Convenient selective synthesis of 5,7,8,9-tetrahydro-4*H*,6*H*-chromeno[2,3-*d*][1,3]oxazin-4-ones*

*Yu. M. Litvinov and A. M. Shestopalov**

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5328. E-mail: amsh@ioc.ac.ru

A method for the synthesis of 5,7,8,9-tetrahydro-4*H*,6*H*-chromeno[2,3-*d*][1,3]oxazin-4-ones was developed. The method involves acid-catalyzed acylation of substituted ethyl 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates with acetic anhydride.

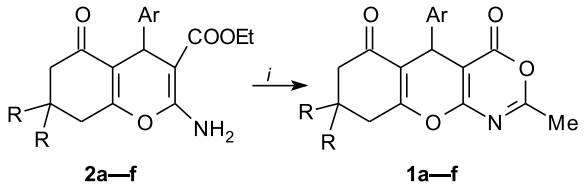
Key words: chromeno[2,3-*d*][1,3]oxazin-4-ones, ethyl 2-amino-4*H*-pyran-3-carboxylates, annulated heterocycles, acylation, acid catalysis.

The recent attention of medicinal chemists has been attracted by high biological activities of annulated oxazinones.[1—8] They are active as substrate inhibitors of various proteases because the oxazinone ring can undergo enzyme-catalyzed opening to give the corresponding stable acyl derivatives. Benzoxazinones and thienooxazinones effectively inhibit human leukocyte elastases (responsible for the degradation of connective tissue),[1—3] herpes proteases,[4] and those of human cytomegalovirus,[5] as well as act as antiinflammatory agents and anticoagulants.[6] Hydrogenated 4*H*-pyrido[4′,3′:4,5]thieno[2,3-*d*][1,3]oxazin-4-ones are active in the selective inhibition of cholesterol esterases and acetylcholinesterase.[7] Some imidazooxazinone nucleosides are effective against HIV.[8] The biological activities of oxygen analogs of benzoxazinones (pyrano[2,3-*d*][1,3]oxazines) have not been examined hitherto. The pyran ring of 2-amino-4*H*-pyrans is unstable in the presence of aqueous protic acids,[9] alcoholic solutions of alkali metal hydroxides,[10] and amines.[11] It is reasonable that the pyran ring would also undergo opening in reactions of pyrano[2,3-*d*][1,3]oxazines with proteases, thus creating additional links with the enzyme.

To date, the acylation of 2-amino-4*H*-pyran-3-carboxylic acid esters in the presence of pyridine has been studied only in two research papers[12,13] both reporting on the formation of 2-(diacetylamino)-4*H*-pyran-3-carboxylic acid esters only. 4*H*,5*H*-Pyrano[2,3-*d*][1,3]oxazin-4-ones were obtained by acylation of substituted 2-amino-4*H*-pyran-3-carboxylic acids.[14] However, these acids are not easily accessible because of possible opening of the pyran ring during their synthesis *via* hydrolysis of appropriate esters of 2-amino-4*H*-pyran-3-carboxylic acids.[9,10]

By selecting the reaction conditions, we developed a method for the synthesis of 4*H*,6*H*-chromeno[2,3-*d*]-[1,3]oxazin-4-ones **1a**—**f** from substituted ethyl 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates **2a**—**f** without preliminary hydrolysis of the ester group. The method involves acetylation of pyrans **2a**—**f** with acetic anhydride in the presence of catalytic amounts of conc. H_2SO_4 (Scheme 1).

Scheme 1



2a—f **1a—f** 52—75%

R = Me (**a**—**e**), H (**f**); Ar = Ph (**a**, **f**), 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 2,6-$Cl_2C_6H_3$ (**e**).
Reagents and conditions: *i*, $(MeCO)_2O$, H_2SO_4 (0.3 equiv.), reflux, 2 h.

