JOURNAL OF combinatorial CHEMISTRY



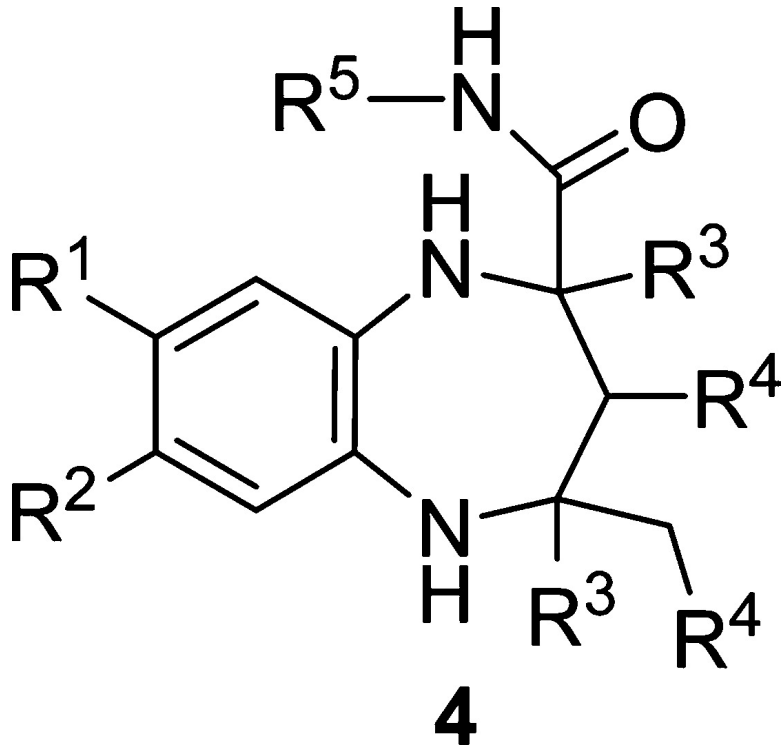
Article

# Novel Multicomponent One-Pot Synthesis of Tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide Derivatives

Ahmad Shaabani, Ali Maleki, and Hamid Mofakham

*J. Comb. Chem.*, **2008**, 10 (4), 595-598• DOI: 10.1021/cc8000635 • Publication Date (Web): 14 June 2008






**4**

## More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article



Journal of Combinatorial Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

# Novel Multicomponent One-Pot Synthesis of Tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide Derivatives

Ahmad Shaabani,* Ali Maleki, and Hamid Mofakham

*Department of Chemistry, Shahid Beheshti University, P.O. Box 19396-4716, Tehran, Iran*

*Received April 20, 2008*

A new approach to the design of multicomponent reactions is introduced. As a result, the novel one-pot synthesis of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide derivatives using an aromatic diamine, a linear or cyclic ketone, an isocyanide, and water in the presence of a catalytic amount of *p*-toluenesulfonic acid at ambient temperature in high yields is described.

## Introduction

Multicomponent reactions (MCRs) offer significant advantages over conventional linear step syntheses, by reducing time and saving money, energy, and raw materials, thus resulting in both economical and environmental benefits. At the same time, diversity can be achieved for building up libraries by simply variation of each component. Because of the unique reactivity of the isocyanide functional group, isocyanide-based MCRs (I-MCRs) are among the most versatile, in terms of number and variety of compounds that can be generated. Such considerations are of particular importance in connection with the design and discovery of novel MCRs.[1]

Benzodiazepines[2] have been the object of intense investigation in medicinal chemistry because of their remarkable central nervous system depressant activity and are now one of the most widely prescribed class of psychotropics.[3] More recently, the area of biological interest of 1,5-benzodiazepines[4] has been extended to antibiotics,[5] and various diseases such as cancer,[6] viral infection (HIV),[7] and cardiovascular disorders.[8] The 1,5-benzodiazepine core is found in compounds active against a variety of target types including peptide hormones,[9] interleukin converting enzymes,[10] and potassium blockers.[8b] Tetrahydrobenzodiazepines have been shown to be effective as inhibitors of farnesyl transferase.[11] Two recently published patents indicate that 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine derivatives carrying carboxamide substituents are potentially important as a therapeutic and prophylactic agent for diabetes, diabetic nephropathy, or glomerulosclerosis.[12]

In continuing our interest in I-MCRs,[13] herein, we report a new reaction that affords 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide derivatives **4a**−**l** via the one-pot condensation of an aromatic diamine **1**, a linear or cyclic ketone **2**, an isocyanide **3,** and water in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH·$H_2O$) in methanol at ambient temperature in high yields (Scheme 1).

