Tetrahedron Letters 51 (2010) 4723–4726

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis, structure and reactivity of 1-(4-nitrobenzyl)-2-chloromethyl benzimidazole

Amanda E. Sparke, Christopher M. Fisher, Ryan E. Mewis, Stephen J. Archibald *

Department of Chemistry, University of Hull, Cottingham Road, Hull HU6 7RX, United Kingdom

ARTICLE INFO

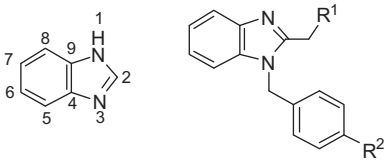
Article history:
Received 15 April 2010
Revised 16 June 2010
Accepted 2 July 2010
Available online 7 July 2010

Keywords:
Benzimidazole
Antagonist
Anti-viral
Chelators synthesis

ABSTRACT

The synthesis of 1-(4-nitrobenzyl)-2-chloromethyl benzimidazole, which undergoes a nucleophilic substitution with pyridine in the absence of additional base, is reported. The key steps are the reaction of 1,2-phenylenediamine to give exclusively the mono-substituted product and the avoidance of minor by-products via the use of glycolic acid for the cyclisation step. The X-ray structures of 1-(4-nitrobenzyl)-2-chloromethyl benzimidazolium chloride and 1-[1-(4-nitrobenzyl)benzimidazol-2-ylmethyl]pyridinium chloride are presented.

The benzimidazole heterocycle is represented in nature as an integral part of the structure of vitamin B_{12} and has been incorporated into pharmaceutical agents to form enzyme inhibitors, receptor binding drugs and DNA intercalators. 1,2-Difunctionalised benzimidazoles of the type we are interested in have been reported as prostaglandin D_2 receptor-antagonists,[1] angiotensin II receptor-agonists[2] and have been patented as dopamine-β-hydroxylase inhibitors.[3] Additionally they have been used as components of metal-chelating ligands.[4]



The synthesis of benzimidazole derivatives functionalised at the 1-position can involve a two-step process with either the initial attachment of a group which will become a 1-position substituent on cyclisation, or initial heterocycle formation followed by electrophilic substitution at the 1-position on reaction with either an alkyl halide or an acid chloride.[5–7] A variety of different routes are reported for the synthesis of benzimidazole derivatives that have been functionalised at the 2-position, including the formation of the five-membered ring using carboxylic acids, solid-phase routes, nitroanilines and orthoesters.[8–13] We attempted to avoid expensive precursors and produce a scalable reaction for the production of multi-gram quantities of the target compound. There are opportunities in the use of substituted aldehydes in the cyclisation step. Das et al. reported the synthesis of a series of compounds in good yields (72–91%)[14] and Gogoi and Konwar developed analogous procedures in aqueous conditions,[15] however, these routes were not exploited in this study.

Our target is a benzimidazole derivative with a reactive moiety at the 2-position and a masked reactive group at the 1-position (preferably 4-aminobenzyl on functional group interconversion). The method investigated involves selective mono-alkylation of 1,2-phenylenediamine either with a benzaldehyde (imine formation followed by reduction) or an alkyl bromide group to produce 1-(4-nitrobenzyl)phenylenediamine, followed by the cyclisation to form the benzimidazole derivative by the reaction with a carboxylic acid to give a chloromethyl benzimidazole. These are well-known reactions but require some attention to produce robust and reproducible procedures on a multi-gram scale. A good example of the effort required to give a reliable synthesis of a related molecule was demonstrated by Hérault et al., where the synthesis of 2-ferrocenyl-1-*n*-butylbenzimidazole by the aromatic nucleophilic substitution of *n*-butylamine onto 2-bromonitrobenzene, followed by reduction of the nitro group to form an amine and finally the condensation with ferrocene carboxaldehyde gave the ferrocene-functionalised benzimidazole (63% overall yield).[6]

Our method uses the standard Phillips synthesis where the 1,2-phenylenediamine precursor is condensed with chloroacetic acid.[16,17] The synthesis of 1-(4-nitrobenzyl)-2-chloromethyl benzimidazole was investigated via two routes, see Scheme 1. *Route 1:* 4-nitrobenzaldehyde in methanol was added to 1,2-phenylenediamine in methanol in the presence of 3 Å molecular sieves and left

