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4-Functionally Substituted 3-Heterylpyrazoles: XIII.* 3-Aryl(heteryl)-4-(4-pyrazolyl)-1,2,3,4-tetrahydropyrimidin-2-ones(thiones)

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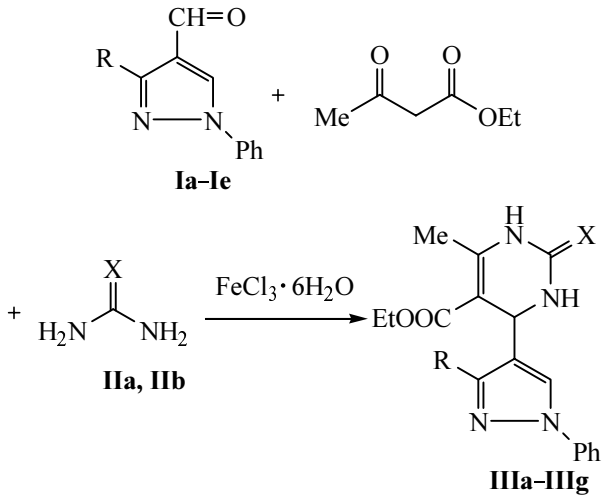
Abstract—Cyclocondesation of 3-aryl(heteryl)pyrazole-4-carbaldehydes with ethyl acetoacetate and urea (thiourea) in the presence of $FeCl_3 \cdot 6H_2O$ afforded 3-aryl(heteryl)-4-(4-pyrazolyl)-1,2,3,4-tetrahydropyrimidin-2-ones(thiones).

Some 1,2,3,4-tetrahydropyrimidin-2-one derivatives were found to exhibit pronounced hypotensive activity and negative inotropic effect [2–5]. The simplest and most convenient approach to such compounds is based on the Biginelli reaction which implies one-step three-component condensation of aromatic or aliphatic aldehydes, β-keto esters, and urea under strongly acidic conditions. This reaction leads to formation of the corresponding alkyl 4-aryl(alkyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates [6]. Among heterocyclic aldehydes, only thiophene-2-carbaldehyde was involved in such condensations [7, 8].

The present communication describes the results of our studies on the synthesis of new 1,2,3,4-tetrahydropyrimidin-2-one derivatives having pyrazolyl substituents in position *4* of the pyrimidine ring. Our attempts to isolate condensation products in reactions of 3-aryl(heteryl)pyrazole-4-carbaldehydes **Ia**–**Ie** with ethyl acetoacetate and urea in the presence of a catalytic amount of concentrated hydrochloric acid were unsuccessful. On the other hand, pyrazole-4-carbaldehydes were used previously to build up bicyclic ensembles consisting of pyrazole and 1,4-dihydropyridine [9] or dihydropyrazole rings [10].

Taking into account recently reported data [11] on the use of iron(III) chloride hexahydrate as catalyst in the Biginelli reaction, we tried to apply an analogous procedure to the syntheses with aldehydes **I**. In fact, by heating a mixture of aldehyde **Ia**–**Ie**, ethyl acetoacetate, urea (**IIa**) or thiourea (**IIb**), and $FeCl_3 \cdot 6H_2O$ at a ratio of 1:1:2:0.6 in boiling ethanol for 3 h we obtained ethyl 3-aryl(heteryl)-2-oxo-4-(4-pyrazolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates **IIIa**–**IIIe** and their 2-thioxo analogs **IIIf** and **IIIg** in 52–66% yield (Scheme 1).

Scheme 1.



I, R = Ph (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 2-thienyl (**e**); **II**, X = O (**a**), S (**b**); **III**, X = O, R = Ph (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 2-thienyl (**e**); X = S, R = Ph (**f**), 4-ClC_6H_4 (**g**).

Compounds **IIIa**–**IIIg** (Tables 1, 2) are colorless high-melting crystalline substances. Their IR spectra contain strong absorption bands due to stretching vibrations of the carbonyl groups in the pyrimidine ring (1675–1690 cm^{-1}) (compounds **IIIa**–**IIIe**) and ester fragment

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Table 1. Yields, melting points, and elemental analyses of ethyl 3-aryl(heteryl)-2-oxo(thioxo)-4-(4-pyrazolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates **IIIa**–**IIIg**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	52	205–207	68.30	5.29	13.71	$C_{23}H_{22}N_4O_3$	68.64	5.51	13.92
IIIb	56	227–229	62.89	4.94	12.61	$C_{23}H_{21}ClN_4O_3$	63.23	4.84	12.82
IIIc	66	222–224	69.55	5.59	13.19	$C_{24}H_{24}N_4O_3$	69.21	5.81	13.45
IIId	60	216–217	66.43	5.68	12.77	$C_{24}H_{24}N_4O_4$	66.65	5.59	12.95
IIIe	61	207–209	61.41	5.06	13.57	$C_{21}H_{20}N_4O_3S$	61.75	4.94	13.72
IIIf	55	211–213	65.60	5.10	13.04	$C_{23}H_{22}N_4O_2S$	66.01	5.30	13.39
IIIg	57	243–244	61.36	4.46	12.11	$C_{23}H_{21}ClN_4OS$	60.90	4.67	12.37

Table 2. IR and ^{1}H NMR spectra of ethyl 3-aryl(heteryl)-2-oxo(thioxo)-4-(4-pyrazolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates **IIIa**–**IIIg**

