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LETTERS TO THE EDITOR

Synthesis of *N*,6-Diaryl-2-imino-4-methyl-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamides

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The Biginelli reaction [1–3] has been recognized as a key method to prepare the substituted 3,4-dihydropyrimidine-2(1*H*)-ones(thiones); such compounds have exhibited antiviral [4], antitumor [5], anti-inflamematory [6], anti-tubercular [7], and antimicrobial [8] activity. In view of this, further development of this reaction as a facile, convenient, and safe procedure to prepare new low-toxic potentially biologically active pyrimidine derivatives is of special interest [9–12].

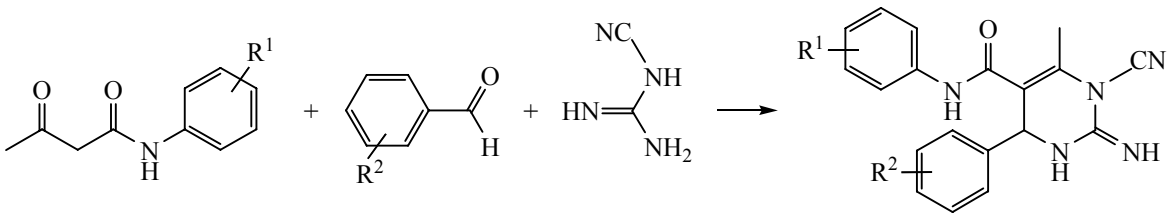
The Biginelli reaction involving cyanoguanidine has been only once described [5]; the reaction has been performed in the presence of catalytic amount of *para*-toluenesulfonic acid to yield 35% of 2-imino-4-methyl-3-cyano-6-phenyl-*N*-2-chlorophenyl-1,2,3,6-tetrahydropyrimidine-5-carboxamide.

Keeping in mind the high pharmaceutical importance of pyrimidine derivatives and potential antitumor activity of cyano-containing compounds [13], in this work we studied the interaction of acetoacetic acid *N*-arylamides with cyanoguanidine and aromatic aldehydes in order to elaborate the preparative procedure of cyanopyrimidines synthesis avoiding any toxic compounds.

It was found that the reaction occurred in bulk in the absence of any catalyst to afford *N*,6-diaryl-2-imino-4-methyl-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamides **I**–**X** with yields of 69–78% (Scheme 1).

The compounds **I**–**X** were colorless of lightly colored substances soluble in DMSO, DMF, acetic acid, and ethanol but insoluble in water. The products structures were confirmed by means of ^{1}H NMR, ^{13}C NMR, and IR spectroscopy as well as mass spectrometry. Splitting of the signals of pyrimidine protons in positions 1 and 6 evidenced the reaction

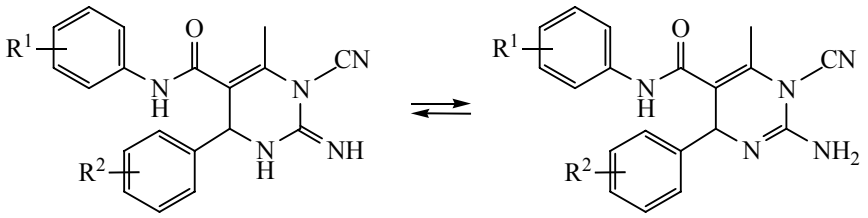
Scheme 1.



I–**X**

R^1 = H, R^2 = H (**I**), 2-Cl (**II**), 4-MeO (**III**), 3-NO_2 (**IV**), 2-MeO (**V**), 2,5-$(MeO)_2$ (**VI**), 4-OH (**VII**); R^1 = 2-Me, R^2 = H (**VIII**), 4-OH (**IX**), 2-Cl (**X**).

Scheme 2.



A **B**

regioselectivity. The doublet ^{1}H NMR signal of the NH proton in position 1 of the pyrimidine cycle confirmed that the products **I**–**X** were formed exclusively in the tautomeric form **A** (Scheme 2).

Mass spectra of compound **I** and **II** contained the peaks of molecular and fragment ions corresponding to the suggested structure.

The obtained data demonstrated that the nature of the substituent in the aromatic ring of the acetoacetic acid arylamide had no significant effect on the reaction course. As far as the substituents in the aromatic aldehyde ring are concerned, the electron-acceptor ones increased the product yield (**II**, **IV**, and **X**), whereas the electron-donor ones decreased the yield (**III**, **V**, and **VI**).