* Corresponding author. Tel.: +44 1482 465488; fax: +44 1482 466410.
E-mail address: s.j.archibald@hull.ac.uk (S.J. Archibald).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.07.010

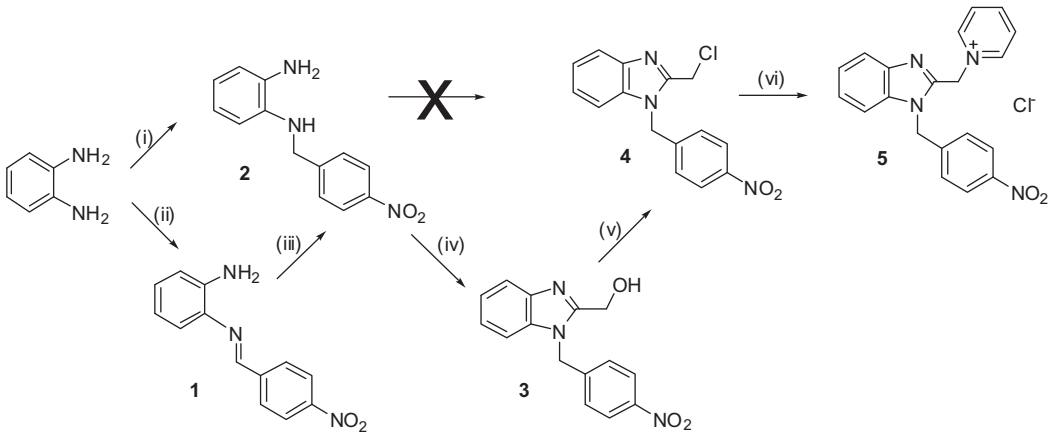
to stir for 72 h at room temperature before the work-up and re-crystallisation from ethanol to give **1** (71% yield). The imine was then reduced to the amine by the addition of an excess of sodium borohydride followed by heating at reflux for 4 h. After the work-up, a white solid **2** was isolated in 74% yield and the ^{1}H NMR spectrum showed a clean loss of the imine peak at 6.81 ppm and the formation of a CH_2 peak at 4.38 ppm.[18] The overall yield of the two steps was 53%, taking ca. four days. *Route 2*: A single step reaction with 4-nitrobenzyl bromide was preferable and proceeded cleanly under the right conditions; 4-nitrobenzyl bromide was added dropwise in methanol to a fivefold excess of 1,2-phenylenediamine and the reaction mixture allowed to stir for 4 h; the product was isolated, recrystallised from a minimum amount of ethanol to remove some of the excess starting material and purified using flash column chromatography (66% yield). We have previously published the single crystal X-ray structure of this compound.[19]

A large number of publications have reported the use of substituted acetic acid derivatives in the reactions with 1,2-phenylenediamine using 5 M HCl as the solvent.[6] The solution is heated at reflux, followed by an alkaline work-up at 0 °C that causes precipitation of the desired compound. In particular, Wilson and Hunt have used this method to form a series of substituted benzimidazoles in ca. 80% yield.[17] The acid catalysis protonates the carbonyl oxygen to form a carbenium ion, followed by nitrogen attack and a dehydration reaction to give the benzimidazole compound. The synthesis of **4** was initially attempted by heating a mixture of 1,2-phenylenediamine and chloroacetic acid to reflux in 5 N HCl with the reaction times varying from 4 to 24 h followed by precipitation of the product with aqueous ammonia in an ice bath, however, we found that this procedure gave the unwanted by-products. The mass spectrometry data showed a peak at m/z = 302, corresponding to **4**, and another smaller peak at 282. Clearly during the work-up, ammonia was partially displacing the chloride causing the formation of 1-(4-nitrobenzyl)-2-aminomethyl benzimidazole (m/z = 282). The reaction was repeated using sodium hydroxide solution in the work-up, but the mass spectrum showed that instead of the amine displacing the chloride, some hydroxymethyl benzimidazole **3** was formed (m/z = 283) in addition to **4**. The work-up was kept cool (below 15 °C) and the reaction was performed in cold by placing the vessel in an ice bath, however, this would be challenging to maintain on a scaled-up procedure.

