Tetrahedron Letters 54 (2013) 3366–3370

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthesis of multi-functionalized 1-azabicycles through MAOS acid catalyzed formal aza-[3+3] cycloaddition of heterocyclic enaminones with oxazolones

Silvio Cunha [a,b,*], Raimundo Francisco dos Santos Filho [a,b], Katharine Hodel Saraiva [c], Alene Vanessa Azevedo-Santos [c], Diego Menezes [c]

[a] Instituto de Química, Universidade Federal da Bahia, Campus de Ondina, Salvador, BA 40170-290, Brazil
[b] Instituto Nacional de Ciência e Tecnologia—INCT em Energia e Ambiente, Universidade Federal da Bahia, Campus de Ondina, Salvador, BA 40170-290, Brazil
[c] Núcleo de Biotecnologia e Bioprospecção (NBBio), Escola Bahiana de Medicina e Saúde Pública, Salvador, BA 40050-420, Brazil

ARTICLE INFO

Article history:
Received 21 March 2013
Revised 10 April 2013
Accepted 15 April 2013
Available online 22 April 2013

Keywords:
Indolizidinones
Quinolizidinones
Erlenmeyer–Plöchl azalactones
$Bi(NO_3)_3{\cdot}5H_2O$
Microwave heating

ABSTRACT

This study describes the combination of microwave heating and green acid catalysis by $Bi(NO_3)_3{\cdot}5H_2O$ and AcOH as a practical one-pot diastereoselective synthetic route to alkaloid-like multi-functionalized 3,4-disubstituted indolizidinones and quinolizidinones from cyclic enaminones and Erlenmeyer–Plöchl azalactone derivatives, as an alternative methodology to access these synthetically and biologically important classes of structural scaffolds in a simple way. The potential biological activity of some synthesized alkaloid-like derivatives was tested against the human tumor lineage hepatoma (HepG-2), and their inhibitory effect evaluated after 24 and 48 h. The indolizidine-like scaffold appears to be crucial to biological activity in the investigated compounds.

Introduction

Polysubstituted and multi-functionalized 1-azabicyclics such as indolizidinones and quinolizidinones are alkaloid-like privileged structural scaffolds which have been studied due to their relevant biological activities.[1–4] In this way, the formal aza-[3+3] cycloaddition has emerged as a powerful[5–7] and sustainable synthetic method to these heterocycles.[8] The subclasses of 3-amido-4-aryl dihydroindolizide-2-one and dihydroquinolizidine-2-one derivatives, and unsaturated analogues, have attracted increased attention due to their potential as peptidomimetics and anticancer compounds.[9,10] In this context, we rationalized that such azabicycles should be accessed by a formal aza-[3+3] cycloaddition of cyclic enaminones and Erlenmeyer–Plöchl azalactones because acyclic enaminones were effective in the synthesis of monocyclic lactams using such approach. In this way, Eynde and co-workers described a thermally induced formal aza-[3+3] cycloaddition reaction of acyclic enaminones with oxazolones,[11] and later extended these reactions to a microwave (MW) solvent-free condition.[12] In an independent work, Chiba and Takahashi reported the synthesis of

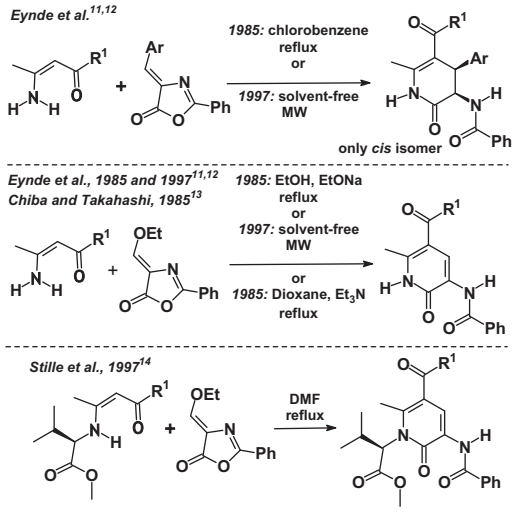


Figure 1. Previously reported formal aza-[3+3] cycloaddition of acyclic enaminones with azalactones.