In summary, we have developed a facile one-pot method to prepare *N*,6-diaryl-2-imino-4-methyl-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamides involving no expensive catalysts, toxic solvents or reactants; the procedure can be used for preparative synthesis of new biologically active pyrimidine derivatives.

2-Imino-4-methyl-*N*,6-diphenyl-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamide (I) *(general procedure)*. A mixture of 1.77 g (0.01 mol) of acetoacetanilide, 1 mL (0.01 mol) of benzaldehyde, and 0.84 g (0.01 mol) of cyanoguanidine was heated at 120–150°C during 5–10 min. The formed crystals were filtered off and washed with ethanol. Yield 2.45 g (74%), colorless crystals, mp 236–238°C (EtOH). IR spectrum, ν, cm^{-1}: 1612 (C=C), 1664 (CON), 2288 (C≡N), 3192 (NH), 3310 (C=NH). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.08 s (3H, 4-CH_3), 5.46 d (1H, H^6, *J* 3.3), 7.03 t (1H, H^4_{Ph}, *J* 7.4), 7.25 d (2H, $H^{2,6}_{Ph}$, *J* 7.4), 7.28 t (2H, $H^{3,5}_{Ph}$, *J* 7.4), 7.30 t (2H, $H^{3',5'}_{Ph}$, *J* 7.6,), 7.37 t (1H, $H^{4'}_{Ph}$, *J* 7.5), 7.53 d (2H, $H^{2',6'}_{Ph}$, *J* 7.6), 8.87 d (1H, N^{1}H, *J* 3.3), 9.69 s (1H, N^{2}H), 9.70 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 16.8 (C^4H_3), 38.8 (C^6H), 54.7 (C–C≡N), 108.1 (C^5); 119.9, 123.3, 126.6, 128.0, 128.8, 128.9, 135.5, 139.0 (C_{Ph}), 142.9 (C^4), 164.8 (NHCO), 163.0 (C^2). Mass spectrum, *m/z* (I_{rel}, %): 331 (12) [*M*]$^+$, 239 (66) [*M*-C_6H_5NH]$^+$, 120 (20) [C_6H_5NHCO]$^+$, 92 (14) [C_6H_5NH]$^+$, 77 (66) [Ph]$^+$. Found, %: C 68.99; H 5.26; N 21.02. $C_{19}H_{17}N_5O$. Calculated, %: C 68.87; H 5.17; N 21.13.

Compounds **II**–**X** were prepared similarly.

2-Imino-4-methyl-*N*-phenyl-6-(2-chlorophenyl)-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamide (II). Yield 2.85 g (78%), colorless crystals, mp 245–247°C (EtOH). IR spectrum, ν, cm^{-1}: 1616 (C=C), 1688 (CON), 2288 (C≡N), 3384 (NH), 3416 (C=NH). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J,* Hz): 2.01 s (3H, 4-CH_3), 5.79 d (1H, H^6, *J* 3.3), 7.01 t (1H, H^4_{Ph}, *J* 7.3), 7.24 t (2H, $H^{3,5}_{Ph}$, *J* 7.4), 7.37 d (2H, $H^{2,6}_{Ph}$, *J* 7.4), 7.40 d (1H, H^3, ArCl, *J* 7.8), 7.30 t (1H, H^4, ArCl, *J* 7.8), 7.33 t (1H, H^5, ArCl, *J* 7.8), 7.49 d (1H, H^6, ArCl, *J* 7.8), 8.74 d (1H, N^{1}H, *J* 3.3), 9.64 s (1H, N^{2}H), 9.67 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 365 (4) [*M*]$^+$, 245 (7) [*M* – C_6H_5NHCO]$^+$, 135 (32) [*M* – C_6H_5NHCO – ClC_6H_4]$^+$, 120 (92) [C_6H_5NHCO]$^+$, 77 (26) [Ph]$^+$. Found, %: C 62.10; H 4.49; N 19.27. $C_{19}H_{16}ClN_5O$. Calculated, %: C 62.38; H 4.41; N 19.14.

2-Imino-4-methyl-*N*-phenyl-6-(4-methoxyphenyl)-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamide (III). Yield 2.34 g (64%). Colorless crystals, mp 254–256°C (EtOH). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J,* Hz): 2.05 s (3H, 4-CH_3), 3.66 s (3H, CH_3O), 5.34 d (1H, H^6, *J* 3.1), 6.92 d (2H, $H^{2,6}_{Ph}$, *J* 8.7), 7.02 t (1H, H^4_{Ph}, *J* 8.5), 7.21 d (2H, H^{3,5}, CH_3OPh, *J* 8.7), 7.25 t (2H, $H^{3,5}_{Ph}$, *J* 8.5), 7.54 d (2H, H^{2,6}, CH_3OPh, *J* 8.6), 8.76 d (1H, N^{1}H, *J* 3.1), 9.72 s (1H, N^{2}H), 9.76 s (1H, NH). Found, %: C 66.60; H 5.22; N 19.49. $C_{20}H_{19}N_5O_2$. Calculated, %: C 66.47; H 5.30; N 19.38.

