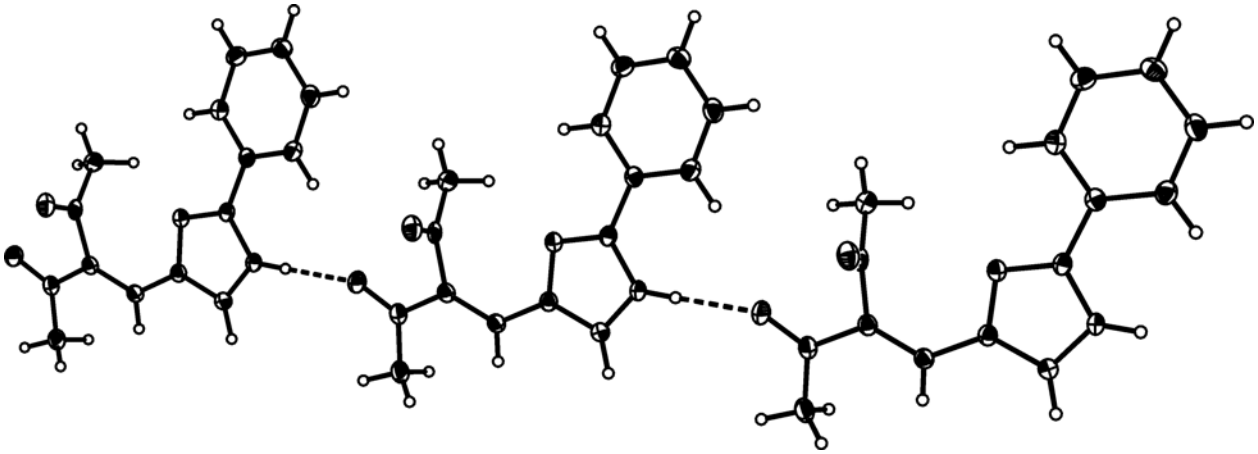


Figure 2. Part of the crystal structure of the compound **2d**, showing the hydrogen bonding (dashed lines). [Symmetry code: (i) x+1, y, z].

distances in imidazole ring vary from 1.319(2) Å for N(1)–C(2) bond to 1.382(2) Å for N(1)–C(5) bond. The C(2)–C(6) distance 1.471(2) Å is appropriate when the "connection" of two (hetero)aromatic rings is considered. The large mesomerical stabilisation reaching from phenyl ring to one of the carbonyl groups is demonstrated by bond lengths C(5)–C(12) = 1.444(2) Å (formally single bond) and C(12)–C(13) = 1.353(2) Å (formally double bond) and by the difference between bond lengths C(13)–C(14) = 1.472(2) Å and C(13)–C(16) = 1.521(2) Å (formally single bonds). Dihedral angles between phenyl and imidazole ring (10.3°), between imidazole ring and C(12)–C(13) double bond (9.6°) and between C(12)–C(13) and C(14)–O(15) double bonds (4.0°) prove nearly planar structure of the mentioned part of molecule. The mesomerical stabilisation could also be affected by contribution of hydrogen bond that causes polarization of the molecule (Fig. 2).

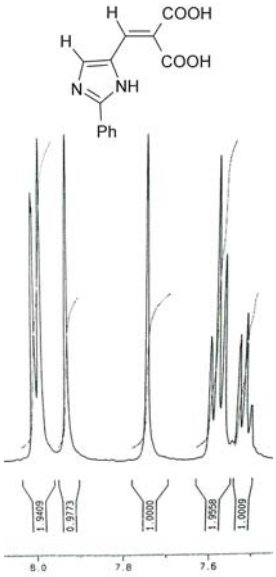


Figure 3. ^{1}H NMR spectrum of **2a** (Table 1).

