A FACILE METHOD FOR SYNTHESIS OF HETEROCYCLES CONTAINING TETRAHYDROBENZO[4,5]THIENO[2,3-*d*]PYRIMIDINE AND COUMARIN MOIETIES

Maxym V. Vasylyev,* Yaroslav V. Bilokin,*[1] Olena V. Branytska, Sergiy M. Kovalenko, Valentyn P. Chernykh

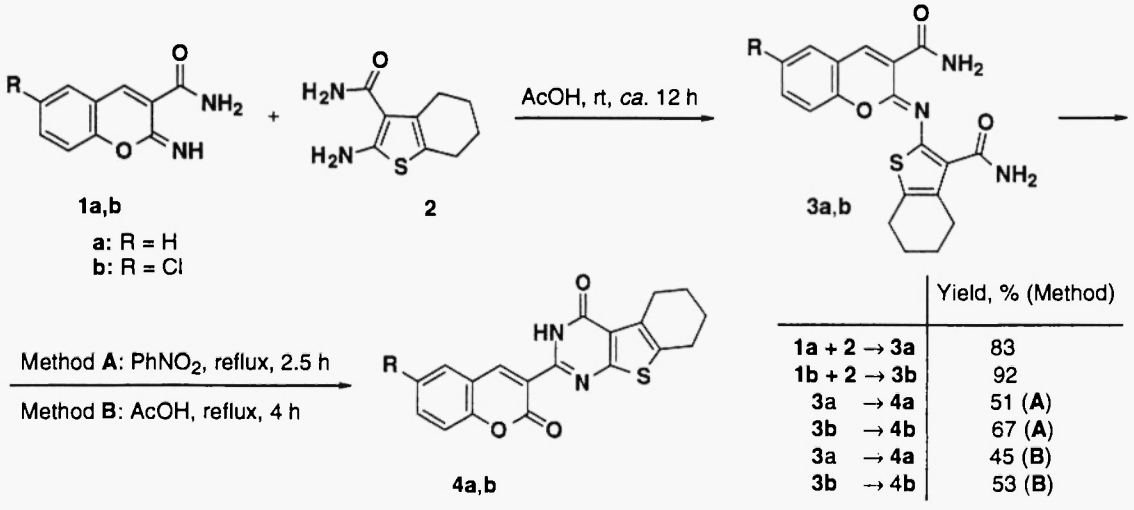
Department of Organic Chemistry, Ukrainian Academy of Pharmacy, Kharkov 310002, UKRAINE

Abstract: 2-(2-Oxo-2*H*-1-benzopyran-3-yl)-5,6,7,8-tetrahydro-3*H*-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-ones (**4a,b**) have been synthesized *via* a rearrangement of 2-(*N*-3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)imino-2*H*-1-benzopyran-3-carboxamides (**3a,b**). The tetrahydrobenzo[*b*]thiophenes **3** have been conveniently prepared by the reaction of 2-imino-2*H*-1-benzopyran-3-carboxamides (**1a,b**) with 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**2**) in glacial acetic acid.

Keywords: coumarins ; benzothiophenes ; benzothienopyrimidines ; imines ; rearrangements

Pyrimidine fused heterocycles have long been subjects for studies of their biological activities. For example, inhibition of epidermal growth factor receptor tyrosine kinase by compounds comprising benzo[4,5]thieno[3,2-*d*]pyrimidine fragment was recently reported (2) and synthesis of their structural analogs (3) is important in gauging their potential as a source of chemotherapeutics. In our recent communication (4) we introduced a novel method for synthesis of compounds containing pyrimidine and coumarin units – 2-(2-oxo-2*H*-1-benzopyran-2-yl)-3*H*-quinazolin-4-ones. It is based on the rearrangement of 2-imino-2*H*-1-benzopyran-3-carboxamides by the action of anthranilic acid as *N*-nucleophile. Applying the same strategy, but varying the methodology, we report herein the result of our studies on transformation reactions of 2-imino-2*H*-1-benzopyran-3-carboxamides **1** with 2-amino-4,5,6,7-tetrahydrobenzo[*b*] thiophene-3-carboxamide (**2**) as a new and efficient pathway to compounds **4** comprising tetrahydrobenzo[4,5]thieno [2,3-*d*]pyrimidine and coumarin fragments.

Scheme 1



	Yield, % (Method)
1a + 2 → 3a	83
1b + 2 → 3b	92
3a → 4a	51 (**A**)
3b → 4b	67 (**A**)
3a → 4a	45 (**B**)
3b → 4b	53 (**B**)

In glacial acetic acid at ambient temperature reactions between 2-imino-2*H*-1-benzopyran-3-carboxamides **1a**,**b** (5) and 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **2** (6) took place without iminolactone ring opening and furnished 2-(*N*-3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)imino-2*H*-1-benzopyran-3-carboxamides **3a**,**b** (7,8) as described in Scheme 1. A mechanism that accounts for the products **3** was elaborated (4,9) and is analogous to acidic hydrolysis of 2-imino-2*H*-1-benzopyrans to the corresponding 2-oxocompounds (10) (reaction with *O*-nucleophiles) and to comprehensively studied (11) reactions of non-cyclic iminoesters with amines. It was revealed that 2-(*N*-3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)imino-2*H*-1-benzopyran-3-carboxamides **3** have the capability to rearrange on refluxing in appropriate solvents (Method A and B, Scheme 1) to the corresponding 2-(2-oxo-2*H*-1-benzopyran-3-yl)-5,6,7,8-tetrahydro-3*H*-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-ones **4** (7,12,13). A possible mechanism of the rearrangement was particularized in reference (4).