2-Imino-4-methyl-*N*-phenyl-6-(3-nitrophenyl)-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamide (IV). Yield 3.35 g (89%). Yellow crystals, mp 203–205°C (EtOH). IR spectrum, ν, cm^{-1}: 1608 (C=C), 1680 (CON), 2288 (C≡N), 3256 (NH), 3408 (C=NH). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J,* Hz): 2.12 s

(3H, C^4H_3), 5.58 d (1H, H^6, *J* 3.0), 7.03 t (1H, H^4_{Ph}, *J* 7.4), 7.26 t (2H, $H^{3,5}_{Ph}$, *J* 7.5), 7.50 d (2H, $H^{2,6}_{Ph}$, *J* 7.4), 7.70 t (1H, H^3, NO_2Ph, *J* 7.7), 7.76 d (1H, H^6, NO_2Ph, *J* 7.7), 8.17 d (1H, H^4, NO_2Ph, *J* 7.6), 8.19 s (1H, H^2, NO_2Ph), 9.10 d (1H, N^1H, *J* 3.0), 9.84 s (1H, N^2H), 9.94 s (1H, NH). Found, %: C 60.51; H 4.37; N 22.45. $C_{19}H_{16}N_6O_3$. Calculated, %: C 60.63; H 4.28; N 22.33.

2-Imino-4-methyl-*N*-phenyl-6-(2-methoxyphenyl)-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamide (V). Yield 2.30 g (64%), colorless crystals, mp 260–262°C (EtOH). ^1H NMR spectrum (500 MHz), δ, ppm (*J,* Hz): 2.05 s (3H, 4-CH_3), 3.65 s (3H, CH_3O), 5.65 d (1H, H^6, *J* 3.1), 6.95 t (1H, H^4_{Ph}, *J* 7.4), 7.00 t (2H, $H^{3,5}_{Ph}$, *J* 7.4), 7.14 d (2H, $H^{2,6}_{Ph}$, *J* 7.4), 7.25 t (1H, H^4, CH_3OPh, *J* 8.0), 7.28 t (1H, H^5, CH_3OPh, *J* 7.8), 7.57 d (2H, $H^{3,6}$, CH_3OPh, *J* 7.9), 8.55 d (1H, N^1H, *J* 3.1), 9.65 s (1H, N^2H), 9.75 s (1H, NH). Found, %: C 66.57; H 5.38; N 19.51. $C_{20}H_{19}N_5O_2$. Calculated, %: C 66.47; H 5.30; N 19.38.

2-Imino-4-methyl-*N*-phenyl-6-(2,5-dimethoxyphenyl)-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamide (VI). Yield 2.69 g (69%), colorless crystals, mp 247–249°C (EtOH). ^1H NMR spectrum (100 MHz), δ, ppm (*J,* Hz): 1.99 s (3H, 4-CH_3), 3.62 s and 3.76 s (6H, $2CH_3O$), 5.57 d (1H, H^6, *J* 3.1), 6.61–7.45 m [8H, C_6H_5, $(CH_3O)_2\underline{C_6H_3}$)], 8.45 d (1H, N^1H, *J* 3.1), 9.56 s (1H, N^2H), 9.65 s (1H, NH). Found, %: C 64.55; H 5.32; N 18.02. $C_{21}H_{21}N_5O_3$. Calculated, %: C 64.44; H 5.41; N 17.89.

2-Imino-4-methyl-*N*-phenyl-6-(4-hydroxyphenyl)-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamide (VII). Yield 2.53 g (70%), pale-yellow crystals, mp 270–272°C (EtOH). IR spectrum, ν, cm^{-1}: 1600 (C=C), 1676 (CON), 2288 (C≡N), 3104 (NH), 3328 (C=NH), 3664 (OH). ^1H NMR spectrum (500 MHz), δ, ppm (*J,* Hz): 2.06 s (3H, 4-CH_3), 5.35 d (1H, H^6, *J* 3.3), 6.73 d (2H, Ph, *J* 7.5), 7.02 t (1H, Ph, *J* 7.4), 7.09 d (2H, $H^{2,6}$, HOPh, *J* 8.5), 7.26 t (2H, Ph, *J* 7.6), 7.53 d (2H, $H^{3,5}$, HOPh, *J* 8.7), 8.82 d (1H, N^1H, *J* 3.3), 9.40 s (1H, N^2H), 9.60 s (1H, NH), 9.72 s (1H, OH). Found, %: C 65.59; H 5.02; 20.03. $C_{19}H_{17}N_5O_2$. Calculated, %: C 65.70; H 4.93; N 20.16.