As an alternative, chloroacetic acid can be replaced by glycolic acid to give 1-(4-nitrobenzyl)-2-hydroxymethyl benzimidazole (**3**) and thionyl chloride can then be used to cleanly convert the hydroxymethyl group into the chloromethyl equivalent.[20] Slightly longer reaction times were required to produce **3** (77% yield), then stirring with thionyl chloride for 24 h gave 1-(4-nitrobenzyl)-2-chloromethyl benzimidazole (**4**) as a cream solid (yield 72% after re-crystallisation).[21] The X-ray crystal structure of **4**·HCl was obtained, the ORTEP plot is shown in Figure 1. The chloride interacts strongly with the protonated imidazole N (bond lengths N–H···Cl 0.949, 2.002 Å; angle 174.99°), but there are no particularly influential π-stacking or edge to face phenyl interactions observed. Only one other X-ray structure was found in the CCDC[22] with a functional group on an N1 benzylic group, in this case a nitrile, however, no reactive group was present at the 2-position in this example.[23]

The alternative approach is to form the benzimidazole compound, followed by substitution, (e.g., with nitrobenzyl bromide), at the benzimidazole N1 position of **4** but we found that these reactions did not proceed cleanly. The substitution of groups directly onto the N1 position of the benzimidazole has been achieved, for example, methyl iodide reacts with benzimidazole in the presence of potassium carbonate using DMF as the solvent (yields greater than 70%),[24] and a related approach has been employed by Li et al. in the synthesis of hepatitis B anti-virals.[25] Similarly, Thomas et al. formed methyl 4′-[(butyl-1*H*-benzimidazol-1-yl)methyl]biphenyl-2-carboxylate,[26] by reacting 2-butylbenzimidazole with a slight excess of methyl 4-(bromomethyl)biphenyl-2-carboxylate and potassium carbonate in dimethylformamide with heating at 100 °C. Care has to be taken in the selection of the base and we found the conditions to be sensitive, and frequently led to the production of minor by-products which are difficult to separate. We also found that dichloromethane/TEA, THF/TEA, DMF/K_2CO_3, sodium hydride/DMF, acetone/potassium carbonate, LDA/THF were similarly unsatisfactory, although there is precedence for their applicability to other precursors and Dubey et al. have had success in the formation of related products using phase-transfer catalysts.[27] The potential for multiple alkylations due to the chloromethyl group can be problematic, and Li et al. have observed the quaternisation reactions.[25] The alkylation of 2-hydroxymethyl benzimidazole was not studied during this work.

The potential for a nucleophilic substitution reaction was investigated by a reaction with pyridine. A modified version of the procedure reported by Iemura et al. was used, where **4** was dissolved in pyridine in the absence of a base and heated at reflux for 30 min.[28] The solvent was removed under reduced pressure, and the resulting cream solid was recrystallised from methanol to give 1-[1-(4-nitrobenzyl)benzimidazol-2-ylmethyl]pyridinium chloride as a white crystalline solid (60% yield).[29] Pyridyl derivatives of benzimidazoles are of interest as anti-virals targeting picornavi-



Scheme 1. Reagents and conditions: (i) 4-nitrobenzyl bromide, MeOH, rt, 4 h (66%); (ii) 4-nitrobenzaldehyde, 3 Å MS, MeOH, rt, 72h; recrystallised from EtOH (71%); (iii) $NaBH_4$, EtOH, reflux, 4 h (74%); (iv) glycolic acid, 5 N HCl, reflux, 48 h; 5% NaOH (77%); (v) $SOCl_2$, rt, N_2, 24 h (72%); (vi) pyridine, reflux, 30 min, recrystallised from MeOH (60%).