According to literature sources, **2d** is structurally similar with two 2-phenylimidazole based compounds, *i.e.* 5-(2,4-diphenyl-1*H*-imidazol-5-yl)-2,4,4,6-tetraphenyl-1,4-dihydropyrimidine and 2-(2,4-diphenylimidazol-5-yl)-1,3,3-triphenyl-2-propen-1-one [12]. Comparing **2d** with both structures, **2d** contains substituent. The constitution of imidazole ring is partially similar except for the C(2)–N(3) bond length being 0.037 Å longer in case of **2d** than in dihydropyrimidine derivative and the N(3)–C(4) bond length being 0.018 Å shorter in **2d** than in ketone. Concerning 4-positioned side chain constructed by aldol condensation, similar unsaturated structure is included in ketone as well as in pyrimidine derivative, where the double bond forms part of dihydropyrimidine heterocycle. This C(12)–C(13) bond (formally double) length in **2d** is

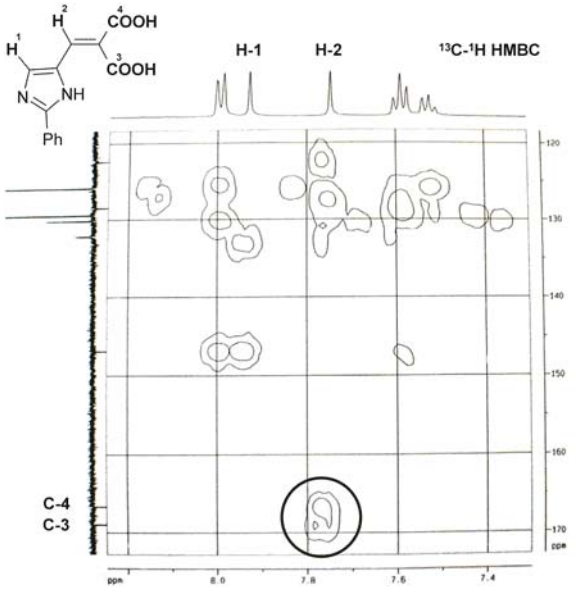


Figure 4. HMBC spectrum of **2a** illustrating the discrimination of two aromatic area singlets in ^{1}H NMR spectrum between vinylic hydrogen (highlighted) and imidazole hydrogen.

similar to both compared substances, whereas the C(5)–C(12) (formally single) bond in **2d** is 0.029 Å shorter than in 5-(2,4-diphenyl-1*H*-imidazol-5-yl)-2,4,4,6-tetraphenyl-1,4-dihydropyrimidine and 0.015 Å shorter than in 2-(2,4-diphenylimidazol-5-yl)-1,3,3-triphenyl-2-propen-1-one, what indicates stronger mesomerical stabilisation in **2d**.

In case of using non-symmetric active methylene compounds in aldol condensation, the problems of mixture formation and *cis-trans* isomerism of the products should arise (Scheme I). The ^{1}H NMR spectra of prepared compounds show only one signal due to the vinylic proton demonstrating the formation of only one of the possible *cis-trans* isomers. In order to determine the configuration of the obtained isomer different NMR experiments have been carried out such as ^{1}H–^{13}C HMBC, HMQC and ^{1}H coupled ^{13}C experiment. *cis-trans* Isomerism of products has been determined according to Cho *et al.* [13].

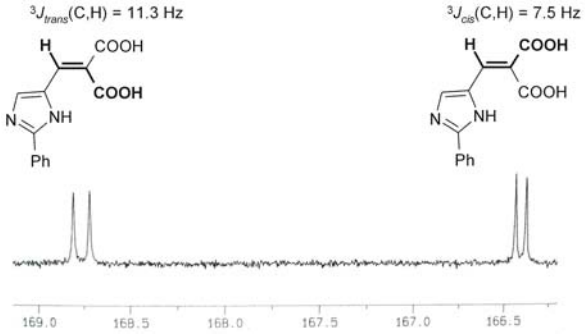


Figure 5. The part of ^{1}H coupled ^{13}C NMR spectrum of **2a** (Table 1) showing different interaction constant of vinylic hydrogen with two carboxylic carbons.

