A Facile Synthesis of an Oxazolo[5,4]pyrimidin-2-one and a Pyrimido[5,4][1,3]oxazin-2-one

Harmen P. Dijkstra, Catherine Gaulon, Dan Niculescu-Duvaz, Caroline J. Springer*

Centre of Cancer Therapeutics, The Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey, SM2 5NG, UK
Fax +44(208)7224205; E-mail: caroline.springer@icr.ac.uk

Received 20 September 2005

Abstract: A facile synthesis is reported for the construction of the five- and six-membered fused carbamate rings of an oxazolo[5,4]pyrimidin-2-one and a pyrimido[5,4][1,3]oxazin-2-one, respectively. The method utilises a controlled two-step procedure in which a reactive *p*-nitrophenylcarbamate intermediate ring closes upon treatment with base, affording the bicyclic pyrimidine-carbamate scaffolds in good yields.

Key words: pyrimidines, cyclic carbamates, ring-closing, heterocyclic chemistry

Pyrimidine derivatives play an important role in many drug discovery programmes in the pharmaceutical industry and amongst them bicyclic pyrimidine ring systems are a very important class of compounds.[1] Bicyclic pyrimidine ring systems also play a crucial role in mammalian systems: the DNA base pairs adenine and guanine are purine derivatives whilst ATP (adenosine triphosphate), a key energy provider substrate in biological signalling pathways, contains a purine moiety. More specifically, the purine group plays an important role in the binding of ATP to protein kinases (an important class of enzymes mediating most signal transduction pathways),[1b,2] resulting in activation of downstream enzymes in the signalling pathway through phosphorylation.[3] It is known that many forms of cancer develop due to mutations of one or several enzymes in these signalling pathways. For this reason, a considerable body of research is directed toward the development of ATP-competitive inhibitors for mutated protein kinases thereby preventing activation of these enzymes and thus blocking the signalling pathway that can lead to cancers.[4] Examples of protein kinase inhibitors in the treatment of cancer are Gleevec© (for leukaemia), Iressa© (for lung cancer) and Sorafeni© (for renal cancer).[5] Thus developing protein kinase inhibitors that strongly compete with ATP have a huge potential in cancer treatments. Pyrimidines have already been shown to be very successful in this area because they possess many key functionalities for crucial binding (mainly hydrogen bonds) to the backbone (hinge region) of the constrained and rather well-defined ATP-pocket of many protein kinases. In addition, due to their versatile chemistry, pyrimidines can be readily decorated with various functionalities to fine-tune their biological activity.[6]

SYNLETT 2006, No. 10, pp 1519–1522
Advanced online publication: 12.06.2006
DOI: 10.1055/s-2006-941604; Art ID: D28805ST
© Georg Thieme Verlag Stuttgart · New York

Our interest in kinase inhibitors led us to develop a novel route towards oxazolo[5,4]pyrimidin-2-ones **1** and pyrimido[5,4][1,3]oxazin-2-ones **2** (Figure 1) with R^2 = benzyl or functionalised benzyl-groups. To our knowledge, no compounds of types **1** and **2** are known in which N-7 and N-9, respectively, are substituted. This was rather surprising since scaffolds **1** and **2** possess many characteristics of a good pharmacophore for binding in the ATP-pocket of kinases. We believe that the absence of compounds of type **1** and **2** in the literature is due to the lack of good and reproducible methods to produce their bicyclic pyrimidine-carbamate ring systems. Herein we report a new proof of concept methodology to construct the bicyclic pyrimidine-carbamate scaffolds of both an oxazolo[5,4]pyrimidin-2-one (**1**) and a pyrimido[5,4][1,3]oxazin-2-one (**2**) bearing a benzyl substituent (R^2, Figure 1) on the positions N-7 and N-9, respectively.

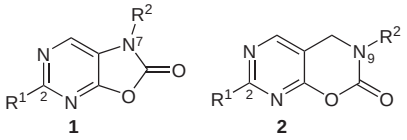
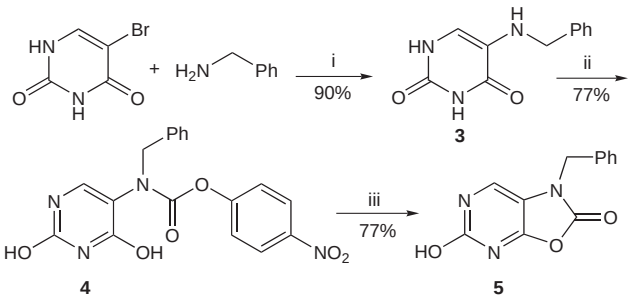


