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Highly Efficient Synthesis of Quinoxalinone-*N*-oxide via Tandem Nitrosation/Aerobic Oxidative C–N Bond Formation

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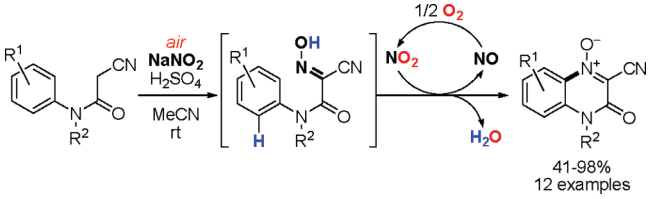
ABSTRACT



An efficient method for constructing quinoxalinone-*N*-oxides from cyanoacetanilides has been developed. This transformation can be achieved using inexpensive reagents and molecular oxygen under mild conditions, thus offering a practical pathway to quinoxalinone-containing pharmaceuticals such as ataquimast and opaviraline.

One of the goals of synthetic organic chemistry is to construct complex and valuable molecules from simple starting materials with inexpensive and readily available reagents. Nitrogen-containing heterocycles constitute medicinally important molecules, and therefore continuous efforts have been made to develop novel efficient methods for their preparation.[1] Transition-metal-catalyzed intramolecular aromatic C–N bond formation, generally by the reaction of a preinstalled amino (or amide) group with (pseudo)haloarene, has been developed as a fundamental reaction for constructing *N*-containing heterocyclic compounds.[2] Recent progress on processes for direct aromatic C–H functionalization/C–N bond formation has enabled more efficient access to *N*-heterocycles from nonprefunctionalized simple arenes.[3−6] After the pioneering work of Buchwald,[4] various oxidative aromatic C–N bond-forming reactions have been devised to synthesize heterocycles,[5,6] for example, utilizing an inexpensive catalyst

(1) (a) Li, J.-J., Corey, E. J., Eds. *Name Reactions in Heterocyclic Chemistry*; Wiley-Interscience: Hoboken, NJ, 2005. (b) For reviews on C–H functionalization for the synthesis of heterocycles, see: (b) Zhang, M. *Adv. Synth. Catal.* **2009**, *351*, 2243. (c) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874.

(2) For reviews, see: (a) Jiang, L.; Buchwald, S. L. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, p 699. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(3) For transition-metal-catalyzed nitrene insertion into aromatic C–H bonds, see: (a) Smitrovitch, J. H.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (c) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500.

(4) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603.

(5) For recent examples, see: (a) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (b) Yamamoto, M.; Matsubara, S. *Chem. Lett.* **2007**, *36*, 172. (c) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (d) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (e) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (f) Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. *Chem.—Eur. J.* **2009**, *15*, 7292. (g) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.

(6) For recent examples using copper catalysts, see: (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (b) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217. For an iron-mediated reaction, see:(c) Zheng, Z.; Tang, L.; Fan, Y.; Qi, X.; Du, Y.; Zhang-Negrerie, D. *Org. Biomol. Chem.* **2011**, *9*, 3714. For metal-free reactions, see:(d) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996. (e) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605.

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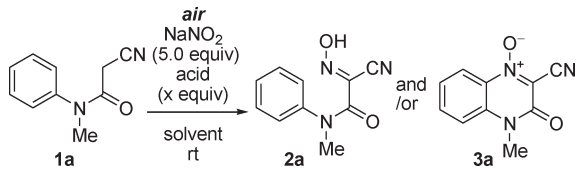
or oxidant.[6] We hypothesized that oxidative aromatic C−N bond-forming strategies together with introduction of a nitrogen-containing functional group should enable a more straightforward synthesis of *N*-heterocycles. We also envisioned a greener process for the oxidative C−N bond formation by utilizing molecular oxygen as the oxidant. Herein, we report introduction of a nitroso group into cyanoacetanilides and simultaneous aerobic oxidative C−N bond formation to construct quinoxalinone-*N*-oxide under transition-metal-free conditions.

We first examined nitrosation of cyanoacetanilide **1a**[7] using $NaNO_2$ and a variety of acids (Table 1). After screening various conditions, we found nitrosation of the active methylene of **1a** was best mediated when H_2SO_4 was employed, and *aci*-nitrosocyanoacetanilide **2a** was obtained in 48% yield (entry 1). Interestingly, when the solvent was changed to AcOH, quinoxalinone-*N*-oxide **3a**,[8] presumably derived from **2a** via oxidation, was obtained in 62% yield (entry 2). The yield of **3a** was improved to 78% when the process was carried out in MeCN (entry 3). Although 5 equiv of H_2SO_4 and $NaNO_2$ were required to obtain **3a** in a decent yield (entry 4), the reaction was readily and successfully scaled up as both reagents are inexpensively available (entry 5). It should be noted that the formation of **3a** was greatly inhibited under an argon flow, and **2a** was obtained in 67% yield (entry 6). This result strongly suggests that the tandem reaction proceeded via **2a** and that molecular oxygen was involved in the oxidation of **2a**. H_2SO_4 seemed to play a crucial role in the tandem reaction since AcOH and TFA were ineffective (entries 7 and 8).