Initially, the dicarboxylic acid **2a** has been studied (Fig. 3). It was necessary to discriminate two singlets in aromatic area between imidazole hydrogen and vinylic hydrogen. ^{1}H–^{13}C HMBC experiment was successful as signal of vinylic proton shown interaction with both carboxylic carbon atoms (Fig. 4). This spin-spin interaction was quantified by ^{1}H coupled ^{13}C experiment that shown $^3J_{trans}$(C,H) = 11.3 Hz and $^3J_{cis}$(C,H) = 7.5 Hz for three-bond interaction (Fig. 5).

The *E* configuration of **2c** was determined by analysis of the ^{1}H coupled ^{13}C NMR spectra measuring the corresponding ^{3}J (C,H). $^3J_{trans}$ = 13.3 Hz for *H–C*N interaction and $^3J_{cis}$ = 6.5 Hz for *H–C*OOCH$_2$CH$_3$ interaction respectively have been found. However, the coupled signal of esteric carbon is affected also by spin-spin interaction with methylene protons of ethyl group (Fig. 6). In case of other unsymmetrically substituted derivatives (**2g**, **2h**, **2i**), the undesired interaction is even stronger.

On the other hand, the coupled signal of cyano-group carbon is affected only by desired three-bond interaction

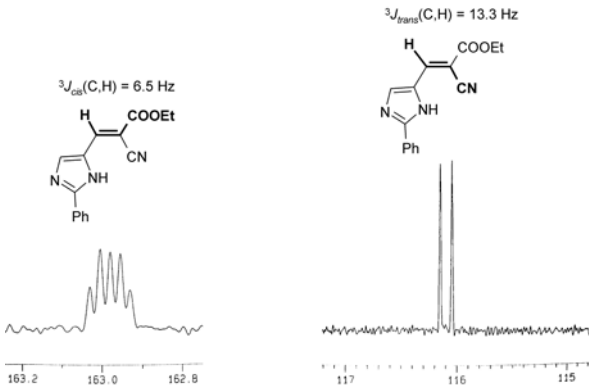


Figure 6. Two parts of ^{1}H coupled ^{13}C NMR spectrum of **2c** (Table 1) showing different intensity of spin-spin interaction of vinylic hydrogen with ethoxycarbonyl-group carbon and cyano-group carbon respectively.

with vinylic proton. As the basic skeleton of all products concerning CN group (**2c**, **2h**, **2i**) is highly similar, the value of J for three-bond C–H interaction can be compared with the value found for **2c** ($^3J_{trans}$ = 13.3 Hz); $^3J_{trans}$ = 14.3 Hz for **2h** and $^3J_{trans}$ = 13.9 Hz for **2i** respectively have been found. This fact proves the *trans* orientation in both cases, the *cis-trans* isomerism of products **2h** and **2i** is therefore *Z*.

Unfortunately, product **2g** can't be determined by ^{1}H coupled ^{13}C NMR experiment at all. According to literature [14], in similar structures a small NOE was detected between vinylic proton and some part of X or Y (Scheme I). The attempts to find similar NOE interaction in **2g** between the vinylic proton and cyclohexane moiety hydrogens (especially the double bond neighbouring CH_2 group) remained unsuccessful. No detectable methylene signal enhancement was observed, if the vinylic proton was irradiated (NOESY spectrum).

Conclusion.

We tried the possibility of use of aldol condensation reaction for side-chain construction of 2-phenylimidazole derivatives in position 4 of imidazole ring. A series of nine new 2-phenylimidazole derivatives (**2a–i**) has been prepared. In case of non-symmetric active methylene compound used, the stereospecific formation of only one *cis-trans* isomer has been observed. *cis-trans* Isomerism of products **2c**, **2h** and **2i** has been determined. The predominant formation of products with bulkier substituents standing opposite on double bond formed by aldol condensation has been proved. Product **2d** has been characterized by single crystal X–ray structural analysis as well.

