FULL PAPER

Synthesis of Novel Pyrazino[2,1-*a*]isoindolediones *via* Intramolecular Hydroamination of 2,3-Dihydro-3-oxo-2-(prop-2-yn-1-yl)-1*H*-isoindole-1-carboxamides

by **Fatemeh Esmaeili-Marandi**[a]), **Issa Yavari**[a]), **Mina Saeedi**[b])[c]), **Mohammad Mahdavi**[d]), and **Abbas Shafiee***[d])

[a]) Department of Chemistry, Tehran Science and Research Branch, Islamic Azad University, Hesarak, Tehran, Iran
[b]) Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran 14176, Iran
[c]) Persian Medicine and Pharmacy Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran
[d]) Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran (phone: +98-21-66406757; e-mail: shafieea@tums.ac.ir)

Novel derivatives of pyrazino[2,1-*a*]isoindolediones were synthesized through 6-*exo-dig* intramolecular hydroamination of 2,3-dihydro-3-oxo-2-(prop-2-yn-1-yl)-1*H*-isoindole-1-carboxamides followed by 1,3-H shift, in the presence of sodium hydride in DMF at 80°. All products were obtained in good yields (60 – 80%) within short reaction time (40 – 60 min).

Keywords: Pyrazino[2,1-*a*]isoindolediones, Isocyanide-based reactions, Propargylamine, 2-Formylbenzoic acids, Hydroamination

Introduction

Hydroamination reaction has been a powerful synthetic tool for the production of functionalized and hindered amines through the addition of an amine to an unsaturated C,C-bond [1]. During recent decades, intramolecular and intermolecular hydroamination reactions have absorbed lots of attention due to the versatile and atom economic procedures for the construction of N-containing heterocycles [2]. In this respect, the use of various catalysts, mostly alkali and lanthanide metal catalysts, has been reported in recent studies. Also, gold-catalyzed intramolecular hydroamination was served for the total synthesis of (−)-epimyrtine [3]. However, the focus has moved to the use of transition metal catalysts since they are usually homogeneous [4 – 6] and development of this kind of catalysts has been the center of attention in current studies [7][8].

Recently, base-catalyzed hydroamination reactions have gained increased importance. In this way, deprotonation of the amine leads to stronger nucleophilicity of N-atom to attack even on unactivated alkenes [9], and the use of bases such as lithium diethylamide [10], monobenzylated piperazine [11], BuLi [12], and ^{t}BuOK [13] have been reported to obtain various *N*-heterocyclic compounds.

N-Heterocycles and their fused systems are the center of attention of organic chemists as well as medicinal chemists due to their promising biological properties. for example, pyrazine derivatives have shown antifungal [14], anti-HIV [15], anticancer [16], and antibacterial [17] activities. Besides, isoindole derivatives possessed cyclooxygenase-2 (COX-2) inhibitory [18] and antimalarial [19] activities as well as affinity for the dopamine D_4 receptor [20]. Compared to the synthesis of other *N*-heterocycles, those of isoindoles and fused derivatives are limited to only a few methods [21]. In this study, pyrazino[2,1-*a*] isoindoles absorbed our attention due to the lack of versatile procedure for their synthesis. Herein, in continuation of our work on the synthesis of novel heterocyclic compounds [22 – 24] as well as hydroamination reaction [13], we describe synthesis of novel pyrazino[2,1-*a*]isoindolediones **5** through the 6-*exo-dig* intramolecular hydroamination of 2,3-dihydro-3-oxo-2-(prop-2-yn-1-yl)-1*H*-isoindole-1-carboxamides **4** (*Scheme*).

