

Synthesis of Novel Benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinone Derivatives via Transition-Metal-Free Intramolecular Hydroamination

Mohammad Mahdavi,^a Niloufar Foroughi,^a Mina Saeedi,^a Maryam Karimi,^a Heshmatollah Alinezhad,^b Alireza Foroumadi,^a Abbas Shafiee,^a Tahmineh Akbarzadeh^{*c,d}

^a Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran

^b Faculty of Chemistry, Mazandaran University, Babolsar, Iran

^c Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran 14176, Iran

^d Persian Medicine and Pharmacy Research Center, Tehran University of Medical Sciences, Tehran, Iran

Fax +98(21)66461178; E-mail: akbarzad@tums.ac.ir

Received: 10.10.2013; Accepted after revision: 01.11.2013

Abstract: Novel benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinone derivatives were synthesized through an efficient *7-exo-dig* hydroamination of 3-substituted-2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-ones in the presence of potassium *tert*-butoxide (KOt-Bu) in DMF at 130 °C.

Key words: hydroamination, 2-aminobenzamides, terminal alkynes, *7-exo-dig*, N-heterocycles

Intramolecular and intermolecular hydroamination reactions constitute a versatile and atom economic synthetic process for the direct formation of a C–N bond leading to nitrogen-containing heterocycles.^{1–3} Various structures such as complex sulfonamide scaffolds,⁴ indolizines,⁵ indolo[1,2-*c*]quinazolines,⁶ azomethine imines,⁷ tetrahydroisoquinoline alkaloids,⁸ N-heterocyclic carbenes,⁹ and pyrazoles¹⁰ have been successfully prepared by this approach. The range of reports concerning hydroamination reactions^{11–14} confirm hydroamination as a strategy for the preparation of N-heterocyclic compounds.

As a part of our ongoing studies on the synthesis of heterocycles and bioactive compounds,¹⁵ we focused on synthetic applications of intramolecular hydroamination to prepare a novel fused benzoxazepine-quinazolinone scaffold.

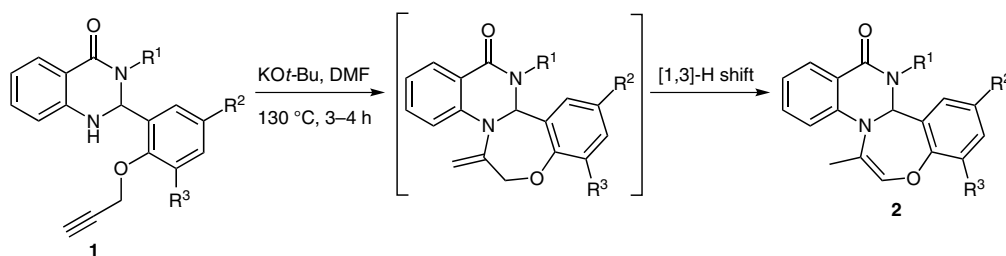
The association of benzoxazepines with various biological activities, such as anticonvulsant and hypnotic,¹⁶ anti-

cancer,¹⁷ and antipsychotic¹⁸ activities is well documented in the literature.

Furthermore, quinazolinone motifs are one of the most important frameworks in natural products such as febri-fugine and isofebri-fugine¹⁹ and a very significant family of compounds displaying various biological properties including antiulcer,²⁰ anti-inflammatory,²¹ anticancer,²² hypolipidemic,²³ and anticonvulsant effects.²⁴ Despite the fact that benzoxazepine and quinazolinone derivatives have been frequently synthesized and evaluated for their bioactivity, there is no report on the synthesis of fused benzoxazepine-quinazolinone derivatives.

In order to obtain the title compounds we concentrated on 3-substituted-2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-one derivatives **1** (Scheme 1) as a potential substrate for the intramolecular hydroamination. In the event, in the presence of strong base, they readily tolerated *7-exo-dig* hydroamination followed by [1,3]-H shift to afford new benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinone derivatives **2** (Scheme 1).