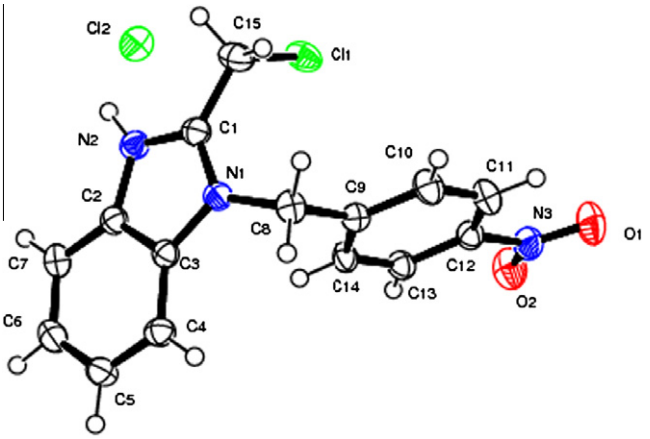


Figure 1. The molecular structure of 1-(4-nitrobenzyl)-2-chloromethyl benzimidazolium chloride **4**·HCl showing the atom labelling and 50% probability ellipsoids for non-H atoms.

ruses and rhinoviruses.[30] The X-ray crystal structure of [**5**]·Cl was obtained. An ORTEP plot of the structure is shown in Figure 2. There is no clear π-stacking or edge to face phenyl interactions, similar to the crystal structure for **4**·HCl, although in this case the chloride group is located in close proximity to the charged pyridinium group. There are some slight differences in the bond lengths and angles which may be attributed to the steric bulk of the pyridyl group. The only X-ray structure of a similar nature deposited at the CCDC has a pyrrolic group attached via a methyl linker in the 2-position of the benzimidazole, but this is not a charged species.[31]

In conclusion, 1-(4-nitrobenzyl)-2-chloromethyl benzimidazole was synthesised via a robust route. A key reaction was between 1,2-phenylenediamine and 4-nitrobenzylbromide in the absence of a base giving exclusively a mono-alkylated product in a single step. Benzimidazole formation by the treatment of **2** with chloroacetic acid in 5 N hydrochloric acid was unsatisfactory due to the consistent presence of by-products, and this was similarly the case with the alkylation of chloromethylbenzimidazole. Therefore, the most reliable route to synthesise this compound was from **3**. Subsequent to the reaction of the chloromethyl group the nitro group could be reduced using sulfurated borohydride offering the potential for further functionalisation at this position. Investigation of these reactions

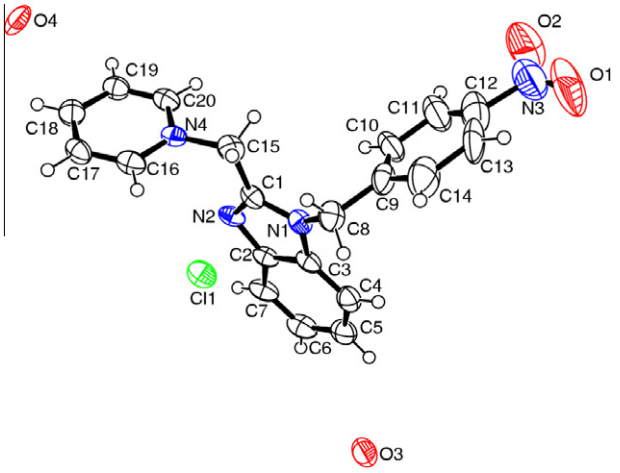


Figure 2. The molecular structure of 1-(4-nitrobenzyl)-2-methylpyridinium benzimidazole chloride **5**, showing the atom labelling and 50% probability ellipsoids for non-H atoms.

forms a part of our ongoing studies, in addition to anti-viral assays[32,33] and chelator formation with these compounds.

Supplementary data

CCDC 772926 and 772927 contain the supplementary crystallographic data for compounds **4**·HCl and **5**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We thank the University of Hull Clinical Biosciences Institute (CMF, AES) and the EPSRC (REM) for funding and the EPSRC National Mass Spectrometry Service for analyses. We also acknowledge the use of the EPSRC Chemical Database Service at Daresbury.