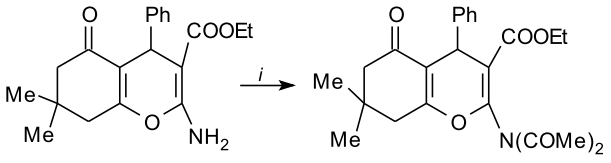
We also studied the acylation of pyrans in the absence of an acid catalyst. In contrast to the synthesis of oxazinones **1a**—**f**, pyran **2a** was exhaustively acylated at the amino group to give ethyl 2-(diacetylamino)-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate **3**. The best yield was achieved when the starting pyran **2a** was heated in acetic anhydride alone for 40 h (TLC) (Scheme 2).

The structures of the products obtained were confirmed by ^{1}H NMR, IR, and mass spectra. The IR spectra of compounds **1** and **3** show no absorption bands at 3400—3100 cm^{-1} (NH stretching). The spectra of oxazines **1a**—**f** exhibit

* On the occasion of the 75th anniversary of the foundation of the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 469—471, February, 2009.

Scheme 2



2a **3** 62%

Reagents and conditions: *i*, $(MeCO)_2O$, reflux, 40 h.

bands at 1752—1760 (lactone carbonyl) and 1656—1664 cm^{-1} (conjugated oxo group). The spectrum of compound **3** contains intense bands at 1736, 1724, 1708, and 1664 cm^{-1} ($\nu_{as}(N(COMe)_2)$ and $\nu_s(N(COMe)_2$, conjugated ester group, and conjugated oxo group, respectively).[15]

The ^1H NMR spectra of compounds **1a—f** show a singlet for the C(5)(H)Ar proton at δ 4.61—5.51, a signal for C(2)—Me at δ 2.32—2.36 (s, 3 H), signals for the aromatic (δ 7.08—7.32) and aliphatic protons (two CH_2 groups at δ 2.14—2.27 and 2.57—2.64 as a singlet or an AB system). The spectrum of compound **3** additionally contains signals for the ethyl substituent at δ 1.06—1.12 (m, 3 H, CH_3) and 4.03 (m, 2 H, CH_2) and for two acetyl groups at δ 2.32 (s, 6 H).

The mass spectrum of oxazine **1a** shows a molecular ion peak (*m/z* 337), while the peak with maximum *m/z* in the mass spectrum of 2-(diacetylamino)pyran **3** corresponds to the deace-tylated fragment (*m/z* 383, $[M - CH_3CO]^+$).

Thus, we demonstrated that easily accessible substituted ethyl 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates **2a—f** can be used as starting materials for the synthesis of earlier unknown oxazines **1a—f** and 2-(diacetylamino)pyran **3**.

Experimental

Melting points were determined on a Kofler hot stage. IR spectra were recorded on a Specord M82 spectrometer in KBr pellets (1 : 200). ^1H NMR spectra were recorded on Bruker WM-250 and Bruker AC-200 instruments (250 and 200 MHz, respectively) in DMSO-d_6. Low-resolution mass spectra were measured on a Kratos MS-30 instrument (EI, 70 eV, direct inlet probe, ionization chamber temperature 200 °C).

The starting ethyl 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates **2a—f** were prepared according to

