Tetrahedron Letters 53 (2012) 6451–6455

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Efficient synthesis and reaction pathway studies of novel fused morpholine oxadiazolines for use as gamma secretase modulators

Xianhai Huang *, Dmitri Pissarnitski, Hongmei Li, Theodros Asberom, Hubert Josien, Xiaohong Zhu, Monica Vicarel, Zhiqiang Zhao, Murali Rajagopalan, Anandan Palani, Robert Aslanian, Zhaoning Zhu, William Greenlee, Alexei Buevich

Department of Medicinal Chemistry, Merck Research Laboratories, 126 East Lincoln Avenue, Rahway, NJ 07065, USA

ARTICLE INFO

Article history:
Received 27 August 2012
Revised 15 September 2012
Accepted 17 September 2012
Available online 25 September 2012

Keywords:
Morpholine
Oxadiazoline
Cyclization
Heterocycles
Gamma secretase modulator
Alzheimer's disease

ABSTRACT

An efficient synthesis of fused morpholine oxadiazoline core structures was accomplished in an effort to identify optimum gamma secretase modulator leads in the treatment of Alzheimer's disease. Reaction pathways were proposed for the key intramolecular cyclization reaction, and chemistry was designed to probe these hypotheses. A highly diastereoselective synthesis of potent GSM **27** was achieved. To further improve the synthesis, a second route was developed which successfully addressed the formation of a fused seven-member ring by-product, and provided opportunities to accelerate future SAR studies.

As one of the most challenging areas for modern drug discovery, Alzheimer's disease (AD) is an ultimately fatal neurodegenerative disorder that is the most common cause of age-related dementia. It is estimated that more than 35 million people suffer from AD worldwide, with an annual cost of over $600 billion and a potential population increase to more than 115 million by 2050.[1] Due to the unmet medical need, both academic and industrial laboratories are working very aggressively to develop therapies to halt or even reverse AD. In our efforts targeting Alzheimer's disease,[2] we have recently identified cyclic hydroxyamidines such as oxadiazolines (**1**) as highly efficacious gamma secretase modulators (GSMs) in both in vitro studies and in vivo animal models. These oxadiazolines were designed as novel isosteric replacements of amides with a consideration of hydrogen bonding characteristics and lack of strong basicity. They were found to not only be chemically stable but also possess highly desirable pharmacokinetic and toxicological profiles.[2d] To further improve the overall profile of this series of compounds, we became interested in fused morpholine oxadiazolines (**2**) which could block potential metabolic hot spot and modify the overall properties such as lipophilicity of the molecule and thus offer lead compounds with optimum profiles. As the construction of this fused ring system turned out to be non-trivial, we herein report our chemistry effort towards the synthesis of such a core unit which provides compounds with further improved $A\beta_{42}$ activities and modulator profiles (selectivity).

As shown in Figure 1, we thought that the desired product (**2**) could be synthesized from morpholine phosphonate (**3**) through the Wittig reaction with an aldehyde, and **3** might be prepared through an intramolecular insertion reaction of diazoalcohol **4**. The only concern for this reaction was that the oxadiazoline ring might not be as electron withdrawing as an ester group for which the insertion was originally employed in an intermolecular fashion.[3] Our synthesis started with the preparation of oxadiazoline intermediate (**9**) which was synthesized in good yield through a [3 + 2] dipolar cycloaddition[4] of imine **8** and nitrile oxide **7** generated from bromooxime **6** in situ by treatment of oxime **5** sequentially with NBS and NEt_3.[5] With **9** in hand, we attempted to introduce the diazo functional group. Disappointingly, upon subjection of compound **9** to the diazonium formation conditions,[6] compound **10** could not be obtained cleanly. Efforts to convert crude product **10** directly into morpholine **3** through alcohol **4** in the presence of $Rh_2(OAc)_2$ were not successful. At this point, the strategy needed to be revised and we thought that an intramolecular SN2 substitution reaction of bromophosphonate **12** was feasible even though possible deprotonation of the alpha carbon to the phosphonate before the cyclization could occur under basic conditions and complicate the reaction. To test this idea, compound **9** was deprotected with TBAF to give alcohol **11** which was subjected to mild radical-initiated bromination reaction conditions[7] to

* Corresponding author. Tel.: +1 732 594 4734.
E-mail address: xianhai.huang@merck.com (X. Huang).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.09.070