Comp. no.	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm
	C=O	N–H	
IIIa	1690, 1760	3250, 3350	0.82 t (3H, CH_3), 2.25 s (3H, CH_3), 3.76–3.84 m (2H, CH_2), 5.40 s (1H, CH), 7.31–7.98 m (11H, H_{arom}, NH), 8.35 s (1H, 5-H), 9.14 s (1H, NH)
IIIb	1685, 1755	3240, 3330	0.88 t (3H, CH_3), 2.26 s (3H, CH_3), 3.77–3.84 m (2H, CH_2), 5.35 s (1H, CH), 7.28–7.86 m (10H, H_{arom}, NH), 8.23 s (1H, 5-H), 9.10 s (1H, NH)
IIIc	1685, 1760	3250, 3320	0.83 t (3H, CH_3), 2.25 s (3H, CH_3), 2.36 s (3H, CH_3), 3.79–3.86 m (2H, CH_2), 5.38 s (1H, CH), 7.29–7.89 m (10H, H_{arom}, NH), 8.32 s (1H, 5-H), 9.15 s (1H, NH)
IIId	1675, 1765	3220, 3360	0.88 t (3H, CH_3), 2.26 s (3H, CH_3), 3.72–3.78 m (2H, CH_2), 3.83 s (3H, CH_3O), 5.37 s (1H, CH), 6.99–7.82 m (10H, H_{arom}, NH), 8.17 s (1H, 5-H), 9.07 s (1H, NH)
IIIe	1680, 1750	3250, 3360	0.87 t (3H, CH_3), 2.29 s (3H, CH_3), 3.80–3.84 m (2H, CH_2), 5.51 s (1H, CH), 7.17–7.78 m (9H, H_{arom}, NH), 8.36 s (1H, 5-H), 9.22 s (1H, NH)
IIIf	1760	3320, 3380	0.82 t (3H, CH_3), 2.28 s (3H, CH_3), 3.78–3.82 m (2H, CH_2), 5.44 s (1H, CH), 7.35–7.92 m (10H, H_{arom}), 8.18 s (1H, 5-H), 9.24 s (1H, NH), 10.01 s (1H, NH)
IIIg	1755	3300, 3390	0.83 t (3H, CH_3), 2.28 s (3H, CH_3), 3.79–3.85 m (2H, CH_2), 5.37 s (1H, CH), 7.38–7.86 m (9H, H_{arom}), 8.38 s (1H, 5-H), 9.72 s (1H, NH), 10.29 s (1H, NH)

(1755–1750 cm^{-1}), as well as of NH groups (3220–3390 cm^{-1}). In the ^{1}H NMR spectra of the products we observed signals typical of substituents in the pyrimidine and pyrazole rings, a singlet from proton in position *4* of the pyrimidine ring (δ 5.35–5.51 ppm), and a singlet from 5-H in the pyrazole ring (δ 8.17–8.38 ppm). The spectral data do not contradict the assumed structure.

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-20 instrument. The ^{1}H NMR spectra were measured on a Varian Gemini spectrometer (300 MHz) from solutions in DMSO-d_6 using TMS as internal reference.

Ethyl 3-aryl(heteryl)-2-oxo-4-(4-pyrazolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates IIIa–IIIe and ethyl 3-aryl(heteryl)-4-(4-pyrazolyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates IIIf and IIIg. A suspension of 0.01 mol of aldehyde **Ia**–**Ie**, 0.02 mol of urea (**IIa**) or thiourea (**IIb**), 1.3 g (0.01 mol) of ethyl acetoacetate, and 0.81 g (0.006 mol) of $FeCl_3 \cdot 6\ H_2O$ in 40 ml of ethanol was heated for 3 h under reflux. The precipitate was filtered off, washed with 50 ml of ethanol and 50 ml of water, dried, and recrystallized from glacial acetic acid.

REFERENCES

1. Bratenko, M.K., Chornous, V.A., and Vovk, M.V., *Russ. J. Org. Chem*., 2003, vol. 39, p. 893.
2. Kastron, V.V., Vitolinya, R.O., Khanina, E.L., Dubur, G.Ya., and Kimenis, A.A., *Khim.-Farm. Zh*., 1987, p. 948.

3. Vitolinya, R.O. and Kimenis, A.A., *Khim.-Farm. Zh*., 1989, p. 285.
4. Atwal, K.S., Rovnyak, G.C., Kimball, D.S., Floyd, D.M., Moreland, S., Swanson, B.N., Gougoutas, J.Z., Schwarts, J., Smillie, K.M., and Malley, M.F., *J. Med. Chem*., 1990, vol. 33, p. 2629.
5. Atwal, K.S., Swanson, B.N., Unger, S.E., Floyd, D.M., Moreland, S., Hedberg, and O'Reilly, B.C., *J. Med. Chem*., 1991, vol. 34, p. 806.
6. Kappe, C.O., *Tetrahedron*, 1993, vol. 49, p. 6937.
7. Kappe, C.O. and Falsone, S.F., *Synlett*, 1998, p. 718.
8. Ramalinya, U., Vijayalakshmi, P., and Kaimal, T.N.B., *Synlett*, 2001, p. 863.
9. Chernyavichus, V.S., Odinets, A.G., Sausyn', A.E., Berzinya, A.Ya., and Zolotoyabko, R.M., *Khim.-Farm. Zh*., 1987, vol. 21, p. 959.
10. Bratenko, M.K., Chornous, V.A., and Vovk, M.V., *Russ. J. Org. Chem*., 2001, vol. 37, p. 556.
11. Lu, J. and Ma, H., *Synlett*, 2000, p. 63.