Table 1. Survey of the Reaction Conditions of **1a**[a]

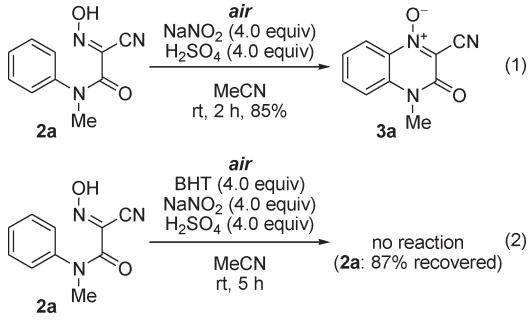


				yield[b] (%)	
entry	acid (equiv)	solvent	time (h)	**2a**	**3a**
1	H_2SO_4 (5.0)	CH_2Cl_2	12	48	0
2	H_2SO_4 (5.0)	AcOH	3	n.d.[c]	62
3	H_2SO_4 (5.0)	MeCN	5	n.d.[c]	78
4[d]	H_2SO_4 (1.5)	MeCN	24	n.d.[c]	48
5[e]	H_2SO_4 (5.0)	MeCN	5	n.d.[c]	79
6[f]	H_2SO_4 (5.0)	MeCN	5	67	12
7	AcOH (5.0)	MeCN	5	4	0
8	TFA (5.0)	MeCN	7	0	0

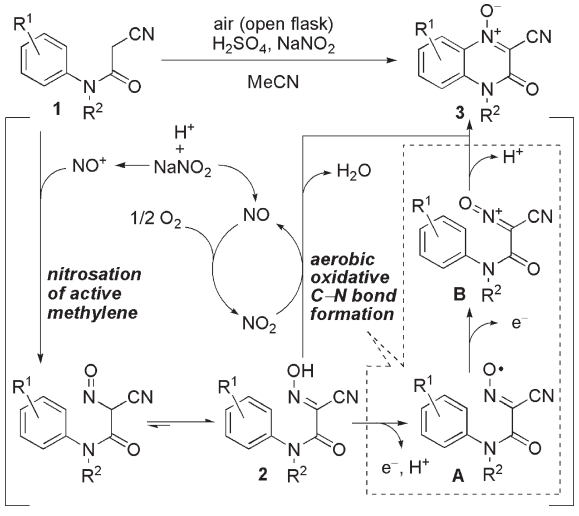
[a] Unless otherwise stated, the reactions were carried out with 1.0 mmol of **1a** under air (open flask). [b] Isolated yields. [c] Not determined. [d] 1.5 equiv of $NaNO_2$ was used. [e] 30 mmol of **1a** was employed. [f] The reaction was carried out under an argon flow.

To gain mechanistic insight into the tandem reaction, we investigated the reactivity of the isolated **2a** (eqs 1 and 2). Oxidative cyclization of **2a** proceeded smoothly to furnish **3a** in 85% yield,[9] substantially under the same conditions as those given in Table 1 (eq 1).[10] In contrast to this result, the reaction of **2a** did not proceed at all in the presence of 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT) as a radical scavenger, suggesting that a single electron transfer process was involved in the present aerobic oxidation.

Taking these results into consideration, a plausible mechanism for the tandem reaction of **1** is shown in Scheme 1. Initially, the active methylene of **1** reacts with a nitrosyl cation to generate *aci*-nitroso species **2** via isomerization. The subsequent aerobic oxidative cyclization would occur through electron transfer from **2** to molecular oxygen by the mediation of NO_2:[11] (1) stepwise single electron transfer would afford the reactive *N*-oxonitrenium intermediate **B**[12] via *N*-oxyl **A**, and (2) intramolecular electrophilic aromatic substitution of **B** would furnish *N*-oxide **3**.[13]



Scheme 1. Hypothesized Mechanism

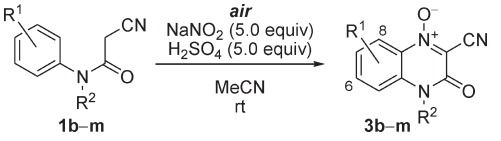


(7) For our previous work using cyanoacetanilides, see: (a) Kobayashi, Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603. (b) Kobayashi, Y.; Harayama, T. *Tetrahedron Lett.* **2009**, *50*, 6665. (c) Kobayashi, Y.; Katagiri, K.; Azumaya, I.; Harayama, T. *J. Org. Chem.* **2010**, *75*, 2741. (d) Kobayashi, Y.; Nakatani, T.; Tanaka, R.; Okada, M.; Torii, E.; Harayama, T.; Kimachi, T. *Tetrahedron* **2011**, *67*, 3457. (e) Kobayashi, Y. *Yakugaku Zasshi* **2011**, *131*, 1037.

