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# SYNTHESIS OF DERIVATIVES OF 2-AMINOIMIDAZOLE AND 2-IMINOIMIDAZOLIDINE BY CYCLIZATION OF 1-ARYL-2-(4,6-DIMETHYLPYRIMIDIN-2-YL)GUANIDINES WITH α-BROMOCARBONYL COMPOUNDS

**A. S. Shestakov[1]*, I. S. Bushmarinov[2], O. E. Sidorenko[1], Kh. S. Shikhaliev[1], and M. Yu. Antipin[2]**

*Cyclization of 1-aryl-2-(4,6-dimethylpyrimidin-2-yl)guanidines with α-bromoacetophenone and ethyl bromoacetate gave derivatives of 1,4-diphenyl-1H-imidazole-2-amine and 2-amino-1-phenylimidazolidin-4-one respectively. The mechanism of the reaction was determined on the basis of quantum-chemical calculations, NOESY NMR spectroscopy, and X-ray crystallography.*

**Keywords**: 2-aminoimidazole, 1-aryl-2-(4,6-dimethylpyrimidin-2-yl)guanidines, 2-iminoimidazoidine, phenacyl bromide, ethyl bromoacetate, *ab initio* calculations, NOESY, X-ray crystallography, cyclization.

2-Aminoimidazole and its derivatives have been the center of attention for the last two decades for specialists in the field of organic synthesis. The reason for this is the antiviral and anticancer activity observed in alkaloids isolated from the marine sponge *Leucetta*. The structural bases of these alkaloids are derivatives of 1-R-2-aminoimidazole [1-4].

Among the preparative methods for preparing 2-aminoimidazole and its derivatives the interaction of α-bromoacetophenone with derivatives of aminoguanidines [5, 6] or acylguanidines [7, 8] are preferred. 2-Aminopyimidine may be considered as a structural analog of cyclic guanidines, alkylation of which with α-bromoacetophenones with subsequent recyclation leads to good yields of the required 2-aminoimidazoles [9, 10].

The basic problem associated with the preparation of derivatives of 2-aminoimidazole on the basis of substituted guanidines is the presence in the structure of the latter of three reactive nucleophilic nitrogen atoms, which gives rise to a mixture of regioisomers. As it turned out, the use of N'-aryl-N''-(4,6-dimethylpyrimidin-2-yl)guanidines in reaction with phenacylbromides and ethyl bromoacetate led to the regioselective synthesis of derivatives 2-aminoimidazole.

* To whom correspondence should be addressed, e-mail: schas@vmail.ru.

[1]Voronezh State University, Universitestskaya Pl., 1, Voronezh 394006, Russia.
[2]A. N. Nesmeyanov Institute of Organoelement Compounds, 28 Vavilova Str., Moscow 119991, Russia; e-mail: bush_i@yandex.ru.

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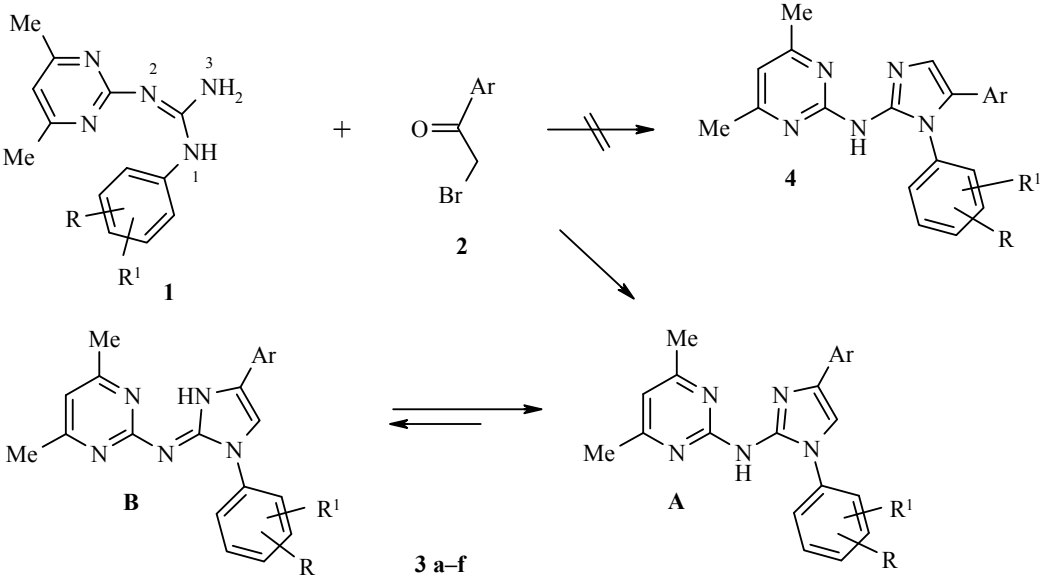
The 1-aryl-2-(4,6-dimethylpyrimidin-2-yl)guanidines **1** used in this work were obtained in good yield by the reaction of 4,6-dimethylpyrimidin-2-ylcyanamide with arylamines [11, 12] or arylbiguanides with pentane-2,4-dione [13, 14].