* Corresponding author.
E-mail address: silviodc@ufba.br (S. Cunha).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.04.055

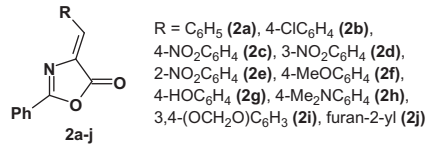
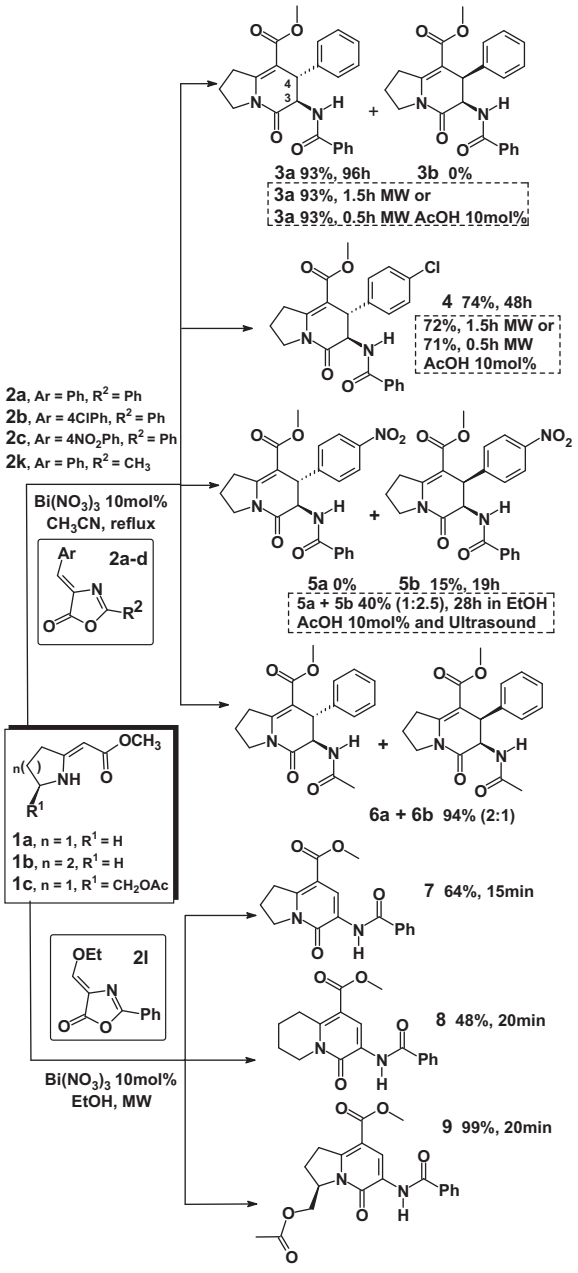


Figure 2. Tested azalactones in the formal aza-[3+3].



Scheme 1. Formal aza-[3+3] cycloaddition of cyclic enaminones.

same 2-pyridones,[13] and Stille and co-workers extended this aza-annulation to a chiral enaminone,[14] Figure 1.

Despite the great achievements abovementioned, the synthetic potential of these formal aza-[3+3] cycloadditions is still limited to acyclic enaminones with the formation of monocyclic heterocycles, and the conditions developed are somewhat harsh and not directly applicable to solid cyclic enaminones. Due to our continued involvement in the synthetic applications of enaminones,[15] we envisioned a strategy to the one-pot synthesis of densely functionalized indolizidinones and quinolizidinones through the reaction of cyclic enaminones with oxazolones, and herein we discovered that the association of acid catalysis and microwave assisted organic synthesis (MAOS) is pivotal to the formation of the multi-functionalized 1-azabicycles, switching diastereoselectivity in relation to previously described monocycles, Figure 1.

Results and discussion

To synthesize a representative set of alkaloid-like multi-functionalized indolizidinones and quinolizidinones, heterocyclic enaminones **1a**,**b**[16] and ten azalactones **2a**–**j**[17] were prepared, Figure 2 and Scheme 1. Whereas all reagents were solids, the solvent-free condition[12] was not applicable, and thus the model reaction of **1a** and **2a** was investigated in several conditions to allow the optimization of reaction parameters in search of the most general one. Toward this end, we first tried the reaction in acetonitrile at room temperature, but the reagents were recovered without any change, and this was the same result under reflux condition, Table 1 (entries 1 and 2). Thus, our enrollment with the synthetic application of bismuth salts in organic synthesis[18,19] prompted us to try such Lewis acids. To our delight, when a small amount of $Bi(NO_3)_3{\cdot}5H_2O$ was added to the reaction mixture, a slow transformation took place and the planned bicyclic lactam **3a** was obtained in excellent yield (Table 1, entry 3 and Scheme 1).

