Pergamon

Tetrahedron Letters 43 (2002) 7553–7556

TETRAHEDRON LETTERS

Isoquinolinone synthesis by S_NAr reaction: a versatile route to imidazo[4,5-*h*]isoquinolin-9-ones

Roger J. Snow,[a,*] Tanja Butz,[a] Abdelhakim Hammach,[a] Suresh Kapadia,[b] Tina M. Morwick,[a] Anthony S. Prokopowicz, III,[a] Hidenori Takahashi,[a] Jonathan D. Tan,[b] Matt A. Tschantz[a] and Xiao-Jun Wang[b]

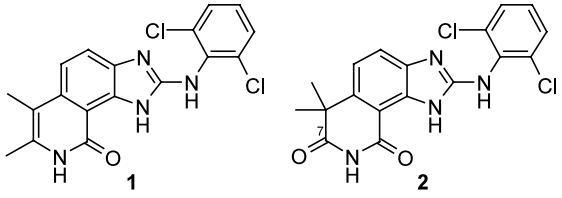
[a]*Department of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, CT 06877, USA*

[b]*Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, CT 06877, USA*

Received 3 June 2002; revised 16 August 2002; accepted 23 August 2002

Abstract—Reaction of 2-chlorobenzonitriles with β-ketoesters in an S_NAr reaction, followed by cyclization in acid provides a versatile route to isoquinolones. Starting from 2,6-dichloro-3-nitrobenzonitrile **7**, sequential displacement of the chlorines by an amine and a β-ketoester leads to imidazo[4,5-*h*]isoquinolin-9-ones **1**, a new class of kinase inhibitor.

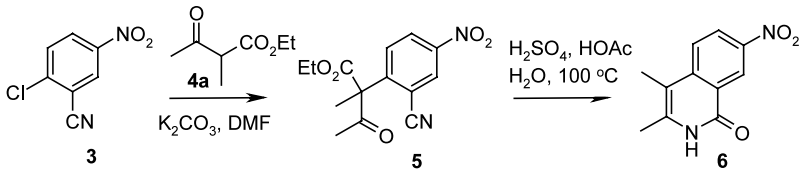
Recently we disclosed a series of phenylamino imidazo[4,5-*h*]isoquinolin-9-ones,[1] exemplified by **1**, as a new class of potent inhibitors of the tyrosine kinase p56lck (lck). These compounds are potentially useful therapeutic agents for treating autoimmune diseases. The discovery of **1** resulted from a structure–activity relationship and molecular modeling study of a screening lead, **2**.



1 **2**

Following this discovery, we needed an improved synthesis of **1** and its analogs for further studies. The original route to **1** proceeded from **2** by selective reduction of the C7 carbonyl, followed by acid treatment to induce a Wagner–Meerwein rearrangement. This had two severe limitations. Firstly, the synthesis of **2** required 10 steps from commercial starting materials. Secondly, the rearrangement to produce **1** was successful only in the dimethyl case. Our analysis of the interaction of **1** with lck[1] indicated that modification of the substituents in the pyridone ring should be beneficial, so we designed a synthetic route that allowed wide variation at these positions, and required fewer steps after introduction of this diversity element. This required a flexible approach to the isoquinolone moiety of **1**, and efficient access to the highly substituted central benzene ring.

Our approach to the isoquinolone (Scheme 1) was based on the S_NAr reaction of 2-chlorobenzonitrile **3** with β-ketoester **4a** to give **5**, followed by cyclization under acid conditions. The ready availability of β-ketoesters would allow a wide range of substitution at



3 **4a** **5** **6**

Scheme 1. Approaches to isoquinolones.

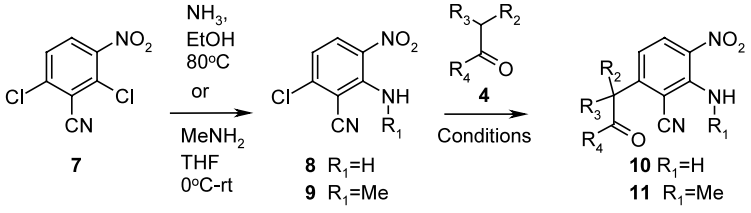
* Corresponding author. Tel.: +1-203-798-4060; fax: +1-203-791-6072; e-mail: rsnow@rdg.boehringer-ingelheim.com

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01802-6

both the 3 and 4 positions of the isoquinolone, and would offer much greater versatility than isoquinolone syntheses based on alkynes[2] or directed lithiation.[3] A conceptually similar route to isoquinolones by a photochemical reaction of 2-bromobenzamide and enolates of simple ketones has been reported.[4] Sommer[5] has described S_NAr reactions of 2-chlorobenzonitriles, including **3**, with phenylacetonitriles under ionic conditions. We expected that the nitro group in **3** would enhance its reactivity, and also provide one of the benzimidazole nitrogens. As a trial reaction, **3** was reacted with **4a** in the presence of K_2CO_3 in DMF at room temperature to give the desired adduct **5** in 47% yield. Heating **5** in a H_2SO_4/water/acetic acid (1:1:3) mixture at 100°C brought about hydrolysis, decarboxylation and cyclization in one step to provide **6** in quantitative yield.