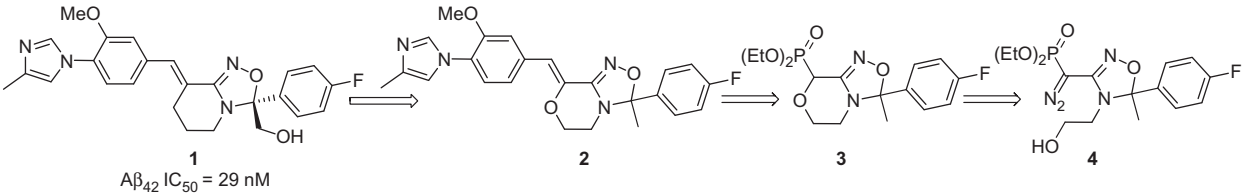
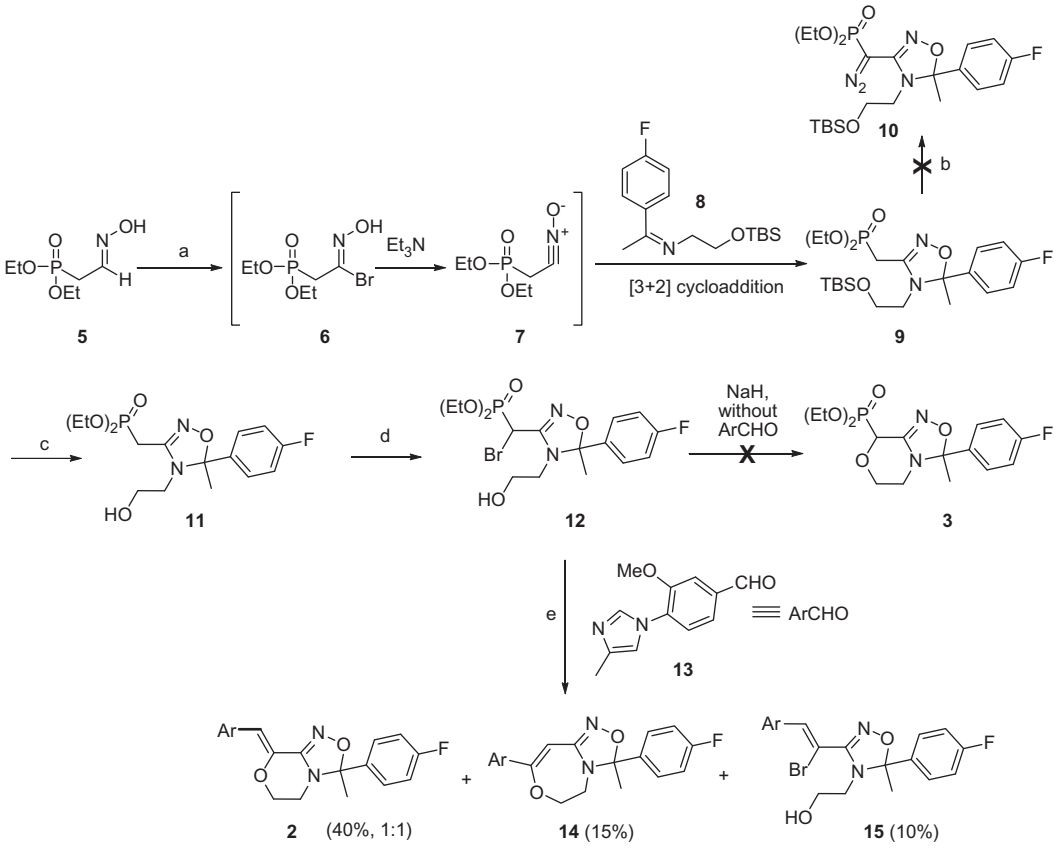


Figure 1. The design of morpholine oxadiazoline gamma secretase modulators.

