Tetrahedron Letters 51 (2010) 337–339

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 3-methoxy-quinoxalin-2-ones from methyl trimethoxyacetate and phenylenediamines

Jennifer D. Venable [a,*], David E. Kindrachuk [a], Matthew L. Peterson [b], James P. Edwards [a]

[a] Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 3210 Merryfield Row, San Diego, CA 92121, USA
[b] TransForm Pharmaceuticals, Inc., 29 Hartwell Avenue, Lexington, MA, USA

ARTICLE INFO

Article history:
Received 19 October 2009
Revised 4 November 2009
Accepted 5 November 2009
Available online 11 November 2009

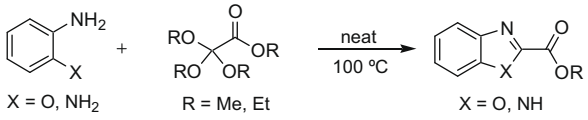
ABSTRACT

Treatment of phenylenediamines with methyl trimethoxyacetate led to the formation of 3-methoxy-quinoxalin-2-ones with the assistance of lanthanide-based Lewis acids.

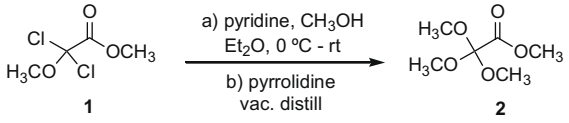
During the course of our research, we became interested in synthesizing structurally diverse examples of benzimidazole-2-carboxylic esters. However, there are relatively few efficient ways to construct this simple chemotype. One method is a two-step procedure involving the formation of 2-trichloromethylbenzimidazoles followed by hydrolysis with an alcoholic solvent.[1] The desired ester oxidation state of the 2-position can also be achieved via formation of a 2-hydroxymethyl benzimidazole followed by oxidation with $KMnO_4$ to obtain the corresponding carboxylic acid.[2] However, yields can be quite variable using this procedure. We were intrigued by the literature report[3] of a one-pot synthesis of benzoxazole and benzimidazole-2-carboxylates from the direct condensation of 2,2,2-trialkoxyacetates with 1,2-aminophenols or 1,2-phenylenediamines, respectively (Scheme 1).

Commercially available 2,2-dichloro-2-methoxy methyl ester (**1**) was treated with methanol and pyridine followed by a vacuum distillation to afford the desired methyl trimethoxyacetate (**2**) in good yields (Scheme 2).[4]

However, direct condensation of **2** with 2,3-diaminotoluene, under the cited conditions,[3] afforded a complex reaction mixture. In order to optimize the reaction conditions, a small solvent screen was initiated (Table 1, entries 1–5). All reactions were performed at reflux. It was found that by using toluene as a solvent with 4 equiv **2** gave 24% yield of a major product (Table 1, entry 5). Since all spectral analysis of this product was consistent with the desired benzimidazole 2-carboxylate, a variety of substituted 1,2-benzenediamines were subjected to the reaction conditions. Surprisingly, when utilizing 4-trifluoromethyl-1,2-phenylenediamine, a mixture of isomeric products was obtained. This result called into question our initial assignment of the benzimidazole 2-carboxylate structure. We thus considered the possibility that the actual products

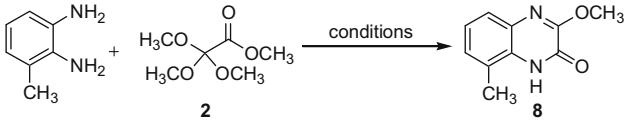


Scheme 1. Synthesis of benzimidazole carboxylic esters.[3]



Scheme 2. Formation of methyl trimethoxyacetate (**2**).

Table 1
Optimization of the synthesis for quioxalin-2-ones

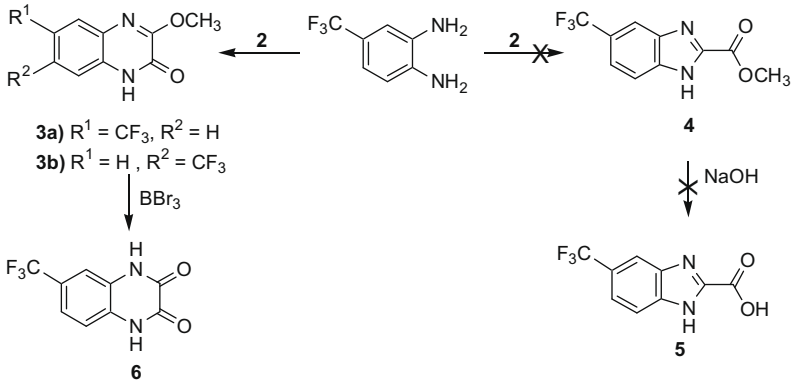


Entry	Solvent[a]	Promoter	Equiv **2**	h	% Yield **8**
1	THF	—	4	24	—
2	1,4-Dioxane	—	4	24	—
3	MeOH	—	4	24	—
4	DMF	—	4	24	—
5	Toluene	—	4	24	24
6	Toluene	1 equiv *p*TsOH	2	24	35
7	Toluene	10 mol % $Sc(OTf)_3$	2	4	63
8	Toluene	10 mol % $Yb(OTf)_3$	2	4	72

[a] All reactions performed at 0.4 M.