As a preliminary we carried out quantum-chemical calculations of the geometry and electronic structure of the guanidines **1** using the GAUSSIAN 03 complex program [15]. The calculations were carried out by the functional density method using the B3LYP function. Complete optimization of the geometry of the molecules was carried out in the 3-21G* basis set. Calculation of the electronic structures was carried out in the 6-31G* basis set. The choice of basis sets and the method of calculation were determined by the circumstance that further increase in the precision of the calculation did not lead to significant change in the values of the energies of the highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO).

The calculations showed that the region where the wave function of the HOMO differed from zero was concentrated on atoms N(1) and N(3). So, with orbital control of the reaction these two atoms should participate in the formation of the ring.

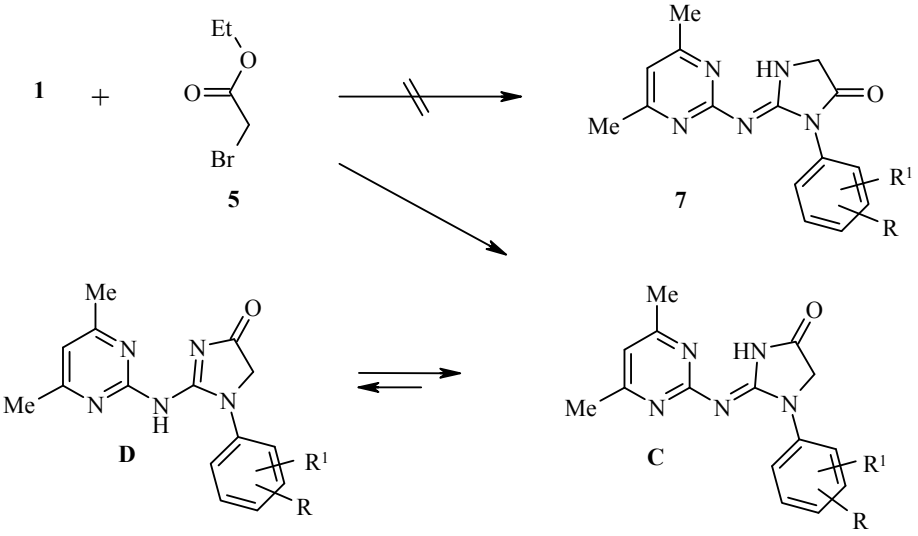
Heating of α-bromoacetophenones **2** with guanidines **1** in dioxane for 8-10 h led to the formation of the corresponding 2-aminoimidazoles **3**. The excess guanidine acted as acceptor for the hydrogen bromide liberated and could be easily regenerated.