References and notes

1. Beaulieu, C.; Wang, Z.; Denis, D.; Greig, G.; Lamontagne, S.; O'Neill, G.; Slipetz, D.; Wang, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3195–3200.
2. Wan, Y.; Wallinder, C.; Plouffe, B.; Beaudry, H.; Mahalingam, A. K.; Wu, X.; Johansson, B.; Holm, M.; Botoros, M.; Karlen, A.; Pettersson, A.; Nyberg, F.; Fandriks, L.; Gallo-Payet, N.; Hallberg, A.; Alterman, M. *J. Med. Chem.* **2004**, *47*, 5995–6008.
3. Kaiser, C.; Kruse, L.I. US4728741, SmithKline Beckman Corporation, 1988.
4. Yang, X.-P.; Kang, B.-S.; Wong, W.-K.; Su, C.-Y.; Liu, H.-Q. *Inorg. Chem.* **2003**, *42*, 169–179.
5. Charton, J.; Girault-Mizzi, S.; Debreu-Fontaine, M. A.; Foufelle, F.; Hainault, I.; Bizot-Espiard, J. G.; Caignard, D. H.; Sergheraert, C. *Bioorg. Med. Chem.* **2006**, *14*, 4490–4518.
6. Hérault, D.; Aelvoet, K.; Blatch, A. J.; Al-Majid, A.; Smethurst, C. A.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 71–75.
7. Raban, M.; Chang, H.; Craine, L.; Hortelano, E. *J. Org. Chem.* **1985**, *50*, 2205–2210.
8. Casella, L.; Gullotti, M.; Pintar, A.; Pinciroli, F.; Viganò, R.; Zanello, P. *J. Chem. Soc., Dalton Trans.* **1989**, 1161–1169.
9. Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W.; Michejda, C. J. *J. Med. Chem.* **1997**, *40*, 4199–4207.
10. Eynde, J. J. V.; Delfosse, F.; Lor, P.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 5813–5818.
11. Farrant, E.; Rahman, S. S. *Tetrahedron Lett.* **2000**, *41*, 5383–5386.
12. Hornberger, K. R.; Adjabeng, G. M.; Dickson, H. D.; Davis-Ward, R. G. *Tetrahedron Lett.* **2006**, *47*, 5359–5361.
13. Abbotto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1996**, *61*, 1761–1769.
14. Das, B.; Holla, H.; Srinivas, Y. *Tetrahedron Lett.* **2007**, *48*, 61–64.
15. Gogoi, P.; Konwar, D. *Tetrahedron Lett.* **2006**, *47*, 79–82.
16. Musser, J. H.; Kubrak, D. M.; Chang, J.; Dizio, S. M.; Hite, M.; Hand, J. M.; Lewis, A. J. *J. Med. Chem.* **1987**, *30*, 400–405.
17. Wilson, J. G.; Hunt, F. C. *Aust. J. Chem.* **1983**, *36*, 2317–2326.
18. 1-(4-Nitrobenzyl)phenylenediamine (**2**). Preferred method: 4-Nitrobenzyl bromide (5 g, 0.023 mol) dissolved in MeOH (300 ml) was added dropwise to a stirred solution of 1,2-phenylenediamine (12.51 g, 0.12 mol) in MeOH (400 ml) over 30 min. The reaction was stirred at room temperature for 4 h. Evaporation of the solvent under reduced pressure gave a red solid, which was dissolved in EtOH (250 ml) with heating, and then allowed to cool. The resulting precipitate was collected and purified by column chromatography using CH_2Cl_2 as the eluent to yield a red/orange solid. R_f: 0.37. Yield 3.92 g (66%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 3.34 (s, 2H), 3.91 (s, 1H), 4.38 (s, 2H), 6.39 (d, 1H, J = 7.3 Hz), 6.65 (m, 3H), 7.49 (d, 2H, J = 8.7 Hz), 8.0 (d, 2H, J = 8.7 Hz). LRMS (ES) m/z (rel int%): 244 ([M+H]$^+$, 100).
19. Silversides, J. D.; Sparke, A. E.; Archibald, S. J. *Acta Crystallogr., Sect. E Struct. Rep. Online* **2006**, *62*, o5944–o5946.
20. 1-(4-Nitrobenzyl)-2-hydroxymethyl benzimidazole (**3**). ^{1}H NMR (400 MHz, CD_3OD): δ 4.83 (s, 2H), 5.69 (s, 2H), 7.29 (m, 4H), 7.60 (d, 2H, J = 8.7 Hz), 8.10 (d, 2H, J = 8.7 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 46.9, 57.0, 110.1, 119.3, 122.9, 123.6, 124.1, 127.5, 135.0, 141.3, 143.2, 147.7, 154.2. MS (ES) m/z (rel int %): 284 ([M+H]$^+$, 100).
21. 1-(4-Nitrobenzyl)-2-chloromethyl benzimidazole (**4**). ^{1}H NMR (400 MHz, CD_3OD): δ 4.97 (s, 2H), 5.79 (s, 2H), 7.36 (m, 4H), 7.82 (d, 2H, J = 8.7 Hz), 8.19 (d, 2H, J = 8.7 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 32.9, 48.9, 114.1, 116.3, 124.8, 127.0, 127.8, 129.4, 131.6, 133.2, 142.1, 148.9, 149.5. MS (ES) m/z (rel int %): 302 ([M+H]$^+$, 100). HRMS m/z: calcd for $C_{15}H_{13}N_3O_2Cl$ 302.0692 ([M+H]$^+$); found 302.0696. Mp 257 °C dec.
22. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746–749.
23. Ping, G.-J.; Liu, Y.-Y.; Han, T.-T.; Ma, J.-F. *Acta Crystallogr., Sect. E Struct. Rep. Online* **2007**, *63*, o4508.
24. Li, Q. X.; Luo, Q. H.; Li, Y. Z.; Duan, C. Y.; Tu, Q. Y. *Inorg. Chim. Acta* **2005**, *358*, 504–512.