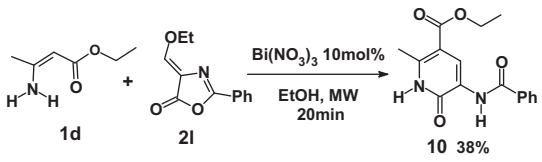
Due to the long reaction time other solvents were investigated (entries 4–6), but only complex mixtures were formed. Despite reagents were consumed with other tested salts (entries 7 and 8), no satisfactory yields were observed, and with $SnCl_2$ a non-selective reaction took place (entry 8), being the sole example where the *cis* isomer **3b** was the major one. In this way, microwave (MW) and ultrasound irradiation were tentatively employed in order to optimize yield and reaction time. The reaction of **1a** and **2a** under MW heating without catalyst afforded compound **3a** in a short reaction time but the yield dropped in comparison to conventional heating (entries 3, 9, and 10; for the stereochemical assignment of **3a**, see below). When the reaction was carried out under MW in the presence of $Bi(NO_3)_3{\cdot}5H_2O$ compound **3a** was isolated with a shorter reaction time and with same excellent yield obtained under conventional heating (entries 3 and 11, Table 1).

The search for additional environmental benign catalyst prompted us to try the reaction using acetic acid, which allowed the isolation of **3a** in yield as good as obtained under both

Table 1
Reaction conditions to the formal aza-[3+3] cycloaddition of enaminone **1a** and azalactones **2a** to yield **3a**

Entry	Solvent	Catalyst (10 mol %)	Condition[a]	Time (h)	Yield (%)
1	CH_3CN	None	rt	48	sm[b]
2	CH_3CN	None	Reflux	48	sm[b]
3	**CH_3CN**	**$Bi(NO_3)_3{\cdot}5H_2O$**	**Reflux**	**96**	**93**
4	Toluene	$Bi(NO_3)_3{\cdot}5H_2O$	Reflux	48	cm[c]
5	Dioxane	$Bi(NO_3)_3{\cdot}5H_2O$	Reflux	48	cm[c]
6	Xylene	$Bi(NO_3)_3{\cdot}5H_2O$	Reflux	48	cm[c]
7	CH_3CN	BiI_3	Reflux	24	11
8	CH_3CN	$SnCl_2$	Reflux	24	52[d]
9	CH_3CN	None	MW 150 W	2	75
10	CH_3CN	None	MW 300 W	1	75
11	**CH_3CN**	**$Bi(NO_3)_3{\cdot}5H_2O$**	**MW 150 W**	**1.5**	**93**
12	CH_3CN	$SnCl_2$	MW 300 W	1	45
13	**CH_3CN**	**AcOH**	**MW 150 W**	**1.5**	**93**
14	**CH_3CN**	**AcOH**	**MW 300 W**	**0.5**	**93**
15	CH_3CN	$Bi(NO_3)_3{\cdot}5H_2O$	))) 80 Hz rt	38	50
16	EtOH	$Bi(NO_3)_3{\cdot}5H_2O$	))) 80 Hz rt	38	45

Best conditions in bold.
[a] MW: microwave irradiation, and))): ultrasound.
[b] sm: Starting material.
[c] cm: Complex mixture.
[d] **3b** Major (**3a**:**3b** 1:1.6).



Scheme 2. Formal aza-[3+3] cycloaddition of acyclic enaminone.

conventional and MW heating with $Bi(NO_3)_3{\cdot}5H_2O$ catalysis, within the shortest observed reaction time (entries 3, 11, and 14). Otherwise, reactions carried out under ultrasound irradiation presented unsatisfactory performance in the model reaction because yields were poor and shown a long reaction time when compared to MW heating (entries 15 and 16).

