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A Novel Highly Stereoselective Synthesis of 2,3-Disubstituted *3H*-Quinazoline-4-one Derivatives

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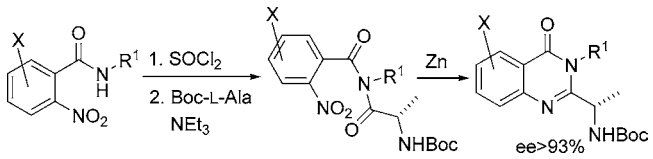
ABSTRACT



An efficient three-step synthesis of chiral 3*H*-quinazoline-4-one derivatives from commercial materials is disclosed. The Mumm reaction of imidoyl chloride with α-amino acids followed by reductive cyclization affords enantiomerically pure (ee >93%) quinazoline-4-ones in good overall yield. A comparison with existing approaches indicates that this method is superior for hindered substrates.

Due to their biological activity, 2,3-disubstituted 3*H*-quinazoline-4-ones represent one of the most interesting groups of heterocycles. In particular, quinazoline-4-one alkaloids such as asperlicin C, possessing cholecystokinin antagonist properties, and benzomalvins, which are neurokinin receptor antagonists, as well as other similar molecules, have attracted significant attention.[1] These alkaloids are often biosynthetically derived from anthranilic acid and chiral amino acids, and as a result contain a chiral center in the α-position of the 2-substituent. Another chiral compound based on the quinazoline-4-one scaffold, a kinesin spindle protein inhibitor ispenisib, is currently in Phase II clinical trials for cancer.[2] Several chiral quinazoline-4-one derivatives selectively inhibiting p110δ kinase, whose potential applications range from autoinflammatory disease to leukemia, have been reported by ICOS scientists.[3]

Many examples of the total synthesis of chiral quinazoline-4-one alkaloids have been reported. The closure of the quinazoline ring while preserving the neighboring chiral center is a critical step in all of these syntheses. There are two main methodologies used to effect the cyclization. One approach, discovered by Mazurkiewicz,[4a] employs isomerization of 4-imino-4*H*-3,1-benzoxazines into quinazoline-4-ones under basic or acidic conditions.[4] This transformation has been used in the stereoselective synthesis of fumiquinazolines A,[4g,k] B,[4g,k] C,[4j,k] E,[4j,k] F,[4f] G,[4c,d,f] H,[4j,k] I,[4g,k] and other

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(1) (a) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659 and references cited therein. For the more recent reviews, see: (b) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 350. (c) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627.

(2) (a) Bergnes, G.; Katjusa, B.; Belmont, L. *Curr. Top. Med. Chem.* **2005**, *5*, 127. (b) Wood, K.; Bergnes, G. *Annu. Rep. Med. Chem.* **2004**, *39*, 173.

(3) (a) Finer, J. T.; Bergnes, G.; Feng, B.; Smith, S. W.; Chabala, J. C.; Morgans, D. J. WO Patent Application 01/98278, 2001. (b) Sadhu, C.; Dick, K.; Treiberg, J.; Sowell, S. J.; Kesicki, E. A.; Oliver, A. U.S. Patent Application 2002/0161014, 2002. (c) Fowler, K. W.; Huang, D.; Kesicki, E. A.; Ooi, H. C.; Oliver, A. R.; Fuqiang, R.; Treiberg, J. WO Patent Application 05/113556, 2005.

(4) (a) Mazurkiewicz, R *Monatsh. Chem.* **1989**, *120*, 973. (b) Snider, B. B.; Zeng, H. *Heterocycles* **2003**, *61*, 173. (c) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432. (d) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397. (e) Hart, D. J.; Magomedov, N. *Tetrahedron Lett.* **1999**, *40*, 5429. (f) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022. (g) Snider, B. B.; Zeng, H. *Org. Lett.* **2000**, *2*, 4103. (h) Witt, A.; Bergman, J. *J. Org. Chem.* **2001**, *66*, 2784. (i) Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892. (j) Snider, B. B.; Zeng, H. *Org. Lett.* **2002**, *4*, 1087. (k) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545. (l) Wang, H.; Sim, M. M. *J. Nat. Prod.* **2001**, *64*, 1497. (m) Wang, H.; Ganesan, A. *J. Comb. Chem.* **2000**, *2, 186*.