* To whom correspondence should be addressed. Phone: +98-21-29902800. Fax: +98-21-22431663. E-mail: a-shaabani@cc.sbu.ac.ir.

To the best of our knowledge, this is the first report of the synthesis of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide derivatives using I-MCR, and this new reaction opens an important field to the use of MCR strategy in heterocyclic synthesis.

## Results and Discussion

In a pilot experiment, *o*-phenylenediamine and acetone were stirred in methanol at room temperature with a catalytic amount of *p*-toluenesulfonic acid. The progress of the reaction was monitored by TLC. After 4 h, benzyl isocyanide and water were added to the reaction mixture, and stirring was continued for 20 h. After completion of the reaction, an aqueous workup afforded compound **4a** in 80% yield.

In view of the success of the above reaction, we explored the scope of this promising reaction by varying the structure of the *o*-phenylenediamine, ketone, and isocyanide components (Table 1). The reaction proceeds very cleanly under mild conditions at room temperature, and no undesirable side reactions were observed under these reaction conditions. The structures of products are shown in Figure 1.

The possible mechanism for the formation of products **4a**−**l** is shown in Scheme 2. It is conceivable that the initial event is the formation of diimine **5** from condensation between *o*-phenylenediamine **1** and 2 mol of ketone **2**.[1] Then, an intramolecular imine−enamine cyclization of **5** affords seven-membered ring **6**. On the basis of the well-established chemistry of the reaction of isocyanides with imines,[1] intermediate **7** was produced by nucleophilic attack of isocyanide **3** to iminium **6**, followed by nucleophilic attack of an $H_2O$ molecule on the nitrilium moiety and production of compound **8**. Finally, tautomerization of intermediate **8** produces the 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide derivatives **4**.

It is important to note that the proposed mechanism is supported by characterization of isolated seven-member ring **6a** by mass, IR, $^1$H NMR, and $^{13}$C NMR spectra (see the Supporting Information).

This reaction was highly regioselective. The $^1$H and $^{13}$C NMR spectra obtained from **5d**−**j** was consistent with the presence of only one isomer. It may be explained that the

