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Synthesis of 2-Aryl-oxazolo[4,5-*c*]quinoline-4(5*H*)-ones and 2-Aryl-thiazolo[4,5-*c*]quinoline-4(5*H*)-ones

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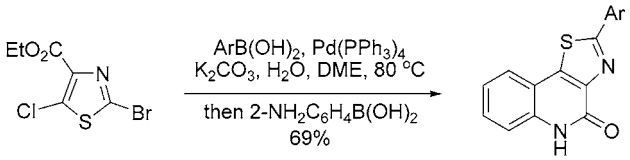
ABSTRACT



13 **2**

Novel and highly efficient syntheses of oxazolo[4,5-*c*]quinoline-4(5*H*)-ones (1) and thiazolo[4,5-*c*]quinoline-4(5*H*)-ones (2) from ethyl 2-chlorooxazole-4-carboxylate (4) and ethyl 2-bromo-5-chlorothiazole-4-carboxylate (13), respectively, are described.

In the search for biologically active compounds as potential drug candidates, the efficient synthesis of both libraries and individual heterocyclic small molecules is of major importance to the pharmaceutical industry. Approaches involving a sequence of regiocontrolled halogenation followed by palladium-catalyzed coupling based upon a heterocyclic scaffold have been successfully developed.[1] We have previously described the regiocontrolled synthesis of substituted thiazoles[2] and oxazoles[3] using such a strategy. As part of a medicinal chemistry project at Neurogen, a series of 2-aryl-oxazolo[4,5-*c*]quinoline-4(5*H*)-ones (**1**) having high affinity for the GABA (γ-aminobutyric acid) receptor were discovered.[4,5] GABA is a major inhibitory neurotransmitter in the central nervous system, and compounds with the appropriate receptor binding profile and functional selectivity have potential pharmaceutical use as anxiolytics, hypnotics, and cognition enhancers.[6] Routes to oxazolo[4,5-*c*]-quinolinones reported in the literature include (i) cyclization of 3-amino-4-hydroxy-2-quinolones with carboxylic acids in polyphosphoric acid (PPA),[7] (ii) Beckmann rearrangement of the oxime of 3-aryl-4-hydroxy-2-quinolones,[8] (iii) reaction of isatoic anhydrides with α-isocyanoacetates,[9] and (iv) thermolysis of 4-azidoquinolones with carboxylic acids in PPA.[10] Limitations to these approaches include the preparation and the reported instability of the 3-amino-4-hydroxy-2-quinolone intermediates[11] and the relatively harsh cyclization conditions,

(1) For excellent reviews of this strategy see: (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1921. (b) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2845. (c) Snieckus, V. *Med. Res. Rev.* **1999**, *19*, 342.

(2) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 1363.

(3) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 2905.

(4) Albaugh, P. U.S. Patent 5,182,290, 1993.

(5) For related series, see: (a) Albaugh, P. A.; Marshall, L.; Gregory, J.; White, G.; Hutchison, A.; Ross, P. C.; Gallagher, D. W.; Tallman, J. F.; Crago, M.; Cassella, J. V. *J. Med. Chem.* **2002**, *45*, 5043. (b) Forbes, I. T.; Johnson, C. N.; Jones, G. E.; Loudon, J.; Nicholass, J. M. Thompson, M. *J. Med. Chem.* **2002**, *45*, 2640 and references therein.

(6) For recent reviews of the therapeutic areas addressed through modulation of GABA, see: (a) Chebib, M.; Johnston, G. A. R. *J. Med. Chem.* **2000**, *43*, 1427. (b) Tallman, J. F.; Cassella, J. V.; White, G.; Gallagher, D. W. *Neuroscientist* **1999**, *5*, 351.

(7) (a) Merchant, J. R.; Shirali, S. S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3075. (b) Ponomarev, O. A.; Brusilt'sev, Y. N.; Grif, V. K.; Mitina, V. G. *Ukr. Khim. Zh.* **1990**, *56*, 272. (c) Ukrainets, I. V.; Taran, S. G.; Sidorenko, L. V.; Gorokhova, O. V.; Turov, A. V. *Chem. Het. Compds.* **1997**, *33*, 1328.

