Journal Name

Dynamic Article Links ►

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

One-pot synthesis of 1-azaspiro frameworks initiated by photooxidation of simple furans

Dimitris Kalaitzakis, Eirini Antonatou and Georgios Vassilikogiannakis*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A range of 1-azaspirocycles, spiroaminals and 1,6-diazaspirocycles has been synthesized, starting from simple and readily accessible furan precursors, using a cascade reaction sequence initiated by singlet oxygen.

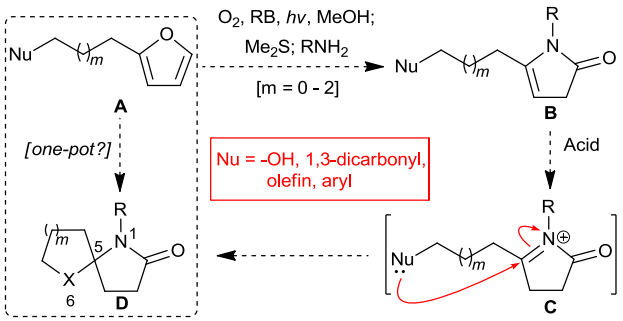
Nitrogen-containing spirocycles of type **D** (Scheme 1) represent a very important class of building blocks as the motif exists in an elaborated form in many natural products and pharmaceuticals including Cylindricine A,[1a] Ansalactam A,[1b] and Grandilodines A-C[1c] (for X=C), Marineosins A and B,[2a] Armeniaspirols A-C,[2b] and Kleinhospitines A-D[2c] (for X=O) and Pandamarine,[3a] and Haplophytine[3b,c] (for X=N).

Out of the known methods for synthesis of 1-azaspirocycles (**D**, X=C),[4] several proceed via *N*-acyliminium (NAI) formation followed by cyclization with an alkene, or an aromatic π-nucleophile.[6-10] However, only one method for the one-step construction of the complete spiro-scaffold (formation of both N1-C5 and C5-C6 bonds of **D**, Scheme 1), via NAI cyclization, has been reported.[7a,8] This method, beginning from a keto amide, was successfully applied to the synthesis of (–)-Lepadiformine,[7a-c] (+)-Cylindricine C[7b-d] and (–)-Fasicularin[7c] and is similar to a strategy originally developed by Speckamp,[6] and extended by Vernon[10] to aromatic π-nucleophiles.

Fewer general methods concerning the efficient synthesis of spiroaminals (**D**, X=O) have been reported.[11] An acid-catalyzed NAI-formation with subsequent cyclization in order to produce the *oxa-aza*-spirocycle has been reported.[12] Only one of these examples was performed in one-step and in this case it began from a specific hydroxy-keto-amide as part of efforts directed towards the synthesis of Marineosin A.[12f]

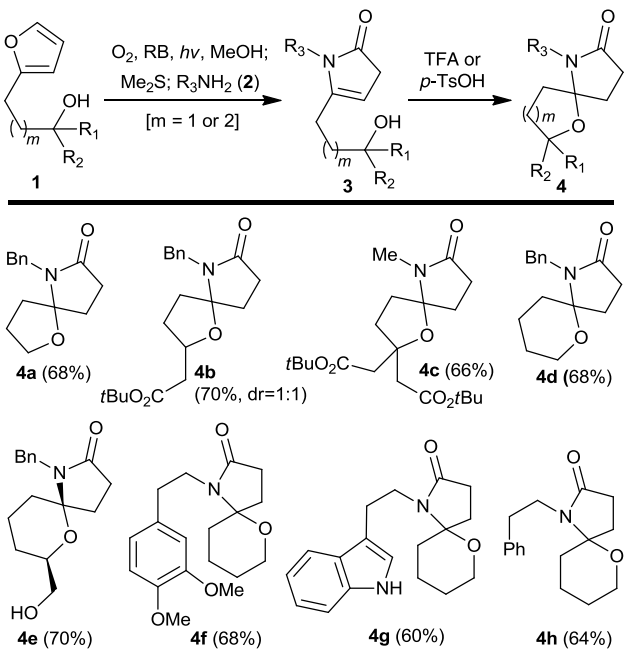
Reports dealing with the construction of 1,6-diazaspirocycles (**D**, X=N) are more limited[13] and only one example utilizing NAI-chemistry has been reported.[14] Recently, a new method has been developed for the construction of the 1,6-diazaspirocycle of Haplophytine based on a semipinacol-type rearrangement[15a] and then applied to the total synthesis of (+)-Haplophytine.[15b,c]