Figure 1 Oxazolo[5,4]pyrimidin-2-ones **1** and pyrimido[5,4][1,3]oxazin-2-ones **2**

Initial screening of the literature for potential suitable methods to create the bicyclic pyrimidine-carbamate ring systems resulted in only two publications by Wetzel et al. describing compounds of type **1** in which R^2 = H.[7] They reported the synthesis of a variety of oxazolo-pyrimidine derivatives of type **1** (R^2 = H) as intermediates in the synthesis of β-lactam antibiotics. In their synthesis, 5-amino-4-hydroxypyrimidines were reacted with phosgene to provide the desired oxazolopyrimidines in moderate to good yields. As mentioned earlier, from a medicinal chemistry point of view, we were keen to introduce substituents, preferably (functionalised) benzyl substituents, on the positions N-7 of **1** and the N-9 of **2**. To explore suitable routes we decided to use a model reaction with R^2 = benzyl. Applying Wetzel's reaction conditions to construct the bicyclic pyrimidine-carbamate scaffold of **1** (R^2 = benzyl) starting from 5-(benzylamino)uracil[8] and phosgene resulted in irreproducible results with poor yields. In the best case, 1-benzyl-5-hydroxyoxazolo[5,4-*d*]pyrimidin-2(1*H*)-one (**5**) was isolated in 8% yield. Replacing the phosgene with triphosgene, another regularly used reagent for this type of reaction resulted in equally

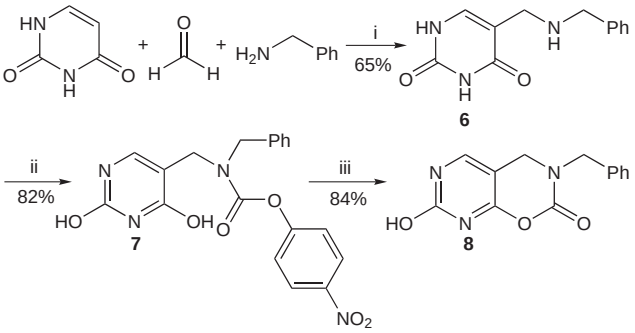
Downloaded by: Nanyang Technological University NTU. Copyrighted material.

poor yields. Since we needed a reproducible method to access products of type **1**, we started to explore a different method to prepare the central pyrimidine-carbamate skeleton. We decided to perform the ring-closing step in a controllable two-step procedure. The synthesis of 1-benzyl-5-hydroxyoxazolo[5,4-*d*]pyrimidin-2(1*H*)-one (**5**) is outlined in Scheme 1. First the reactive 4-nitrophenyl carbamate **4** was synthesised from 5-benzylaminouracil **3**, which is available from 5-bromouracil and benzylamine.[8] Uracil **3** was found to be insufficiently soluble to react with 4-nitrophenyl chloroformate to afford intermediate **4**: only up to 30% conversion was observed even after prolonged reaction times (>72 h) and elevated temperatures (reflux in THF). To overcome this problem, **3** was first treated with an excess of *N*,*N*-diethyltrimethylsilylamine, giving the completely THF-soluble bis(silyloxy) ether, and subsequent treatment of this soluble intermediate with 4-nitrophenyl chloroformate in the presence of triethylamine followed by an aqueous work-up, gave the 4-nitrophenyl carbamate **4** in 77% yield.[9] Subsequent treatment of **4** with potassium *tert*-butoxide in THF at reflux conditions resulted in the formation of the desired bicyclic carbamate structure **5** in 77% yield[9] and in 60% overall yield starting from **3**.[9] Using the ethyl carbamate intermediate, which is more commonly used in the literature to synthesise cyclic carbamates, instead of the 4-nitrophenyl derivative, failed to the give the final cyclic product **5**. This is probably a result of the rather poor nucleophilicity of the 4-OH functionality of the pyrimidine combined with the poor leaving group ability of the ethoxide group relative to the 4-nitrophenol group.



Scheme 1 *Reagents and conditions*: *i*. neat, 160 °C, 3 h;[8] *ii*. *N*,*N*-diethyltrimethylsilylamine, THF, reflux, 1 h, followed by 4-nitrophenyl chloroformate, Et_3N, THF, 0 °C, r.t., 3 h; *iii*. *t*-BuOK, THF, reflux, 1.5 h.