10.1021/cc8000635 CCC: $40.75 
Published on Web 06/14/2008

**Scheme 1.** Synthesis of 2,3,4,5-Tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide Derivatives **4a**−**l**

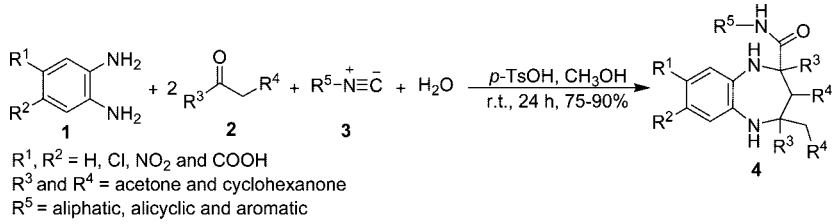



**Table 1.** Synthesis of 2,3,4,5-Tetrahydro-1H-1,5-benzodiazepine-2-carboxamides **4a**−**l**

| entry | diamine | ketone | isocyanide | product | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | *o*-phenylenediamine | acetone | benzyl | **4a** | 80 |
| 2 | 4,5-dichloro-1,2-phenylenediamine | acetone | benzyl | **4b** | 84 |
| 3 | 4,5-dichloro-1,2-phenylenediamine | acetone | cyclohexyl | **4c** | 78 |
| 4 | 4-nitro-1,2-phenylenediamine | acetone | cyclohexyl | **4d** | 90 |
| 5 | 4-nitro-1,2-phenylenediamine | acetone | *tert*-butyl | **4e** | 88 |
| 6 | 4-nitro-1,2-phenylenediamine | acetone | benzyl | **4f** | 85 |
| 7 | 4-nitro-1,2-phenylenediamine | acetone | 2,6-dimethylphenyl | **4g** | 75 |
| 8 | 4-nitro-1,2-phenylenediamine | acetone | 1,1,3,3-tetramethylbutyl | **4h** | 87 |
| 9 | 3,4-diaminobenzoic acid | cyclohexanone | cyclohexyl | **4i** | 82 |
| 10 | 3,4-diaminobenzoic acid | cyclohexanone | benzyl | **4j** | 80 |
| 11 | 4,5-dichloro-1,2-phenylenediamine | cyclohexanone | *tert*-butyl | **4k** | 86 |
| 12 | 4,5-dichloro-1,2-phenylenediamine | cyclohexanone | benzyl | **4l** | 80 |

[a] Isolated yield.

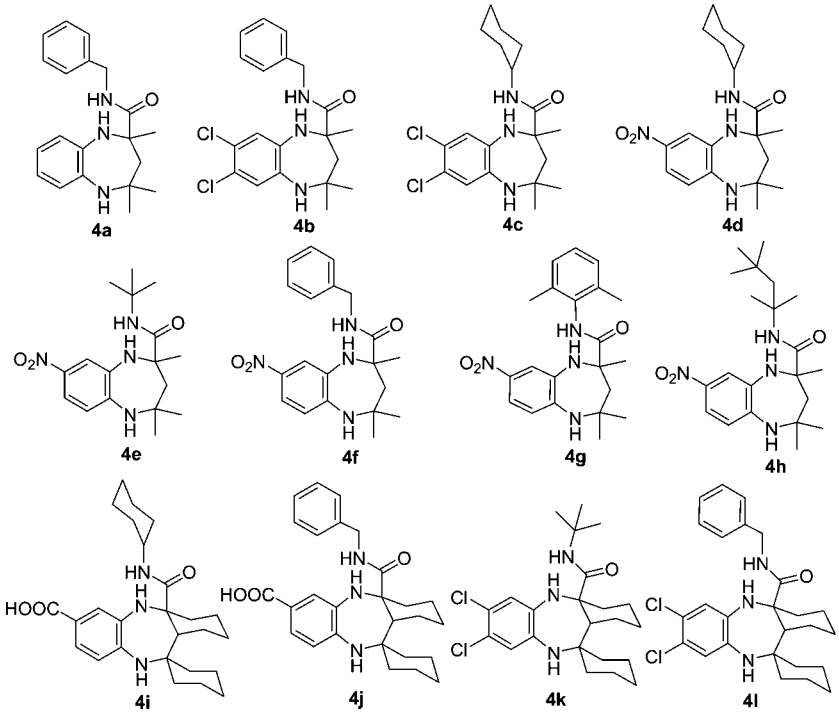



**Figure 1.** Structure of products **4a**−**l**.

selectivity is the result of the electronic effect of the electron-withdrawing groups such as $NO_2$ and COOH, which deactivate the *p*-amino group, and the reaction is initiated by the *m*-amino group to give iminium ion **6** as favored intermediates (Figure 2).[4]

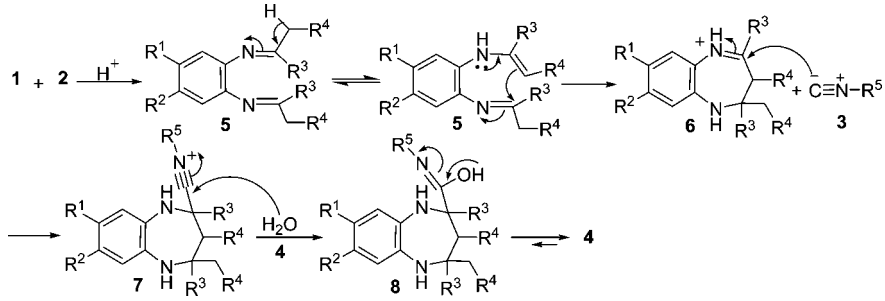
Another interesting aspect of this reaction was the high purity of the product. All of the products (except **4a**, **4g**, and **4l**) were sufficiently pure after an aqueous workup and did not require any further purification. In the case of products **4a**, **4g**, and **4l**, they were crystallized from acetone to give high purity crystalline products.