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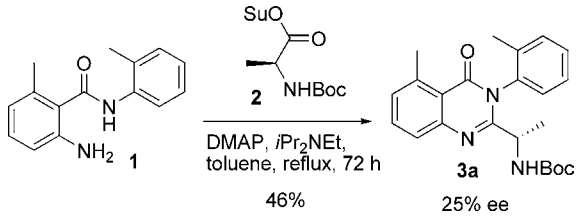
fumiquinazoline analogues,[4m] as well as fiscalin B,[4c,d,f] alantrypinone,[4e,i] glyantrypine,[4f] circumdatins C[4h] and F,[4h] and verrucines A and B.[4l] Another widely used cyclization method is an aza-Wittig cyclization of imines (Eguchi protocol).[5] This protocol has been successfully applied to the stereoselective synthesis of amauromine and 5-*N*-acetylardeemin,[6] fumiquinazoline G and its dehydro-derivative,[7] glyantrypine, fumiquinazoline F, and other 2,4-dihydro-1*H*-pyrazino[2,1-b]quinazoline-3,6-diones,[8] as well as asperlicin[9a] and benzomalvin A.[9b]

As a part of our research on p110δ kinase inhibitors we found it necessary to prepare a series of 2,3-disubstituted 3*H*-quinazoline-4-ones possessing a chiral 2-substituent. In this letter we would like to disclose a novel highly stereoselective approach to such molecules. This approach has shown superior results when directly compared with the other known cyclization methods on the example of compound **3a**.

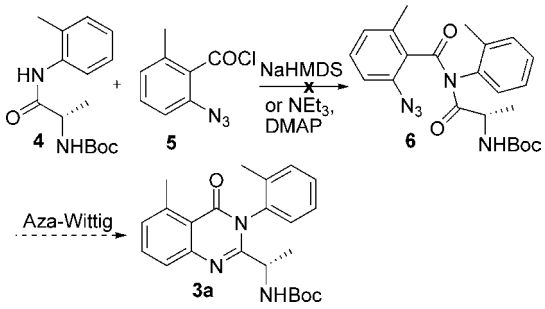
The difficulty of the formation of the quinazoline ring of **3a** is due to the steric hindrance around the 3-nitrogen created by the *o*-tolyl substituent, as well as to the fact that another methyl group, positioned ortho to the carbonyl, prevents the amide from taking the planar configuration necessary for the cyclization. As can be expected from the literature on thermal cyclization,[10] the cyclization of **1** and **2** in refluxing toluene afforded partially epimerized product (Scheme 1):

Scheme 1



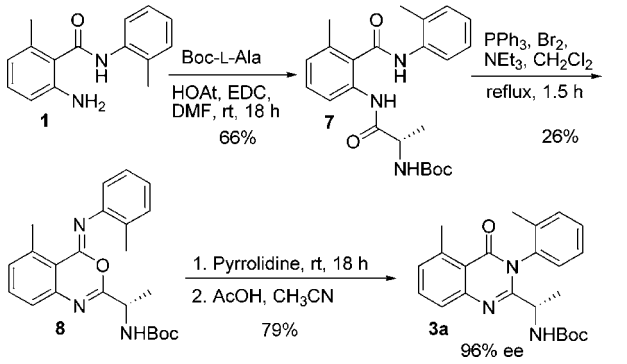
Our attempts to prepare **3a** via the Egichi protocol were not successful (Scheme 2), as no reaction of amide **4** with acid chloride **5** was observed in the presence of either NaHMDS[6a] or NEt_3, DMAP.[9a] A likely explanation for this failure is the decreased reactivity of both the amide nitrogen and the acid chloride carbonyl resulting from their ortho-substitution.