EXPERIMENTAL

All commercially available chemicals and solvents have been used without further purification. 2-Phenylimidazole-4-

carbaldehyde [15], ethyl benzimidate hydrochloride [16] and Meldrum's acid [17] were prepared according to literature procedures.

^{1}H NMR spectra were recorded with Bruker AVANCE 500 instrument at 500 MHz using DMSO-d_6 as a solvent. The ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker AVANCE 500 instrument at 125 MHz. Digital resolution 0.45 Hz. Additional NMR techniques such as ^{1}H-^{1}H COSY, ^{1}H coupled ^{13}C experiment (the gated ^{1}H decoupling technique [18]), HMBC and HMQC were used. Chemical shifts are reported in ppm with residual DMSO-d_6 (2.55 and 39.51 ppm respectively) as reference. J values are given in hertz.

The mass spectra were measured on GC/MS configuration of Agilent Technologies - gas chromatograph 6890N (HP-5MS column, length 30 m, I.D. 0,25 mm, film 0,25 μm) with 5973 Network MS detektor (EI 70 eV, mass range 33 – 550 Da).

IR spectra were recorded on a Perkin Elmer Spectrum BX spectrometer.

Single crystal X-ray diffraction study of **2d**. Empirical formula $C_{15}H_{14}N_2O_2$; formula weight 254.28; crystal dimensions 0.40 x 0.40 x 0.30 mm; a = 9.806(5) Å, b = 8.698(5) Å, c = 16.225(5) Å, β = 107.396(5)°, U = 1320.6 (1) Å^3, Z = 4, space group *P* $2_1/n$, D_{calcd} = 1.279 g. cm^{-3}; F_{000} = 536; μ (MoKα) = 0.086 mm^{-1}; $2\theta_{max}$ = 50°; no. of reflections collected/unique 7449/2329 (R_{int}=0.02); limiting indices $-11 \le h \le 11$, $-10 \le k \le 6$, $-19 \le l \le 19$; no. of variables 174; refinement based on F^2; final indices [I>2σ(I)]: R = 0.037; R_w = 0.088; $\Delta\rho_{max}$ = 0.274 e. Å^{-3} ; $\Delta\rho_{min}$= -0.194 e. Å^{-3} .

Data were collected on a four-circle κ-axis diffractometer Xcalibur2 (Oxford Diffraction Ltd.) equipped with the Sapphire2 CCD detector at 105 K. The CrysAlis software package [19] was used for data collection and reduction. The structure was solved by the SIR97 program [20] incorporated in the WinGX system (Version 1.70.00) [21] and refined anisotropically using full-matrix least-squares procedure [SHELXL-97] [22]. All hydrogen atoms of **2d** were localized in difference Fourier maps, idealized and refined a 'riding' model, with the C–H distances of 0.95 and 0.98 Å and the N–H distances of 0.88 Å, and with U_{iso}(H) = 1.2U_{eq} (CH, CH_2 and NH) or 1.5U_{eq} (CH_3) was used.

Crystal data for the structure of **2d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 286042. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: C44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

[(2-Phenylimidazol-4-yl)methylene]propanedioic acid (**2a**).

2-Phenylimidazole-4-carbaldehyde (0.005 mol), finely powdered malonic acid (0.015 mol) and piperidine (5 drops) were heated in methanol (10 ml) to reflux for 3 hours. White crystals of product were precipitating during heating. After cooling the crude product was collected by filtration and washed with methanol (5 ml). No further purification was necessary. Yield 78%, mp 226–229 °C; ^{1}H nmr (DMSO-d_6): δ 7.52 (t, 1H, J = 7.0, Ar*H*), 7.59 (t, 2H, J = 7.6, Ar*H*), 7.75 (s, 1H, –C*H*=), 7.93 (s, 1H, H_{im}), 7.99 (d, 2H, J = 8.2, Ar*H*), 14.02 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 122.4, 125.9, 128.5, 129.4, 130.1, 132.2, 146.9, 166.7, 169.0; ir (neat): 3112, 2565, 1715, 1608, 1575, 1476, 1414, 1362, 1330, 1295, 1226, 1139, 1098, 960, 853, 821, 774, 703, 679 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.5; H, 3.9; N, 10.9. Found: C, 60.3; H, 4.0; N, 11.1.

