MULTICOMPONENT SYNTHESIS OF 2,5-DIOXO- AND 4-ARYL-5-OXO-2-THIOXO-1,2,3,4,5,6,7,8-OCTAHYDROQUINAZOLINES

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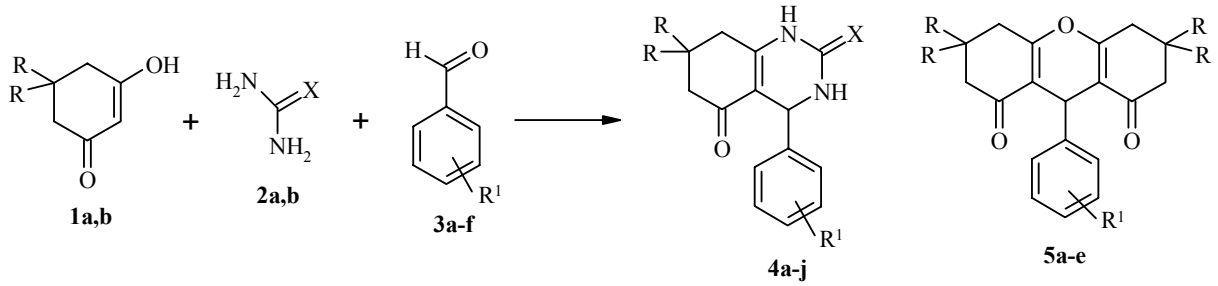
Ten 2,5-dioxo- and 4-aryl-5-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolines have been synthesized in three-component interactions of 1,3-cyclohexanedione or dimedone, urea or thiourea, and substituted benzaldehydes (3-bromo-, 4-bromo-, 4-fluoro-, 4-methoxy-, 3,4-methylenedioxy-, and 3-nitro-). 9-Aryl-4,5-dioxo-1,2,3,4,5,6,7,8-octahydro-9H-xanthenes were also formed in these reactions.

Keywords: 2,5-dioxo- and 5-oxo-2-thioxo-4-aryl-1,2,3,4,5,6,7,8-octahydroquinazolines, substituted benzaldehydes, ureas, 1,3-cyclohexanediones, three-component synthesis.

Among the large diversity of multicomponent reactions involving 1,3-dicarbonyl compounds, aldehydes and various C- and N-nucleophiles [1-14] the variant of the Bidginelli condensation involving 1,3-cyclohexanedione, an aromatic aldehyde, and urea, leading to quinazoline derivatives is unknown. In these reactions the formation of the corresponding 9-aryl-4,5-dioxo-1,2,3,4,5,6,7,8-octahydroxanthenes might be expected as side products.



1 a R= H; **b** R = Me; **2 a** X= O; **b** X = S; **3 a** R^1= 3-Br, **b** R^1 = 4-Br, **c** R^1 = 4-F, **d** R^1 = 4-OMe, **e** R^1 = 3,4-OCH_2O, **f** R^1 = 3-NO_2; **4 a** R, R^1, X = H, 4-Br, O; **b** H, 4-F, O; **c** H, 4-F, S; **d** H, 4-OMe, O; **e** H, 4-OMe, S; **f** H, 3,4-OCH_2-O-, O; **g** H, 3-NO_2, O; **h** Me, 3-Br, O; **i** Me, 4-F, O; **j** Me, 4-OMe, O; **5 a** R,R^1 = H, 4-F; **b** R,R^1 = Me, 4-F; **c** R,R^1 = H, OMe; **d** R,R^1 = Me, OMe; **e** R,R^1 = H, OCH_2O

We used 1,3-cyclohexanedione (**1a**) or dimedone (**1b**), urea (**2a**) or thiourea (**2b**), and substituted benzaldehydes **3a-f** as starting materials. Reactions were carried out by continuously (9-10 h) boiling equimolar quantities of diketone **1**, aldehyde **3** and 3 equivalents of urea or thiourea **2** in ethanol in the presence of catalytic amounts of H_2SO_4. In the case of 4-fluoro-, 4-methoxy-, or 3,4-methylenedioxybenzaldehydes a

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precipitate of the corresponding octahydroxanthenes **5** formed from the reaction mixture on cooling. After separating it and removing a portion of the solvent a mixture of octahydroquinazolines **4** and octahydroxanthenes **5** was precipitated with water. Sequential treatment of the mixture with hot ethanol and chloroform leads to pure quinazolines **4**.