Scheme 2. Attempted Preparation of **3a** by the Eguchi Method



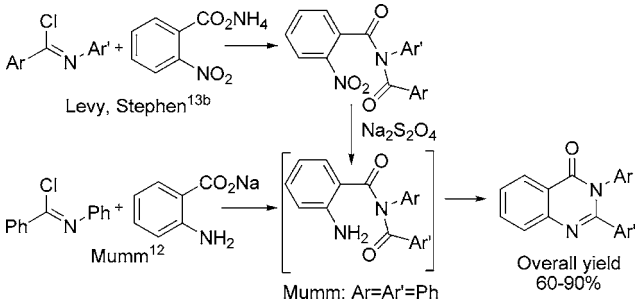
The benzoxazine approach following the Mazurciewitcz–Ganesan procedure[4b] (Scheme 3) afforded **3a** with high ee; however, the overall yield was disappointing (14% from **1**).

Scheme 3



As we were looking for an alternative, more efficient cyclization method, our attention was attracted by the reaction of imidoyl chlorides with carboxylic acids (Mumm rearrangement)[11] and the following cyclization of the resulting imides to 3*H*-quinazoline-4-ones (Scheme 4).

Scheme 4. Original Mumm synthesis and Its Modification by Levy and Stephen



The prototype of this cyclization was also discovered by Mumm.[12] Asahina and Ohta,[13a] followed by Stephen and Levy,[13b] incorporated a reduction of the nitro-group as the final step (Scheme 4), further improving the synthesis.

(5) (a) Takeuchi, H.; Eguchi, S. *Tetrahedron Lett.* **1989**, *30*, 3313. (b) Takeuchi, H.; Hagivara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375.

(6) (a) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143. (b) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953.

(7) He, F.; Snider, B. *Synlett* **1997**, 483.

(8) (a) Hernández, F.; Lumetzberger, A.; Avendaño, C.; Söllhuber, M. *Synlett* **2001**, 1387. (b) Cledera, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **2000**, *65*, 1743. (c) Buenadicha, F. L.; Avendaño, C.; Söllhuber, M. *Tetrahedron*: *Asymmetry* **2001**, *12*, 3019.

(9) (a) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417. (b) Sugimori, T.; Okawa, T.; Eguchi, S.; Kakehu, A.; Yashima, E.; Okamoto, Y. *Tetrahedron* **1998**, *54*, 7997.

(10) Significant enantiomeric erosion was observed during the microwave synthesis of fumiquinazoline F: Li, J.-F.; Ye, P.; Zhang, B.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 6339.

Table 1. Synthesis of Chiral Quinazoline-4-one Derivatives **3**

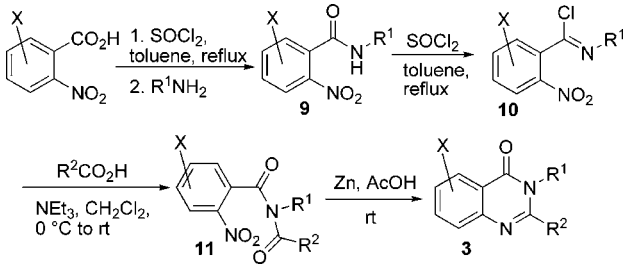
series	X	R^1	yield of **9** (%)	R^2CO_2H	R^2	yield of **11** (%)	yield of **3** (%)	ee of **3** (%)
a	6-Me	2-methylphenyl	89	Boc-L-alanine	*S*-CH(Me)NHBoc	88	58	>99[a]
b	6-Me	Ph	100	Boc-L-alanine	*S*-CH(Me)NHBoc	80	60	98[a]
c	6-Me	3,5-difluorophenyl	58	Boc-L-alanine	*S*-CH(Me)NHBoc	63	40	94[a]
d	H	Bn	84	Boc-L-alanine	*S*-CH(Me)NHBoc	71	71	>99[a]
e	H	Ph	*c*	Boc-L-serine	*R*-CH(CH_2OH)NHBoc	40	57	94[b]
f	6-F	Ph	99	Boc-D-α-Abu-OH	*R*-CH(Et)NHBoc	55	67	>98[g]
g	H	2,6-difluorophenyl	97	Boc-L-alanine	*S*-CH(Me)NHBoc	*d*,*e*	49[f]	93[a]
h	6-Me	2,6-difluorophenyl	45	Boc-L-alanine	*S*-CH(Me)NHBoc	*d*,*e*	20[f]	>99[a]