The investigation described herein focuses on the facile one-pot synthesis of all three of the azaspiro-frameworks introduced above (**D**, Scheme 1). The reaction sequence is initiated by singlet oxygen-mediated oxidation of very simple and easily accessible 2-substituted furans.[16] The one-pot protocol begins with the formation of 2-pyrrolidinone **B**,[17] an intermediate which is then protonated *in situ* to yield an NAI **C** that is attacked by a pendant nucleophile to furnish the final spirocycle **D** (Scheme 1).

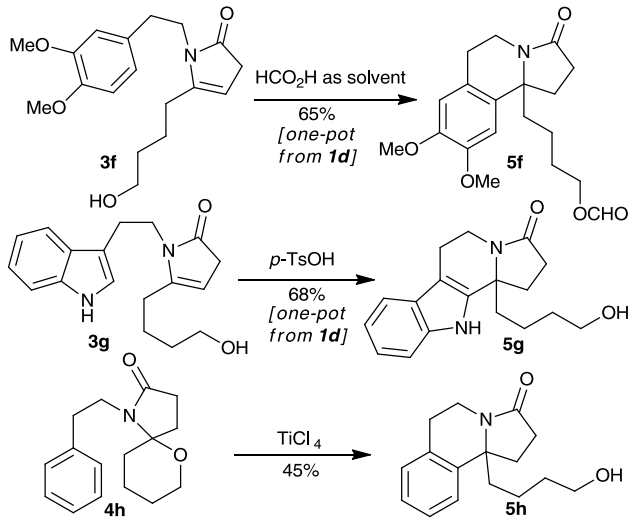


Scheme 1 General concept for the synthesis of 1-azaspirocyclic lactams.

The investigation began with simple 2-(γ-hydroxyalkyl) and 2-(δ-hydroxyalkyl) furans as substrates (**1**, Scheme 2). Irradiation of a solution of these furans (in MeOH containing 10^{-4} M rose Bengal and with oxygen gently bubbling through it) with visible light for 8 min, followed by treatment with 4 eq of dimethyl sulfide (DMS) and 0.9 eq of an amine (**2**), resulted in the formation of the intermediate 2-pyrrolidinone[17] (**3**, Scheme 2). Treatment of this 2-pyrrolidinone **3** with a Brønsted acid (TFA or



Scheme 2 One-pot synthesis of spiroaminals starting from simple furans.

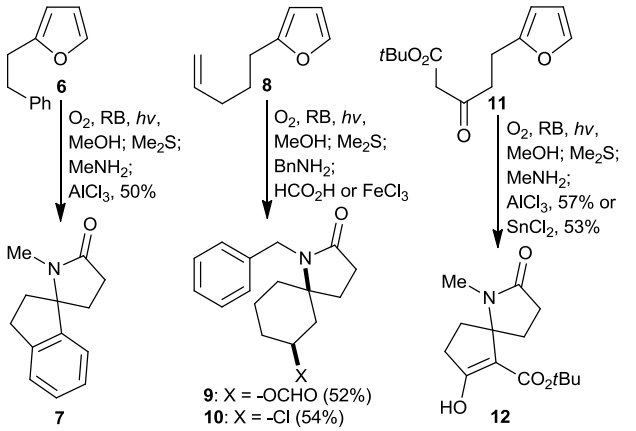


Scheme 3 Pictet-Spengler cyclization to fused bicyclic lactams.

p-TsOH) followed by 5-*exo*, or 6-*exo* cyclization, of the intermediate NAI of type **C** (Scheme 1) led to the exclusive formation of both [5,5]- (**4a-c**) and [5,6]-spiroaminals (**4d-h**, Scheme 2) in 60-70% isolated yield. *p*-TsOH (0.2 eq) was found to be more suitable in the case of [5,6]-spiroaminal **4e** (isolated as single diastereoisomer) because the free hydroxy group of the final product could easily be esterified with TFA.