**3 a** R = R$^1$ = H, Ar = *p*-Br$C_6H_4$, **b** R = *m*-Me, R$^1$ = *p*-Me, Ar = *p*-Et$C_6H_4$, **c** R = *m*-Me, R$^1$ = *p*-Me, Ar = *p*-Br$C_6H_4$, **d** R = H, R$^1$ = *o*-Br, Ar = *p*-Et$C_6H_4$, **e** R = H, R$^1$ = *p*-Cl, Ar = 2-naphthyl, **f** R = H, R$^1$ = *p*-O-Ph, Ar = Ph

Strictly speaking, the products of this reaction, along with 1,4-diaryl-1H-imidazole-2-amine **3,** are 5 other isomeric 2-aminoimidazoles, but the quantum-chemical calculations described above allowed us to exclude four of the six possible cyclization products, and to discuss only compounds **3** and **4**. Analysis of the literature data showed that the interaction of α-bromoacetophenones **2** with heterocyclic amidines [16, 17], 2-aminopyridines [28, 29], 2-aminopyrimidines [9, 10], and 2-aminoimidazoles [20-22], the carbon atom in compound **2** bonded to the bromine atom invariably formed a bond with the endocyclic nitrogen atom in the heterocyclic starting material. Subsequent interaction of the carbonyl carbon atom with exocyclic nitrogen atom led to the formation of an annelated imidazole. It may be suggested that in our case the interaction of guanidine **1** with the α-bromoacetophenone begins with electrophilic attack at the secondary atom N(1) and concludes with the formation of a bond between the carbonyl carbon atom and the primary atom N(3) to give formation of compound **3**.

To confirm these suggestions we the used the NOESY experiment. In the spectrum of compound **3c** intense correlation peaks were observed at δ 7.19/9.20 and 7.24/9.20 ppm which corresponded to the interaction of the phenyl group *ortho* protons with the imidazole fragment proton. This interaction is possible only for the regioisomer **3**. The data of this experiment, namely, the presence of cross peaks at 7.19/9.20 and 7.24/9.20 ppm permitted the conclusion that this isomer existed in the tautomeric form **A**. In fact such spin interactions are only possible for the *ortho* protons of the phenyl groups and the proton on the exocyclic nitrogen atom.

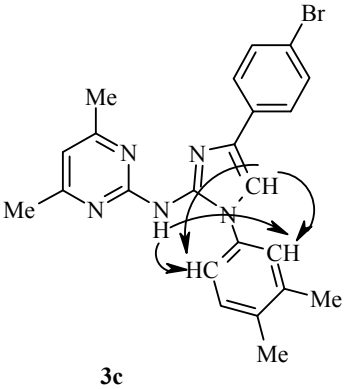


**6 a–e**

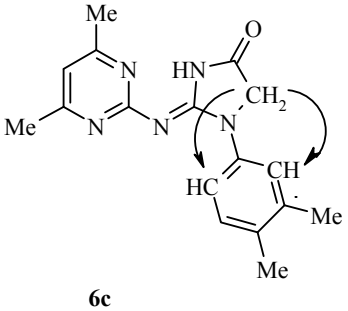
**6 a** R = H, $R^1$ = *p*-Me, **b** R = H, $R^1$ = *p*-MeO, **c** R = *m*-Me, $R^1$ = *p*-Me,
**d** R = *o*-Cl, $R^1$ = *p*-Cl, **e** R = *m*-Cl, $R^1$ = *p*-F

The other possible asymmetric two-carbon electrophile is ethyl bromoacetate **5**, which on reaction with guanidine **1** gave 2-iminoimidazolidin-4-ones **6**. As with phenacyl bromide, the reaction occurred with a two-fold molar excess of the guanidine.

The formation of the regioisomer **6** (and not **7**) was confirmed by the result of the NOESY experiment, as in the previous example. The interaction of the methylene protons with the protons of the *ortho*-phenyl group, which is possible only for the iminoimidazolidinone **6**, is expressed by the presence of intense correlation peaks at δ 4.44/7.47 and 4.44/7.63 ppm in the spectrum of compound **6c**.