Results and Discussion

Isocyanide-based multicomponent reactions (IMCRs) have attracted lots of attention due to the production of versatile products which may act as bifunctional starting materials. On the other hand, they have tackled various problems related to the production of structural diversity and molecular complexity [25]. In this work, we profited from IMCRs benefits and prepared different 2,3-dihydro-3-oxo-2-(prop-2-yn-1-yl)-1*H*-isoindole-1-carboxamide derivatives **4** as a desired starting material. As previously described in the literature [26 – 28], reactions among 2-formylbenzoic acid, isocyanides, and various amines leads to the formation of different *N*-heterocycles. Hence, considering these reactions, compounds **4** were easily

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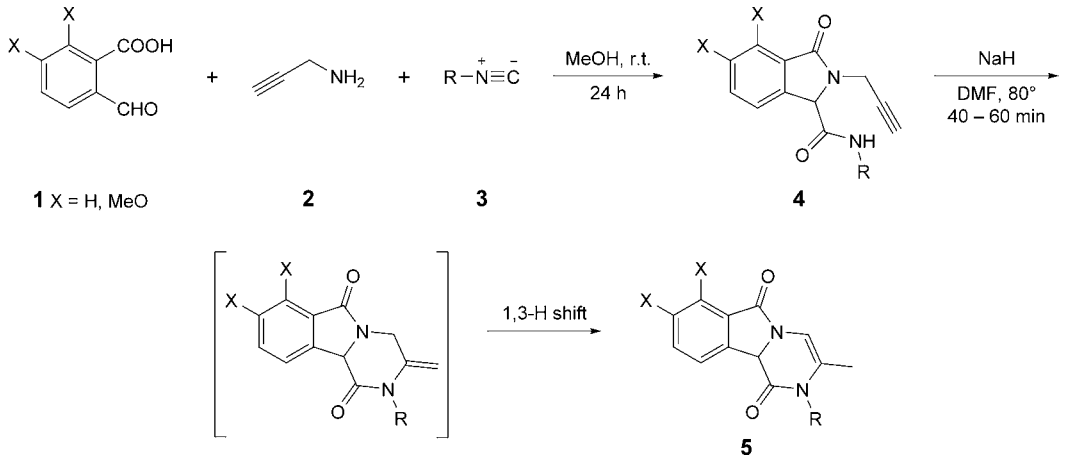
Scheme. Synthesis of pyrazino[2,1-*a*]isoindolediones **5**



1 X = H, MeO **2** **3** **4** **5**

prepared by the reaction of 2-formylbenzoic acids **1**, $HC{\equiv}CCH_2NH_2$ (**2**), and isocyanides **3** (*Scheme*). For this purpose, the above mentioned compounds **1** – **3** reacted in MeOH for 24 h at room temperature to afford pure products **4**. It is worth mentioning that isolated compounds **4a** – **4f** were completely pure and they did not need further purification. Characterization of compound **4a** has been described as a representative product in the *Exper. Part* to confirm the accuracy of the synthetic procedure as well as the structure of **4a**.

In the next step, the corresponding intramolecular hydroamination was investigated. For this purpose, *N*-cyclohexyl-2,3-dihydro-3-oxo-2-(prop-2-yn-1-yl)-1*H*-isoindole-1-carboxamide (**4a**) was selected as the model substrate to conduct the cyclization reaction using various bases (NaH, KOH, EtONa, and ^{t}BuOK) and solvents (DMF, EtOH, and THF). Some results are shown in *Table 1*. As can be seen in *Table 1*, NaH was the most efficient base leading to the formation of the corresponding product **5a** in good yield (80%) within short reaction time (40 min). It was also found that DMF was the most appropriate solvent and the others did not give the product in satisfactory yield. Temperature screening revealed that conducting the model reaction at 80° is the best condition and increasing the temperature did not lead to better yield. However, running the reaction at room temperature resulted in low yield and long reaction time. In continuation of our investigation, we also screened the optimized amount of NaH and observed that equivalent amount of NaH was sufficient to give the promising yield of product **5a** (80%).

Table 1. Investigation of various conditions for the formation of **5a**

Entry	Solvent	Base	Temperature [°]	Time [min]	Yield [%][a])
1	DMF	NaH	r.t.	120	Trace
2	DMF	NaH	80	40	80
3	DMF	NaH	100	60	80
4	THF	NaH	80	120	20
5	EtOH	EtONa	80	120	25
6	DMF	KOH	80	60	15
7	DMF	^{t}BuOK	80	60	15

[a]) Yield of isolated product.

After confirmation of the structure of **5a** using IR, ^{1}H- and ^{13}C-NMR spectroscopy as well as chemical analysis, the scope of the reaction was studied using 6-formyl-2,3-dimethoxybenzoic acid and different isocyanides (*Table 2*). All 2,3-dihydro-3-oxo-2-(prop-2-yn-1-yl)-1*H*-isoindole-1-carboxamides **4** tolerated 6-*exo-dig* hydroamination followed by 1,3-H shift to give product **5**.