Finally, the structure of the favored isomer of **4e** was confirmed unambiguously by single-crystal X-ray analysis (The Cambridge Crystallographic Data Centre (CCDC) no. 681385) (Figure 3).[14]

## Conclusions

In summary, we have developed a novel condensation reaction leading to 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide derivatives starting from simple and readily available precursors. This novel reaction can be regarded as a new approach for the preparation of synthetically and pharmaceutically important 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide systems, especially, spirocyclic ones (**4i**−**l**). This one-pot reaction includes some important aspects like the easy workup procedure, high atom economy,

**Scheme 2.** Possible Mechanism for the Formation of Products **4a**−**l**



selectivity, very good yields, combinatorial diversity, and mild reaction conditions.

## Experimental Section

**Typical Procedure: Synthesis of Compound 4a.** First, a solution of *o*-phenylenediamine (0.108 g, 1 mmol) and acetone (0.116 g, 2 mmol) in the presence of *p*-TsOH·$H_2O$ (0.095 g, 5 mol%) was stirred for 4 h in 5 mL of methanol at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1), benzyl isocyanide (0.117 g, 1 mmol) and water (0.5 mL) were added to the reaction mixture. Then the resulting mixture was stirred for 20 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 4/1), the product was filtered off, washed further with water, and then crystallized from acetone to give **4a** as yellow crystals (0.258 g, 80%): mp 137−140 °C; IR (KBr, $cm^{-1}$) 3412, 3380, 3292, 3025, 2934, 2853, 1634, 1543, 1440; $^1$H NMR (300.13 MHz, DMSO-$d_6$) $\delta$ 1.06 (3H, s, $CH_3$), 1.09 (3H, s, $CH_3$), 1.28 (3H, s, $CH_3$), 1.56 (1H, d, $J$ = 14.2 Hz, $CH_2$), 2.25 (1H, d, $J$ = 14.1 Hz, $CH_2$), 4.13 (1H, br s, NH), 4.26−4.31 (2H, m, $CH_2$ of benzyl), 4.99 (1H, br s, NH), 6.56−6.75 (4H, m, H−Ar), 7.16−7.24 (5H, m, H−Ar), 7.96 (1H, m, NH−CO); $^{13}$C NMR (75.47 MHz, DMSO-$d_6$) $\delta$ 30.1, 30.4, 32.2, 42.9, 48.7, 52.8, 60.2, 119.4, 120.1, 121.6, 127.0, 127.5, 128.6, 138.2, 139.9, 176.3; MS *m*/*z* 323 ($M^+$, 8), 189 (100), 133 (65), 91 (20), 65 (15); Anal. Calcd for $C_{20}H_{25}N_3O$ C 74.27, H 7.79, N 12.99; Found C 74.42, H 7.64, N 13.85.