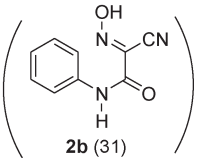
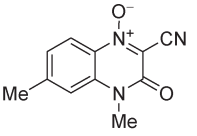
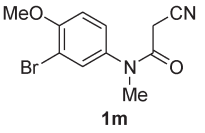
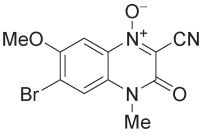
(8) Ahmad, Y.; Habib, M. S.; Ziauddin *Tetrahedron* **1964**, *20*, 1107.

With an optimized set of reaction conditions, we next investigated the scope and limitation of the tandem reaction (Table 2). The reaction of secondary anilide **1b** afforded **2b** exclusively in 31% yield, whose cyclization to **3b** seemed to be prohibited presumably due to conformational reasons[14] (entry 1). However, the tandem reaction of cyanoacetanilides **1c**,**d** substituted at amide nitrogen with ethyl and benzyl groups took place smoothly to afford the desired quinoxalinone-*N*-oxides **3c**,**d** in 70% and 98% yields, respectively (entries 2 and 3). Notably, the *N*-oxides **3e**,**f** were obtained in high yields (entries 4, 5) since the halogenated products could in principle be further functionalized by way of transition-metal-catalyzed coupling reactions. Importantly, the tandem reactions successfully proceeded with arenes bearing strong electron-withdrawing substituents **1g**–**j** (entries 6–9). The prolonged reaction time and decreased chemical yield (entry 9) support the mechanism proposed above via intramolecular electrophilic substitution. The following results indicate that the cyclization step is sensitive to the steric hindrance: (1) the cyclization of *meta*-substituted cyanoacetanilide **1l**,**m** occurred almost exclusively *para* to the methyl and bromo group to afford 6-substituted qunoxalinone-*N*-oxide **3l**,**m** in 75% and 50% yields, respectively (entries 11 and 12); and (2) *ortho*-substituted cyanoacetanilide **1n** was ineffective in the tandem reaction (entry 13). It should be worth noting that the isolation of all products **3c**–**l** could be readily accomplished by precipitation and filtration.[15]

Table 2. Scope and Limitation of Tandem Nitrosation/Aerobic Oxidative Cyclization of Cyanoacetanilides **1b**–**n**[a]



1b–**m** → **3b**–**m**

entry	**1** (R^1, R^2)	time(h)	**3** (% yield[b])
			3b (0)
1	**1b** (H, H)	5	 **2b** (31)
2	**1c** (H, Et)	5	**3c** (70)
3	**1d** (H, Bn)	5	**3d** (98)
4	**1e** (*p*-Br, Me)	5	**3e** (81)
5	**1f** (*p*-Cl, Me)	5	**3f** (84)
6	**1g** (*p*-F, Me)	5	**3g** (61)
7	**1h** (*p*-F, Bn)	5	**3h** (56)
8	**1i** (*p*-CF_3, Me)	5	**3i** (63)
9	**1j** (*p*-NO_2, Me)	24	**3j** (41)
10	**1k** (*p*-Me, Me)	5	**3k** (84)
11	**1l** (*m*-Me, Me)	5	 **3l** (75)
12	 **1m**	5	 **3m** (50)
13	**1n** (*o*-Me, Me)	5	**3n** (trace)

[a] All reactions were carried out with 1.0 mmol of **1** under air (open flask). [b] Isolated yields.