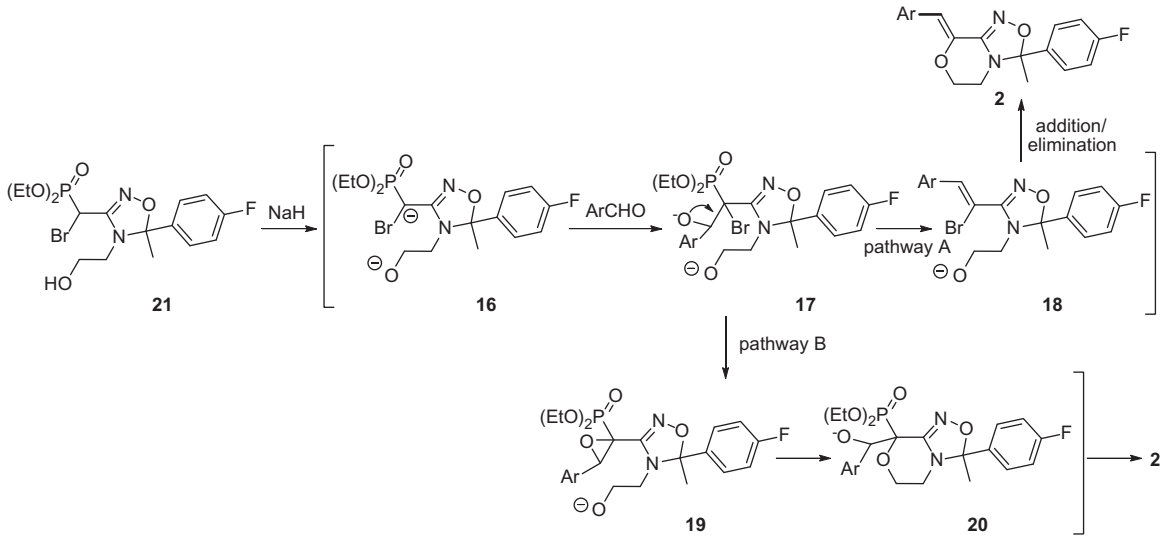
smoothly give compound **12** and set the stage for the cyclization reaction. Upon treatment of **12** with NaH in THF, a rather complex mixture of products was observed and clean product **3** was not able to be isolated. To overcome this problem, we decided to try the reaction in a one pot fashion so that the anion generated alpha to the phosphonate could be trapped by an aldehyde in situ. When a mixture of compound **12** and aldehyde **13** in DMF was treated with excess NaH, desired product **2** was isolated in 40% yield as a mixture of 1:1 *E*/*Z* mixture in addition to the isolation of seven member ring by-product **14** and vinylbromide **15**.

While the formation of compounds **2** and **15** was understandable, the presence of **14** was surprising. In order to understand the origin of **14** and improve the synthesis of **2**, possible reaction pathways were proposed as shown in Scheme 2. Upon treatment of **12** with excess NaH (3.0 equiv), dianion **16** was generated. In the presence of aldehyde **13**, the dianion was trapped to give **17**. Two possible reactions could happen to **17**. In pathway A, alkene intermediate **18** could form through a typical Wittig reaction. The oxygen anion in **18** could then attack the vinylbromide through an intramolecular addition/elimination process to provide the desired product **2**. Unreacted intermediate **18** would give rise to by-product **15**. On the other hand, in pathway B, an epoxide intermediate **19** could be generated from **17**. The oxygen anion in **19** could then attack the epoxide to give Wittig type intermediated **20** which would generate the desired alkene product **2** through Wittig elimination. We thought that pathway B was less likely since this required the anion in **19** to attack a more hindered quaternary centre to form the desired product **2**. However, pathway A could not explain the formation of the seven member ring product **14** either.

Bearing this question in mind, we carried out the synthesis towards more advanced analogues such as compound **27**. Our goal was to synthesize this compound diastereoselectively since it was known from previous structure–activity relationship (SAR) studies that the (C3-*S*, C6-*R*) diastereomer would provide the best activity, and at the same time to further study possible mechanistic pathways of the morpholine ring formation reaction. We started the synthesis from enantiomerically pure ketimine **21** (prepared from (*R*)-2-hydroxypropylamine and ethyl 3,5-difluorobenzoylformate) which underwent [3 + 2] dipolar cycloaddition with