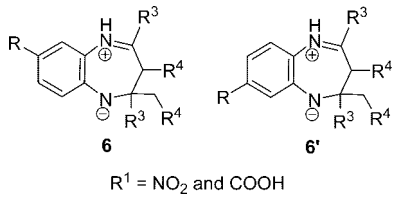


**Figure 2.** Structure of intermediates **6** and **6′**.

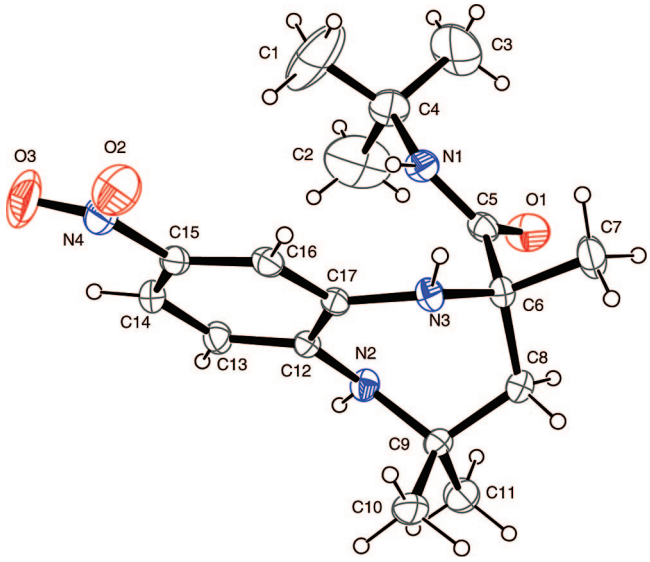


**Figure 3.** ORTEP representation of compound **4e**.

**Acknowledgment.** We gratefully acknowledge financial support from the Iran National Science Foundation (INSF) and Research Council of Shahid Beheshti University.

**Supporting Information Available.** Crystallographic data for **4e** (CIF), experimental procedures, and mass, IR, $^1$H NMR, and $^{13}$C NMR spectra for compounds **4a**−**l** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References and Notes

(1) (a) Zhu, J., Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(2) (a) Randall, L. O.; Kappel, B. In *Benzodiazepines*; Garattini, S., Mussini, E., Randall, L. O., Eds.; Raven Press: New York, 1973; p 27. (b) Schutz, H. *Benzodiazepines*; Springer: Heidelberg, Germany, 1982. (c) Landquist, J. K. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon; Oxford, U.K., 1984; Vol. 1, p 166. (d) Archer, G. A.; Sternbach, L. H. *Chem. Rev.* **1968**, *68*, 747–784. (e) Langnickel, R.; Bluth, R.; Ott, T. *Pharmazie* **1986**, *41*, 689–694. (f) Parola, A. L.; Yamamura, H. I.; Laird, H. E. *Life Sci.* **1993**, *52*, 1329–1342.

(3) Michelini, S.; Cassano, G. B.; Frare, F.; Perugi, G. *Pharmacopsychiatry* **1996**, *29*, 127–134.

(4) (a) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791–5793. (b) Leimgruber, W.; Batcho, A. D.; Schenker, F. *J. Am. Chem. Soc.* **1965**, *87*, 5793–5795. (c) Li, Z.; Sun, Y.; Ren, X.; Shi, Y.; Ouyang, P. *Heterocycles* **2007**, *71*, 453–458. (d) Fazaeli, R.; Aliyan, H.; Tangestaninejad, Sh. *Heterocycles* **2007**, *71*, 805–814. (e) Reddy, K. S.; Reddy, Ch. V.; Mahesh, M.; Reddy, K. R.; Raju, P. V.; Reddy, V. V. *Can. J. Chem.* **2007**, *85*, 184–188. (f) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **2001**, *42*, 3193–3195. (g) Yadav, J. S.; Reddy, B. V. S.; Eshwaraiah, B.; Anuradha, K. *Green Chem.* **2002**, *4*, 592–594. (h) Reddy, B. M.; Sreekanth, P. M. *Tetrahedron Lett.* **2003**, *44*, 4447–4449. (i) Sabitha, G.; Reddy, G. S. K.; Reddy, K. B.; Reddy, N. M.; Yadav, J. S. *Adv. Synth. Catal.* **2004**, *346*, 921–923. (j) Chen, W.-Y.; Lu, J. *Synlett* **2005**, *8*, 1337–1339. (k) Yadav, J. S.; Reddy, B. V. S.;

Praveenkumar, S.; Nagaiah, K. *Synthesis* **2005**, *3*, 480–484. (l) Varala, R.; Enugala, R.; Nuvula, S.; Adapa, S. R. *Synlett* **2006**, *7*, 1009–1014. (m) Kuo, C.-W.; More, S. V.; Yao, C.-F. *Tetrahedron Lett.* **2006**, *47*, 8523–8528. (n) Shaabani, A.; Maleki, A. *Iran. J. Chem. Chem. Eng.* **2007**, *26*, 93–97.