Recently, our research group has developed the use of isatoic anhydride (**3**, Scheme 2) as a versatile starting material to obtain various heterocyclic compounds.^{15c,25} Herein, relying on this earlier work, we report the preparation of novel fused benzoxazepine-quinazolinones **2** starting from **3**. Initially, various 2-aminobenzamide derivatives **5** were prepared by the reaction of equimolar



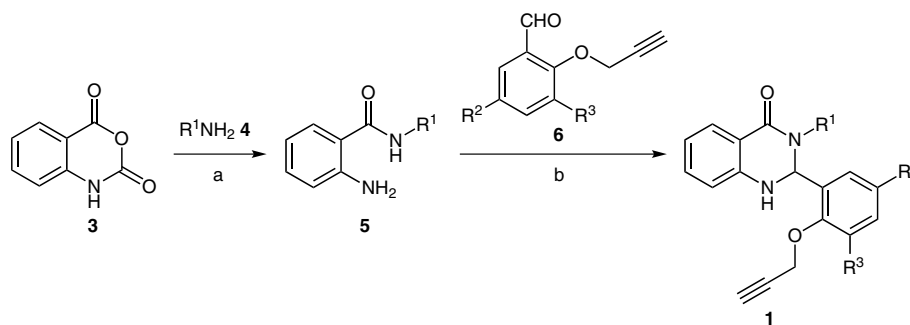
Scheme 1 Synthesis of benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinones **2**

SYNLETT 2014, 25, 0385–0388

Advanced online publication: 06.12.2013

DOI: 10.1055/s-0033-1340310; Art ID: ST-2013-D0957-L

© Georg Thieme Verlag Stuttgart · New York



Scheme 2 Synthesis of 3-substituted-2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-ones **1a–i**. Reagents and conditions: (a) H₂O, r.t., 2–3 h; (b) 2-(prop-2-yn-1-yloxy)benzaldehyde derivatives, K₂CO₃, DMF, 80 °C, 10–12 h.

amounts of isatoic anhydride (**3**) and amines **4** in water at room temperature for 2–3 hours.

Next, these were efficiently reacted with a range of 2-(prop-2-yn-1-yloxy)benzaldehyde derivatives **6** in the presence of potassium carbonate (K₂CO₃) in DMF at 80 °C to give 3-substituted 2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-ones **1a–i** in good yields (60–75%).

In the next step, we investigated the subsequent intramolecular cyclization reaction of starting material **1** to form benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinones **2**. For our initial optimization studies, we selected 3-(2-chlorobenzyl)-2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-one (**1f**) as a substrate and examined various conditions for the best performance of hydroamination reaction.

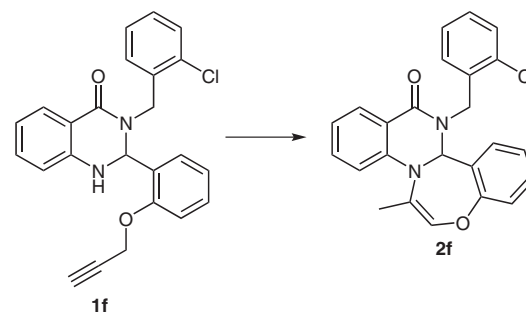
A scrutiny of publications devoted to hydroamination reactions revealed that they usually need to be catalyzed by various metals.² Therefore, developing an efficient and easy procedure in the absence of complex and expensive catalysts would be worthwhile. Recently, Trofimov et al.²⁶ introduced base/DMSO systems for α -vinylation of aromatic, aliphatic, and cycloaliphatic ketones with aryl-acetylenes. Influenced by their results, we investigated similar systems for the hydroamination reaction in Scheme 1. Preliminary base and solvent screening was performed and some results are shown in Table 1. From these studies we concluded that utilizing KO*t*-Bu in DMF led to the formation of the corresponding product **2f** in the best yield.

We also screened for the optimal amount of KO*t*-Bu and temperature. We were pleased to observe that when the model reaction was conducted in the presence of two equivalents of KO*t*-Bu in DMF at 130 °C, **2f** could be isolated in a promising yield (80%, Table 1, entry 5). Changing the amount of base to threefold did not result in better yield (Table 1, entry 6).