Conclusion

In conclusion, we developed an efficient protocol for 6-*exo-dig* hydroamination of 2,3-dihydro-3-oxo-2-(prop-2-yn-1-yl)-1*H*-isoindole-1-carboxamides followed by 1,3-H shift in the presence of NaH in DMF at 80° to obtain novel pyrazino[2,1-*a*]isoindoledione derivatives in good yields and short reaction time (40 – 60 min).

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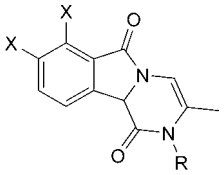
Experimental Part

General

M.p.: *Kofler* hot stage apparatus; uncorrected. ^{1}H- and ^{13}C-NMR: *Bruker FT-500* (500 and 125 MHz, resp.); (D_6)DMSO; δ in ppm rel. to Me_4Si as internal standard, J in Hz. IR Spectra: *Nicolet Magna FT-IR 550* spectrophotometer; in KBr; $\tilde{\nu}$ in cm^{-1}. Elemental analysis:

Table 2. Synthesis of pyrazino[2,1-*a*]isoindolediones **5**



5

Entry	R	X	Product **5**	Yield [%][a])
1	cHex[b])	H	**5a**	80
2	*t*Bu	H	**5b**	75
3	1,1,3,3-Tetramethylbutyl	H	**5c**	65
4	cHex	MeO	**5d**	75
5	*t*Bu	MeO	**5e**	70
6	1,1,3,3-Tetramethylbutyl	MeO	**5f**	60

[a]) Yield of isolated product. [b]) cHex, Cyclohexyl.

VarioEL (*Elementar Analysensysteme GmbH*, Germany), CHNS mode; in %.

Synthesis of 2,3-Dihydro-3-oxo-2-(prop-2-yn-1-yl)-1H-isoindole-1-carboxamides **4**. *Typical Procedure.* A mixture of 2-formylbenzoic acids **1** (1 mmol), $HC{\equiv}CCH_2NH_2$ (**2**; 1 mmol), and isocyanide derivatives **3** (1.2 mmol) in MeOH (10 ml) was stirred at r.t. for 24 h. After completion of the reaction (checked by TLC), H_2O (15 ml) was added to the mixture, and the resulting yellow precipitate was filtered off, washed with H_2O, and used for the next reactions without further purifications. The physical and spectroscopic data of **4a** is described below as the representative derivative.

***N*-Cyclohexyl-2,3-dihydro-3-oxo-2-(prop-2-yn-1-yl)-1*H*-isoindole-1-carboxamide** (**4a**). White crystals. Yield: 0.24 g (80%). M.p. 173 – 175°. IR: 3300, 3230, 2955, 2850, 2245, 1670, 1652, 1610. ^{1}H-NMR: 1.16 – 1.81 (*m*, 10 H, cHex); 3.34 (*t*, *J* = 2.5, 1 CH); 3.56 – 3.59 (*m*, NCH); 3.79 (*dd*, *J* = 17.5, 2.5, 1 CH_2); 4.70 (*dd*, *J* = 17.5, 2.5, 1 CH_2); 5.29 (*s*, H–C(1)); 7.55 (*t*, *J* = 7.5, H–C(5)); 7.58 (*d*, *J* = 7.5, H–C(7)); 7.65 (*td*, *J* = 7.5, 1.0, H–C(6)); 7.72 (*d*, *J* = 7.5, H–C(4)); 8.66 (*d*, *J* = 8.0, 1 NH). ^{13}C-NMR: 24.4; 24.5; 25.2; 30.3; 32.3; 39.1; 48.2; 62.2; 75.4; 78.4; 122.5; 123.2; 129.0; 130.9; 132.3; 141.7; 165.2; 167.4. Anal. calc. for $C_{18}H_{20}N_2O_2$ (296.37): C 72.95, H 6.80, N 9.45; found: C 72.81, H 6.72, N 9.34.