Quinoxalinone derivatives, including 3,4-dihydroquinoxalinone, show important biological and pharmacological properties and are widely used in material sciences.[16,17] Therefore a number of synthetic methods have been reported to date.[18,19] We hypothesized that quinoxalinone-*N*-oxides[20] could be used as intermediates for their preparation.[21] In particular, the CN group at the C2 position of **3** could be

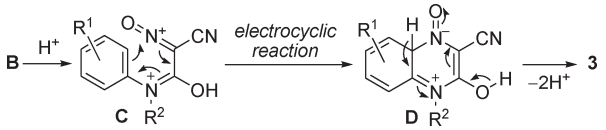
(9) Although the aerobic oxidative cyclization of *aci*-nitroso species **2** has not been reported to our knowledge, a few cyclization reactions of the related α-arylimino oximes have been reported; see: (a) Maroulis, A. J.; Domzaridou, K. C.; Hadjiantoniou-Maroulis, C. P. *Synthesis* **1998**, 1769. (b) Xekoukoulotakis, N. P.; Hadjiantoniou-Maroulis, C. P.; Maroulis, A. J. *Tetrahedron Lett.* **2000**, *41*, 10299. (c) Aggarwal, R.; Sumran, G.; Saini, A.; Singh, S. P. *Tetrahedron Lett.* **2006**, *47*, 4969.

(10) No cyclization of **2a** was observed in the absence of $NaNO_2$ or H_2SO_4.

(11) For a gaseous NO_2-mediated oxidative cyclization, see: (a) Pasinszki, T.; Havasi, B.; Hajgató, B.; Westwood, N. P. C. *J. Phys. Chem. A* **2009**, *113*, 170. For selected recent examples for aerobic alcohol oxidation utilizing NO_2, see: (b) Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem. Soc.* **2004**, *126*, 4112. (c) Uyanik, M; Fukatsu, R.; Ishihara, K. *Chem.—Asian J.* **2010**, *5*, 456. (d) Shibuya, M.; Osada, Y.; Sasano, Y.; Tomizawa, M.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2011**, *133*, 6497.

(12) Wang, K.; Fu, X.; Liu, J.; Liang, Y.; Dong, D. *Org. Lett.* **2009**, *11*, 1015.

(13) In the strongly acidic reaction media, an alternative mechanism via an electrocyclic reaction of the dicationic intermediate **C** cannot be ruled out.



(14) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177 and references cited therein.

(15) For experimental details, see the Supporting Information.

(16) For recent examples of quinoxalinone derivatives, see: (a) Saoudi, N.; Bellaouchou, A.; Guenbour, A.; Bachir, A. B.; Essassi, E.; Achouri, M. E. *Bull. Mater. Sci.* **2010**, *33*, 313. (b) Galal, S. A.; Abdelsamie, A. S.; Tokuda, H.; Suzuki, N.; Lida, A.; ElHefnawi, M. M.; Ramadan, R. A.; Atta, M. H. E.; El Diwani, H. I. *Eur. J. Med. Chem.* **2011**, *46*, 327.

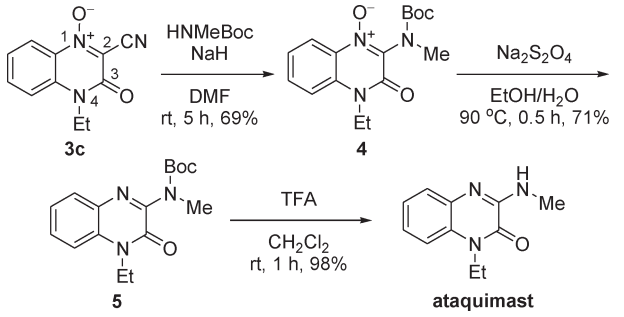
(17) For recent reviews on quinoxalinone scaffolds, see: (a) Li, X.; Yang, K.; Li, W.; Xu, W. *Drugs Future* **2006**, *31*, 979. (b) Carta, A.; Piras, S.; Loriga, G.; Paglietti, G. *Mini-Rev. Med. Chem.* **2006**, *6*, 1179.

(18) For selected recent examples for quinoxalinones, see: (a) Bi, F. C.; Aspnes, G. E.; Guzman-Perez, A.; Walker, D. P. *Tetrahedron Lett.* **2008**, *49*, 1832. (b) Chen, D.; Wang, Z.-J.; Bao, W. *J. Org. Chem.* **2010**, *75*, 5768.

(19) For selected recent examples for 3,4-dihydroquinoxalinones, see: (a) Luo, X.; Chenard, E.; Martens, P.; Cheng, Y.-X.; Tomaszewski, M. J. *Org. Lett.* **2010**, *12*, 3574. (b) Rueping, M.; Tato, F.; Schoepke, F. R. *Chem.—Eur. J.* **2010**, *16*, 2688. (c) Chen, D.; Bao, W. *Adv. Synth. Catal.* **2010**, *352*, 955. (d) Xue, Z.-Y.; Jiang, Y.; Peng, X.-Z.; Yuan, W.-C.; Zhang, X.-M. *Adv. Synth. Catal.* **2010**, *352*, 2132. (e) Tanimori, S.; Kashiwagi, H.; Nishimura, T.; Kirihata, M. *Adv. Synth. Catal.* **2010**, *352*, 2531.

substituted by a variety of nucleophiles, readily enabling the derivatization.