The structure of 8-(2-chlorobenzyl)-1-methyl-7b,8-dihydro-9*H*-benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolin-9-one (**2f**) was clearly confirmed by mass spectrometry, IR and NMR spectroscopy. In the IR spectrum of **2f**, three absorption bands at 3053, 2929, and 2850 cm⁻¹, one sharp absorption band at 1665 cm⁻¹, and one sharp absorption

band at 1652 cm⁻¹ were observed which could be related to aromatic and aliphatic C–H, C=O, and C=C stretching frequencies. The MS peak ($m/z = 404/402$) associated with the molecular ion was in accordance with the calculated mass for C₂₄H₁₉ClN₂O₂. The ¹H NMR spectrum of **2f** consisted of two series of signals at high field. A singlet at $\delta = 1.98$ ppm and two doublets at $\delta = 4.20$ and 5.39 ppm ($J = 16.0$ Hz) relating to protons of the CH₃ and NCH₂ groups, respectively. Two singlets at $\delta = 6.00$ and 6.68 ppm correspond to two CH groups and 12 aromatic pro-

Table 1 Investigation of Various Conditions for the Hydroamination of **1f** to Obtain the Corresponding Product **2f**



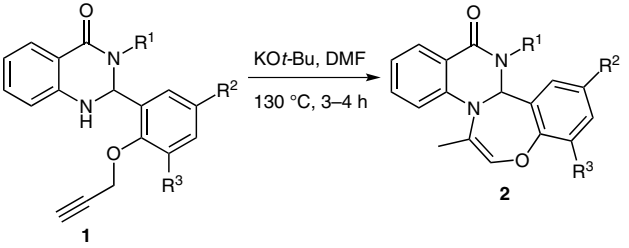
Entry	Solvent	Base (equiv)	Temp (°C)	Yield (%) ^a
1	DMF	KO <i>t</i> -Bu (1)	60	55
2	DMF	KO <i>t</i> -Bu (2)	80	58
3	DMF	KO <i>t</i> -Bu (2)	100	60
4	DMF	KO <i>t</i> -Bu (1)	130	65
5	DMF	KO <i>t</i> -Bu (2)	130	80
6	DMF	KO <i>t</i> -Bu (3)	130	80
7	DMF	KOH (2)	100	20
8	DMF	NaOH (2)	100	20
9	DMSO	KO <i>t</i> -Bu (2)	60	35
10	DMSO	KO <i>t</i> -Bu (2)	130	40
11	DMSO	KOH (2)	100	20
12	DMSO	NaOH (2)	130	20

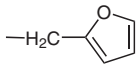
^a Isolated yields.

tons which appeared between $\delta = 6.78$ and 7.81 ppm. As expected, the ^{13}C spectrum showed 24 distinct resonances.

With these results in hand, we prepared various benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinone derivatives **2a–i** (Table 2).²⁷ Substrates **1** possessing both electron-rich as well as electron-poor substituents on aromatic rings underwent 7-*exo-dig* hydroamination followed by [1,3]-H shift to give the desired products **2**.

Table 2 Synthesis of Benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinones **2**²⁷



Entry	R ¹	R ²	R ³	Product	Yield (%) ^a
1	Bu	H	H	2a	68
2	Bu	H	OMe	2b	70
3	Bn	H	H	2c	80
4	4-FC ₆ H ₄ CH ₂	H	H	2d	74
5	4-FC ₆ H ₄ CH ₂	Br	H	2e	85
6	2-ClC ₆ H ₄ CH ₂	H	H	2f	80
7	4-MeC ₆ H ₄ CH ₂	H	H	2g	82
8	Ph	Br	H	2h	71
9		H	OMe	2i	70

^a Isolated yields.

The structures of all products **2a–i** were elucidated from their spectroscopic analyses as described herein for **2f**.

In summary, a convenient and applicable protocol for the intramolecular hydroamination reaction of 3-substituted 2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-ones has been developed in the absence of transition-metal catalysts.