Since we were also interested in 6-membered cyclic carbamates fused to a pyrimidine ring (**2**, Figure 1) as scaffolds for drug-like molecules, we decided to investigate whether this new method could also be applied to the construction of the bicyclic scaffold of type **2**. To do so, a similar approach was followed (Scheme 2). In the first step, uracil was subjected to Mannich reaction conditions using paraformaldehyde and benzylamine in an ethanol–water mixture (4:1), affording 5-(benzylaminomethyl)uracil (**6**) in 65% yield.[10] The presence of a considerable amount of water (ca. 20%) in the solvent mixture was found to be crucial in order to get satisfying yields and reproducible results. This is probably due to the fact that water is necessary to solubilise all reagents under the applied reaction conditions.



Scheme 2 *Reagents and conditions*: *i*. EtOH–H_2O (4:1), reflux, 20 h; *ii*. 4-nitrophenyl chloroformate, THF, Et_3N, 0 °C, r.t., 20 h; *iii*. *t*-BuOK, THF, reflux, 2 h.

Treatment of uracil derivative **6** with 4-nitrophenyl chloroformate in THF in the presence of triethylamine afforded the reactive carbamate intermediate **7** in 82% yield. Reaction of **7** with potassium *tert*-butoxide in THF at reflux conditions resulted in the formation of the desired pyrimido-oxazinone **8** in 84% yield.[11] Also here, we first attempted to synthesise **8** directly from **6** using phosgene or triphosgene and the conditions described by Wetzel et al., however, in this case we were unable to isolate any desired product. Via the new controlled two-step procedure, however, we were able to obtain the desired product **8** in 67% overall yield starting from uracil derivative **6**.

In conclusion, we report a facile two-step procedure to synthesise the bicyclic pyrimidine-carbamate skeleton of oxazolo[5,4]pyrimidin-2-ones and pyrimido[5,4][1,3]oxazin-2-ones. For the first time an oxazolo[5,4]pyrimidin-2-one and a pyrimido[5,4][1,3]oxazin-2-one are described with an alkyl substituent at N-7 and N-9, respectively. Whereas the more conventional methods (using phosgene and triphosgene) failed, this method afforded the desired fused pyrimidine-carbamate products in good yields, creating the possibility to access a wide variety of these bicyclic carbamate substrates. This in combination with the rich chemistry already developed for functionalising pyrimidines[6,12] and the known key hydrogen bond donating/accepting abilities of bicyclic pyrimidine systems for binding to biological targets, make these fused pyrimidine-carbamate systems interesting building blocks in medicinal chemistry.

Acknowledgment

We would like to thank Cancer Research-UK (grant numbers C309/A2187 and C107/A3096), the Institute of Cancer Research and Wellcome Trust for the funding of this work. We are grateful to our colleagues Lawrence Davies, Ion Niculescu-Duvaz, Esteban Roman and Ian Scanlon (at the ICR) and to Richard Taylor and Adrian Gill (Astex Technology Ltd) for fruitful discussions.

Downloaded by: Nanyang Technological University NTU. Copyrighted material.

References and Notes

(1) For purine kinase inhibitors, see for example: (a) Meijer, L.; Raymond, E. *Acc. Chem. Res.* **2003**, *36*, 417. (b) Laufer, S. A.; Domeyer, D. M.; Scior, T. R. F.; Albrecht, W.; Hauser, D. R. J. *J. Med. Chem.* **2005**, *48*, 710.

(2) (a) Manning, G.; Whyte, D. B.; Martinez, R.; Hunter, T.; Sudarsanam, S. *Science* **2002**, *298*, 1912. (b) Manning, G.; Whyte, D. B.; Martinez, R.; Hunter, T.; Sudarsanam, S. *Science* **2002**, *298*, 1933.

(3) Huse, M.; Kuriyan, J. *Cell* **2002**, *109*, 275.

(4) For a review on protein kinase inhibitors, see: Bridges, A. J. *Chem. Rev.* **2001**, *101*, 2541.

(5) Levitzki, A. *Acc. Chem. Res.* **2003**, *36*, 462; this review includes references to gleevec, iressa and sorafenib.

(6) Brown, D. J. *Comprehensive Heterocyclic Chemistry*, Vol. 3; Boulton, A. J.; McKillop, A., Eds.; Pergamon Press: Oxford, **1985**, 57.

(7) (a) Wetzel, B.; Woitun, E.; Reuter, W.; Maier, R.; Lechner, U. *Drug. Res.* **1985**, *35*, 343. (b) Wetzel, B.; Woitun, E.; Reuter, W.; Maier, R.; Lechner, U.; Goeth, H. Eur. Pat. Appl., EP 4499265, **1982**. (c) Maier, R.; Wetzel, B.; Woitun, E.; Reuter, W.; Lechner, U.; Appel, K.-R. *Arzneim.-Forsch.* **1986**, *9*, 1297.