The structures of the quinazoline derivatives **4** were confirmed by data of ^{1}H NMR spectra. In all cases the proton signals at the neighboring $C_{(4)}$ (5.09-5.32 ppm, ^3J = 3 Hz) and $N_{(3)}$ (7.65-7.83 ppm, ^3J = 3 Hz) atoms were clearly recorded. In the 2-thioxo derivatives **4c,e** the signals of $N_{(1)}$-H and $N_{(3)}$-H were displaced towards low field (**4c** 10.56 and 9.61, **4e** 10.58 and 9.66 ppm) compared with the 2-oxo derivatives. The signals of the protons of the carbocyclic fragment of molecules **4** and the proton at the $C_{(4)}$ atom, bearing an aromatic substituent, are observed in the expected regions. Absorption bands for the vibrations of the NH bonds of compound **4** were displayed in the IR spectra in the range of 3050-3370 cm^{-1}, and the bands of the carbonyl groups at 1700-1712 for $C_{(2)}$=O and at 1610-1628 cm^{-1} for $C_{(5)}$=O. Octahydroxanthenes **5c-e** formed in the reactions were obtained by the known procedures of [15,16] and the known compounds **5a,b** were synthesized by the procedure [16] for the first time (Tables 1, 2).

EXPERIMENTAL

The IR spectra were taken on a Specord IR 75 instrument for suspensions in nujol (1500-1800 cm^{-1}) and in hexachlorobutadiene (2000-3600 cm^{-1}, the absorption bands for the C–H stretching vibrations at 2800-3050 cm^{-1} are not given). The ^{1}H NMR spectra were recorded on a Bruker WH 90/DS (90 MHz) spectrometer for solutions in $CDCl_3$ and DMSO-d_6, internal standard was HMDS.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal (S)		
4a	$C_{14}H_{13}BrN_2O_2$	52.12 / 52.36	3.92 / 4.08	8.51 / 8.72	24.60 / 24.87	270-271	56
4b	$C_{14}H_{13}FN_2O_2$	64.80 / 64.61	4.87 / 5.03	10.61 / 10.76		275-276	19
4c	$C_{14}H_{13}FN_2OS$	60.78 / 60.85	4.61 / 4.74	10.02 / 10.14	(11.40) / (11.60)	258-260	30
4d	$C_{15}H_{16}N_2O_3$	65.97 / 66.16	5.80 / 5.92	10.11 / 10.29		271-272	13
4e	$C_{15}H_{16}N_2O_2S$	62.30 / 62.47	5.66 / 5.59	9.59 / 9.71	(10.90) / (11.12)	271-272	17
4f	$C_{15}H_{14}N_2O_4$	62.73 / 62.93	4.99 / 4.93	9.73 / 9.79		279-281	13
4g	$C_{14}H_{13}N_3O_4$	58.60 / 58.53	4.49 / 4.56	14.70 / 14.63		291-292	61
4h	$C_{16}H_{17}BrN_2O_2$	54.85 / 55.03	4.77 / 4.91	7.81 / 8.02	22.60 / 22.88	229-230	23
4i	$C_{16}H_{17}FN_2O_2$	66.60 / 66.65	5.81 / 5.94	9.60 / 9.72		274-275	14
4j	$C_{17}H_{20}N_2O_3$	67.21 / 67.98	6.60 / 6.71	9.12 / 9.33		273-274	14
5a	$C_{19}H_{17}FO_3$	72.95 / 73.07	5.40 / 5.49			253-254	72
5b	$C_{23}H_{25}FO_3$	74.80 / 74.97	6.77 / 6.84			208-210	77