In summary, the reactions described above constitute a useful strategy for preparation of benzothienopyrimidines of type **4** utilizing simple precursors **1** and **2**. Expansion of the scope of the method based on the rearrangements resulting from the reactions of 2-imino-2*H*-1-benzopyran-3-carboxamides with *N*-nucleophiles could open a new avenue for the synthesis of different 3-heterosubstituted coumarin derivatives.

References and Notes

(1) Present address: Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

(2) A review on recent advances in tyrosine kinase inhibitors by D. W. Fry, *Ann. Rep. Med. Chem.* 31, 151 (1996)

(3) (a) For synthesis of 3*H*-benzo[4,5]thieno[3,2-*d*]pyrimidin-4-ones, see: A. J. Bridges, H. Zhou, *J. Heterocycl. Chem.* 34, 1163 (1997); and (b) For a review on synthesis and pharmacological aspects of heterocycles possessing thieno-fragment, see, also: R. Pech, R. Böhm, *Pharmazie* 39, 4 (1984)

(4) Y. V. Bilokin, S. N. Kovalenko, I. E. Bylov, V. P. Chernykh, *Heterocycl. Commun.* 4, 257 (1998) and references cited therein

(5) For synthesis of 2-imino-2*H*-1-benzopyran-3-carboxamides **1**, see: **1a**: (a) G. P. Schiemenz, *Chem. Ber.* 95, 483 (1962); and (b) P. Czerney, H. Hartmann, *J. Prakt. Chem.* 323, 691 (1981). **1b**: C. N. O'Callaghan, *Proc. Roy. Irish. Acad.* 77B, 533 (1977)

(6) For a procedure to synthesize 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **2** from cyclohexanone, 2-cyanoacetamide, and sulfur by the application of Gewald reaction, see: V. P. Arya, *Indian J. Chem.* 10, 1141 (1972)

(7) All new compounds described in Scheme 1 were fully characterized by ^{1}H NMR- and IR-analyses and by elemental microanalysis. Mp (°C) of compounds synthesized: **3a**: > 300; **3b**: 273-4; **4a**: 267-8; **4b**: 242-3

(8) Selected spectral data for *2-(N-3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)imino-2H-1-benzopyran-3-carboxamide* (**3a**): ^{1}H NMR (400MHz, DMSO-d_6): δ 8.96 (br s, 1H, CONH$_2$); 8.33 (s, 1H, **H-4**); 7.87 (br s, 1H, CONH$_2$); 7.84 (br s, 1H, CONH$_2$); 7.79 (dd, 1H, *J* = 7.8, 1.4Hz, **H-5**); 7.64 (ddd, 1H, *J* = 8.6, 8.2, 1.4Hz, **H-7**); 7.48 (d, 1H, *J* = 8.2Hz, **H-8**); 7.36 (dd, 1H, *J* = 8.6, 7.8Hz, **H-6**); 7.31 (br s, 1H, CONH$_2$); 2.74 (br t, 2H *J* = 5.0Hz, CH$_2$); 2.66 (br t, 2H *J* = 5.0Hz, CH$_2$); 1.76 (m, 4H, CH$_2$-CH$_2$)

(9) A manuscript on a facile method for synthesis of tetrahydrobenzo[*b*]thiophenes of type **3** is in preparation and will appear in due course: M. V. Vasylyev, Y. V. Bilokin, S. M. Kovalenko, O. V. Branytska, V. P. Chernykh, 'manuscript in preparation'

(10) A. A. Karasev, L. L. Lukatskaya, M. I. Rubtsov, E. K. Zhikol, S. N. Yarmolenko, O. A. Ponomarev, *Zh. Obshch. Khim.* 65, 1547 (1995); *Chem. Abstr.* 124, 342517p (1996)

(11) E. S. Hand, W. P. Jencks, *J. Am. Chem. Soc.* 84, 3505 (1962)

(12) Selected spectral data for *2-(2-oxo-2H-1-benzopyran-3-yl)-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one* (**4a**): ^{1}H NMR (400MHz, DMSO-d_6): δ 12.03 (br s, 1H, NH); 9.00 (s, 1H, **H-4**); 8.04 (dd, 1H, *J* = 7.8, 1.6Hz, **H-5**); 7.78 (ddd, 1H, *J* = 8.3, 7.3, 1.6Hz, **H-7**); 7.56 (d, 1H, *J* = 8.3Hz, **H-8**); 7.48 (dd, 1H, *J* = 7.8, 7.3Hz, **H-6**); 2.91 (br t, 2H *J* = 5.9Hz, 8-CH$_2$); 2.78 (br t, 2H *J* = 5.9Hz, CH$_2$); 1.81 (m, 4H, CH$_2$-CH$_2$)

(13) The structure of compound **4b** was additionally corroborated by X-ray diffraction analysis and the data will be published elsewhere

Received February 10, 1999