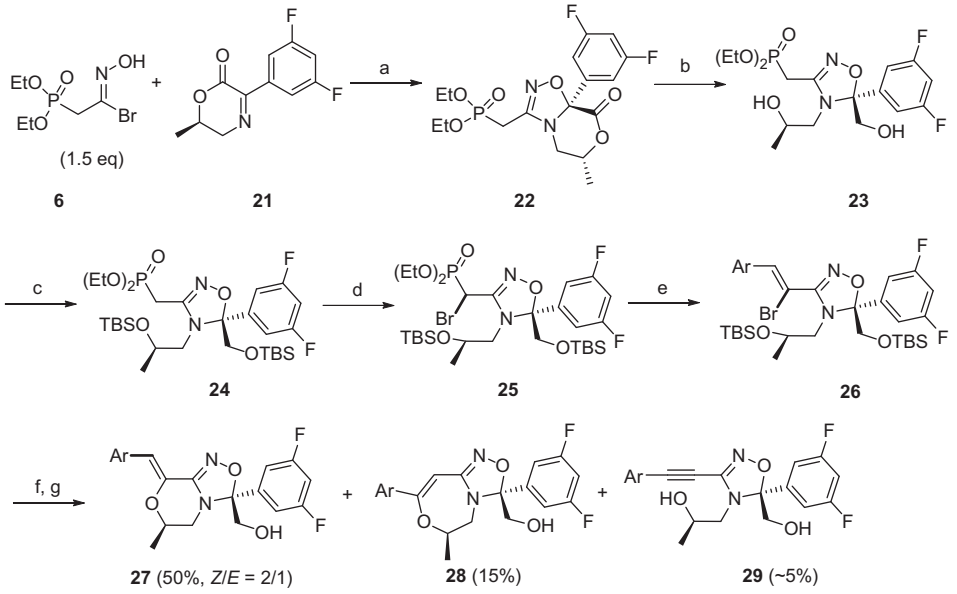
Scheme 1. Initial synthetic route towards fused morpholine oxadiazolines. Reagents and conditions: (a) NBS, DMF, then NEt_3, **8**, 50%. (b) TsN_3, NaH, THF. (c) TBAF, THF, 72%; (d) NBS, benzoyl peroxide, CCl_4, 80%; (e) NaH, DMF, 0 °C to rt.



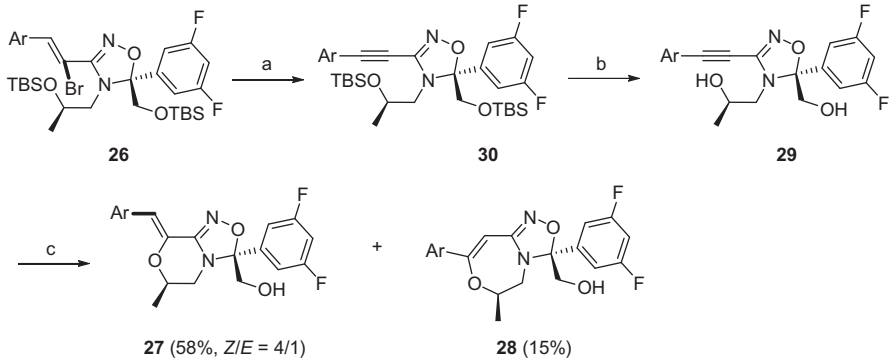
Scheme 2. Initially proposed reaction pathway.

bromooxime **6** in a highly diastereoselective fashion to provide oxadiazoline lactone **22** in good yield. Lactone **22** was reduced smoothly with $NaBH_4$ to give diol **23**. At this point, diol **23** could be brominated to introduce a bromide alpha to the phosphonate which might be converted into the desired products as described in Scheme 1. However, in order to understand the reaction pathway, we decided to first protect the diol with TBS groups to give compound **24**, which was brominated in the presence of NBS and benzoyl peroxide to furnish bromide **25**. As discussed in Scheme 2, to determine which pathway was more plausible, we treated compound **25** with aldehyde **13** under basic conditions and vinylbromide **26** was the only major product isolated with no epoxide intermediate observed. This result suggested that pathway B was not the dominant pathway. At this point, the diols were revealed from **26** with TBAF deprotection to set up the stage to test the cyclization reaction. Upon treatment of the diol intermediate with KOt-Bu, the desired morpholine oxadiazoline **27** was indeed obtained in addition to the seven-member ring product **28**, which suggested that pathway A should be a more likely route for the formation of these fused morpholine oxadiazolines. But it still could not explain how by-product **28** was produced. Fortunately, a small amount of by-product **29** was carefully isolated and characterized. This finding prompted us to think that the alkyne intermediate might be the true reactive species giving rise to both products **27** and **28**.