**3c**



**6c**

TABLE 1. Characteristics of Compounds **3a-f** and **6a-c**

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **3a** | $C_{21}H_{18}BrN_5$ | 59.88 / 60.01 | 4.38 / 4.32 | 16.54 / 16.66 | 225-227 | 71 |
| **3b** | $C_{25}H_{27}N_5$ | 75.67 / 75.54 | 6.77 / 6.85 | 17.60 / 17.62 | 209-210 | 81 |
| **3c** | $C_{23}H_{22}BrN_5$ | 61.69 / 61.61 | 4.87 / 4.95 | 15.63 / 15.62 | 234-236 | 66 |
| **3d** | $C_{23}H_{22}BrN_5$ | 61.52 / 61.61 | 5.02 / 4.95 | 15.51 / 15.62 | 192-193 | 55 |
| **3e** | $C_{25}H_{20}ClN_5$ | 70.62 / 70.50 | 4.79 / 4.73 | 16.34 / 16.44 | 235-236 | 76 |
| **3f** | $C_{27}H_{23}N_5O$ | 74.81 / 74.81 | 5.42 / 5.35 | 16.12 / 16.15 | 180-181 | 64 |
| **6a** | $C_{16}H_{17}N_5O$ | 64.95 / 65.07 | 5.83 / 5.80 | 23.82 / 23.71 | 197-198 | 64 |
| **6b** | $C_{16}H_{17}N_5O_2$ | 61.67 / 61.72 | 5.47 / 5.50 | 22.42 / 22.49 | 171-172 | 59 |
| **6c** | $C_{17}H_{19}N_5O$ | 65.89 / 66.00 | 6.04 / 6.19 | 22.69 / 22.64 | 153-154 | 56 |
| **6d** | $C_{15}H_{13}Cl_2N_5O$ | 51.52 / 51.45 | 3.81 / 3.74 | 19.93 / 20.00 | 208-209 | 34 |
| **6e** | $C_{15}H_{13}ClFN_5O$ | 53.97 / 53.98 | 3.99 / 3.93 | 21.09 / 20.98 | 195-196 | 52 |