2-[(2-Phenylimidazol-4-yl)methylene]cyclohexanone (**2g**).

2-Phenylimidazole-4-carbaldehyde (0.001 mol) and cyclohexane (0.003 mol) were mixed in 5 ml of methanol. The resulting mixture was heated to 40°C and subsequently 2 ml of sodium hydroxide solution (10% wt. in water) were added dropwise during 30 minutes. The reaction mixture was stirred at r. t. and followed on TLC (ethyl acetate). The end of reaction was indicated by a disappearance of starting aldehyde. The reaction was quenched with water and extracted twice with 10 ml of ethyl acetate. Organic extract was washed with water and dried with sodium sulphate. After filtration and evaporation of solvent at reduced pressure, the residue was afforded to column chromatography (silica gel, ethyl acetate). Yield 64%, mp 200–202 °C; ^{1}H nmr (DMSO-d_6): δ 1.82–1.89 (m, 4H, 2 × CH_2), 2.45 (t, 2H, J = 5.5, CH_2), 2.70 (m, 1H), 3.06 (m, 1H), 7.41 + 7.64 (2 × s, 2H, –C*H*=, H_{im}), 7.45 (t, 1H, J = 6.7, Ar*H*), 7.53 (t, 2H, J = 7.3, Ar*H*), 8.02 (d, 2H, J = 7.9, Ar*H*), 12.98 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 22.6, 22.8, 28.5, 39.5, 77.7, 100.2, 125.2, 128.7, 128.8, 130.0, 132.0, 143.1, 147.1, 198.9; ms: (m/z) 252 (M$^+$, 100), 223 (22), 195 (33), 104 (17), 93 (13), 77 (11); ir (neat): 3278, 2936, 2438, 1658, 1567, 1452, 1385, 1275, 1197, 1149, 1070, 918, 834, 707, 691 cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.2; H, 6.4; N, 11.1. Found: C, 75.9; H, 6.2; N, 11.1.

General Procedure for Method A.

2-Phenylimidazole-4-carbaldehyde (0.005 mol) and methylene compound (0.005 mol) were mixed in 5 ml of methanol. Piperidine (2 drops) and glacial acetic acid (2 drops) were added. The mixture was stirred at r. t. and the reaction was monitored on TLC (ethyl acetate). The end of reaction was indicated by a disappearance of starting aldehyde. After evaporation of solvent at reduced pressure, the crude product was purified by column chromatography (silica gel, ethyl acetate).

Diethyl [(2-phenylimidazol-4-yl)methylene]propanedioate (**2b**).

Prepared from **1** and diethyl malonate by method A as light yellow powder, yield 94%, mp 144–146 °C; ^{1}H nmr (DMSO-d_6): δ 1.29 (t, 6H, J = 7.1, CH_3), 4.25 (q, 2H, J = 7.1, CH_2), 4.37 (q, 2H, J = 7.1, CH_2), 7.45 (t, 1H, J = 7.1, Ar*H*), 7.53 (t, 2H, J = 7.5, Ar*H*), 7.60 (s, 1H, –C*H*=), 7.87 (s, 1H, H_{im}), 7.97 (d, 2H, J = 7.9, Ar*H*), 13.09 (s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 13.8, 14.1, 60.6, 60.7, 108.2, 120.8, 125.2, 128.9, 129.0, 129.8, 133.0, 135.7, 147.4, 164.2, 166.2; ms: (m/z) 314 (M$^+$, 93), 268 (78), 240 (8.3), 223 (72), 196 (100), 168 (18), 140 (15), 104 (21), 77 (9.8); ir (neat): 3245, 2974, 1725, 1661, 1626, 1475, 1404, 1375, 1272, 1244, 1204, 1128, 1070, 780, 694, 655 cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.9; H, 5.8; N, 8.9. Found: C, 64.8; H, 5.9; N, 8.9.