Synthesis of Pyrazino[2,1-a]isoindolediones **5**. *Typical Procedure*. A mixture of crude 2,3-dihydro-3-oxo-2-(prop-2-yn-1-yl)-1*H*-isoindole-1-carboxamide derivative **4** (1 mmol) and NaH (1 mmol) in DMF (8 ml) was stirred at 80° for 40 – 60 min. After completion of the reaction (checked by TLC), H_2O (8 ml) was added to the mixture, and the precipitated white product was filtered off, washed with H_2O, and recrystallized from EtOH to give pure product **5**.

2-Cyclohexyl-3-methylpyrazino[2,1-*a*]isoindole-1,6(2*H*,10b*H*)-dione (**5a**). White crystals. Yield: 0.24 g (80%). M.p. 175 – 177°. IR: 3115, 2959, 1720, 1652, 1601. ^{1}H-NMR: 1.21 – 1.89 (*m*, 10 H, cHex); 2.11 (*s*, Me); 3.70 – 3.71 (*m*, CHN); 5.19 (*s*, 1 CH); 6.16 (*s*, H–C(4)); 7.51 (*t*, *J* = 7.0, H–C(8)); 7.63 – 7.66 (*m*, H–C(9,10)); 8.03 (*d*, *J* = 7.0, H–C(7)). ^{13}C-NMR: 23.0; 28.1; 28.2; 32.2; 33.3; 50.6; 56.3; 60.3; 102.1; 113.9; 116.4; 117.1; 124.7; 132.3; 134.9; 145.2; 163.6; 163.8. Anal. calc. for $C_{18}H_{20}N_2O_2$ (296.37): C 72.95, H 6.80, N 9.45; found: C 73.15, H 6.94, N 9.58.

2-*tert*-Butyl-3-methylpyrazino[2,1-*a*]isoindole-1,6(2*H*,10b*H*)-dione (**5b**). White crystals. Yield: 0.20 g (75%). M.p. 141 – 143°. IR: 3126, 2960, 1725, 1640, 1602. ^{1}H-NMR: 1.30 (*s*, Me_3C); 2.10 (*s*, Me); 5.31 (*s*, 1 CH); 6.16 (*s*, H–C(4)); 7.53 (*t*, *J* = 7.5, H–C(8)); 7.60 (*d*, *J* = 7.5, H–C(10)); 7.65 (*t*, *J* = 7.5, H–C(9)); 7.71 (*d*, *J* = 7.5, H–C(7)). ^{13}C-NMR: 28.3; 30.2; 50.8; 62.4; 102.8; 118.1; 122.8; 123.0; 128.7; 132.7; 133.0; 141.8; 165.8; 167.3. Anal. calc. for $C_{16}H_{18}N_2O_2$ (270.33): C 71.09, H 6.71, N 10.36; found: C 71.24, H 6.92, N 10.45.

3-Methyl-2-(2,4,4-trimethylpentan-2-yl)pyrazino[2,1-*a*]isoindole-1,6(2*H*,10b*H*)-dione (**5c**). White crystals. Yield: 0.21 g (65%). M.p. 122 – 124°. IR: 3120, 2959, 1721, 1647, 1601. ^{1}H-NMR: 0.98 (*s*, 3 Me); 1.29 (*s*, Me); 1.37 (*s*, Me); 1.49 (*d*, *J* = 14.5, 1 CH_2); 1.98 (*d*, *J* = 14.5, 1 CH_2); 2.21 (*s*, Me); 5.32 (*s*, 1 CH); 5.87 (*s*, H–C(4)); 7.53 (*t*, *J* = 7.5, H–C(8)); 7.60 (*d*, *J* = 7.5, H–C(10)); 7.65 (*t*, *J* = 7.5, H–C(9)); 7.71 (*d*, *J* = 7.5, H–C(7)). ^{13}C-NMR: 28.8; 29.2; 30.0; 31.2; 31.3; 50.0; 62.40; 102.1; 112.9; 122.5; 123.1; 130.8; 131.9; 134.8; 141.9; 165.0; 165.7. Anal. calc. for $C_{20}H_{26}N_2O_2$ (326.44): C 73.59, H 8.03, N 8.58; found: C 73.70, H 7.91, N 8.38.