TABLE 2. $^1$H NMR Spectra of Compounds **3a-f** and **6a-c**

| Compound | Chemical shifts, δ, ppm (*J*, Hz)* |
|---|---|
| **3a** | 2.09 (6H, s, $2CH_3$); 6.42 (1H, s, H-5 Pyr); 7.30 (1H, t, *J* = 7.5, H-4 Ar); 7.36-7.49 (4H, m, Ar); 7.58 (2H, d, *J* = 8.8, H-3,5 Ar'); 7.76 (2H, d, *J* = 8.8, H-2,6 Ar'); 7.98 (1H, s, H-4 Im); 9.28 (1H, s, NH) |
| **3b** | 1.21 (3H, t, *J* = 7.6, $CH_3$); 2.12 (6H, s, $2CH_3$); 2.20 (6H, s, $2CH_3$); 2.61 (2H, q, *J* = 7.6, $CH_2$); 6.46 (1H, s, H-5 Pyr); 7.14 (2H, d, *J* = 7.5, H-3,5 Ar'); 7.19-7.28 (3H, m, H-2,5,6 Ar); 7.69 (1H, s, H-4 Im); 7.72 (2H, d, *J* = 7.5, H-2,6 Ar'); 9.07 (1H, s, NH) |
| **3c** | 2.11 (6H, s, $2CH_3$); 2.18 (6H, s, $2CH_3$); 6.44 (1H, s, H-5 Pyr); 7.13 (2H, d, *J* = 9.5, H-5,6 Ar); 7.24 (1H, s, H-2 Ar); 7.55 (2H, d, *J* = 8.2, H-3,5 Ar'); 7.75 (2H, d, *J* = 8.2, H-2,6 Ar'); 7.90 (1H, s, H-4 Im); 9.20 (1H, s, NH) |
| **3d** | 1.25 (3H, t, *J* = 7.6, $CH_3$); 2.19 (6H, s, $2CH_3$); 2.66 (2H, q, *J* = 7.6, $CH_2$); 6.31 (1H, s, H-5 Pyr); 7.15 (2H, d, *J* = 7.7, H-3,5 Ar'); 7.21 (1H, d, *J* = 7.8, H-6 Ar); 7.31 (1H, t, *J* = 7.6, H-4 Ar); 7.45 (1H, s, H-4 Im); 7.51 (1H, d, *J* = 7.8, H-3 Ar); 7.63-7.69 (3H, m, H-5 Ar + H-2,6 Ar'); 9.09 (1H, s, NH) |
| **3e** | 2.12 (6H, s, $2CH_3$); 6.46 (1H, s, H-5 Pyr); 7.41-7.57 (6H, m, H Ar); 7.82-8.05 (5H, m, H Ar); 8.31 (1H, s, H-4 Im); 9.32 (1H, s, NH) |
| **3f** | 2.14 (6H, s, $2CH_3$); 6.42 (1H, s, H-5 Pyr); 6.89 (2H, d, *J* = 7.6, H Ar); 6.98 (2H, d, *J* = 7.7, H Ar); 7.11 (1H, t, *J* = 7.5, H Ar); 7.19 (1H, t, *J* = 7.6, H Ar); 7.33 (4H, m, H Ar); 7.46 (2H, d, *J* = 7.6, H Ar); 7.68 (1H, s, H-4 Im); 7.79 (2H, d, *J* = 7.5, H Ar); 9.09 (1H, s, NH) |
| **6a** | 2.33 (3H, s, $CH_3$); 2.39 (6H, s, $2CH_3$); 4.41 (2H, s, $CH_2$); 6.70 (1H, s, H-5 Pyr); 7.18 (2H, d, *J* = 8.7, H-3,5 Ar); 7.71 (2H, d, *J* = 8.7, H-2,6 Ar); 11.47 (1H, br. s, NH) |
| **6b** | 2.40 (6H, s, $2CH_3$); 3.81 (3H, s, $OCH_3$); 4.42 (2H, s, $CH_2$); 6.69 (1H, s, H-5 Pyr); 6.93 (2H, d, *J* = 8.8, H-3,5 Ar); 7.71 (2H, d, *J* = 8.6, H-2,6 Ar); 11.62 (1H, br. s, NH) |
| **6c** | 2.20 (3H, s, $CH_3$); 2.23 (3H, s, $CH_3$); 2.34 (6H, s, $2CH_3$); 4.44 (2H, s, $CH_2$); 6.78 (1H, s, H-5 Pyr); 7.14 (1H, d, *J* = 8.5, H-6 Ar); 7.47 (1H, s, H-2 Ar); 7.63 (1H, d, *J* = 8.0, H-5 Ar); 11.44 (1H, br. s, NH) |
| **6d** | 2.41 (6H, s, $2CH_3$); 4.40 (2H, s, $CH_2$); 6.72 (1H, s, H-5 Pyr); 7.46 (2H, d, *J* = 9.2, H-6 Ar); 7.59 (1H, s, H-3 Ar); 7.68 (1H, d, *J* = 9.4, H-5 Ar); 11.65 (1H, br. s, NH) |
| **6e** | 2.42 (6H, s, $2CH_3$); 4.46 (2H, s, $CH_2$); 6.69 (1H, s, H-5 Pyr); 7.27 (1H, m, H Ar); 7.94 (1H, m, H Ar); 8.28 (1H, m, H Ar); 11.77 (1H, br. s, NH) |

* Im – imidazolyl.

The absence of cross-peaks, corresponding to the interaction of the proton of the exocyclic nitrogen atom and the *ortho* protons of the phenyl group allows the conclusion that compound **6** exists in the tautomeric form **C**. The presence in character and disposition of the signals of the NH protons in the spectra of compounds **6** and **3** is in complete agreement with this suggestion. Thus the proton on the exocyclic nitrogen atom of compound **3** gives a sufficiently narrow singlet in the 9.05-9.35 ppm range. The broad signal of the proton on this nitrogen atom in compound **6** is found at a weaker field (11.40-11.80 ppm).

A final confirmation that compounds **6** are formed during the course of the reaction between guanidines **1** and ethyl bromoacetate **5** was provided by the X-ray crystallographic data for compounds **6a** and **6c** (Fig. 1).