Having found a route to the isoquinolone, the next challenge was introduction of the benzimidazole nitrogens of **1**. The synthesis of **2** took six steps to insert these nitrogens. An attractive commercial precursor that contains the 1,2,3,4-tetrasubstitued benzene required for the central ring is 2,6-dichloro-3-nitro benzonitrile (**7**). We reasoned that it might be possible to displace the two chlorines sequentially, using one to introduce the second nitrogen, and the other to carry out the S_NAr reaction (Scheme 2). There is evidence that the chlorine at C2 is more readily displaced in this kind of system.[6] Treatment of **7** with ammonia in ethanol in a sealed tube or methylamine in THF led to the formation of **8** (68%) and **9** (83%), respectively. In both cases the product crystallized from the reaction mixture in >95% purity in the indicated yield. The mother liquor from **9** contained more product, along with the regioisomer (4–6% yield) and a small amount of the diamine (2%). The position of the amine was confirmed chemically by conversion to the benzimidazole.

With **8** and **9** in hand we investigated the S_NAr reaction with ketoester **4a** (Table 1). Using K_2CO_3 in DMF, the products **10a** and **11a** were formed in 46 and 56% yield, respectively. The optimum conditions used 1.1 equiv. of base and 1.5 equiv. of ketoester. Functionalized ketoesters **4c** and **4g** gave similar yields. Subsequently it was found that the reaction was faster and generally higher yielding with Cs_2CO_3. Potassium *t*-butoxide also worked well, giving **11a** in 69% yield. Polar solvents such as DMF or DMSO were preferred. Amine bases or phase transfer conditions were unsatisfactory. In contrast to the other examples, reaction of ethyl substituted ketoester **4b** with **8** gave poor yields of **10b** with either K_2CO_3 or Cs_2CO_3. In this case a by-product that appeared to arise from dimerization of **8** was observed. However, a much better yield of the *N*-methyl analog **11b** was obtained when **4b** was reacted with **9** in the presence of Cs_2CO_3. In other cases, the main by-prod-

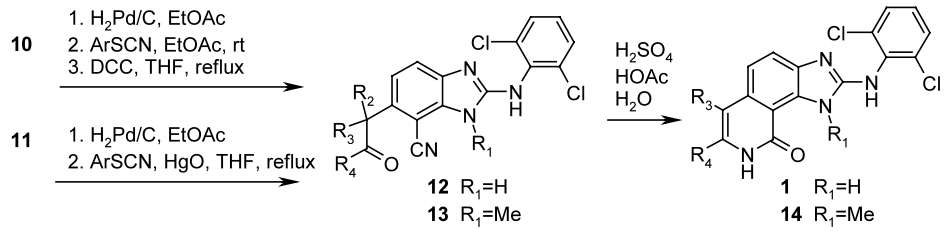


Scheme 2. Synthesis of tetrasubstituted benzene precursor.

Table 1. Examples of S_NAr reaction

Ketone	Nitrile	R_2	R_3	R_4	Conditions[a]	Product	Yield[b]
4a	**8**	CO_2Et	Me	Me	A	**10a**	46
4a	**9**	CO_2Et	Me	Me	A	**11a**	56
4a	**9**	CO_2Et	Me	Me	B	**11a**	80
4a	**9**	CO_2Et	Me	Me	C	**11a**	69
4b	**8**	CO_2Et	Et	Me	A	**10b**	25
4b	**8**	CO_2Et	Et	Me	B	**10b**	16
4b	**9**	CO_2Et	Et	Me	B	**11b**	59
4c	**8**	CO_2Et	CH_2CO_2Et	Me	A	**10c**	40
4c	**9**	CO_2Et	CH_2CO_2Et	Me	B	**11c**	70
4d	**9**	CO_2Et	$(CH_2)_2CO_2Et$	Me	B	**11d**	55
4e	**9**	H	CO_2Me	Me	A	**11e**	84
4f	**8**	CO_2tBu	H	Me	A	**10f**[c]	49
4f	**9**	CO_2tBu	H	Me	B	**11f**[c]	58
4g	**8**	CO_2tBu	H	CH_2OBn	A	**10g**	46
4h	**8**	Ph-4-OMe	H	Me	A	**10h**	41
4i	**9**	CO_2Et	$(CH_2)_3$		B	**11i**	49
4j	**9**	H	$C(=O)(CH_2)_3$		B	**11j**	85

[a] Conditions: A: K_2CO_3, DMF, rt 24–48 h. B: Cs_2CO_3, DMF, rt, 2–6 h. C: KO*t*Bu, DMSO, 25–40°C.
[b] Yields of pure product after chromatography.
[c] R_2 = H, isolated after cleavage of CO_2tBu by treatment with TFA.



Scheme 3. Conversion of ketoesters to imidazo[4,5-*h*]isoquinolin-9-ones.