(8) Zoorob, H. H.; Hamama, W. S. *Egypt. J. Chem.* **1986**, *29*, 325.

(9) Suzuki, M.; Matsumoto, K.; Miyoshi, M.; Yoneda, N.; Ishida, R. *Chem. Pharm Bull.* **1977**, *25*, 2602.

(10) Steinschifter, W.; Fiala, W.; Stadlbauer, W. *J. Het. Chem.* **1994**, *31*, 1647 and references therein.

(11) Ukrainets, I. V.; Taran, S. G.; Sidorenko, L. V.; Gorokhova, O. V.; Turov, A. V.; Ogirenko, A. A. *Chem. Heterocycl. Compd.* **1997**, *33*, 815.

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heating to 120−150 °C in PPA, which are incompatible with sensitive functionality. We were also interested in the synthesis of the related thiazolo analogues, although to the best of our knowledge thiazolo[4,5-*c*]-quinoline-4(5*H*)-ones (**2**) have not previously been reported in the chemical literature.

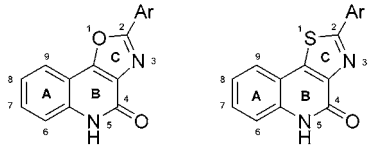
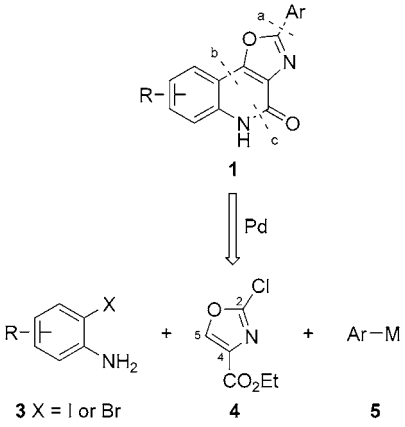


Figure 1.

We required efficient and flexible routes, such that modifications at the 2-position and on the A-ring could easily be accomplished. Three disconnections, a, b, and c, indicated that **1** could be constructed from readily available starting materials: 2-haloaniline **3**, ethyl 2-chlorooxazole-4-carboxylate (**4**),[3] an organometallic reagent **5** and a sequence of palladium-catalyzed reactions (Scheme 1). We have previously established that a variety of substituents could be incorporated at the 2-position of the oxazole **4**[3] using various palladium-catalyzed reactions (disconnection a).[12] Introduction of the second aryl ring, destined to become the A-ring, should be possible via a palladium-catalyzed Heck[13] reaction of a 2-haloaniline **3** and the 5-position of the oxazole (disconnection b).[14] Cyclization between the aniline and the 4-carboxyl functionality of the oxazole should complete the synthesis of **1** (disconnection c). Reversing the order of the disconnections b and c, amide bond formation followed by intramolecular Heck reaction, should also lead to **1**.