2-Imino-4-methyl-*N*-2-methylphenyl-6-phenyl-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamide (VIII). Yield 2.35 g (68%), colorless crystals, mp 265–267°C (EtOH). IR spectrum, ν, cm^{-1}: 1600 (C=C), 1676 (CON), 2288 (C≡N), 3104 (NH), 3328 (C=NH). ^1H NMR spectrum (500 MHz), δ, ppm (*J,* Hz): 1.85 s (3H, 4-CH_3); 2.05 s (3H, $\underline{CH_3}C_6H_4$), 5.80 d (1H, H^6, *J* 3.3), 7.05 t (1H, Ph, *J* 7.6), 7.10 d (2H, Ph, *J* 7.4), 7.40 d (2H, Ar, *J* 7.4), 7.34 t (2H, Ar, *J* 7.4), 7.46 t (2H, Ph, *J* 7.6), 8.85 d (1H, N^1H, *J* 3.3), 9.35 s (1H, N^2H), 9.70 s (1H, NH). Found, %: C 69.55; H 5.45; N 20.16. $C_{20}H_{19}N_5O$. Calculated, %: C 69.55; H 5.54; N 20.28.

2-Imino-4-methyl-*N*-2-methylphenyl-6-(4-hydroxyphenyl)-3-cyano-1,2,3,6-tetrahydropyrimidine-5-carboxamide (IX). Yield 2.53 g (70%), pale-yellow crystals, mp 270–272°C (EtOH). IR spectrum, ν, cm^{-1}: 1600 (C=C), 1676 (CON), 2288 (C≡N), 3104 (NH), 3328 (C=NH), 3664 (OH). ^1H NMR spectrum (300 MHz), δ, ppm (*J,* Hz): 1.89 s (3H, 4-CH_3), 2.13 s (3H, $\underline{CH_3}C_6H_4$), 5.35 d (1H, H^6, *J* 3.3), 6.74–7.14 m (8H, $CH_3\underline{C_6H_4}$, $HO\underline{C_6H_4}$), 8.82 d (1H, N^1H, *J* 3.3), 9.19 s (1H, OH), 9.49 s (1H, N^2H), 9.65 s (1H, NH). Found, %: C 66.34; H 5.39; N 19.49. $C_{20}H_{19}N_5O_2$. Calculated, %: C 66.47; H 5.30; N 19.38.

2-Imino-4-methyl-3-cyano-*N*-2-methylphenyl-6-(2-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-5-carboxamide (X). Yield 3.15 g (83%), colorless crystals, mp 274–276°C (EtOH). IR spectrum, ν, cm^{-1}: 1610 (C=C), 1648 (CON), 2288 (C≡N), 3150 (NH), 3348 (C=NH). ^1H NMR spectrum (300 MHz), δ, ppm (*J,* Hz): 1.85 s (3H, 4-CH_3), 2.08 s (3H, $\underline{CH_3}C_6H_4$), 5.84 d (1H, H^6, *J* 3.0), 7.05–7.45 m (8H, $CH_3\underline{C_6H_4}$, ClC_6H_4), 8.89 d (1H, N^1H , *J* 3.0), 9.35 s (1H, N^2H), 9.76 s (1H, NH). Found, %: C 63.36; H 4.86; N 18.57. $C_{20}H_{18}ClN_5O$. Calculated, %: C 63.24; H 4.78; N 18.44.

IR spectra of the compounds suspensions in mineral oil were recorded on a Specord M-80 spectrometer. ^1H NMR spectra of the solutions in DMSO-d_6 were recorded on Bruker 500 (500.13 MHz), Bruker 300 (300 MHz), BS-567A (100 MHz) spectrometers with TMS as internal reference. ^{13}C NMR spectra of the solutions in DMSO-d_6 were recorded using a Bruker-300 (75 MHz) spectrometer. Mass spectra were obtained using a Finnigan MAT INCOS-50 instrument under conditions of electron ionization at 70 eV. Elemental analysis was performed using a Perkin Elmer 2400 instrument. Melting points were determined using an M-565 device.

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