The direct application of the best protocols to azalactones **2b–j** depicted in Figure 2 was not at all satisfactory. Furthermore, only azalactones **2b** and **2c** afforded clean reactions under the best conditions highlighted in Table 1, once the reaction of enaminone **1a** and **2g–j** resulted in complex mixtures, and reagents were recovered in the reactions with **2d–f**. Indeed, azalactone **2k** derived from *N*-acetylglycine (not shown in Fig. 2) was able to afford a clear reaction. Thus, azalactone **2b** afforded indolizidinone **4** with almost the same good yield under the three heating conditions presented in Scheme 1 (yield was only 40% under ultrasound; data not shown). Otherwise, in the reaction of azalactone **2c** and enaminone **1a** with conventional heating and $Bi(NO_3)_3{\cdot}5H_2O$ catalysis, the *cis* indolizidinone **5b** was solely isolated albeit in low yield, which formed as a complex mixture either under MW or conventional heating in the absence of Lewis acid, Scheme 1. On the other hand, in the catalysis by AcOH, indolizidinones **5a** and **5b** were isolated in better yield as a mixture of diastereomers (1:2.5, respectively). Interestingly, the *cis* isomer was the major one, in contrast to the observed behavior to indolizidinones **3**–**4** and to the reaction with azalactone **2k** where diastereomers **6a** (*trans* major) and **6b** were formed.

With isolated isomers **3a** and **4**, and mixtures of pairs of inseparable diastereomers **3a–3b**, **5a–5b**, and **6a–6b** in hand, the designation of which isomer was formed as the major or sole compound could be possible. The stereochemical assignment was done taking into account the relative *cis–trans* stereochemical distinction

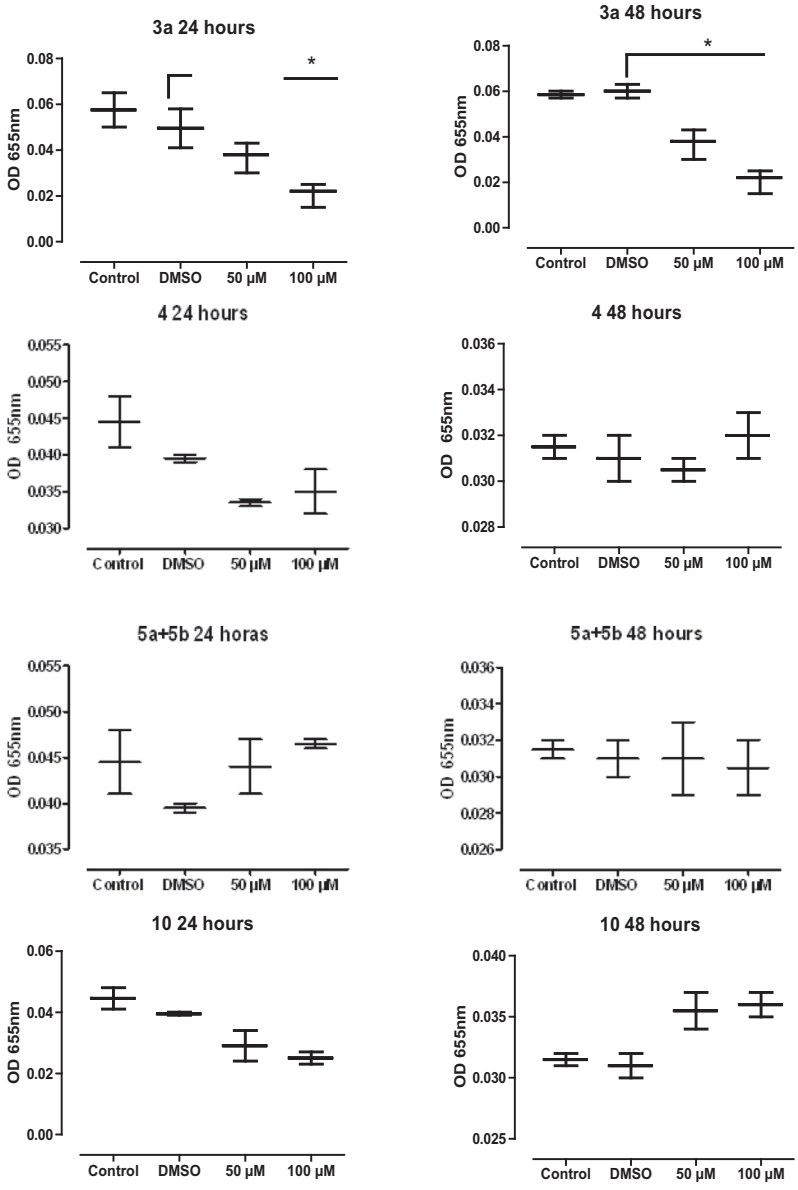


Figure 3. In vitro effect on HepG2 proliferation of **3a**, **4**, **5a+b**, and **10** after 24 and 48 h. *P <0.05 statistically different (Dunnett).