(8) For the synthesis of **3**, see: Gaulon, C.; Dijkstra, H. P.; Springer, C. J. *Synthesis* **2005**, *13*, 2227.

(9) **Synthesis of 4-Nitrophenyl Benzyl(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)carbamate (4).**
N,*N*′-Diethyltrimethylsilylamine (5.5 mL, 30.32 mmol) was added to a suspension of 5-(benzylamino)uracil (1.75 g, 7.58 mmol) in THF (120 mL) and the resulting mixture was heated to reflux for 1 h, affording a clear solution. The reaction mixture was cooled to ambient temperature and subsequently all volatiles were removed in vacuo, affording the disilylated intermediate as a sticky white residue. The intermediate was dissolved in THF (120 mL) and cooled to 0 °C. Then, Et_3N (1.02 mL, 7.58 mmol) was added, followed by the dropwise addition of *p*-nitrophenyl chloroformate in THF (10 mL). The temperature of the resulting mixture was allowed to rise to r.t. and stirring was continued for 3 h. The reaction mixture was filtered to remove Et_3N salts and H_2O (5 mL) was added to the filtrate to hydrolyse the trimethylsilyl–oxygen bonds. Next, the THF layer was concentrated to dryness, leaving a yellow solid. This solid was redissolved in THF (50 mL) and filtered to remove traces of insoluble material. The filtrate was concentrated to ca. 20 mL and upon addition of Et_2O (ca. 20 mL), an off-white solid precipitated. This precipitate was collected by filtration, washed with Et_2O (2 × 10 mL) and dried in vacuo, affording the product as an off-white solid; yield 2.23 g (77%). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.50–4.91 (m, 2 H, CH_2, different rotamers exist), 7.32–7.50 (m, 8 H, ArH + $PyrH_6$), 8.29 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, ArH), 11.01 (br s, 1 H, NH), 11.42 (br s, 1 H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 52.93, 114.39, 115.71, 122.67, 125.11, 126.09, 127.46, 128.27, 128.32, 136.37, 144.52, 150.50, 156.06, 161.17. MS (ES^+): *m/z* = 406.09 [$M + Na^+$].
Synthesis of 1-Benzyl-5-hydroxyoxazolo[5,4-*d*]pyrimidin-2(1*H*)-one (5).
4-Nitrophenyl benzyl(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)carbamate (**4**, 1.58 g, 4.13 mmol) was dissolved in THF (140 mL) and *t*-BuOK (0.97 g, 8.26 mmol) was added in one portion and the resulting mixture was heated to reflux for 1.5 h. After cooling the reaction mixture to r.t., the reaction mixture was concentrated to dryness. Then, H_2O (25 mL) was added to the brightly yellow-coloured solid and this mixture was stirred vigorously for 5 min. Next, this layer was acidified with 1 M HCl aq (ca. 15 mL), resulting in an off-white precipitate. The precipitate was collected by filtration, washed with H_2O (2 × 15 mL) and Et_2O (2 × 30 mL) and dried in vacuo, affording the product as an off-white solid; yield 0.77 g (77%). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.88 (s, 2 H, CH_2), 7.33–7.42 (m, 5 H, ArH), 7.66 (s, 1 H, PyrH), 11.60 (br s, 1 H, OH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 45.40, 111.98, 123.72, 127.68, 127.79, 127.91, 128.61, 134.56, 151.06, 154.93. HRMS: *m/z* calcd for $C_{12}H_{10}N_3O_3$ [$M + H^+$]: 244.0722. Found: 244.0726. Anal. Calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.16; H, 4.17; N, 17.64.
For the use of *p*-nitrophenol esters in the synthesis of carbamates, see also: (a) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 2223. (b) Vigroux, A.; Bergon, M.; Zedde, C. *J. Med. Chem.* **1995**, *38*, 3983.