Following the successful synthesis of spiroaminals **4f-h** (Scheme 2) using amines of type $ArCH_2CH_2NH_2$ each bearing an aromatic unit with a different degree of nucleophilicity (a phenyl ring activated by two methoxy substituents in **4f**, an indole ring in **4g** and a simple phenyl ring in **4h**), our investigation moved on to examination of the possibility of a 6-*endo* cyclization with the amine's aromatic ring (Pictet-Spengler[18] aromatic substitution, Scheme 3) of intermediates **3f-h** by adjusting the type and the amount of the acid used. In particular, by adding either HCOOH (as solvent), or *p*-TsOH (0.4 eq), the Pictet-Spengler cyclization was achieved furnishing exclusively the corresponding fused bicyclic lactams **5f** and **5g** (Scheme 3). It is important to mention here that both these reactions were performed as one-pot processes starting from furan **1d** (m=2, R_1=R_2=H, Scheme 2). Moreover, if isolated, [5,6]-spiroaminals **4f** and **4g** could be exclusively transformed to the corresponding fused bicyclic lactams **5f** and **5g** if treated with HCOOH (as solvent), or *p*-TsOH (0.4 eq), respectively. For the formation of bicyclic lactam **5h**, isolation of spiroaminal **4h** was necessary before treatment with $TiCl_4$ (3.0 eq, Scheme 3).[19]

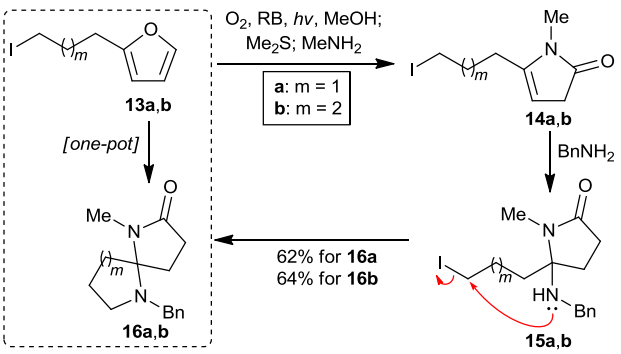
Exploration of different nucleophiles appended to the 2-alkyl side chain of the starting furans was next investigated with the aim of preparing of 1-azaspirocycles (**D**, X=C, Scheme 1). For this purpose, three alternative types of cyclizations (Pictet-Spengler,[18] *aza*-Prins[20] and Mannich[21]) for the final stage of this one-pot process were studied. Furans **6**, **8** and **11** (Scheme 4) were selected, bearing different nucheophiles on the 2-alkyl side chain (a phenyl ring, an olefin and a β-ketoester, respectively). Application of the developed protocol to furan **6** using $AlCl_3$ as the Lewis acid, afforded the Pictet-Spengler product **7** (Scheme 4). In the case of furan **8**, two different azaspirocycles were obtained through an *aza*-Prins cyclization by tailoring the choice of acid at the final stage of the one-pot process. Use of HCOOH



Scheme 4 One-pot synthesis of various 1-azaspirocycles.

(as solvent)[6] afforded azaspirocycle **9**, while termination of this one-pot process with $FeCl_3$ (2.0 eq)[22] gave azaspirocycle **10**. Both azaspirocycles **9** and **10** were obtained as single diastereoisomers (Scheme 4). $SnCl_4$ mediated *aza*-Prins cyclization was also attempted, but a mixture of regioisomers of **10** was isolated; this observation is in agreement with a previously reported one applying to a similar situation, but where $TiCl_4$ is used as the Lewis acid.[9b] Finally, β-ketoester **11** was employed for the formation of the [5,5]-1-azaspirocycle **12** through a Mannich cyclization. The reaction proceeded smoothly leaving the sensitive β-ketoester group untouched through the early stages of this complex cascade reaction sequence producing the intermediate 2-pyrrolidinone of type **B** (Scheme 1). Since Brønsted acid-mediated Mannich cyclizations are known to be difficult,[7d] efforts were focused on employing Lewis acidic conditions. After intensive screening ($TiCl_4$ in the presence of AcOH[23] does not give reproducible results), $AlCl_3$ (2.0 eq) and $SnCl_2$ (3.5 eq) were found to be the best Lewis acids for the formation of the desired compound **12**.