Table 1. Yields, physical constants, and spectroscopic characteristics of compounds **1a—f** and **3**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR ν/cm^{-1} ν(C=O), ν(C=C)	^1H NMR, δ (*J*/Hz)
1a	75	212—214	71.25 71.20	5.72 5.68	4.09 4.15	$C_{20}H_{19}NO_4$	1756, 1664, 1624	0.98, 1.07 (both s, по 3 H, C(8)$(Me)_2$); 2.19—2.27 (m, 2 H, CH_2); 2.36 (s, 3 H, C(2)Me); 2.64 (s, 2 H, CH_2); 4.61 (s, 1 H, H(5)); 7.25 (m, 5 H, Ph)
1b	52	203—205	67.35 67.60	5.13 5.11	4.09 3.94	$C_{20}H_{18}FNO_4$	1756, 1668, 1628	0.98, 1.07 (both s, 3 H each, C(8)$(Me)_2$); 2.19—2.27 (m, 2 H, CH_2); 2.36 (s, 3 H, C(2)Me); 2.64 (s, 2 H, CH_2); 4.64 (s, 1 H, H(5)); 7.08 (m, 2 H, Ar), 7.22 (m, 2 H, Ar)
1c	48	199—201	64.78 64.61	4.63 4.88	3.91 3.77	$C_{20}H_{18}ClNO_4$	1760, 1660, 1620	0.97, 1.06 (both s, 3 H each, C(8)$(Me)_2$); 2.15—2.31 (m, 2 H, CH_2); 2.36 (s, 3 H, C(2)Me); 2.62 (s, 2 H, CH_2); 4.60 (s, 1 H, H(5)); 7.27 (d, 2 H, H(2′), H(6′), *J* = 7.9), 7.33 (d, 2 H, H(3′), H(5′), *J* = 7.8)
1d	65	205—207	57.46 57.71	4.28 4.36	3.51 3.36	$C_{20}H_{18}BrNO_4$	1752, 1656, 1628	0.96, 1.05 (both s, 3 H each, C(8)$(Me)_2$); 2.22 (AB-system, 2 H, CH_2, *J* = 16.4); 2.34 (s, 3 H, C(2)Me); 2.62 (s, 2 H,CH_2); 4.58 (s, 1 H, H(5)); 7.20 (d, 2 H, H(2′),H(6′), *J* = 7.9); 7.46 (d, 2 H, H(3′), H(5′), *J* = 7.8)
1e	67	247—250	58.94 59.13	4.29 4.22	3.14 3.45	$C_{20}H_{17}Cl_2NO_4$	1752, 1656, 1624	1.00, 1.07 (both s, 3 H each, C(8)$(Me)_2$); 2.07—2.30 (m, 2 H, CH_2); 2.38 (s, 3 H, C(2)Me); 2.58 (s, 2 H, CH_2); 5.51 (s, 1 H, H(5)); 7.20—7.31 (m, 2 H, Ar); 7.42—7.46 (m, 1 H, Ar)
1f	62	243—246	69.72 69.89	4.99 4.89	4.72 4.53	$C_{18}H_{15}NO_4$	1756, 1664, 1628	1.97—2.02 (m, 2 H, CH_2); 2.30 (s, 2 H, CH_2); 2.34 (s, 3 H, C(2)Me); 2.63–2.81 (s, 2 H, CH_2); 4.62 (s, 1 H, H(5)); 7.27 (m, 5 H, Ph)
3	62	161—163	67.62 67.75	6.51 6.40	3.15 3.29	$C_{24}H_{27}NO_6$	1736, 1724, 1708 1664 1640	0.93 (s, 3 H, C(7)Me); 1.06—1.12 (m, 6 H, C(7)Me + $COOCH_2C\underline{H}_3$); 2.14 (AB-system, 2 H, CH_2, *J* = 14.7); 2.32 (s, 6 H, N($COC\underline{H}_3)_2$); 2.57 (AB-system, 2 H, CH_2, *J* = 17.7); 4.03 (m, 2 H, $COOC\underline{H}_2CH_3$); 4.82 (s, 1 H, H(5)); 7.19—7.32 (m, 5 H, Ph)

a standard three-component procedure[16,17] from equimolar amounts of malononitrile, dimedone (**2a—e**), or cyclohexane-1,3-dione (**2f**) and an appropriate aromatic aldehyde.

5-Aryl-2-methyl-5,7,8,9-tetrahydro-4*H*,6*H*-chromeno-[2,3-*d*][1,3]oxazine-4,6-diones (1a—f) (general procedure). Concentrated H_2SO_4 (0.09 g, 0.9 mmol) was added to a solution of pyran **2a—f** (3 mmol) in acetic anhydride (3 mL). The reaction mixture was refluxed for 2 h (monitoring by TLC). On cooling to 4 °C, colorless needle-like crystals of products **1a—f** were filtered off, successively washed with ethanol (2 mL), water (3×3 mL), ethanol (2 mL), and light petroleum (2 mL), recrystallized from acetic anhydride, and dried at 150 °C to a constant weight. The yields, physical constants, elemental analysis data, and IR and ^{1}H NMR spectra of compounds **1a—f** are given in Table 1.

2,8,8-Trimethyl-5-phenyl-5,7,8,9-tetrahydro-4*H*,6*H*-chromeno[2,3-*d*][1,3]oxazine-4,6-dione (1a). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 337 $[M]^+$ (100), 294 $[M - CH_3CO]^+$ (54), 266 $[M - CH_3CO - CO]^+$ (39), 260 $[M - Ph]^+$ (92), 240 $[M - CH_3CO - C_4H_7]^+$ (71), 218 $[M - CH_3CO - Ph]^+$ (64).