25. Li, Y. F.; Wang, G. F.; He, P. L.; Huang, W. G.; Zhu, F. H.; Gao, H. Y.; Tang, W.; Luo, Y.; Feng, C. L.; Shi, L. P.; Ren, Y. D.; Lu, W.; Zuo, J. P. *J. Med. Chem.* **2006**, *49*, 4790–4794.
26. Thomas, A. P.; Allott, C. P.; Gibson, K. H.; Major, J. S.; Masek, B. B.; Oldham, A. A.; Ratcliffe, A. H.; Roberts, D. A.; Russell, S. T.; Thomason, D. A. *J. Med. Chem.* **1992**, *35*, 877–885.
27. Dubey, P. K.; Reddy, P. V. V. P.; Srinivas, K. *Synth. Commun.* **2007**, *37*, 1675–1681.
28. Iemura, R.; Kawashima, T.; Fukada, T.; Ito, K.; Tsukamoto, G. *J. Heterocycl. Chem.* **1987**, *24*, 31–35.
29. 1-[1-(4-Nitrobenzyl)benzimidazol-2-ylmethyl]pyridinium chloride (**5**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (s, 2H), 6.97 (s, 2H), 7.30 (m, 4H), 7.65 (d, 1H, J = 6.4 Hz), 7.93 (m, 5H, ArCH), 8.35 (t, 1H, ArCH, J = 7.6 Hz), 9.67 (d, 2H, ArCH, J = 5.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.8, 56.0, 110.3, 120.3, 123.5, 124.1, 124.7, 127.7, 127.9, 135.8, 142.1, 143.3, 145.7, 146.1, 146.7, 147.4. MS (ES) *m/z* (rel int %): 345 ($[M-Cl]^+$, 100). HRMS *m/z*: calcd for $C_{20}H_{17}N_4O_2$ 345.1346 ($[M-Cl]^+$); found 345.1349. Mp 197 °C dec.
30. Sato, N.; Kuriyama, H.; Agoh, M. US4818761, Maruishi Seiyaku Kabushiki Kaisha, 1989.
31. Parvez, M. *Acta Crystallogr., Sect. C Cryst. Struct. Commun.* **1996**, *52*, 904.
32. Valks, G. C.; McRobbie, G.; Lewis, E. A.; Hubin, T. J.; Hunter, T. M.; Sadler, P. J.; Pannecouque, C.; De Clercq, E.; Archibald, S. J. *J. Med. Chem.* **2006**, *49*, 6162–6165.
33. Khan, A.; Nicholson, G.; Greenman, J.; Madden, L.; McRobbie, G.; Pannecouque, C.; De Clercq, E.; Ullom, R.; Maples, D. L.; Maples, R. D.; Silversides, J. D.; Hubin, T. J.; Archibald, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 3416–3417.