Finally, our focus shifted to the construction of 1,6-diazaspirocycles (**16a**,**b** Scheme 5). As free amines are sensitive to singlet oxygen-photooxygenation conditions,[24] the application of the developed protocol to a furan of type **A** (Scheme 1) where Nu=-NHR, was not a viable option. Instead, the intermolecular attack of a second amine on to the NAI arising from 2-pyrrolidinones **14a**,**b** and a subsequent intramolecular substitution of an iodide at γ-, or δ-positions, of the alkyl side chain of intermediates **15a**,**b** (Scheme 5) was investigated. This idea was successfully applied to iodo-furans **13a** and **13b**,[19] using



Scheme 5 One-pot synthesis of 1,6-diazaspirocycles.

$MeNH_2$ for the formation of 2-pyrrolidinones **14a**,**b**, followed by addition of a second amine ($BnNH_2$) in refluxing chloroform. The desired [5,5]- and [5,6]-1,6-diazaspirocycles **16a**,**b** were isolated. The total yields for these processes (62% for **16a** and 64% for **16b**) are remarkable if the intricate nature of the cascade reaction sequence that leads to their formation is taken into account. Crude ^{1}H NMR spectra, taken before completion of the final step (**15a** → **16a**) of this one-pot sequence, revealed the formation of intermediate **15a**, suggesting that the proposed sequence of events (initial formation of **15a**,**b** followed by the intramolecular nucleophilic substitution of the primary iodide) is indeed correct.

We have developed a practical and highly controllable one-pot reaction sequence for the synthesis of a variety of different 1-azaspiro frameworks, including 1-azaspirocycles, spiroaminals and 1,6-diazaspirocycles. The reaction sequence is initiated by singlet oxygen-mediated oxidation of simple and readily accessible furans. This novel technology answers the call for new sustainable processes from a number of different perspectives; namely, a dramatic increase in molecular complexity in one synthetic operation has been achieved, protecting groups are not required and the oxidant is metal- and toxic residue-free. In addition, singlet oxygen is generated using benign conditions and its employment maximizes atom-economy.

The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC Grant Agreement No. 277588.

Notes and references

Department of Chemistry, University of Crete, 71003 Iraklion, Crete, Greece. Fax: +30 2810 545001; Tel: +30 2810 545074; E-mail: vasil@chemistry.uoc.gr

† Electronic Supplementary Information (ESI) available: [Experimental procedures, full spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds, as well as copies of the NOE experiments]. See DOI: 10.1039/b000000x/

1 (*a*) A. J. Blackman, C. Li, *Tetrahedron* 1993, **49**, 8645; (*b*) M. C. Wilson, S.-J. Nam, T. A. M. Gulder, C. A. Kauffman, P. R. Jensen, W. Fenical, B. S. Moore, *J. Am. Chem. Soc.* 2011, **133**, 1971; (*c*) W.-S, Yap, C.-Y. Gan, Y.-Y. Low, Y.-M. Choo, T. Etoh, M. Hayashi, K. Komiyama, T.-S. Kam, *J. Nat. Prod.* 2011, **74**, 1309.

2 (*a*) C. Boonlarppradab, C. A. Kauffman, P. R. Jensen, W. Fenical, *Org. Lett.* 2008, **10**, 5505; (*b*) C. Dufour, J. Wink, M. Kurz, H. Kogler, H. Olivan, S. Sablé, W. Heyse, M. Gerlitz, L. Toti, A. Nuβer, A. Rey, C. Couturier, A. Bauer, M. Brönstrup, *Chem. Eur. J.* 2012, **18**, 16123; (*c*) C.-X. Zhou, L. Zou, L.-S. Gan, Y.-L. Cao, *Org. Lett.* 2013, **15**, 2734.

3 (*a*) L. T. Byrne, B. Q. Guevara, W. C. Patalinghug, B. V. Recio, C. R. Ualat, A. H. White, *Aust. J. Chem.* 1992, **45**, 1903; (*b*) E. F. Rogers, H. R. Snyder, R. F. Fischer, *J. Am. Chem. Soc.* 1952, **74**, 1987; (*c*) P. Yates, F. N. MacLachlan, I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, M. P. Cava, M. Behforouz, M. V. Lakshmikantham, W. Zeiger, *J. Am. Chem. Soc.* 1973, **95**, 7842.