realized by Eynde and co-workers in the thermally induced formal aza-[3+3] cycloaddition reaction of acyclic enaminones with oxazolones.[11,12] Although these described reactions resulted in the formation of *cis*-3,4-dihydro-2-pyridones selectively, they also synthesized another set of monocyclic *cis*- and *trans*-3,4-dihydro-2-pyridones structurally analogous to compounds presented in Scheme 1. Two reported aspects of the ^{1}H NMR were crucial to the distinction of relative stereochemistry: the chemical shift of CH hydrogens at positions 3 and 4 is more deshielded for the *cis* isomer (δ_{H3cis} 4.8–5.0 and δ_{H4cis} 4.2–4.4 ppm; $\delta_{H3trans}$ 4.4–4.6 and $\delta_{H4trans}$ 3.9–4.1 ppm), and the vicinal coupling constant is larger for the *cis* isomer also ($^3J_{H3H4cis}$ 7 and $^3J_{H3H4trans}$ 2 Hz).[11,12]

Application of the above criteria to the mentioned pair of diastereomers **3a**–**3b**, **5a**–**5b**, and **6a**–**6b** allowed *cis*–*trans* discrimination because they were formed in different amounts distinguished by the ^{1}H NMR spectra. In this way, for the set of deshielded hydrogens H3/H4, signals are in the range of δ_{H3} 5.0–5.2/δ_{H4} 4.5–4.8 ppm ($^3J_{H3H4}$ 7.5–8.1 Hz), and for the other set of less deshielded H3/H4 the corresponding values are δ_{H3} 4.8–5.0/δ_{H4} 4.2–4.4 ppm ($^3J_{H3H4}$ 3.3–4.2 Hz). Thus, comparison of these data with the reported values fits the first and second hydrogen sets to *cis* and *trans* isomers, respectively.[11,12] In this way, application of these criteria revealed the preferential *trans* diastereoselectivity for almost all 3,4-dihydro azabicyclic compounds **3**–**8** synthesized, whereas the preference to only *cis* isomer **5b** in the reaction of **2c** was observed which has a very strong electron withdrawing NO_2 group at the phenyl ring. Furthermore, switching diastereoselectivity to *trans* by the use of acid catalysis was differential in the synthesis of these 1-azabycycles, in contrast to previously described *cis* diastereoselectivity in the formal aza-[3+3] cycloaddition of acyclic enaminones and Erlenmeyer–Plöchl azalactones.[11,12] Curiously, the vicinal coupling constant of hydrogen H3 with amidic NH presents a larger value than the coupling with H4. This was proved in a chemical exchange experiment with D_2O for compound **3a**, wherein the double doublet at 4.97 ppm (^3J 8.5 and 4.0 Hz) changed to a doublet (^3J 3.6 Hz).

With a secure procedure developed to the formal aza-[3+3] cycloaddition, we planned to increase the scope of alkaloid-like compounds accessed by varying the nature of the electrophilic component. In this sense, extension of the bismuth catalysis to the reaction with biselectrophile **2l** afforded azabicycle **7** with a 2-pyridone core embedded in its structure and decorated with new substitution patterns, Scheme 1. The reaction was also extended to the six membered enaminone **1b**, and quinolizidinone **8** could thus be isolated. The lower yield for this less reactive enaminone is in accordance to other related azaannulations.[15b] Additionally, chiral enaminone **1c** afforded indolizidinone **9** quantitatively, as indicated through analysis of ^{1}H NMR spectrum of crude reaction mixture, although it suffered decomposition when submitted to chromatographic purification. As mentioned before, the combination of bismuth catalysis and MW irradiation was efficient in the synthesis of densely substituted bicyclic heterocycles in a *trans*-selective one-pot reaction, as can be seen in Scheme 1.

To compare the performance of developed methodology with those previously described to acyclic liquid enaminone by Eynde[12] or Chiba and Takahashi,[13] enaminone **1d** was reacted with Erlenmeyer–Plöchl azalactone **2l** under microwave heating and catalysis by $Bi(NO_3)_3{\cdot}5H_2O$. The developed methodology was not as effective as the described methods because yield was low, Scheme 2.