TABLE 2. Spectral Characteristics of the Synthesized Compounds

Compound	IR spectra, ν, cm^{-1}	^1H NMR spectra, δ, ppm (coupling constant, *J*, Hz)
4a	1712, 1674, 1616, 1500; 3350, 3260-3150	DMSO-d_6. 1.67-2.67 (6H, m, $3CH_2$); 5.16 (1H, d, ^3J = 3, CH); 7.09-7.56 (4H, m, C_6H_4); 7.74 (1H, d, ^3J = 3, NH); 9.46 (1H, br. s, NH)
4b	1702, 1672, 1650, 1624, 1510; 3350, 3260, 3150	DMSO-d_6. 1.78-2.54 (6H, m, $3CH_2$); 5.23 (1H, d, ^3J = 3, CH); 7.07-7.43 (4H, m, C_6H_4); 7.83 (1H, d, ^3J = 3, NH); 9.58 (1H, br. s, NH)
4c	1630, 1610, 1570, 1515; 3250, 3200	DMSO-d_6. 1.85-2.63 (6H, m, $3CH_2$); 5.21 (1H, d, ^3J = 3, CH); 7.20-7.99 (4H, m, C_6H_4); 9.61 (1H, br. s, NH); 10.56 (1H, br. s, NH)
4d	1700, 1650, 1606, 1515; 3240, 3100	DMSO-d_6. 1.78-2.67 (6H, m, $3CH_2$); 3.69 (3H, s, CH_3); 5.12 (1H, d, ^3J = 3, CH); 6.81 (2H, m, ^3J = 8, C_6H_4); 7.16 (2H, m, ^3J = 8, C_6H_4); 7.65 (1H, br. s, NH); 9.38 (1H, br. s, NH)
4e	1628, 1572, 1510; 3260, 3200	DMSO-d_6. 1.78-2.58 (6H, m, $3CH_2$); 3.71 (3H, s, CH_3); 5.16 (1H, d, ^3J = 3, CH); 6.87 (2H, m, ^3J = 8, C_6H_4); 7.27 (2H, m, ^3J = 8, C_6H_4); 9.66 (1H, d, ^3J = 3, NH); 10.58 (1H, br. s, NH)
4f	1708, 1680, 1616, 1500; 3350-3050	DMSO-d_6.1.74-2.53 (6H, m, $3CH_2$); 5.09 (1H, d, ^3J = 3, CH); 5.92 (2H, s, CH_2); 6.73 (3H, center m, C_6H_4); 7.67 (1H, d, ^3J = 3, NH); 9.45 (1H, br. s, NH)
4g	1710-1700, 1652, 1610, 1530; 3350, 3260, 3100	DMSO-d_6. 1.69-2.56 (6H, m, $3CH_2$); 5.32 (1H, d, ^3J = 3, CH); 7.52-8.07 (5H, m, C_6H_4, NH); 9.56 (1H, br. s, NH)
4h	1702, 1660, 1622, 1575, 1535; 3370, 3260, 3140	DMSO-d_6. 0.89 (3H, s, CH_3); 1.07 (3H, s, CH_3); 2.12 (2H, m, CH_2); 2.41 (2H, m, CH_2); 5.18 (1H, d, ^3J = 3, CH); 7.23-7.49 (4H, m, C_6H_4); 7.81 (1H, br. s, NH); 9.56 (1H, br. s, NH)
4i	1707, 1660, 1615, 1530; 3300, 3220, 3130	DMSO-d_6. 0.88 (3H, s, CH_3); 1.07 (3H, s, CH_3); 2.03 (2H, m, CH_2); 2.34 (2H, m, CH_2); 5.18 (1H, d, ^3J = 3, CH); 6.98-7.36 (4H, m, C_6H_4); 7.81 (1H, br. s, NH); 9.54 (1H, br. s, NH)
4j	1710, 1674, 1616, 1515; 3320, 3240, 3150	DMSO-d_6. 0.92 (3H, s, CH_3); 1.05 (3H, s, CH_3); 2.05 (2H, m, CH_2); 2.31 (2H, m, CH_2); 3.72 (3H, s, CH_3); 5.14 (1H, d, ^3J = 3, CH); 6.83 (2H, m, ^3J = 8, C_6H_4); 7.25 (2H, m, ^3J = 8, C_6H_4); 7.74 (1H, br. s, NH); 9.45 (1H, br. s, NH)
5a	1680, 1660, 1622, 1602, 1510	DMSO-d_6.1.93-2.66 (12H, m, $6CH_2$); 4.58 (1H, s, CH); 6.94-7.33 (4H, m, C_6H_4, NH)
5b	1685, 1668, 1633, 1518	$CDCl_3$. 0.96 (6H, s, $2CH_3$); 1.09 (6H, s, $2CH_3$); 2.16 (4H, s, $2CH_2$); 2.46 (4H, s, $2CH_2$); 4.94 (1H, s, CH); 6.81-7.36 (4H, m, C_6H_4)