The corresponding benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinone derivatives were readily obtained using two equivalents of KO^{*t*}-Bu in DMF at 130 °C in good yields. We believe that this method could be applicable in the drug discovery area.

Acknowledgement

This research was supported by grants from the research council of Tehran University of Medical Sciences and Iran National Science Foundation (INSF).

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

References and Notes

- Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.
- Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.
- Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104.
- Gregory, A. W.; Jakubec, P.; Turner, P.; Dixon, D. J. *Org. Lett.* **2013**, *15*, 4330.
- Siddiqui, I. R.; Abumhdi, A. A. H.; Shamim, S.; Shireen Waseem, M. A.; Rahila Srivastava, A.; Srivastava, A. *RSC Adv.* **2013**, *3*, 10173.
- Xu, M.; Xu, K.; Wang, S.; Yao, Z.-J. *Tetrahedron Lett.* **2013**, *54*, 4675.
- Hunt, A. D.; Dion, I.; Neves, N. D.; Taing, S.; Beauchemin, A. M. *J. Org. Chem.* **2013**, *78*, 8847.
- (a) Pouilhès, A.; Baltaze, J.-P.; Kouklovsky, C. *Synlett* **2013**, *24*, 1805. (b) Ogata, T.; Kimachi, T.; Yamada, K.-I.; Yamamoto, Y.; Tomioka, K. *Heterocycles* **2012**, *86*, 469.
- López-Gómez, M.-J.; Martin, D.; Bertrand, G. *Chem. Commun.* **2013**, *49*, 4483.
- Yoshimatsu, M.; Ohta, K.; Takahashi, N. *Chem. Eur. J.* **2012**, *18*, 15602.
- Nguyen, T. M.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9588.
- Roth, T.; Wadepohl, H.; Wright, D. S.; Gade, L. H. *Chem. Eur. J.* **2013**, *19*, 13823.
- Strom, A. E.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8909.
- Wang, Y.; Rapakousiou, A.; Latouche, C.; Daran, J.-C.; Singh, A.; Ledoux-Rak, I.; Ruiz, J.; Saillard, J.-Y.; Astruc, D. *Chem. Commun.* **2013**, *49*, 5862.
- (a) Akbarzadeh, T.; Rafinejad, A.; Mollaghasem, J. M.; Safavi, M.; Fallah-Tafti, A.; Pordeli, M.; Ardestani, S. K.; Shafiee, A.; Foroumadi, A. *Arch. Pharm. Chem. Life Sci.* **2012**, *345*, 386. (b) Akbarzadeh, T.; Tabatabai, S. A.; Khoshnoud, M. J.; Shafaghani, B.; Shafiee, A. *Bioorg. Med. Chem.* **2012**, *11*, 769. (c) Mahdavi, M.; Asadi, M.; Saeedi, M.; Rezaei, Z.; Moghbel, H.; Foroumadi, A.; Shafiee, A. *Synlett* **2012**, *23*, 2521.
- Deng, X.-Q.; Song, M.-X.; Wei, C.-X.; Sun, Z.-G.; Quan, Z.-S. *Med. Chem. Res.* **2011**, *20*, 996.
- Banerji, B.; Pramanik, S. K.; Sanphui, P.; Nikhar, S.; Biswas, S. C. *Chem. Biol. Drug Des.* **2013**, *82*, 401.
- Liégeois, J. F.; Deville, M.; Dilly, S.; Lamy, C.; Mangin, F.; Résimont, M.; Tarazi, F. I. *J. Med. Chem.* **2012**, *55*, 1572.
- (a) Koepfli, J. B.; Mead, J. F.; Brockman, J. A. Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1837. (b) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175.
- Terashima, K.; Shimamura, H.; Kawase, A.; Tanaka, Y.; Tanimura, T.; Kamisaki, T.; Ishizuka, Y.; Sato, M. *Chem. Pharm. Bull.* **1995**, *43*, 2021.
- Rather, B. A.; Raj, T.; Reddy, A.; Ishar, M. P. S.; Sivakumar, S.; Paneerselvam, P. *Arch. Pharm. Chem. Life Sci.* **2010**, *343*, 108.
- Cao, S. L.; Feng, Y. P.; Jiang, Y. Y.; Liu, S. Y.; Ding, G. Y.; Li, R. T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1915.
- Kurogi, Y.; Inoue, Y.; Tsutsumi, K.; Nakamura, S.; Nagao, K.; Yohsitsugu, H.; Tsuda, Y. *J. Med. Chem.* **1996**, *39*, 1433.
- Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. *J. Med. Chem.* **1990**, *33*, 161.
- (a) Asadi, M.; Ebrahimi, M.; Mahdavi, M.; Saeedi, M.; Ranjbar, P. R.; Yazdani, F.; Shafiee, A.; Foroumadi, A. *Synth. Commun.* **2013**, *43*, 2385. (b) Shafii, B.; Saeedi, M.; Mahdavi, M.; Foroumadi, A.; Shafiee, A. *Synth. Commun.* **2014**, *44*, 215. (c) Farzipour, S.; Mahdavi, M.; Saeedi, M.;