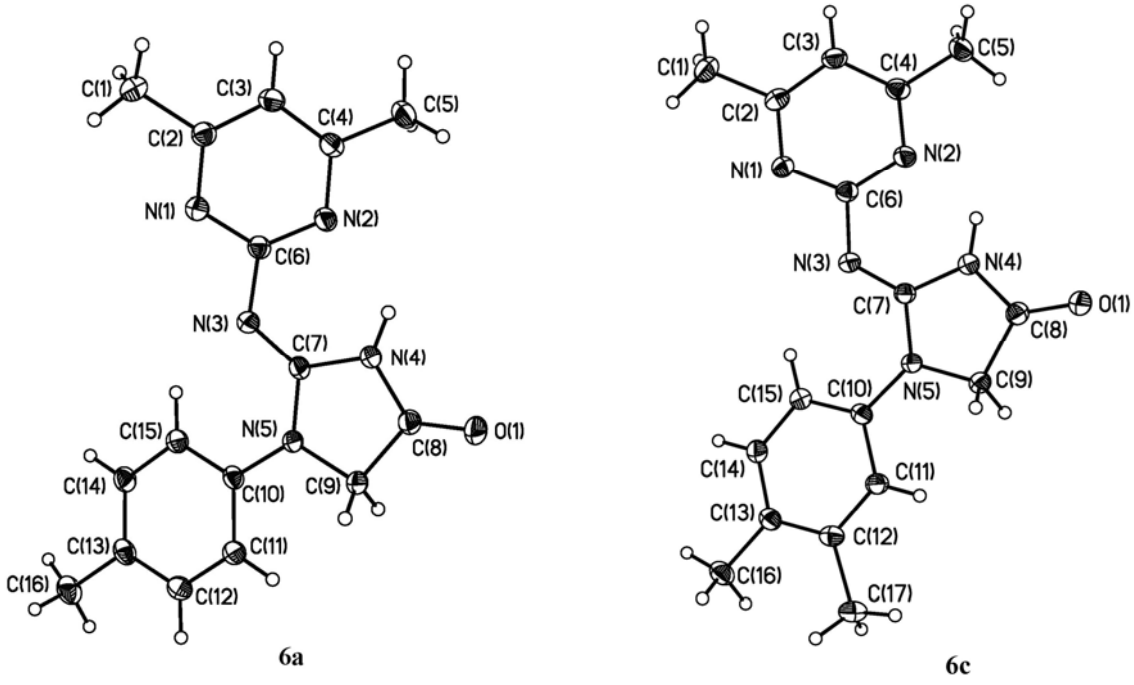



Fig. 1. General view of molecules **6a** and **6c** in the crystals. Atoms are shown as thermal ellipsoids ($p$ = 50%).

Compounds **6a** and **6c** crystallized as crystal hydrates containing one molecule of dioxane for two molecules of compound. The parameters of the unit cells of compounds **6a** and **6c** are close (Table 3) which is explained by the very similar character of the crystal packing in the crystals of these compounds. The bond lengths in both compounds are close and demonstrate typical values for C–C, C–N and C=O (Table 4). In both compound **6a** and compound **6c** the rotation angles of the phenyl and imidazole units are not large and equal 6-7°, whereas the rotation angles of the pyrimidine unit relative to the imidazole ring are considerably larger, 40.8(2)° in compound **6a** and 29.8(2)° in compound **6c**. In the crystals of both compounds the hydrogen atom H(4N) forms a forked hydrogen bond, participating in an intramolecular interaction with atom N(2) and an intermolecular interaction with atom O(1). The remaining spatial contacts in the crystals are exhausted by weak van der Waals interactions.

## EXPERIMENTAL

$^1$H NMR spectra were recorded with a Bruker AC-300 (300 MHz) in DMSO-$d_6$ at 20°C with TMS as internal standard, and 2D $^1$H NMR spectra with a Bruker DRX-500 (500 MHz) in DMSO-$d_6$ at 20°C. Purity of

synthesized compounds and the course of experiments were monitored by TLC on Merck UV-254 plates (20:1 chloroform–methanol as eluent).