Scheme 1



The 2-phenyl substituent was introduced by Suzuki−Miyaura[15] coupling of the oxazole **4** with phenylboronic acid and gave **6** in 87% yield. The introduction of the second aryl group at the 5-oxazole position via a palladium-catalyzed Heck reaction[13] was then investigated. Optimal conditions for 2-iodonitrobenzene proved to be $Pd(OAc)_2$, PPh_3, and Cs_2CO_3 in DMF at 140 °C for 3 h, which gave an 83% yield of the coupled product **7**. To widen the breadth of potential aryl substituents, 2-bromo- and 2-chloronitrobenzene were also examined in the reaction. Under the same conditions 2-bromonitrobenzene gave clean coupling and an excellent 80% yield of **7**, whereas 2-chloronitrobenzene gave a modest 31% yield. Aryl chlorides are generally very poor electrophiles in the Heck reaction; however, the electron-withdrawing nitro substituent enhances the rate of the oxidative addition step during the catalytic cycle. Heating the reaction longer than 3 h did not increase the yield of **7** presumably because of palladium complex decomposition. To prolong the life of palladium complexes, PPh_3 ligands have been replaced by the more bulky P(*o*-tolyl)$_3$, the assumption being that the bulkier phosphine forms a more stable PdL_2 species and that quaternization of the phosphorus by the aryl halide is minimized.[16] Gratifyingly, the use of P(*o*-tolyl)$_3$ in place of PPh_3 in the reaction of **4** with 2-chloronitrobenzene gave a 78% yield of **7**. The nitro group of **7** was then hydrogenated, using 10% Pd/C as the catalyst, and gave following workup, somewhat surprisingly, only the uncyclized aniline **8**. Indeed, the ^{1}H NMR of a d_6-DMSO solution of the aniline **8** remained unchanged after several hours at room temperature. To complete the cyclization, the aniline **8** was refluxed in a solution of DME and aqueous K_2CO_3 and gave, following recrystallization, pure 2-phenyl-oxazolo[4,5-*c*]-quinoline-4(5*H*)-one (**9**)[7c] in 77% yield (Scheme 2).

An alternative method for the introduction of the 5-aryl substituent was investigated next. The oxazole **6** was brominated at the 5-position by treatment with an excess of *N*-bromosuccinimide in refluxing chloroform and gave the bromide **10** in 86% yield. Under Suzuki−Miyaura conditions the 5-bromooxazole **10** was treated with commercially

(12) For other examples of palladium-catalyzed reactions of oxazoles, see: (a) Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry*; Pergamon Press: Elmsford, Oxford, 2000; Chapter 8, pp 321−333. (b) Sakamoto, T.; Nagata, H.; Kondo, Y.; Shiraiwa, M.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 823. (c) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415. (d) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4633. (e) Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1998**, *63*, 8640. (f) Boto, A.; Ling, M.; Meek, G.; Pattenden G. *Tetrahedron Lett.* **1998**, *39*, 8167. (g) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011. (h) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469. (i) Smith, A. B., III; Minibiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. (j) Clapham, B.; Sutherland, A. J. *J. Org. Chem.* **2001**, *66*, 9033.

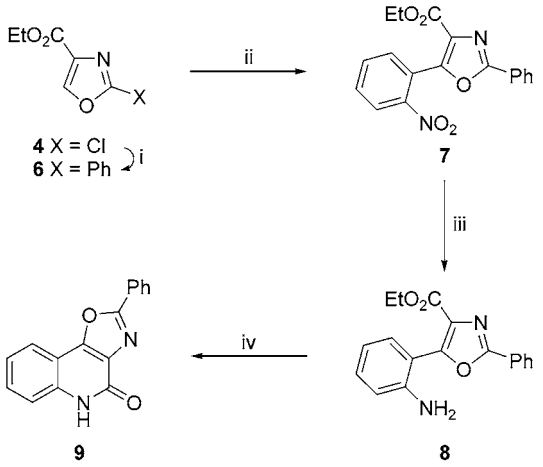
(13) For reviews, see: (a) Heck, R. F. *Org. React.* **1982**, *27*, 345−390. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. For mechanistic insight, see: (c) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (d) Amatore, C.; Jutland, A. *Acc. Chem. Res.* **2000**, *33*, 314.

(14) For an example of a Heck reaction at the 5-position of an oxazole, see: (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. For other heteroaryl Heck reactions, see: (b) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301. (c) McClure, M. S.; Glover, B.; McSorley, E.; Maillar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677. (d) Hii, K. K.; Claridge, T. D. W.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 984. (e) Itahara, T. J. *J. Org. Chem.* **1985**, *50*, 5272.

(15) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem Rev.* **1995**, *95*, 2457. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(16) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.