[a] Ee was determined by removing the Boc-group with TFA/CH_2Cl_2. The resulting amine was reacted with racemic and with (*R*)-1-(1-naphthyl)ethyl isocyanate, and HPLC traces of these two samples were compared. [b] Ee was determined by reacting **3e** with racemic and with (*S*)-α-methoxyphenylacetyl chloride and comparing HPLC traces of these two samples. [c] Commercially available. [d] Made via KHMDS procedure. [e] Intermediate not isolated. [f] Yield over two steps. [g] Ee was determined by chiral HPLC.

Similarly to the azide in the Eguchi protocol, the nitro-group in the Mumm synthesis serves as the amine equivalent. The few known examples in the literature suggest that these two methodologies have similar scope. It remains unclear to us why the Mumm synthesis has been forgotten[14] while the Eguchi protocol, which employs the potentially dangerous aryl azide, has gained prominence.

On the basis of this research, we envisioned the synthesis beginning with the preparation of imidoyl chloride followed by the reaction with a chiral amino acid (Scheme 5).

Scheme 5. Stereoselective Synthesis of 2,3-Disubstituted 3*H*-Quinazoline-4-one Derivatives via the Mumm Reaction



Importantly, during the Mumm rearrangement with amino acids the chirality is preserved.[15] The reduction−cyclization of the resulting chiral *N*-acyl-2-nitrobenzamide can then be effected under mild conditions avoiding epimerization of the chiral center.

Reaction of **9a** and thionyl chloride afforded imidoyl chloride **10a** in quantitative yield. Because **10a** is unstable to air, it was treated directly with Boc-L-alanine, affording a good yield of **11a** (88%). Out of several reducing agents tried (H_2/Pd, H_2/Pd(OH)$_2$, $Na_2S_2O_4$, Al/NH_4Cl, Raney Ni, $NiCl_2$/$NaBH_4$, $SnCl_2$, Fe/HCl, Fe/NH_4Cl, Pd/polymethylhydrosiloxane) for the cyclization, zinc powder in acetic acid gave the best yield of **3a** (58%). To our great satisfaction, a single enantiomer of **3a** formed almost exclusively (ee >99%, see Table 1).

Several other 3*H*-quinazoline-4-ones with different 5- and 3-substituents have been prepared successfully starting with corresponding anilides (or benzylamide) of 2-nitrobenzoic acids and Boc-protected amino acids (Table 1). The yields on both steps are moderate to good, and the ee of the products is uniformly high (>93%). Somewhat lower yields in the case of Boc-L-serine are the result of side reactions of the hydroxy-group.

If desired, chromatographic purification of the intermediate imide **11** can be avoided, and a crude reaction mixture can be used in the subsequent reductive cyclization after a minimal workup. Conversion of **9a** into **3a** under these conditions proceeded in a 43% yield as compared to 51% for the two-step procedure. For the reason of convenience, the syntheses of **3g**,**h** were conducted without purification of the intermediate imine.