TABLE 3. Basic Crystallographic Data and Refinement Parameters of Compounds **6a** and **6c**

| | **6a** | **6c** |
|---|---|---|
| Empirical formula | $C_{16}H_{17}N_5O_2 \cdot 0.5C_4H_8O_2$ | $C_{17}H_{19}N_5O \cdot 0.5C_4H_8O_2$ |
| *M* | 339.40 | 353.42 |
| T, K | 120 | 120 |
| Crystal system | Triclinic | Triclinic |
| Space group | *P*-1 | *P*-1 |
| *Z* | 2 | 2 |
| *a*, Å | 7.2819(7) | 7.2350(15) |
| *b*, Å | 10.9886(10) | 10.909(2) |
| *c*, Å | 11.1754(11) | 11.645(2) |
| α, deg. | 73.387(2) | 100.613(4) |
| β, deg. | 77.977(2) | 104.681(5) |
| γ, deg. | 89.190(2) | 92.587(4) |
| *V*, Å$^3$ | 837.12(14) | 869.8(3) |
| $d_{calc}$, g·cm$^{-3}$ | 1.346 | 1.349 |
| μ, cm$^{-1}$ | 0.92 | 0.91 |
| *F*(000) | 360 | 376 |
| $2\theta_{max}$, deg. | 58 | 58 |
| Number of reflections | | |
| measured | 9556 | 9923 |
| independent | 4631 | 4791 |
| with $I>2\sigma(I)$ | 4022 | 3923 |
| Number of parameters refined | 229 | 243 |
| *R*1 | 0.0538 | 0.0568 |
| *wR*2 | 0.1601 | 0.1603 |
| *GOOF* | 1.002 | 1.000 |
| Residual electron density e·Å$^{-3}$ ($d_{min}/d_{max}$) | 0.664/-0.350 | 0.501/-0.273 |

TABLE 4. Basic Bond Lengths (*l*) in Compounds **6a** and **6c**

| Bond | *l*, Å | |
|---|---|---|
| | **6a** | **6c** |
| O(1)–C(8) | 1.2176(14) | 1.2156(16) |
| N(1)–C(2) | 1.3385(15) | 1.3401(16) |
| N(1)–C(6) | 1.3485(15) | 1.3462(16) |
| N(2)–C(6) | 1.3425(14) | 1.3469(16) |
| N(2)–C(4) | 1.3484(14) | 1.3501(16) |
| N(3)–C(7) | 1.2853(14) | 1.2897(16) |
| N(3)–C(6) | 1.3908(14) | 1.3936(15) |
| N(4)–C(8) | 1.3627(15) | 1.3621(16) |
| N(4)–C(7) | 1.4004(13) | 1.3967(16) |
| N(5)–C(7) | 1.3737(14) | 1.3771(15) |
| N(5)–C(10) | 1.4146(13) | 1.4176(15) |
| N(5)–C(9) | 1.4581(13) | 1.4600(16) |

Table 5. Bond Angles (ω) in Compounds **6a** and **6c**

| Angle | ω, deg | |
|---|---|---|
| | **6a** | **6c** |
| C(2)–N(1)–C(6) | 116.13(10) | 116.41(11) |
| C(6)–N(2)–C(4) | 116.59(10) | 116.83(11) |
| C(7)–N(3)–C(6) | 121.63(10) | 121.24(11) |
| C(8)–N(4)–C(7) | 112.56(9) | 112.88(10) |
| C(7)–N(5)–C(10) | 128.14(9) | 128.55(10) |
| C(7)–N(5)–C(9) | 110.70(9) | 110.36(10) |
| C(10)–N(5)–C(9) | 120.86(9) | 120.63(10) |
| N(1)–C(2)–C(3) | 121.72(10) | 121.59(12) |
| N(1)–C(2)–C(1) | 116.85(10) | 117.75(12) |
| N(2)–C(4)–C(3) | 121.08(11) | 121.04(12) |
| N(2)–C(4)–C(5) | 116.73(10) | 117.40(11) |
| N(2)–C(6)–N(1) | 126.43(10) | 126.01(11) |
| N(2)–C(6)–N(3) | 119.93(10) | 113.65(11) |
| N(1)–C(6)–N(3) | 113.57(10) | 120.31(11) |
| N(3)–C(7)–N(5) | 124.21(10) | 124.34(11) |
| N(3)–C(7)–N(4) | 128.81(10) | 128.61(11) |
| N(5)–C(7)–N(4) | 106.90(9) | 107.02(10) |
| O(1)–C(8)–N(4) | 127.11(11) | 127.01(12) |
| O(1)–C(8)–C(9) | 126.52(10) | 126.91(11) |
| N(4)–C(8)–C(9) | 106.37(9) | 106.08(10) |
| N(5)–C(9)–C(8) | 103.14(9) | 103.35(9) |
| C(11)–C(10)–N(5) | 118.16(10) | 117.96(11) |
| C(15)–C(10)–N(5) | 123.03(10) | 123.36(11) |