(10) (a) A modification from a literature procedure was used: Delia, T. J.; Scovill, J. P.; Munslow, W. D. *J. Med. Chem.* **1976**, *19*, 344. (b) **Synthesis of 5-(Benzylaminomethyl)uracil (6).** Paraformaldehyde (2.91 g, 97.0 mmol) and benzylamine were mixed in EtOH (320 mL) and this mixture was stirred at r.t. for 10 min. Subsequently, uracil (10.0 g, 88.2 mmol) was added in one portion followed by the addition of H_2O (80 mL) and the resulting mixture was heated at reflux for 20 h. Next, the filtrate was evaporated to dryness, leaving a white solid. After washing with acetone (3 × 25 mL) and drying in vacuo, the product was obtained as a white solid; yield 13.2 g (65%). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.29 (s, 2 H, CH_2), 3.66 (s, 2 H, CH_2), 7.17–7.31 (m, 5 H, ArH), 7.32 (s, 1 H, PyrH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 44.26, 52.10, 110.61, 126.49, 127.82, 128.07, 138.46, 140.70, 151.26, 164.42. MS (ES^+) *m/z* = 232 [$M + H^+$].

(11) **Synthesis of 4-Nitrophenyl Benzyl[(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]carbamate (7).**
5-(Benzylaminomethyl)uracil (2.0 g, 8.7 mmol) was dissolved in THF (40 mL) and cooled to 0 °C with an ice-bath. Then, Et_3N (1.2 mL, 8.7 mmol) was added followed by the dropwise addition of a solution of *p*-nitrophenyl chloroformate in THF (10 mL). The temperature was allowed to rise to r.t. and stirring was continued for 20 h at that temperature. Next, all volatiles were evaporated, leaving a yellow solid. This solid was washed with H_2O (2 × 20 mL), Et_2O (2 × 20 mL), and CH_2Cl_2 (2 × 20 mL) and dried in vacuo. Afterwards, THF (15 mL) was added to this solid and the resulting suspension was stirred at r.t. for 10 min. Subsequently, Et_2O (30 mL) was added and the precipitate was collected and dried in vacuo, leaving a slightly yellow solid; yield: 2.82 g (82%). ^{1}H NMR (250 MHz, DMSO-d_6, 100 °C): δ = 4.24 (s, 2 H, CH_2), 4.66 (s, 2 H, CH_2), 7.30–7.44 (m, 8 H, ArH + PyrH), 8.24 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, ArH), 10.48 (br s, 2 H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6, 100 °C): δ = 43.53, 50.24, 107.46, 122.77, 125.07, 127.01, 127.31, 128.53, 137.52, 141.24, 144.41, 151.14, 153.12, 156.17, 164.25. HRMS: *m/z* calcd for $C_{19}H_{17}N_4O_6$ [$M + H^+$] 397.1148; found: 397.1145.
Synthesis of 3-Benzyl-7-hydroxy-3,4-dihydropyrimido[5,4-*e*][1,3]oxazin-2-one (8).
4-Nitrophenyl benzyl[(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]carbamate (**7**, 1.0 g, 2.5 mmol) was dissolved in THF (100 mL) and *t*-BuOK (0.57 g, 5.1 mmol) was added in one portion. The resulting solution was heated to reflux for 2 h and subsequently cooled to r.t. and concentrated to dryness. Then, H_2O (20 mL) was added to the yellow solid and this mixture was stirred vigorously for 5 min. This layer was acidified with 1 M HCl aq (ca. 20 mL), resulting in a white precipitate. The precipitate was collected, washed with H_2O (2 × 10 mL) and Et_2O (2 × 15

Downloaded by: Nanyang Technological University NTU. Copyrighted material.

mL) and dried in vacuo, affording the product as a white solid; yield 0.50 g (84%). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.15 (s, 2 H, CH_2), 4.60 (s, 2 H, CH_2), 7.31–7.41 (m, 5 H, ArH), 7.94 (s, 1 H, PyrH), 11.95 (br s, 1 H, OH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 42.54, 51.65, 95.35, 127.70, 127.77, 128.65, 135.47, 144.67, 148.65, 155.87, 166.03. HRMS: *m/z* calcd for $C_{13}H_{11}N_3O_3Na$ [M + Na^+]: 280.0698; found: 280.0696. Anal. Calcd for $C_{13}H_{11}N_3O_3 \cdot 0.2H_2O$: C, 59.86; H, 4.41; N, 16.11. Found: C, 60.02; H, 4.37; N, 15.73.

(12) Some examples can be found in the following papers: (a) Sandosham, J.; Undheim, K. *Heterocycles* **1994**, *37*, 501. (b) Sandosham, J.; Undheim, K.; Rise, F. *Heterocycles* **1993**, *35*, 235. (c) Sugimoto, O.; Mori, M.; Tanji, K. *Tetrahedron Lett.* **1999**, *40*, 7477.

Downloaded by: Nanyang Technological University NTU. Copyrighted material.