Ethyl (2*E*)-2-cyano-3-(2-phenylimidazol-4-yl)propenoate (**2c**).

Prepared from **1** and ethyl cyanoacetate by method A as light yellow crystals, yield 52%, mp 162–165 °C; ^{1}H nmr (DMSO-d_6): δ 1.32 (t, 3H, J = 7.1, CH_3), 4.30 (q, 2H, J = 7.1, CH_2), 7.47 (t, 1H, J = 7.3, Ar*H*), 7.54 (t, 2H, J = 7.5, Ar*H*), 8.06 (d, 2H, J = 7.3, Ar*H*), 8.21 (s, 1H, –C*H*=), 8.22 (s, 1H, H_{im}), 13.50 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 14.1, 61.8, 96.4, 116.1, 125.7, 129.0, 129.2, 129.6, 131.2, 134.8, 145.8, 148.8, 163.0; ms: (m/z) 267 (M$^+$, 100),

239 (6.8), 220 (60), 194 (51), 166 (8.1), 140 (9.5), 104 (25), 77 (15), 64 (17); ir (neat): 3301, 2225, 1676, 1600, 1372, 1268, 1230, 1113, 1095, 1018, 951, 785, 761, 742, 712, 693, 658 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.4; H, 4.9; N, 15.7. Found: C, 67.4; H, 4.9; N, 15.9.

3-[(2-Phenylimidazol-4-yl)methylene]pentane-2,4-dione (**2d**).

Prepared from **1** and acetyl acetone using method A as yellow powder, yield 63%, mp 177–178 °C; ^{1}H nmr (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.40 (t, 1H, J = 7.4, Ar*H*), 7.49 (t, 2H, J = 7.7, Ar*H*), 7.53 (s, 1H, –C*H*=), 7.75 (s, 1H, H_{im}), 7.95 (d, 2H, J = 7.9, Ar*H*), 13.14 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 26.1, 31.9, 125.0, 125.6, 129.2, 129.4, 130.0, 131.6, 136.3, 138.4, 148.1, 197.3, 205.3; ms: (m/z) 254 (M^+, 100), 239 (37), 221 (16), 211 (21), 197 (82), 183 (18), 169 (41), 104 (26), 77 (14); ir (neat): 3201, 1705, 1631, 1593, 1485, 1368, 1272, 1226, 1176, 1122, 992, 952, 900, 789, 714, 700, 658 cm^{-1}.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.9; H, 5.6; N, 11.0. Found: C, 70.9; H, 5.6; N, 11.1.

2,2-Dimethyl-5-[(2-phenylimidazol-4-yl)methylene]-1,3-dioxane-4,6-dione (**2e**).

Prepared from **1** and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) using method A as bright yellow crystals, yield 92%, mp 210.5–212.5 °C; ^{1}H nmr (DMSO-d_6, 350 K): δ 1.78 (s, 6H, CH_3), 7.55 (t, 1H, J = 7.2, Ar*H*), 7.60 (t, 2H, J = 7.2, Ar*H*), 8.08 (d, 2H, J = 8.4, Ar*H*), 8.44 + 8.77 (2 × s, 2H, –C*H*=, H_{im}), 13.45 (br s, 1H, N*H*); ir (neat): 3210, 1694, 1551, 1505, 1454, 1388, 1346, 1285, 1267, 1202, 1171, 1077, 1006, 900, 782, 705, 683 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.4; H, 4.9; N, 9.5.