* Corresponding author.
E-mail address: jvenable@its.jnj.com (J.D. Venable).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.11.017



Scheme 3. Formation of quinoxalin-2-ones **3a**, **3b**.

of the condensation were the isomeric quinoxalin-2-ones **3a** and **3b** (Scheme 3).

Additionally, if the putative benzimidazole **4** had formed, it should hydrolyze to the corresponding carboxylic acid **5** when treated with sodium hydroxide, however, only starting material was recovered when subjected to strongly basic conditions (Scheme 3). Interestingly, treatment of the isolated isomeric mixture with boron tribromide afforded the known quinoxalin-dione **6** as a single product giving chemical proof of structures **3a** and **3b**.

After scanning the materials that had been synthesized thus far for crystallinity, we were able to determine the X-ray crystal structure of the product obtained from the condensation of 3-chloro-5-trifluoromethylphenylene diamine and **2**. The structure was determined to be the quinoxalin-2-one **7** instead of the anticipated benzimidazole carboxylate (Fig. 1).

With this discovery, we set out to further optimize the reaction conditions for the formation of the 6,6-sytem**.** Using toluene as the solvent, we examined the effect Bronsted and Lewis acids had on the reaction rate and outcome. Treatment of 2,3-diaminotoluene with 2 equiv of **2** in refluxing toluene (Dean–Stark) for 12 h gave the product **8** in 35% yield. The best results were obtained by running the reaction in the presence of catalytic quantities (10 mol %) of either scandium or ytterbium triflate for 4 h at 110 °C in a sealed tube. After 4 h under these conditions, 63% and 72% of the desired quinoxalin-2-one product **8** could be isolated, respectively.

This reaction could be expanded to include a variety of substituents around the arene ring (Fig. 2). For 3-substituted 1,2-phenylenediamines, only a single regioisomeric product was obtained (**7**–**9**). Presumably the first intermediate is oxonium ion formation of **2** resulting in the loss of methanol. This can then condense with the least sterically hindered amine to give an imine intermediate. Finally, intramolecular cyclization of the more hindered amine, preferentially with the pendant ester, would give rise to the isolated quinoxalin-2-one products as a single isomer. The

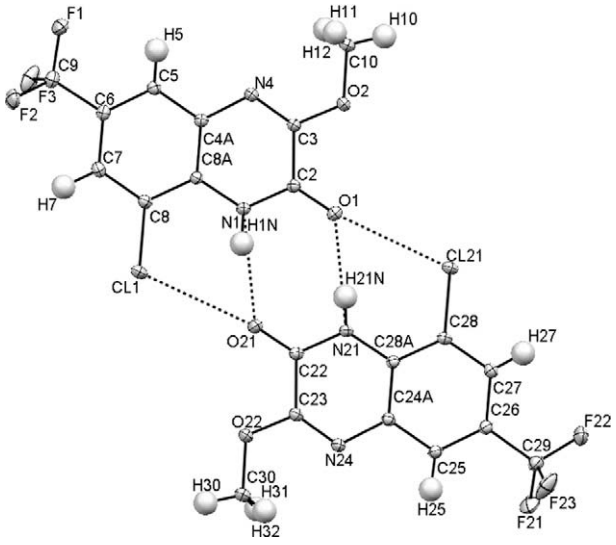


Figure 1. Ortep diagram (50% ellipsoids for non-hydrogen atoms) of the two crystallographically unique molecules in the asymmetric unit from the X-ray crystal structure of **7**. Atom names and the numbering scheme employed are shown. Short contacts between heavy atoms are indicated by dashed lines.