Yavari, H.; Mirzahekmati, M.; Ghaemi, N.; Foroumadi, A.; Shafiee, A. *Synth. Commun.* **2013**, in press.

- (26) (a) Trofimov, B. A.; Schmidt, E. Yu.; Ushakov, I. A.; Zorina, N. V.; Skital'tseva, E. V.; Protsuk, N. I.; Mikhaleva, A. I. *Chem. Eur. J.* **2010**, *16*, 8516. (b) Trofimov, B. A.; Schmidt, E. Y.; Zorina, N. V.; Ivanova, E. V.; Ushakov, I. A. *J. Org. Chem.* **2012**, *77*, 6880.
- (27) **Synthesis of Benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinone Derivatives 2 – General Procedure**
A mixture of 3-substituted 2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-one **1** (1 mmol) and KO*t*-Bu (2 mmol) in DMF (5 mL) was stirred at 130 °C for 3–4 h. Upon completion of reaction, checked by TLC, the reaction mixture was poured into cold H₂O, the precipitate was filtered off, and the residue was purified using plate chromatography eluting with PE–EtOAc (4:1). **8-Butyl-1-methyl-7b,8-dihydro-9*H*-benzo[6,7][1,4]-oxazepino[4,5-*a*]quinazolin-9-one (2a)**

Yield 0.23 g (68%); yellow oil. IR (KBr): 3060, 2957, 2850, 1659 (C=O), 1614, 1482 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 0.87 (t, *J* = 7.2 Hz, 3 H, NCH₂CH₂CH₂CH₃), 1.27–1.33 (m, 2 H, NCH₂CH₂CH₂CH₃), 1.54–1.63 (m, 2 H, NCH₂CH₂CH₂CH₃), 2.02 (s, 3 H, CH₃), 2.84–2.91 (m, 1 H, NCH₂^aCH₂CH₂CH₃), 4.04 (m, 1 H, NCH₂^bCH₂CH₂CH₃), 5.76 (s, 1 H, CH, H₂), 6.67 (s, 1 H, CH), 6.72 (d, *J* = 7.6 Hz, 1 H, H₁₃), 6.82 (t, *J* = 7.6 Hz, 1 H, H₁₁), 6.88 (d, *J* = 7.0 Hz, 1 H, H₄), 6.99 (t, *J* = 7.0 Hz, 1 H, H₆), 7.05 (d, *J* = 7.0 Hz, 1 H, H₇), 7.24 (dt, *J* = 7.0, 1.2 Hz, 1 H, H₅), 7.29 (dt, *J* = 7.6, 1.2 Hz, 1 H, H₁₂), 7.77 (dd, *J* = 7.6, 1.2 Hz, 1 H, H₁₀). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 14.1, 20.0, 20.3, 30.3, 45.3, 70.6, 107.1, 113.7, 115.9, 119.4, 121.2, 123.9, 124.9, 128.3, 130.5, 131.2, 134.1, 143.5, 143.7, 155.1, 162.0. Anal. Calcd for C₂₁H₂₂N₂O₂: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.28; H, 6.78; N, 8.19.

Data for compounds **2b–i** are given in the Supporting Information.