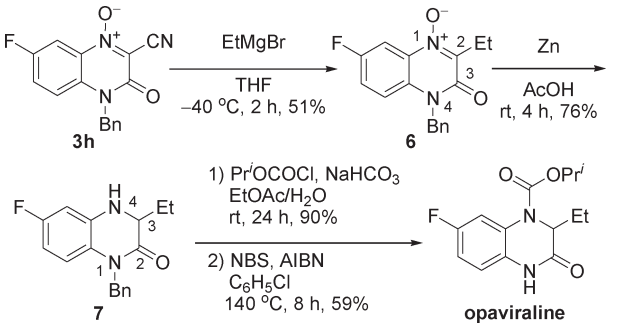
Scheme 2. Synthesis of Ataquimast



In this context, we investigated the rapid synthesis of ataquimast[22] which is useful in the treatment of chronic obstructive bronchopneumopathies such as asthma (Scheme 2). To our delight, introduction of the nitrogen-containing functional group at the C2 position of **3c** could be achieved by substitution of the CN group with HNMeBoc under basic conditions, giving the corresponding carbamate **4** in 69% yield. Reduction of *N*-oxide **4** with $Na_2S_2O_4$ followed by deprotection of the Boc group of **5** furnished ataquimast in good yield.

We also hypothesized that substitution of CN groups of **3** with carbon nucleophiles allows rapid entry into the anti-HIV-1 reverse transcriptase inhibitor[23] such as opaviraline (GW-420867X). To this end, the treatment of **3h** with a Grignard reagent was examined (Scheme 3). As a result, EtMgBr could be successfully substituted for the CN group to give 2-ethyl-quinoxalinone-*N*-oxide **6** in 51% yield, which was then reduced with zinc powder in acetic acid to provide 3,4-dihydroquinoxalinone **7**. After carbamate protection

Scheme 3. Synthesis of Opaviraline



of the amino group, cleavage of the *N*-benzyl group furnished opaviraline.[19e]

In conclusion, we have developed a highly efficient method for constructing quinoxalinone-*N*-oxide through the tandem nitrosation/aerobic oxidative cyclization of cyanoacetanilides with inexpensive reagents. The CN groups of **3** were successfully substituted with not only a carbon nucleophile but also a nitrogen nucleophile. This strategy enables rapid access to various substituted quinoxalinone derivatives. In addition, we proposed a mechanistically novel oxidative aromatic C–N bond-forming reaction of *aci*-nitroso species **2** utilizing molecular oxygen as the sole oxidant. More detailed mechanistic studies as well as extension of the present chemistry to the synthesis of other quinoxalinone-containing pharmaceuticals are under investigation.

Acknowledgment. We thank Instrument Analysis Center of Mukogawa Women's University for the NMR and MS measurements.

Supporting Information Available. Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) For selected recent examples, see: (a) Meyer, C.; Zapol'skii, V. A.; Adam, A. E. W.; Kaufmann, D. E. *Synthesis* **2008**, 2575. (b) Özpınar, G. A.; Erdem, S. S.; Meyer, C.; Kaufmann, D. E. *J. Org. Chem.* **2009**, *74*, 4727 and references cited therein.

(21) Only a few reactions of quinoxalinone-*N*-oxides have been reported; see: (a) Reference 8. (b) Ahmad, Y.; Habib, M. S.; Iqbal, M.; Ziauddin *Bull. Chem. Soc. Jpn.* **1965**, *38*, 562. (c) Ahmad, Y.; Habib, M. S.; Ziauddin, Bashir, N. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1654.

(22) Patoisear, J.-F.; Tarayre, J.-P.; Autin, J.-M. PCT Int. Appl. WO 9626928 A1 19960906, 1996.

(23) (a) Roesner, M.; Billhardt-Troughton, U.-M.; Kirsch, R.; Kleim, J.-P.; Meichsner, C.; Riess, G.; Winkler, I. Eur. Pat. Appl. EP 708093 A1 19960424, 1996. (b) Balzarini, J.; De Clercq, E.; Carbonez, A.; Burt, V.; Kleim, J.-P. *AIDS Res. Hum. Retroviruses* **2000**, *16*, 517. (c) Cass, L. M.; Moore, K. H. P.; Dallow, N. S.; Jones, A. E.; Sisson, J. R.; Prince, W. T. *J. Clin. Pharmacol.* **2001**, *41*, 528.