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NEW DIRECTION IN THE REACTION OF THIOCARBOXAMIDES WITH N-SUBSTITUTED MALEIMIDES

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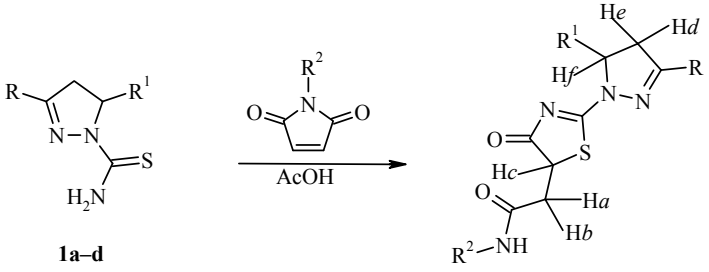
The reaction of both aliphatic and aromatic thioamide derivatives with N-substituted maleimides under various conditions leads to the formation of complex polycyclic systems [1, 2]. No information is available on the reaction of N-arylmaleimides with heterocyclic thiocarboxamide derivatives.

We have found that the reaction of 1-aminothiocarbonyl-3,5-diarylpyrazolines **1a-1d** [2] with N-substituted maleimides upon heating for 10 min in acetic acid at reflux leads to N-aryl-2-[2-(3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-yl]acetamides **2a-d** in high yield. This reaction permits broad variation of the substituents R, R^1, and R^2 in the pyrazolinothiazolone molecules **2**, which allows us to synthesize large combinatorial libraries of such compounds.



1a–d **2a–d**

1 a R = R^1 = Ph, **b** R = 4-$MeOC_6H_4$, R^1 = 4-MeC_6H_4, **c** R = 4-FC_6H_4, R^1 = 3-ClC_6H_4, **d** R = 2-C_4H_3S, R^1 = Ph; **2 a** R = R^1 = R^2 = Ph, **b** R = 4-$MeOC_6H_4$, R^1 = 4-MeC_6H_4, R^2 = 4-F, 3-ClC_6H_3, **c** R = R^2 = 4-FC_6H_4, R^1 = 3-ClC_6H_4, **d** R = 2-C_4H_3S, R^1 = Ph, R^2 = 3-$MeOC_6H_4$

The structure of products **2a-d** was indicated by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

The ^1H and ^{13}C NMR spectra were taken on a Varian Mercury VX-200 spectrometer at 200 and 50 MHz, respectively, in $CDCl_3$ with TMS as the internal standard. The IR spectra were taken on a Perkin Elmer One FTIR spectrometer for KBr pellets. The electron impact mass spectra were taken on a Varian 1200L mass spectrometer at 70 eV.

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Pyrazolines **1a-c** were prepared according to Rezessy et al. [3] and pyrazoline **1d** was prepared according to Kaplancikli et al. [4].

Acetamides 2a-d (General Method). A mixture of (1 mmol) 1-aminothiocarbonyl-3,5-diaryl-4,5-dihydro-1H-pyrazole **1** and N-arylmaleimide (1 mmol) in acetic acid (0.8 ml) was heated at reflux for 10 min. The reaction mixture was cooled and diluted with acetone (10 ml). The precipitate of acetamide **2** was filtered off, washed with acetone, and dried in the air.

N-Phenyl-2-[2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-yl]acetamide (2a) was obtained in 75% yield; mp 259-260°C (acetone). IR spectrum, ν, cm^{-1}: 1532, 1602, 1681, 3318. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.65 (1H, dd, ^3J = 11.3, ^2J = 16.5, H*a*); 3.21 (1H, dd, ^3J = 3.7, ^2J = 16.5, H*b*); 3.38 (1H, dd, ^3J = 4.0, ^2J = 18.3, H*d*); 4.11 (1H, dd, ^3J = 11.3, ^2J = 18.3, H*e*); 4.39 (1H, dd, ^3J = 3.7, ^3J = 11.3, H*c*); 5.80 (1H, dd, ^3J = 4.0, ^3J = 11.3, H*f*); 7.0-7.9 (15H, m, ArH); 10.1 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 40.0, 43.2, 50.1, 63.4, 119.1, 123.1, 125.3, 127.0, 127.5, 128.3, 128.5, 128.6, 129.6, 131.1, 138.5, 140.1, 160.3, 168.2, 176.8, 187.5. Found, %: N 12.40. $C_{26}H_{22}N_4O_2S$. Calculated, %: N 12.33.