Table 2. Yields for the conversion of ketoesters to imidazo[4,5-*h*]isoquinolin-9-ones

SM	R_1	R_2	R_3	R_4	Benzimidazole	Yield[a]	Product	Yield
10a	H	CO_2Et	Me	Me	**12a**	47	**1a**	72
11a	Me	CO_2Et	Me	Me	**13a**	51	**14a**	88
11c	Me	CO_2Et	CH_2CO_2Et	Me	**13c**	69	**14e**	78[b]
11d	Me	CO_2Et	$(CH_2)_2CO_2Et$	Me	**13d**	74	**14d**	62[b]
11e	Me	H	CO_2Me	Me	**13e**	77	**14e**	70[c]
10f	H	H	H	Me	**12f**	87	**1f**	48
11f	Me	H	H	Me	**13f**	61	**14f**	90
11i	Me	CO_2Et	$(CH_2)_3$		**13i**	92	**14i**	43

[a] Overall isolated yield for conversion of **10** to **12** or **11** to **13**, respectively.
[b] Yield after re-esterification with $EtOH/H_2SO_4$.
[c] Cyclization in H_2SO_4, 0°C–rt.

ucts were dark baseline material and unreacted nitrile. While most examples used ketoesters, diketones (**4j**) and ketones with additional stabilization by an aromatic ring (**4h**) also gave satisfactory results. The success of this reaction on a highly functionalized system, even in cases where the product contains a quaternary center, provided rapid access to the core of **1**.

To convert **10a** to **1**, either the pyridone or the benzimidazole ring could be formed first. Closure of the pyridone ring, as in the model system, succeeded, but subsequent steps were hampered by the extremely poor solubility of the resulting isoquinolone. Several final compounds were prepared in this way. A more satisfactory procedure was to reduce **10** to the diamine and convert this to the benzimidazole **12** before forming the pyridone ring (Scheme 3). For **12** the diamine was converted to the thiourea, then cyclized with DCC in a separate step. For the *N*-methyl benzimidazoles **13**, treating the diamine with the isothiocyanate and HgO in a one-pot procedure was found to be more reliable. Closure of the pyridone ring by heating **12** and **13** in acid gave **1** and **14** (Table 2). Side chain esters hydrolyzed during the reaction, and were re-esterified prior to isolation. The final product precipitated on neutralization, in most cases in good yield, and did not require further purification. One exception was ester **13e**, which gave a mixture of the ester **14e** and decarboxylated product **14f** under the standard conditions. To obtain **14e** cleanly, **13e** was treated with H_2SO_4 alone, without heating. To access **14f**, the unsubstituted ketone **11f**, obtained from the *t*-butyl ester by treatment with TFA, was treated under the standard conditions. Attempts to hydrolyze the methyl ester of **13e** under basic conditions prior to cyclization led instead to deacetylation.

This approach represents a significant improvement in the synthesis of **1**. The number of steps was reduced from twelve to six, and the added flexibility provided access to analogs for SAR studies, including compounds with functional groups suitable for further elaboration. Certain analogs showed enhanced biological activity, details of which will be reported elsewhere.[7]

Acknowledgements

We thank Drs. Neil Moss and Daniel Goldberg for helpful discussions and critical reading of the manuscript.

References

1. Snow, R. J.; Cardozo, M. G.; Morwick, T. M.; Busacca, C. A.; Dong, Y.; Eckner, R. J.; Jacober, S.; Jakes, S.; Kapadia, S.; Lukas, S.; Panzenbeck, M.; Peet, G. W.; Peterson, J. D.; Prokopowicz, A. S., III; Sellati, R.; Tolbert, R. M.; Tschantz, M. A.; Moss, N. *J. Med. Chem.* **2002**, *45*, 3394–3405.
2. (a) Wu, M.-J.; Chang, L.-J.; Wei, L.-M.; Lin, C.-F. *Tetrahedron* **1999**, *55*, 13193–13200; (b) Sakamoto, T.; Miura, N.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2760–2765.
3. (a) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Synthesis* **2000**, 273–280; (b) Fisher, L. E.; Muchowski, J. M.; Clark, R. D. *J. Org. Chem.* **1992**, *57*, 2700–2705.
4. Bois-Choussy, M.; Beugelmans, R. *Synthesis* **1981**, 729–731.
5. Sommer, M. B.; Bergtrup, M.; Bogeso, P. *J. Org. Chem.* **1990**, *55*, 4817–4821.

6. Capps, D. B.; Dunbar, J.; Kesten, S. R.; Shillis, J.; Werbel, L. M.; Plowman, J.; Ward, D. L. *J. Med. Chem.* **1992**, *35*, 4770–4778.
7. Goldberg, D. R.; Butz, T.; Cardozo, M. G.; Eckner, R. J.; Hammach, A.; Huang, J.; Jakes, S.; Kapadia, S.; Kashem, M.; Lukas, S.; Morwick, T. M.; Moss, N.; Panzenbeck, M.; Patel, U.; Pav, S.; Peet, G. W.; Peterson, J. D.; Prokopowicz, A. S., III; Snow, R. J.; Sellati, R.; Takahashi, H.; Tan, J.; Tschantz, M. A.; Wang, X.; Wang, Y.; Wolak, J.; Xiong, P. *J. Med. Chem.*, submitted.