Further increase of the hindrance around the aromatic ring R^1 from one ortho-substituent (2-methyl, **3a**) to two ortho-substituents (2,6-difluoro, **3g**,**h**) dramatically diminished the reactivity of the corresponding imidoyl chlorides. Imidoyl chlorides **10g** and **10h** failed to react with Boc-L-alanine under standard conditions in dichloromethane. Heating the reaction to 85 °C in toluene or addition of catalytic DMAP had no effect. To remedy this, we deprotonated **9g**,**h** with KHMDS and then treated the anion with the succinimide ester of Boc-L-alanine to give **11g**,**h** (Scheme 6). This approach was successful (albeit low-yielding) even in the case of **11h** when a total of four ortho-substituents were

(11) (a) Mumm, O. *Chem. Ber.* **1910**, *43*, 886. For the mechanism see: (b) Brady, K.; Hegarty, A. *J. Chem. Soc., Perkin Trans. 2* **1980**, *121*.

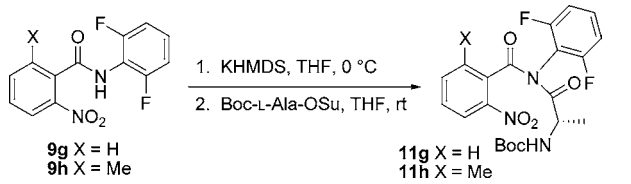
(12) Mumm, O.; Hesse, H. *Chem. Ber.* **1910**, *43*, 2505. For more examples see: Spath, E.; Platzer, N. *Chem. Ber.* **1935**, *68*, 2221.

(13) (a) Asahina, Y.; Ohta, T. *Yakugaku Zasshi* **1928**, *48*, 313; *Chem. Abstr.* **1928**, *22*, 29031. (b) Levy, P. B.; Stephen, H. *J. Chem. Soc.* **1956**, *985*.

(14) To the best of our knowledge, the Mumm rearrangement or the following reductive cyclization has never been used in the synthesis of chiral 3*H*-quinazoline-4-one derivatives. There are only three other articles that involve preparation of any 3*H*-quinazoline-4-ones via reduction of *N*-acyl-2-nitrobenzamides, and neither article mentions the original authors. Two of them utilized impractical CO with heating and pressure as the reducing agent. (a) Motohiro, A.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1993**, *58*, 310. (b) Nishiyama, Y.; Hirose, M.; Kitagaito, W. *Tetrahedron Lett.* **2002**, *43*, 1855. (c) The third paper, dealing with the synthesis of deoxyvasicinone, appeared during preparation of this paper: Ziaee, V.; Jalalizadeh, H.; Iranshahi, M.; Shafiee, A. *Iran. J. Chem. Chem. Eng.* **2004**, *23*, 33.

(15) Gruszecki, W.; Gruszecka, M.; Bradaczek, H. *Liebigs Ann. Chem.* **1988**, *331*.

Scheme 6. Alternative Imide Formation via KHMDS



9g X = H
9h X = Me

11g X = H
11h X = Me

present. For comparison, a similar step in the Eguchi protocol (reaction of chloride **5** with the anion of **4**) failed (see Scheme 2). In the reactions of the amide anion and a neutral electrophile, hindrance around the anion generally affects the reaction rate much less than hindrance around a neutral electrophile. This may explain why the Eguchi protocol is so sensitive to the *o*-methyl substitution in the acid chloride (**5**). The fact that the hindrance in the reaction in Scheme 6 is present only in the amide anion creates an inherent advantage of our method over the Eguchi protocol in its applicability to the hindered substrates.

In conclusion, we have found a novel approach to the synthesis of chiral 2,3-disubstituted 3*H*-quinazoline-4-one derivatives. This method is efficient (3 steps from commercial starting materials), affords materials of high enantiomeric purity (ee >93%), and is, particularly for hindered substrates, superior to other known methods.

Supporting Information Available: Experimental procedures and characterization for compounds **1**, **3a**−**h**, **7**, **8**, **9a**−**h**, **10a**,**d**,**e**, and **11a**−**f**, as well as procedures for ee determination for compounds **3a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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