4 For a review, see: (*a*) G. Dake, *Tetrahedron* 2006, **62**, 3467 and references therein. For representative examples dealing with the formation of N1-C5 or C5-C6 bond at spirocyclization step see: (*b*) L. Caggiano, J. Davies, D. J. Fox, D. C. Moody, S. Warren, *Chem. Commun.* 2003, **39**, 1648; (*c*) T. J. Donohoe, C. K. A. Callens, A. L. Thompson, *Org. Lett.* 2009, **11**, 2305; (*d*) C. M. Griffiths-Jones, D. W. Knight, *Tetrahedron* 2010, **66**, 4150; (*e*) H. Liang, M. A. Ciufolini, *Chem. Eur. J.* 2010, **16**, 13262; (*f*) M. Fujitani, M. Tsuchiya, K. Okano, K. Takasu, M. Ihara, H. Tokuyama, *Synlett* 2010, 822; (*g*) L. I. Palmer, J. Read de Alaniz, *Angew. Chem. Int. Ed.* 2011, **50**, 7167; (*h*) M. Puppala, A. Murali, S. Baskaran, *Chem. Commun.* 2012, **48**, 5778; (*i*) M. A. Perry, R. R. Hill, S. D. Rychnovsky, *Org. Lett.* 2013, **15**, 2226; (*j*) M.-C. P. Yeh, C.-J. Liang, C.-Y. Liu, Y. Shih, I-C. Lee, H.-F. Liu, J.-L. Wang, *Org. Biomol. Chem.* 2013, **11**, 3393; (*k*) K.-J. Xiao, J.-M. Luo, X.-E. Xia, Y. Wang, P.-Q. Huang, *Chem. Eur. J.* 2013, **19**, 13075.

5 (*a*) W. N. Speckamp, H. Hiemstra, *Tetrahedron* 1985, **41**, 4367; (*b*) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* 2004, **104**, 1431.

6 (*a*) H. E. Schoemaker, W. N. Speckamp, *Tetrahedron Lett.* 1978, **19**, 1515; (*b*) H. E. Schoemaker, W. N. Speckamp, *Tetrahedron* 1980, **36**, 951.

7 (*a*) H. Abe, S. Aoyagi, C. Kibayashi, *Angew. Chem. Int. Ed.* 2002, **41**, 3017; (*b*) J. Liu, R. P. Hsung, S. D. Peters, *Org. Lett.* 2004, **6**, 3989; (*c*) H. Abe, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* 2005, **127**, 1473; (*d*) J. Liu, J. J. Swidorski, S. D. Peters, R. P. Hsung, *J. Org. Chem.* 2005, **70**, 3898.

8 H. Abe, K. Takaya, K. Watanabe, S. Aoyagi, C. Kibayashi, T. Katoh, *Heterocycles* 2007, **74**, 205.

9 (*a*) P. Sun, C. Sun, S. M. Weinreb, *Org. Lett.* 2001, **3**, 3507; (*b*) T. Ito, N. Yamazaki, C. Kibayashi, *Synlett* 2001, 1506.

10 (*a*) P. D. Bailey, K. M. Morgan, D. I. Smith, J. M. Vernon, *Tetrahedron Lett.* 1994, **35**, 7115; (*b*) P. D. Bailey, K. M. Morgan, D. I. Smith, J. M. Vernon, *Tetrahedron* 2003, **59**, 3369; (*c*) A. A. Bahajaj, M. H. Moore, J. M. Vernon, *Tetrahedron* 2004, **60**, 1235.

11 For a review, see: (*a*) M.-E. Sinibaldi, I. Canet, *Eur. J. Org. Chem.* 2008, 4391 and references therein; (*b*) A. Y. Sukhorukov, A. V. Lesiv, Y. A. Khomutova, S. L. Ioffe, Y. V. Nelyubina, *Synthesis* 2008, 1205; (*c*) J. Robertson, A. J. Tyrrell, P. T. Chovatia, S. Skerratt, *Tetrahedron Lett.* 2009, **50**, 7141; (*d*) E. L. Cropper, A.-P. Yuen, A. Ford, A. J. P. White, K. K. Hii, *Tetrahedron* 2009, **65**, 525; (*e*) A. Martín, I. Pérez-Martín, E. Suárez, *Tetrahedron* 2009, **65**, 6147; (*f*) X.-C. Cai, X. Wu, B. B. Snider, *Org. Lett.* 2010, **12**, 1600; (*g*) A. P. J. Pal, P. Kadigachalam, A. Mallick, V. R. Doddi, Y. D. Vankar, *Org. Biomol. Chem.* 2011, **9**, 809.