(5) (a) Knabe, J.; Buech, H. P.; Bender, S. *Arch. Pharm.* **1995**, *328*, 59–66. (b) Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1980**, *20*, 161–178.

(6) Atwal, K. S.; Bergey, J. L.; Hedberg, A.; Moreland, S. *J. Med. Chem.* **1987**, *30*, 635–640.

(7) (a) Merluzzi, V.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shih, C.-K.; Eckner, K.; Hattox, S.; Adams, J.; Rosenthal, A. S.; Faanes, R.; Eckner, R. J.; Koup, R. A.; Sullivan, J. L. *Science* **1990**, *250*, 1411–1413. (b) Di Braccio, M.; Grossi, G.; Roma, G.; Vargiu, L.; Mura, M.; Marongiu, M. E. *Eur. J. Med. Chem.* **2001**, *36*, 935–949. (c) Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; Mirands, M.; Rodgers, J. D.; Sherrill, R. G.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L. J.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1991**, *34*, 3187–3197. (d) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 97–100.

(8) (a) Werner, W.; Baumgart, J.; Burckhardt, G.; Fleck, W. F.; Geller, K.; Gutsche, W.; Hanschmann, H.; Messerschmidt, A.; Roemer, W. *Biophys. Chem.* **1990**, *35*, 271–276. (b) Claremon, D. A.; Liverton, N.; Smith, G. R.; Selnick, H. G. U. S. Patent 5 725 171, 1998.

(9) Tranquillini, M. E.; Cassara, P. G.; Corsi, M.; Curotto, G.; Donati, D.; Finizia, G.; Pentassuglia, G.; Polinelli, S.; Tarzia, G.; Ursini, A.; Van Amsterdam, F. T. M. *Arch. Pharm.* **1997**, *330*, 353–357.

(10) Batchelor, M. J.; Bebbington, D.; Bemis, G. W.; Fridman, W. H.; Gillespie, R. J.; Golec, J. M. C.; Lauffer, D. J.; Livingston, D. J.; Matharu, S. S.; Mullican, M. D.; Murcko, M. A.; Murdoch, R.; Zelle, R. E. U. S. Patent 6 423 840, 2002.

(11) Ding, C. Z.; Batorsky, R.; Bhide, R.; Chao, H. J.; Cho, Y.; Chong, S.; GulloBrown, J.; Guo, P.; Kim, S. H.; Lee, F.; Leftheris, K.; Miller, A.; Mitt, T.; Patel, M.; Penhallow, B. A.; Ricca, C.; Rose, W. C.; Schmidt, R.; Slusarchyk, W. A.; Vite, G.; Yan, N.; Manne, V.; Hunt, J. T. *J. Med. Chem.* **1999**, *42*, 5241–5253.

(12) (a) Ohtake, Y., Fukaya, Y. E. European Patent 1 820 799 A1, 2007. (b) Finch, H.; Shah, P.; Carr, R. A. E. U.S. Patent 5 585 376, 1996.

(13) (a) Shaabani, A.; Maleki, A.; Moghimi-Rad, J. *J. Org. Chem.* **2007**, *72*, 6309–6311. (b) Shaabani, A.; Maleki, A.; Mofakham, H.; Moghimi-Rad, J. *J. Org. Chem.* **2008**, *73*, 3925–3927. (c) Shaabani, A.; Soleimani, E.; Maleki, A. *Tetrahedron Lett.* **2006**, *47*, 3031–3034. (d) Shaabani, A.; Rezayan, A. H.; Rahmati, A.; Sarvary, A. *Synlett* **2007**, 1458–1460. (e) Shaabani, A.; Maleki, A.; Mofakham, H.; Khavasi, H. R. *J. Comb. Chem.* **2008**, *10*, 323–326.

(14) *X-STEP32*, version 1.07b; Stoe & Cie GmbH: Darmatadt, Germany, 2000.

CC8000635