4-(4-Bromophenyl)- (4a), 4-(4-Fluorophenyl)- (4b), 4-(4-Methoxyphenyl)- (4d), 4-(3,4-Methylenedioxyphenyl)- (4f), 4-(3-Nitrophenyl)-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinazolines (4g), 4-(4-Fluorophenyl)- (4c), 4-(4-Methoxyphenyl)-5-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolines (4e), 4-(3-Bromophenyl)- (4h), 4-(4-Fluorophenyl)- (4i), and 4-(4-Methoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinazolines (4j). Solution of diketone **1** (5 mmol), aldehyde **3** (5 mmol), and urea or thiourea (15 mmol) in ethanol (30 ml) was boiled for 10 h in the presence of concentrated H_2SO_4 (0.15 ml). In the case of quinazolines **4b,d,e,f,i,j** a precipitate of the corresponding octahydroxanthene **5** (10-15% calculated on the aldehyde, identification is given below) was formed on cooling the ethanolic solution. The xanthene **5** precipitate was filtered off, ethanol (~20 ml) was distilled from the filtrate, the residue was poured into water (70 ml), the solution neutralized to pH 7 with aqueous KOH solution, and left for 24 h. The precipitated solid, sometimes oily, was filtered off or decanted from water. The substance obtained was triturated sequentially with hot ethanol and chloroform to remove octahydroxanthene derivatives. The quinazolines **4**, obtained in this way are pure substances according to TLC data. Recrystallization of them from THF or DMF led to significant loss, but the melting point did not change.

Octahydroxanthenes **5c**, **5d**, and **5e** obtained in the synthesis of quinazolines **4d**, **4f**, and **4j** gave no depression of melting point with known samples [15,16]. 9-(4-Fluorophenyl)-4,5-dioxo-1,2,3,4,5,6,7,8-octahydro-9H-xanthenes **5a,b** were also obtained by us for the first time by the reaction of diketones **1a,b** with 4-fluorobenzaldehyde. Their characteristics are given in Tables 1 and 2.

REFERENCES

1. C. O. Kappe. *Acc. Chem. Res.*, **33**, 879 (2000).
2. C. O. Kappe, *Eur. J. Med. Chem.*, **35**, 1043 (2000).
3. C. O. Kappe, D. Kumar, and R. S. Varma, *Synthesis*, 1799 (1999).
4. M. Boisbrun, L. Jeannin, L. Toupet, and J.-Y. Laronze, *Eur. J. Org. Chem.*, 3051 (2000).
5. A. A. Hassanien, M. A. Zahran, M. S. A. El-Gaby, and M. M. Ghorab, *J. Indian Chem. Soc.*, **76**, 350 (1999).
6. W. C. Wong, W. Sun, B. Lagu, D. Tian, M. R. Marzabadi, F. Zhang, D. Nagarathnam, S. W. Miao, J. M. Wetzel, J. Peng, C. Forray, R. S. L. Chang, T. B. Chen, R. Ransom, S. O'Malley, T. P. Broten, P. Kling, K. P. Vyas, K. Zhanh, and C. Gluchowski, *J. Med. Chem.*, **42**, 4804 (1999).
7. E. H. Hu, D. R. Sidler, and U.-H. Dolling, *J. Org. Chem.*, **63**, 3454 (1998).
8. A. J. Ortiz, A. Sanchez, and M. Nogueras, *J. Heterocycl. Chem.*, **35**, 231 (1998).
9. J. B. Sainani, A. C. Shah, and V. P. Arya, *Indian J. Chem. B*, **33**, 526 (1994).
10. A. L. Mikhal'chuk and O. V. Gulyakevich, *Izv. Akad. Nauk, Ser. Khim.*, 2353 (1996).
11. S. G. Krivokolysko, V. D. Dyachenko, A. N. Chernega, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 733 (2000).
12. S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1691 (1999).
13. S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 230 (1999).
14. V. D. Dyachenko, N. N. Nesterov, S. G. Krivokolysko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 785 (1997).
15. E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).
16. D. Vorländer, *Z. Anal. Chem.*, **77**, 241 (1929).