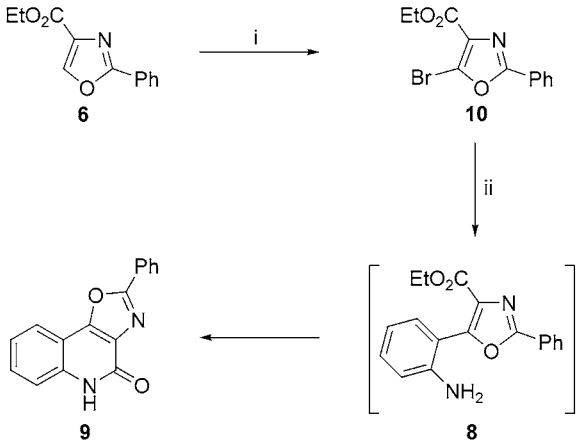
Scheme 2[a]



[a] Reaction conditions: (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, PhMe, H_2O, K_2CO_3, 90 °C (87%); (ii) 2-$IC_6H_4NO_2$, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, DMF, 140 °C (83%); (iii) 10% Pd/C, MeOH, H_2; (iv) DME, H_2O, K_2CO_3, reflux (77%).

available 2-aminophenylboronic acid, which presumably gave the 5-aryl oxazole **8**, although on this occasion and under the conditions of the reaction, cyclization occurred and gave **9** in 78% yield (Scheme 3).

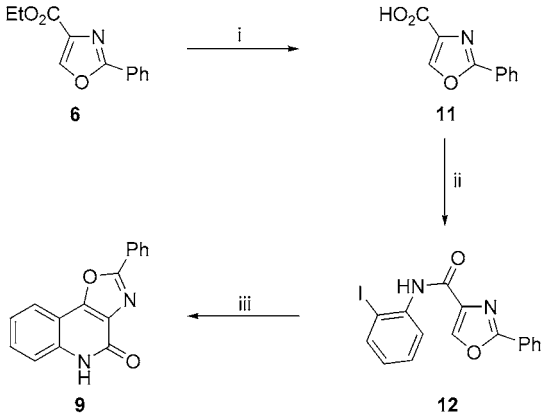
Scheme 3[a]



[a] Reaction conditions: (i) NBS, $CHCl_3$, 60 °C (86%); (ii) 2-$NH_2C_6H_4B(OH)_2$, $Pd(PPh_3)_4$, DME, H_2O, K_2CO_3, 80 °C (78%).

The palladium-catalyzed intramolecular diaryl coupling has previously been used for the synthesis of several tricyclic systems,[17] and we chose to investigate its application to the synthesis of 2-phenyl-oxazolo[4,5-*c*]quinoline-4(5*H*)-one (**9**) (Scheme 4). To this end the ester **6** was hydrolyzed with

Scheme 4[a]



[a] Reaction conditions: (i) NaOH, EtOH, rt (89%); (ii) BOP, 2-$IC_6H_4NH_2$, Et_3N, CH_2Cl_2, rt (78%); (iii) $Pd(OAc)_2$, PPh_3, Cs_2CO_3, DMF, 140 °C (63%).

sodium hydroxide and gave the acid **11** in 89% yield. BOP[18] coupling of the acid **11** with 2-iodoaniline gave the amide **12** in 78% yield. Exposure of the iodide **12** to the Heck conditions described earlier gave cyclization to **9** in 63% isolated yield, although no attempts were made to optimize the conditions of this reaction.

The wide range of organometallic reagents available for the introduction of the 2-substituent and the large array of compatible reagents for installation of the aryl group at the oxazole 5-position (destined to become the A-ring) offer considerable flexibility for the synthesis of substituted oxazolo[4,5-*c*]quinoline-4(5*H*)-ones from a single precursor, ethyl 2-chlorooxazole-4-carboxylate (**4**).