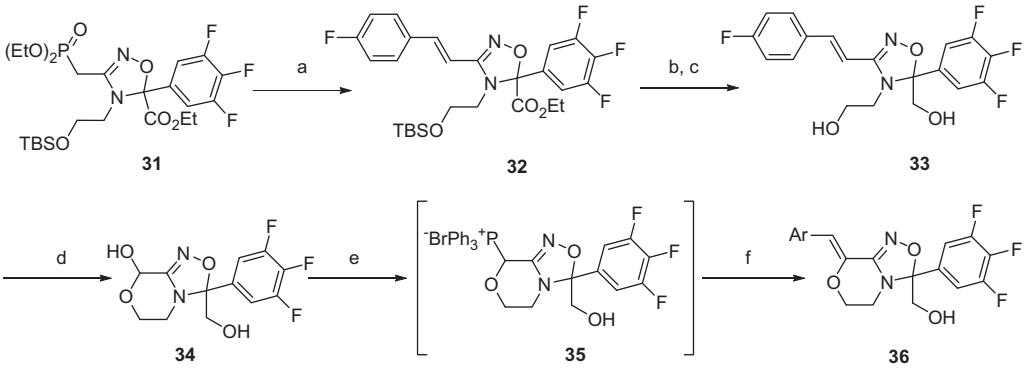
To test this hypothesis, vinyl bromide **26** was converted into **30** in good yield upon treatment with NaHMDS (Scheme 4). Alkyne diol **29** was prepared in a large quantity from **30** by deprotection of the silyl groups with TBAF. Gratifyingly, upon treatment of **29** with NaH, products **27** and **28** were obtained in similar yields as discussed in Scheme 3. An improved ratio of *Z*/*E* isomer (in favour of the desired *Z* isomer) of **27** was observed when the reaction solvent was 1:1 mixture of DMF and THF instead of neat DMF. This synthetic sequence clearly supported the hypothesis that the intra-



Scheme 3. Diastereoselective synthesis of compound **27**. Reagents and conditions: (a) NEt_3, DMF, 74%; (b) $NaBH_4$, THF/MeOH, 72%; (c) TBSCl, imidazole, DMF, 94%; (d) NBS, benzoyl peroxide, CCl_4, 58%; (e) KOt-Bu, **13**, DMF, 80%; (f) TBAF, THF, 88%; (g) KOt-Bu, DMF.



Scheme 4. Reaction pathway Studies. Reagents and conditions: (a) NaHMDS, THF, 70%; (b) TBAF, THF, 83%; (c) NaH (3 equiv), DMF/THF (v/v = 1/1), 0 °C to rt.



Scheme 5. Second synthetic route towards fused morpholine oxadiazolines. Reagents and conditions: (a) LHMDS, 4-fluorobenzaldehyde, −78 to 0 °C, 70%; (b) $NaBH_4$, THF, 82%; (c) TBAF, THF, 85%; (d) O_3, MeOH, CH_2Cl_2, −78 °C, 72%; (e) PPh_3·HBr, $CH_3CN/ClCH_2CH_2Cl$, 80 °C; (f) **13**, LHMDS, THF/DMF, 0 °C to rt, 30% over two steps.

molecular cyclization proceeded through an alkyne intermediate. The *Z*-isomer of **27** was tested in biological assays and proved to be a very potent GSM ($A\beta_{42}$ IC_{50} = 16 nM).

In an attempt to eliminate the fused seven member ring side product and further improve the synthesis, a second route was designed (Scheme 5). Compound **31** was synthesized using a similar route to compound **9** (Scheme 1). Alkene **32** was used as a temporary surrogate of an aldehyde and was obtained upon treatment of **31** under typical Wittig reaction conditions. Compound **32** was reduced with $NaBH_4$ followed by deprotection with TBAF to give diol **33**. The double bond in **33** was cleaved with ozonolysis to reveal the aldehyde masked as lactal **34** which was stable and could be purified with silica gel flash chromatography without any decomposition. Compound **34** was treated with PPh_3·HBr to generate phosphonium salt **35**[8] which was used without further purification and converted into the desired product **36** (*Z*/*E* = 2.5/1) upon treatment with NaH and aldehyde **13**. This synthetic route was straightforward, and the seven member ring by-product was eliminated.