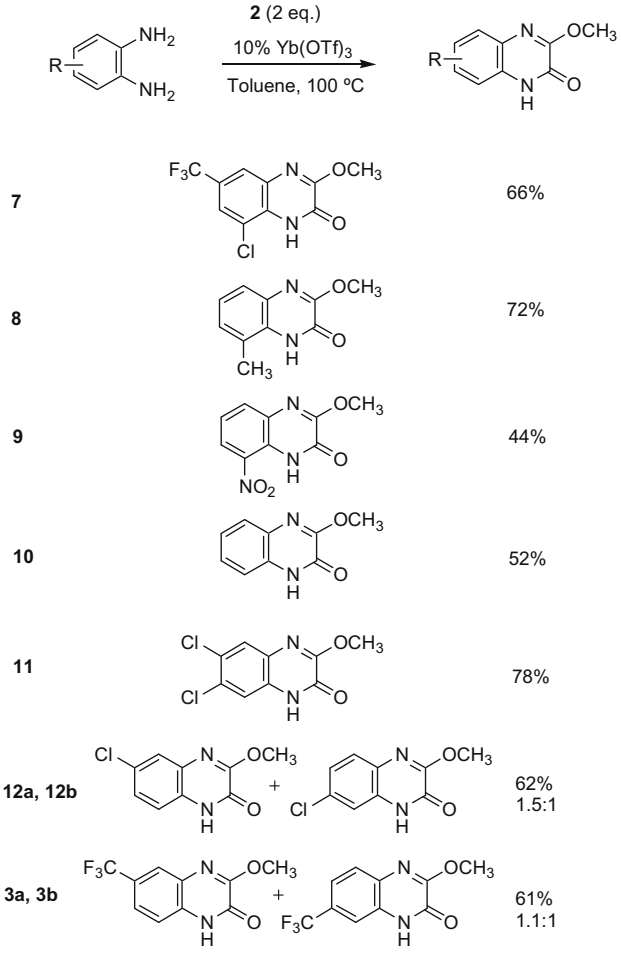


Figure 2. 3-Methoxyquinoxalin-2-ones **3**, **7**–**12**.

symmetrical 1,2-phenylenediamine and 4,5-dichloro-1,2-phenylenediamine gave the corresponding quinoxalin-ones **10** and **11** in good yields. As previously seen when steric bulk is removed from the ortho position, mixtures of regioisomers are obtained as demonstrated by utilizing 4-chloro (**12a** and **12b**) or 4-trifluoromethyl (**3a** and **3b**) phenylenediamine under the reaction conditions to give a mixture of isomeric products which can be separated by silica gel chromatography. Structural confirmation of the individual isomers were determined by NOE correlation.

In conclusion, a new one-step method for synthesizing differentiated quinoxalin-2-ones has been developed utilizing $Yb(OTf)_3$ as a Lewis acid catalyst.[5] The 3-methoxy substituent provides a handle for further functionalization of these molecules.

Acknowledgments

The authors thank Jiejun Wu for assistance with compound structural determination and John Keith for editing the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.017.

References and notes

1. (a) Garuti, L.; Marinella, R.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2707; (b) Young, J. R.; Huang, S. X.; Walsh, T. F.; Wyvratt, M. J., Jr.; Yang, Y. T.; Yudkovitz, J. B.; Cui, J.; Mount, G. R.; Ren, R. N.; Wu, T.-J.; Shen, X.; Lyons, K. A.; Mao, A.-H.; Carlin, J. R.; Karanam, B. V.; Vincent, S. H.; Cheng, K.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 827.
2. (a) Copeland, R. A.; Day, A. R. *J. Am. Chem. Soc.* **1943**, *65*, 1072; (b) Orjales, A.; Alonso-Cires, L.; Lopez-Tudanca, P.; Tapia, I.; Mosquera, R.; Labeaga, L. *Eur. J. Med. Chem.* **1999**, *34*, 415.
3. (a) Musser, J. H.; Bailey, H. T. T. *Synth. Commun.* **1984**, *14*, 947; for other examples see: Fouchard, D. M. D.; Tillekeratne, L. M. V.; Hudson, R. A. *J. Org. Chem.* **2004**, *69*, 2626; (b) Boger, D. L.; Schmitt, H. W.; Fink, B. E.; Hedrick, M. P. *J. Org. Chem.* **2001**, *66*, 6654.
4. (a) Jones, R. G. *J. Am. Chem. Soc.* **1951**, *73*, 5168; (b) Kantlehner, W.; Kapassakalidis, J. J.; Maier, T. *Liebigs Ann.* **1980**, *9*, 1448; (c) Kantlehner, W.; Dinkeldein, U.; Bredereck, H. *Liebigs Ann.* **1979**, *9*, 1346.
5. *Typical experimental conditions for the synthesis of 3-methoxy-qyinoxalin-2-ones*: 3-Methoxy-8-methyl-1*H*-quinoxalin-2-one (**8**): A mixture of 2,3-diamino toluene (0.20 g, 1.64 mmol, 1.0 equiv), methyl trimethoxyacetate (1.07 g, 6.54 mmol, 2.0 equiv), and ytterbium triflate (0.10 g, 0.16 mmol, 0.10 equiv) in toluene (4 mL, 0.4 M) was heated at 100 °C for 4 h in a sealed tube. The reaction was cooled, and the precipitate was collected by vacuum filtration. After washing with hot ethyl acetate (2 × 10 mL), the precipitate was dried in vacuo to afford 0.22 g (72%) of 3-methoxy-8-methyl-1*H*-quinoxalin-2-one. ^{1}H NMR (400 MHz, $CDCl_3$): 11.34 (br s, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.12 (m, 2H), 4.14 (s, 3H), 2.59 (s, 3H).