5-[(2-Phenylimidazol-4-yl)methylene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**2f**)

Prepared from **1** and pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (barbituric acid) by method A as orange-yellow powder, yield 95%, mp 182 °C decomp.; ^{1}H nmr (DMSO-d_6): δ 7.46–7.67 (br s, 3H, Ar*H*), 8.07 (d, 2H, J = 7.0, Ar*H*), 8.35 + 8.60 (2 × br s, 2H, –C*H*=, H_{im}), 11.26–11.48 (br s, 2H, $N_{amid}H$), 13.91 (br s, 1H, $N_{imid}H$); ir (neat): 2989, 2815, 1749, 1703, 1651, 1559, 1538, 1507, 1390, 1346, 1220, 1174, 1079, 1019, 844, 775, 708 cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.6; H, 3.6; N, 19.8. Found: C, 59.4; H, 3.6; N, 19.7.

General Procedure for Method B.

2-Phenylimidazole-4-carbaldehyde (0.001 mol) and methylene compound (0.001 mol) were mixed in 5 ml of methanol. Sodium methoxide (0.2 g) was added and the reaction mixture was stirred at 60°C under stream of argon until tlc (ethyl acetate) showed reaction completion. Afterwards, the reaction mixture was poured into cold water (10 ml) and stirred for 15 minutes. Crude product was collected by filtration and purified by column chromatography (silica gel, ethyl acetate).

(2*Z*)-2-phenyl-3-(2-phenylimidazol-4-yl)propennitrile (**2h**).

Prepared from **1** and benzyl cyanide using method B as yellow crystals, yield 62%, mp 197.5–199.5 °C; ^{1}H nmr (DMSO-d_6): δ 7.40 (t, 1H, J = 7.3, Ar*H*), 7.45 (t, 1H, J = 7.4, Ar*H*), 7.51 (t, 2H, J = 7.8, Ar*H*), 7.54 (t, 2H, J = 7.8, Ar*H*), 7.75 (d, 2H, J = 7.2, Ar*H*) 7.89 (s, 1H, –C*H*=), 7.99 (s, 1H, H_{im}), 8.09 (d, 2H, J = 7.6, Ar*H*), 13.23 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 105.6, 118.6, 122.7, 125.3, 125.5, 128.5, 129.0, 129.1, 129.3, 129.8, 134.3, 135.2, 137.1, 147.1; ms: (m/z) 271 (M^+, 100), 168 (18), 140 (28), 114 (10), 104 (15), 77 (11); ir (neat): 3036, 2658, 2207, 1592, 1456, 1406, 1280, 1193, 1152, 1109, 963, 884, 754, 717, 684 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}N_3$: C, 79.7; H, 4.8; N, 15.5. Found: C, 79.6; H, 5.0; N, 15.5.

(2*Z*)-3-(2-phenylimidazol-4-yl)-2-pyridin-2-ylpropennitrile (**2i**).

Prepared from **1** and 2-pyridylacetonitrile by method B as orange-yellow solid, yield 95%, mp 179–180 °C; ^{1}H NMR (DMSO-d_6) 7.41 (t, 1H, J = 6.6, Ar*H*), 7.47 (t, 1H, J = 7.4, Ar*H*), 7.56 (t, 2H, J = 7.5, Ar*H*), 7,88 (d, 1H, *J* = 7.9, Ar*H*), 7.95 (t, 1H, J = 8.6, Ar*H*), 8.09 (d, 2H, J = 8.4, Ar*H*) 8.11 (s, 1H, H_{im}), 8.43 (s, 1H, –C*H*=), 8.67 (d, 1H, J = 4.6, Ar*H*), 12.85 (br s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) 104.9, 118.1, 119.9, 123.0, 125.4, 126.4, 128.9, 129.0, 129.7, 135.5, 136.2, 137.7, 147.7, 149.6, 151.3; ms: (m/z) 272 (M^+, 44), 271 (100), 168 (9.4), 142 (23), 114 (5.4), 104 (14), 77 (6.0); ir (neat): 3063, 2216, 1604, 1588, 1564, 1457, 1429, 1279, 1192, 1141, 1099, 776, 706, 688, 655.