In summary, efforts to identify optimum GSM leads for the treatment of Alzheimer's disease, drove us in the synthesis of novel fused morpholine oxadiazoline core structures. In the initial synthetic route, a fused seven-member ring by-product was observed in addition to the desired product. Possible reaction pathways were proposed and reactions were designed to probe these hypotheses, which resulted in a clear understanding of the reaction pathway and helped to improve the synthesis. A highly diastereoselective synthesis of potent GSM **27** was achieved. To further improve the synthesis, a second route was worked out and successfully addressed the formation of the fused seven member ring by-product, providing an opportunity to speed up future SAR studies.

Acknowledgments

We thank Drs. Christopher Boyce, Andrew Stamford, and Jing Su for comments on the preparation of the manuscript. We thank Dr. Eric Parker for his strong support of the program. We thank Dr. Li-Kang Zhang for technical support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.070.

References and notes

1. Wimo, A.; Prince, M. *World Alzheimer Report 2010: The Global Economic Impact of Dementia*; Alzheimer's Disease International (ADI): London, U.K., 2010.
2. (a) Huang, X.; Aslanian, R.; Zhou, W.; Zhu, X.; Qin, J.; Greenlee, W.; Zhu, Z.; Zhang, L.; Hyde, L.; Chu, I.; Cohen-Williams, M.; Palani, A. *ACS Med. Chem. Lett.* **2010**, *1*, 184–187; (b) Qin, J.; Dhondi, P.; Huang, X.; Mandal, M.; Zhao, Z.; Pissarnitski, D.; Zhou, W.; Aslanian, R.; Zhu, Z.; Greenlee, W.; Clader, J.; Zhang, L.; Cohen-Williams, M.; Jones, N.; Hyde, L.; Palani, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 664; (c) Qin, J.; Zhou, W.; Huang, X.; Dhondi, P.; Palani, A.; Aslanian, R.; Zhu, Z.; Greenlee, W.; Cohen-Williams, M.; Jones, N.; Hyde, L.; Zhang, L. *ACS Med. Chem. Lett.* **2011**, *2*, 471; (d) Sun, Z.-Y.; Asberom, T.; Bara, T.; Bennett, C.; Burnett, D.; Chu, I.; Clader, J.; Cohen-Williams, M.; Cole, D.; Czarniecki, M.; Durkin, J.; Gallo, G.; Greenlee, W.; Josien, H.; Huang, X.; Hyde, L.; Jones, N.; Kazakevich, I.; Li, H.; Liu, X.; Lee, J.; MacCoss, M.; Mandal, M. B.; McCracken, T.; Nomeir, A.; Mazzola, R.; Palani, A.; Parker, E. M.; Pissarnitski, D. A.; Qin, J.; Song, L.; Terracina, G.; Vicarel, M.; Voigt, J.; Xu, R.; Zhang, L.; Zhang, Q.; Zhao, Z.; Zhu, X.; Zhu, Z. *J. Med. Chem.* **2012**, *55*, 489; (e) Caldwell, J. P.; Bennett, C. E.; McCracken, T. M.; Mazzola, R. D.; Bara, T.; Buevich, A. V.; Burnett, D. A.; Chu, I.; Cohen-Williams, M.; Jones, N. T.; Josien, H.; Hyde, L. A.; Lee, J.; McKittrick, B.; Song, L.; Terracina, G.; Voigt, J. H.; Zhang, L.; Zhu, Z. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5380.
3. Cox, G. G.; Kulagowski, J. J.; Moody, C. J.; Sie, E.-R. H. B. *Synlett* **1992**, 975.

4. (a) Alcaide, B.; Mardomingo, C. L.; Plumet, J.; Cativiela, C.; Mayoral, J. A. *Can. J. Chem.* **1987**, *65*, 2050; (b) El-Abadelah, M. M.; Hussein, A. Q.; Awadallah, A. M. *Heterocycles* **1989**, *29*, 1957.
5. (a) Azizian, J.; Madani, M.; Souzangarzadeh, S. *Synth. Commun.* **2005**, *35*, 765; (b) Tsuge, O.; Kanemasa, S.; Suga, H.; Nakagawa, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2463.
6. Lee, J. C.; Yuk, J. Y. *Synth. Commun.* **1995**, *25*, 1511.
7. Paulini, K.; Reissig, H. U. *Chem. Ber.* **1994**, *127*, 685.
8. Kimura, T.; Kawano, K.; Doi, E.; Kitazawa, N.; Takaishi, M.; Ito, K.; Kaneko, T.; Sasaki, T.; Sato, N.; Miyagawa, T.; Hagiwara, H. U.S. 2,007,011,7798, 2007.