**X-ray Crystallographic Investigation of Compounds 6a and 6c.** Monocrystals of compounds **6a** and **6c**, suitable for X-ray crystallography, were obtained from dioxane. Low temperature X-ray diffraction studies of the compounds were carried out with a SMART APEX 1000 CCD diffractometer (MoKα-radiation, graphite monochromator, ω-scanning). The structures were determined by direct methods and refined by least squares analysis in the anisotropic complete matrix approximation with $F^2_{hkl}$. Hydrogen atoms by geometric considerations and refined by the "riding" model, with the exception of the hydrogen atoms of the NH groups which were found from a difference Fourier map. The structures of compounds **6a** and **6c** have been deposited in the Cambridge Structure Database (deposits CCDC 762873 and 762874 respectively). All calculations were carried out with the SHELXTL PLUS complex of programs [23].

**N-(1,4-Diaryl-1H-imidazol-2-yl)-4,6-dimethylpyrimidine-2-amines 3a-f (General Method)**. A solution of the corresponding guanidine **1** (20 mmol) and the corresponding phenacyl bromide **2** (11 mmol) in dioxane (40 ml) was heated at 90°C for 10 h. The guanidine hydrobromide which precipitated on cooling was filtered off and the filtrate was evaporated. The residue was recrystallized from a mixture of 2-propanol and DMF, to give N-[4-(4-bromophenyl)-1-phenyl-1H-imidazol-2-yl]-4,6-dimethylpyrimidine-2-amine (**3a**), N-[1-(3,4-dimethylphenyl)-4-(4-ethylphenyl)-1H-imidazol-2-yl]-4,6-dimethylpyrimidine-2-amine (**3b**), N-[4-(4-bromophenyl)-1-(3,4-dimethylphenyl)-1H-imidazol-2-yl]-4,6-dimethylpyrimidine-2-amine (**3c**), N-[1-(2-bromophenyl)-4-(4-ethylphenyl)-1H-imidazol-2-yl]-4,6-dimethylpyrimidine-2-amine (**3d**), 4,6-dimethyl-N-[1-(4-chlorophenyl)-4-(2-naphthyl)-1H-imidazol-2-yl]pyrimidine-2-amine (**3e**), and 4,6-dimethyl-N-[1-(4-phenoxyphenyl)-4-phenyl-1H-imidazol-2-yl]-pyrimidine-2-amine (**3f**).

**2-[4,6-Dimethylpyrimidin-2-yl)imino]-1-phenylimidazolidin-4-ones 6a-e (General Method).** The ester **5** (1.2 ml, 11 mmol) was added dropwise to a solution of the corresponding guanidine **1** (20 mmol) in dioxane (40 ml) and the mixture was heated at 90°C for 5 h. The guanidine hydrobromide which separated on cooling was filtered off and the filtrate was evaporated. The residue was recrystallized twice from 2-propanol to give 2-[(4,6-dimethylpyrimidin-2-yl)imino]-1-*p*-tolylimidazolidin-4-one (**6a)**, 2-[(4,6-dimethylpyrimidin-2-yl)-

imino]-1-(3-methoxyphenyl)imidazolidin-4-one (**6b**), 1-(3,4-dimethylphenyl)-2-[(4,6-dimethylpyrimidin-2-yl)-imino]imidazolidin-4-one (**6c**), [1-(2,4-dichlorophenyl)-2-(4,6-dimethylpyrimidin-2-yl)imino]imidazolidin-4-one (**6d**), and 2-[(4,6-dimethylpyrimidin-2-yl)imino]-1-(3-chloro-4-fluorophenyl)imidazolidin-4-one (**6e**).

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