N-(3-Chloro-4-fluorophenyl)-2-[2-(3-(4-methoxyphenyl)-5-*p*-tolyl-4,5-dihydro-1H-pyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-yl]acetamide (2b) was obtained in 72% yield, mp 247-248°C (acetone). IR spectrum, ν, cm^{-1}: 1510, 1541, 1608, 1677, 3307. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 2.72 (1H, dd, ^3J = 11.0, ^2J = 16.4, H*a*); 3.21 (1H, dd, ^3J = 3.5, ^2J = 6.4, H*b*); 3.28 (1H, dd, ^3J = 4.0, ^2J = 18.0, H*d*); 3.83 (3H, s, CH_3O); 4.06 (1H, dd, ^3J = 11.1, ^2J = 18.0, H*e*); 4.37 (1H, dd, ^3J = 3.5, ^3J = 11.0, H*c*); 5.74 (1H, dd, ^3J = 4.0, ^3J = 11.1, H*f*); 7.0-8.0 (12H, m, ArH); 10.36 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 550 $[M]^+$ (2), 378 (14), 224 (19), 145 (23), 117 (64), 55 (100). Found, %: N 10.22. $C_{28}H_{24}ClFN_4O_3S$. Calculated, %: N 10.17.

N-(4-Fluorophenyl-2-[2-(5-(3-chlorophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-yl]acetamide (2c) was obtained in 68% yield; mp 278-279° (acetone). IR spectrum, ν, cm^{-1}: 1508, 1533, 1674, 1693, 3273, 3297. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.72 (1H, dd, ^3J = 11.1, ^2J = 16.4, H*a*); 3.15 (1H, dd, ^3J = 3.6, ^2J = 16.4, H*b*); 3.5 (1H, dd, ^3J = 4.0, ^2J = 18.0, H*d*); 4.10 (1H, dd, ^3J = 11.1, ^2J = 18.0, H*e*); 4.4 (1H, dd, ^3J = 3.6, ^3J = 11.1, H*c*); 5.8 (1H, dd, ^3J = 4.0, ^3J = 11.1, H*f*); 7.0-8.0 (12H, m, ArH); 10.15 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 524 $[M]^+$ (16), 386 (100), 258 (20), 211 (16), 162 (26), 137 (24), 121 (24), 110 (38). Found, %: N 10.78. $C_{26}H_{19}ClF_2N_4O_2S$. Calculated, %: N 10.67.

N-(3-Methoxyphenyl)-2-[2-(5-phenyl-3-(2-thienyl)-4,5-dihydro-1H-pyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-yl]acetamide (2d) was obtained in 70% yield; mp 273-274°C (acetone). IR spectrum, ν, cm^{-1}: 1533, 1615, 1679, 1703, 3319. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.70 (1H, dd, ^3J = 11.3, ^2J = 16.4, H*a*); 3.21 (1H, dd, ^3J = 3.5, ^2J = 16.4, H*b*); 3.40 (1H, dd, ^3J = 3.9, ^2J = 18.0, H*d*); 3.80 (3H, s, CH_3O); 4.12 (1H, dd, ^3J = 11.1, ^3J = 18.0, H*e*); 4.38 (1H, dd, ^3J = 3.5, ^3J = 11.3, H*c*); 5.78 (1H, dd, ^3J = 3.9, ^3J = 11.1, H*f*); 6.6-7.9 (13H, m, ArH); 10.1 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 490 $[M]^+$ (10), 340 (74), 227 (17), 203 (17), 176 (27), 149 (44), 103 (100). Found, %: N 11.47. $C_{25}H_{22}N_4O_3S_2$. Calculated, %: N 11.42.

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