Ethyl 2-(diacetylamino)-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (3). A solution of pyran **2a** (1.02 g, 3 mmol) in acetic anhydride (3 mL) was refluxed for 40 h (monitoring by TLC). On cooling to 4 °C, the precipitate of product **3** that formed was filtered off, successively washed with ethanol (2 mL), water (3×3 mL), ethanol (2 mL), and light petroleum (2 mL), recrystallized from acetic anhydride, and dried at 120 °C to a constant weight. The yields, physical constants, elemental analysis data, and IR and ^{1}H NMR spectra of compound **3** are given in Table 1.

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 383 $[M - CH_3CO]^+$ (14), 307 $[M - CH_3CO - Ph]^+$ (14), 307 $[M - 2CH_3CO - Ph]^+$ (100).

References

1. A. Krantz, R. W. Spencer, T. F. Tam, T. J. Liak, L. J. Copp, E. M. Thomas, S. P. Rafferty, *J. Med. Chem.*, 1990, **33**, 464.
2. M. Gütschow, U. Neumann, *J. Med. Chem.*, 1998, **41**, 1729.
3. M. Gütschow, L. Kuerschner, U. Neumann, M. Pietsch, R. Löser, N. Koglin, K. Eger, *J. Med. Chem.*, 1999, **42**, 5437.
4. R. L. Jarvest, I. L. Pinto, S. M. Ashman, C. E. Dabrowski, A. V. Fernandez, L. J. Jennings, P. Lavery, D. G. Tew, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 443.
5. I. L. Pinto, R. L. Jarvest, B. Clarke, C. E. Dabrowski, A. Fenwick, M. M. Gorczyca, L. J. Jennings, P. Lavery, E. J. Sternberg, D. G. Tew, A. West, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 449.
6. P.-W. Hsieh, T.-L. Hwang, C.-C. Wu, F.-R. Chang, T.-W. Wanga, Y.-C. Wu, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2786.
7. M. Pietsch, M. Gütschow, *J. Med. Chem.*, 2005, **48**, 8270.
8. Y. Saito, M. Nakamura, T. Ohno, C. Chaicharoenpong, E. Ichikawa, S. Yamamura, K. Kato, K. Umezawa, *J. Chem. Soc., Perkin Trans. 1*, 2001, 298.
9. C. Wiener, C. H. Schroeder, B. D. West, K. P. Link, *J. Org. Chem.*, 1962, **27**, 3086.
10. H. H. Otto, O. Rinus, H. Schmelz, *Monatsh. Chem.*, 1979, **110**, 115.
11. A. I. De Lucas, J. Fernandez-Gadea, N. Martin, C. Seoane, *Tetrahedron*, 2001, **57**, 5591.
12. N. Martin, A. Martinez-Grau, C. Seoane, J. L. Marco, *Tetrahedron Asymmetry*, 1995, **6**, 255.
13. H. M. F. Madkour, M. R. Mahmoud, A. M. Sakr, M. M. Habashy, *Sci. Pharm.,* 2001, **69**, 33.
14. A. H. Zeinab, *J. Chem. Res. (M)*, 1996, **9**, 2421.
15. K. Nakanishi, *Infrared Absorption Spectroscopy*, Holden-Day, Inc., San Francisco; Nanuodo Company Ltd., Tokyo, 1962.
16. A. M. Shestopalov, Yu. M. Emel´yanova, V. N. Nesterov, *Izv. Akad. Nauk, Ser. Khim.*, 2003, **52**, 1103 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 1164].
17. L. G. Sharanina, V. N. Nesterov, G. V. Klokol, L. A. Rodinovskaya, V. E. Shklover, Yu. A. Sharanin, Yu. T. Struchkov, V. K. Promonenkov, *Zh. Org. Khim.*, 1986, **22**, 1315 [*J. Org. Chem. USSR*, 1986, **22**, 1185].

Received November 7, 2008;
in revised form January 14, 2009