Anal. Calcd. for $C_{17}H_{12}N_4$: C, 75.0; H, 4.4; N, 20.6. Found: C, 74.8; H, 4.4; N, 20.6.

Acknowledgements.

Authors gratefully acknowledge The Ministry of Education, Youth and Sports of Czech Republic for financial support (grant no. MSM0021627501). One of the authors (Z.T.) would like to thank The Ministry of Education, Youth and Sports for financial support (grant no. MSM6198959218).

REFERENCES

[1] E. Knoevenagel, *Chem. Ber.*, **31**, 2585 (1898).
[2] G. Jones, *Org. React.*, **15**, 204 (1967).
[3] R. Tanikaga, N. Konya, K. Hamamura and A. Kaji, *Bull. Chem. Soc. Jpn.*, **61**, 3211 (1988).
[4] S. Murahashi, T. Naota, H. Taki, M. Mizuno, H. Takaya, S. Komiya, Y. Mizuho, N. Oyasato, M. Hiraoka, M. Hirano and A. Fukuoka, *J. Am. Chem. Soc.*, **117**, 12436 (1995).
[5] J. Yadav, B. Subba Reddy, A. Basak, B. Visali, A. Narsaiah and K. Nagaiah, *Eur. J. Org. Chem.*, **3**, 546 (2004).
[6] E. Anselmi, J. Blazejewski and C. Wakselman, *J. Fluorine Chem.*, **107**, 315 (2001).
[7] R. Kitbunnadaj, O. Zuiderveld and B. Christophe, *J. Med. Chem.*, **47**, 2414 (2004).
[8] R. Silvestri, M. Artico, R. La Regina, A. Di Pasquali, G. De Martino, F. D. D`Auria, L. Nencioni and A. T. Palamara, *J. Med. Chem.*, **47**, 3924 (2004).
[9] F. Bureš and J. Kulhánek, *Tetrahedron:Asymmetry*, **16**, 1347 (2005).
[10] I. Sirkar, G. Bobowski, J. Bristol, R. Weishaar and D. Evans, *J. Med. Chem.*, **29**, 261 (1986).
[11] H. McNab and C. Thornley, *J. Chem. Soc., Perkin Trans. I*, 2203 (1997).
[12] P. Langer, M. Doring, D. Seyferth and H. Gorls, *Eur. J. Org. Chem.*, **2003**, 1948 (2003).
[13] H. Cho, T. Iwashita, M. Hamaguchi and Y. Oyama, *Chem. Pharm. Bull.*, **39**, 3341 (1991).
[14] U. Costantino, M. Curini, F. Montanari, M. Nocchetti and O. Rosati, *J. Mol. Cat. A-Chem.*, **195**, 245 (2003).
[15] P. Rolf, J. A. Brockman, W. A. Hallett, J. W. Hanifin, M. E. Tarrant, L. W. Torley, F. M. Callahan, P. F. Fabio, B. D. Johnson, R. H. Lenhard, R. E. Schaub and A. Wissner, *J. Med. Chem.*, **28**, 1704 (1985).
[16] R. Kupfer, M. Nagel, E. Wuerthwein and R. Allmann, *Chem. Ber.*, **118**, 3089 (1985).

[17] D. Davison and S. Bernhard, *J. Am. Chem. Soc*., **70**, 3426 (1948).

[18] S. Braun, H.-O. Kalinowski and S. Berger, 150 and More Basic NMR Experiments, Wiley-VCH, Weinheim, 1997, pp 117-131.

[19] Oxford Diffraction (2005). CrysAlis CCD and CrysAlis RED software (Ver. 1.171.24), Oxford Diffraction Ltd., Abingdon, Oxfordshire, England.

[20] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo,A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr*., **32**, 115 (1999).

[21] L. J. Farrugia: WinGX (Ver. 1.70.00), *J. Appl. Crystallogr*., **32**, 837 (1999).

[22] G. M. Sheldrick: SHELX-97. Programs for Crystal Structure Analysis (Release 97–2), University of Göttingen, Germany, 1997.