Thiazolo[4,5-*c*]-quinoline-4(5*H*)-ones (**2**) have not previously been reported in the chemical literature, and in principle any of the approaches outlined in Schemes 2−4 could be adapted. The most direct route proved to be the one-pot synthesis of **2** from the readily available ethyl 2-bromo-5-chlorothiazole-4-carboxylate (**13**)[2,19] and consecutive palladium-catalyzed coupling reactions. Using standard Suzuki−Miyaura conditions, the thiazole **13** was treated with 1 equiv of 3,4-dimethoxyphenyl boronic acid at 80 °C. After 4 h none of the starting material (**13**) remained by TLC. A further 5 mol % of $Pd(Ph_3P)_4$ and 1.5 equiv of commercially available 2-aminophenyl boronic acid were added, and the reaction was reheated to 80 °C for a further 4 h. Following aqueous workup and recrystallization, the cyclized product **2** was isolated in 69% yield. The formation of the quinolinone **2** confirmed that the initial coupling was selective for the 2-position and gave the intermediate **14** and that the second coupling at the 5-position gave the intermediate **15** and, under the conditions of the reaction, cyclization to the tricycle **2** (Scheme 5).

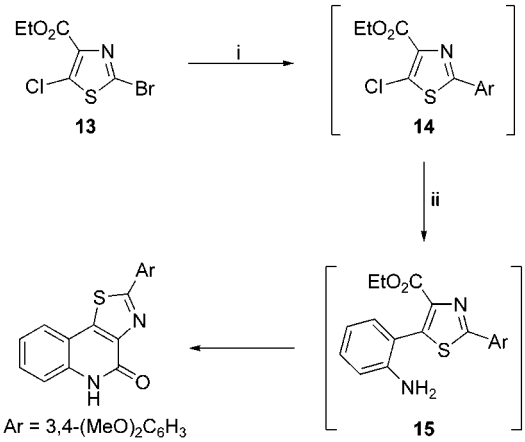
We have described two novel synthetic routes to 2-substituted-oxazolo[4,5-*c*]quinoline-4(5*H*)-ones (**1**) from the

(17) For examples, see: (a) Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919. (b) Kuroda, T.; Suzuki, F. *Tetrahedron Lett.* **1991**, *32*, 6915. (c) Hernandez, S.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2003**, *5*, 1095. For a general review, see: (d) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447.

(18) Castro, B.; Dormoy, J. R.; Evin, G.; Selvey, C. *Tetrahedron Lett.* **1975**, 1219.

(19) Okonya, J. F.; Al-Obeidi, F. *Tetrahedron Lett.* **2002**, *43*, 7051.

Scheme 5[a]



[a] Reaction conditions: (i) 3,4-$(MeO)_2C_6H_3B(OH)_2$, $Pd(PPh_3)_4$, DME, H_2O, K_2CO_3, 80 °C; then (ii) 2-$NH_2C_6H_4B(OH)_2$, $Pd(PPh_3)_4$, 80 °C (69%).

same precursor, ethyl 2-chlorooxazole-4-carboxylate (**4**). In both approaches the 2-substituent was introduced by a Suzuk−Miyaura reaction, although we have previously shown that a wide variety of organometallic reagents could also be used for this step. In the first approach, intermolecular Heck or Suzuki−Miyaura coupling reactions were used to introduce aryl substituents to the oxazole 5-position. The aryl group then became the A-ring of the oxazolo[4,5-*c*]quinoline-4(5*H*)-one (**1**) following cyclization. In the second approach, an intramolecular palladium-catalyzed coupling reaction between an aryl iodide and the oxazole 5-position was the key step in the synthesis. The synthesis of 2-substituted-thiazolo[4,5-*c*]quinoline-4(5*H*)-ones (**2**) was also described. The one-pot introduction of both the 2-substituent and the A-ring and subsequent cyclization from the readily available ethyl 2-bromo-5-chloro-4-thiazole carboxylate (**13**), without the need for chromatography, is noteworthy. The efficiency of the reactions and the diversity of compatible starting materials and reagents make the described methodologies attractive and flexible entries into 2-substituted-oxazolo[4,5-*c*]quinoline-4(5*H*)-ones (**1**) and 2-substituted-thiazolo[4,5-*c*]quinoline-4(5*H*)-ones (**2**).

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **4**, **6**−**13**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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