2-Cyclohexyl-7,8-dimethoxy-3-methylpyrazino[2,1-*a*]isoindole-1,6(2*H*,10b*H*)-dione (**5d**). White crystals. Yield: 0.27 g (75%). M.p. 138 – 139°. IR: 3128, 2961, 1727, 1642, 1603. ^{1}H-NMR: 1.18 – 1.87 (*m*, 10 H, cHex); 2.10 (*s*, Me); 3.67 – 3.68 (*m*, CHN); 3.80 (*s*, MeO); 3.89 (*s*, MeO); 5.30 (*s*, 1 CH); 6.25 (*s*, H–C(4)); 7.08 (*d*, *J* = 8.0, H–C(9)); 7.67 (*d*, *J* = 8.0, H–C(10)). ^{13}C-NMR: 23.3; 28.4; 28.9; 33.5; 50.3; 55.3; 55.6; 60.9; 100.2; 114.3; 116.6; 117.6; 123.4; 132.8; 145.3; 153.2; 163.3; 163.4. Anal. calc. for $C_{20}H_{24}N_2O_4$ (356.42): C 67.40, H 6.79, N 7.86; found: C 67.27, H 6.87, N 7.71.

2-*tert*-Butyl-7,8-dimethoxy-3-methylpyrazino[2,1-*a*]isoindole-1,6(2*H*,10b*H*)-dione (**5e**). White crystals. Yield: 0.23 g (70%). M.p. 149 – 151°. IR: 3126, 2690, 1727, 1641, 1604. ^{1}H-NMR: 1.28 (*s*, Me_3C); 2.20 (*s*, Me); 3.82 (*s*, MeO); 3.87 (*s*, MeO); 5.14 (*s*, 1 CH); 5.81 (*s*, H–C(4)); 7.22 (*d*, *J* = 8.0, H–C(9)); 7.30 (*d*, *J* = 8.0, H–C(10)). ^{13}C-NMR: 28.3; 30.1; 55.3; 55.5; 58.3; 61.6; 101.2; 114.4; 116.0; 117.8; 123.9; 139.5; 144.0; 152.0; 162.3; 162.4. Anal. calc. for $C_{18}H_{22}N_2O_4$ (330.38): C 65.44, H 6.71, N 8.48; found: C 65.32, H 6.88, N 8.32.

7,8-Dimethoxy-3-methyl-2-(2,4,4-trimethylpentan-2-yl)pyrazino[2,1-*a*]isoindole-1,6(2*H*,10b*H*)-dione (**5f**). White crystals. Yield: 0.23 g (60%). M.p. 165 – 167°. IR: 3123, 2960, 1726, 1655, 1604. ^{1}H-NMR: 0.98 (*s*, 3 Me); 1.28 (*s*, Me); 1.35 (*s*, Me); 1.51 (*d*, *J* = 14.5, 1 CH_2); 1.99 (*d*, *J* = 14.5, 1 CH_2); 2.26 (*s*, Me); 3.82 (*s*, MeO); 3.87 (*s*, MeO); 5.17 (*s*, 1 CH); 6.02 (*s*, H–C(4)); 7.22 (*d*, *J* = 8.0, H–C(9)); 7.30 (*d*, *J* = 8.0, H–C(10)). ^{13}C-NMR: 28.8; 29.3; 30.0;

31.2; 31.3; 54.6; 56.2; 56.3; 61.3; 102.4; 114.4; 118.9; 119.2; 122.4; 134.3; 145.0; 142.9; 165.0; 165.2. Anal. calc. for $C_{22}H_{30}N_2O_4$ (386.49): C 68.37, H 7.82, N 7.25; found: C 68.51, H 7.71, N 7.38.