12 (*a*) F. C. Uhle, F. Sallmann, *J. Am. Chem. Soc.* 1960, **82**, 1190; (*b*) A. S. Kende, J. I. M. Hernando, J. B. J. Milbank, *Org. Lett.* 2001, **3**, 2505; (*c*) J.-F. Zheng, W. Chen, S.-Y. Huang, J.-L. Ye, P.-Q. Huang, *Beilstein J. Org. Chem.* 2007, **3**, 1:41; (*d*) J. D. Panarese, L. C. Konkol, C. B. Berry, B. S. Bates, L. N. Aldrich, C. W. Lindsley, *Tetrahedron Lett.* 2013, **54**, 2231; (*e*) G. Li, X. Zhang, Q. Li, P. Feng, Y. Shi, *Org. Biomol. Chem.* 2013, **11**, 2936; (*f*) L. N. Aldrich, C. B. Berry, B. S. Bates, L. C. Konkol, M. So, C. W. Lindsley, *Eur. J. Org. Chem.* 2013, 4215.

13 (*a*) K. H. Büchel, A. K. Bocz, F. Korte, *Chem. Ber.* 1966, **99**, 724; (*b*) O. Tsuge, H. Watanabe, K. Masuda, M. M. Yousif, *J. Org. Chem.* 1979, **44**, 4543.

14 M. J. Martín-López, F. Bermejo, *Tetrahedron* 1998, **54**, 12379.

15 (*a*) K. Matsumoto, H. Tokuyama, T. Fukuyama, *Synlett* 2007, 3137; (*b*) H. Ueda, H. Satoh, K. Matsumoto, K. Sugimoto, T. Fukuyama, H. Tokuyama, *Angew. Chem. Int. Ed.* 2009, **48**, 7600; (*c*) K. C. Nicolaou, S. M. Dalby, S. Li, T. Suzuki, D. Y.-K. Chen, *Angew. Chem. Int. Ed.* 2009, **48**, 7616.

16 B. König, *Science of Synthesis* 2000, **9**, 183.

17 For generation of 2-pyrrolidinone **B** via photooxidation of 2-substituted furans, see: (*a*) D. Kalaitzakis, T. Montagnon, I. Alexopoulou, G. Vassilikogiannakis, *Angew. Chem., Int. Ed.* 2012, **51**, 8868; (*b*) D. Kalaitzakis, T. Montagnon, E. Antonatou, N. Bardají, G. Vassilikogiannakis, *Chem. Eur. J.* 2013, **19**, 10119; (*c*) D. Kalaitzakis, T. Montagnon, E. Antonatou, G. Vassilikogiannakis, *Org. Lett.* 2013, **15**, 3714.

18 (*a*) A. Pictet, T. Spengler, *Ber. Dtsch. Chem. Ges.* 1911, **44**, 2030; (*b*) E. D. Cox, J. M. Cook, *Chem. Rev.* 1995, **95**, 1797.

19 See Supporting Information for full details.

20 For a review, see: C. Olier, M. kaafarani, S. Gastaldi, M. P. Bertrand, *Tetrahedron* 2010, **66**, 413.

21 J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* 2004, **104**, 2311.

22 R. M. Carballo, M. A. Ramírez, M. L. Rodríguez, V. S. Martín, J. I. Padrón, *Org. Lett.* 2006, **8**, 3837.

23 Y. Koseki, H. Sato, Y. Watanabe, T. Nagasaka, *Org. Lett.* 2002, **4**, 885.

24 (*a*) R. S. Davidson, K. R. Trethewey, *J. Chem. Soc., Perkin Trans. 2* 1977, 173; ibid 178; (*b*) E. Baciocchi, T. Del Giacco, O. Lanzalunga, A. Lapi, *J. Org. Chem.* 2007, **72**, 9582; (*c*) G. Jiang, J. Chen, J.-S. Huang, C.-M. Che, *Org. Lett.* 2009, **11**, 4568.