REFERENCES

[1] T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev. (Washington, DC, U.S.)* **2008**, *108*, 3795.
[2] M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.
[3] T. T. Huyen Trinh, K. H. Nguyen, P. de Aguiar Amaral, N. Gouault, *Beilstein J. Org. Chem.* **2013**, *9*, 2042.
[4] M. R. Gagné, T. J. Marks, *J. Am. Chem. Soc.* **1989**, *111*, 4108.
[5] Y. Li, P.-F. Fu, T. J. Marks, *Organometallics* **1994**, *13*, 439.
[6] G. A. Molander, H. Hasegawa, *Heterocycles* **2004**, *64*, 467.
[7] N. Mizuno, M. Tabata, T. Uematsu, M. Iwamoto, *J. Catal.* **1994**, *146*, 249.
[8] K. Motokura, N. Nakagiri, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa, K. Kaneda, *Org. Lett.* **2006**, *8*, 4617.
[9] J. Seayad, A. Tillack, C. G. Hartung, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 795.
[10] V. Khedkar, A. Tillack, C. Benisch, J.-P. Melder, M. Beller, *J. Mol. Catal. A: Chem.* **2005**, *241*, 175.
[11] K. Kumar, D. Michalik, I. Garcia Castro, A. Tillack, A. Zapf, M. Arlt, T. Heinrich, H. Böttcher, M. Beller, *Chem. – Eur. J.* **2004**, *10*, 746.
[12] A. Ates, C. Quinet, *Eur. J. Org. Chem.* **2003**, 1623.
[13] M. Mahdavi, N. Foroughi, M. Saeedi, M. Karimi, H. Alinezhad, A. Foroumadi, A. Shafiee, T. Akbarzadeh, *Synlett* **2014**, *25*, 385.
[14] H. Tang, C. Zheng, J. Lü, J. Wu, Y. Li, H. Yang, B. Fu, C. Li, Y. Zhou, J. Zhu, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 979.
[15] A. Petrocchi, P. Jones, M. Rowley, F. Fiore, V. Summa, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4245.
[16] I. Ortín, J. F. González, E. de la Cuesta, C. Manguan-García, R. Perona, C. Avendaño, *Bioorg. Med. Chem.* **2009**, *17*, 8040.
[17] R. K. Tiwari, D. Singh, J. Singh, V. Yadav, A. K. Pathak, R. Dabur, A. K. Chhillar, R. Singh, G. L. Sharma, R. Chandra, A. K. Verma, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 413.
[18] V. R. Khayrullina, A. Y. Gerchikov, A. A. Lagunin, F. S. Zarudii, *Biochemistry Moscow* **2015**, *80*, 74.
[19] E. del Olmo, B. Barboza, L. D. Chiaradia, A. Moreno, J. Carrero-Lérida, D. González-Pacanowska, V. Muñoz, J. L. López-Pérez, A. Giménez, A. Benito, A. R. Martínez, L. M. Ruiz-Pérez, A. San Feliciano, *Eur. J. Med. Chem.* **2011**, *46*, 5379.
[20] T. R. Belliotti, W. A. Brink, S. R. Kesten, J. R. Rubin, D. J. Wustrow, K. T. Zoski, S. Z. Whetzel, A. E. Corbin, T. A. Pugsley, T. G. Heffner, L. D. Wise, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499.
[21] K. Speck, T. Magauer, *Beilstein J. Org. Chem.* **2013**, *9*, 2048.
[22] F. Goli-Garmroodi, M. Omidi, M. Saeedi, F. Sarrafzadeh, A. Rafinejad, M. Mahdavi, G. R. Bardajee, T. Akbarzadeh, L. Firoozpour, A. Shafiee, A. Foroumadi, *Tetrahedron Lett.* **2015**, *56*, 743.
[23] S. Nahavandian, S. Allameh, M. Saeedi, S. Ansari, M. Mahdavi, A. Foroumadi, A. Shafiee, *Helv. Chim. Acta* **2015**, *98*, 1028.
[24] F. Esmaeili-Marandi, M. Saeedi, M. Mahdavi, I. Yavari, A. Foroumadi, A. Shafiee, *Synlett* **2014**, *25*, 2605.
[25] A. Dömling, *Chem. Rev. (Washington, DC, U.S.)* **2006**, *106*, 17.
[26] S. V. Ley, S. J. Taylor, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1813.
[27] C. Faggi, M. García-Valverde, S. Marcaccini, G. Menchi, *Org. Lett.* **2010**, *12*, 788.
[28] A. Shaabani, F. Hajishaabanha, M. Mahyari, H. Mofakham, S. W. Ng, *Tetrahedron* **2011**, *67*, 8360.

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