To gain an insight into the potential biological activity of synthesized alkaloid-like compounds, derivatives **3**, **4**, and **5a**–**b** were tested against the human tumor lineage hepatoma (HepG-2), being their inhibitory effect evaluated after 24 and 48 h, in the tested concentration, Figure 3. Compounds **3a**, **4** and the mixture **5a**–**b** were active after 24 h. However, only compound **3a** maintained its inhibitory effect after 48 h, and shown a significant statistic difference when compared to DMSO in both the tested times. Additionally, it has an increased effect with respect to dose and exposure time on the tumor cells of HepG2.

It is noteworthy that the indolizidine-like scaffold appears to be crucial to biological activity, because when monocyclic derivative **10** was tested in the same conditions of indolizidinones **3a**, **4**, and **5a**–**b**, it was less effective than **3a** and **4** in 24 h. Curiously, the effect after 48 h was up modulation instead of the inhibitory effect, Figure 3.

In conclusion, this study shows that the combination of microwave heating and green acid catalysis by $Bi(NO_3)_3{\cdot}5H_2O$ or AcOH constitutes a practical synthetic route to alkaloid-like multi-functionalized indolizidinones and quinolizidinones from heterocyclic enaminones and Erlenmeyer–Plöchl azalactone derivatives, as an alternative methodology to access synthetically and biologically important classes of structural scaffolds in a simple way.[20]

Acknowledgments

The authors gratefully acknowledge the financial support of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB). We also thank CNPq for fellowship to R.F.S.F., and a research fellowship to S.C., and Professor Mauricio Victor for discussion and comments.

Supplementary data

Supplementary data (experimental procedures, IR, ^{1}H NMR and ^{13}C NMR spectra for **3**–**10**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.055.

References and notes

1. Boto, A.; Miguélez, J.; Marin, R.; Diaz, M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3402–3407.
2. Bourguet, C. B.; Goupil, E.; Tassy, D.; Hou, X.; Thouin, E.; Polyak, F.; Hébert, T. E.; Claing, A.; Laporte, S. A.; Chemtob, S.; Lubell, W. D. *J. Med. Chem.* **2011**, *54*, 6085–6097.
3. (a) Hanessian, S.; Auzzas, L. *Acc. Chem. Res.* **2008**, *41*, 1241–1251; (b) Maison, W.; Prenzel, A. H. G. P. *Synthesis* **2005**, 1031–1048; (c) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670–2680.
4. Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222–3231.
5. Ghosh, S. K.; Buchanan, G. S.; Long, Q. A.; Wei, Y.; Al-Rashid, Z. F.; Sklenicka, H. M.; Hsung, R. P. *Tetrahedron* **2008**, *64*, 883–893.
6. Buchanan, G. S.; Dai, H.; Hsung, R. P.; Gerasyuto, A. I.; Schienebeck, C. M. *Org. Lett.* **2011**, *13*, 4402–4405.
7. Buchanan, G. S.; Feltenberger, J. B.; Hsung, R. P. *Curr. Org. Synth.* **2010**, *7*, 363–401. and reference therein.
8. Candeias, N. R.; Branco, L. C.; Gois, P. M. P.; Afonso, C. A. M.; Trindade, A. F. *Chem. Rev.* **2009**, *109*, 2703–2802.
9. Cheng, Y.; Yang, H.-B.; Wang, M.-X.; Williams, D. J. *Tetrahedron* **2002**, *58*, 2821–2829.
10. Jiang, X.-P.; Cheng, Y.; Shi, G.-F.; Kang, Z.-M. *J. Org. Chem.* **2007**, *72*, 2212–2215.
11. Maquestiau, A.; Eynde, J. J. V.; Paplleux, P. *Bull. Soc. Chim. Belg.* **1985**, *94*, 849–857.
12. Eynde, J. J. V.; Labuche, N.; Haverbeke, Y. V. *Synth. Commun.* **1997**, *27*, 3683–3690.
13. Meyer, H.; Bossert, F.; Horstmann, H. *Liebigs Ann. Chem.* **1978**, 1483–1490.
14. Chiba, T.; Takahashi, T. *Chem. Pharm. Bull.* **1985**, *33*, 2731–2734.
15. (a) Cunha, S.; Gomes, A. T. *Tetrahedron Lett.* **2012**, *53*, 6710–6713; (b) Cunha, S.; Damasceno, F.; Ferrari, J. *Tetrahedron Lett.* **2007**, *48*, 5795–5798; (c) Cunha, S.; Bastos, R. M.; Silva, P. O.; Costa, G. A. N.; Vencato, I.; Lariucci, C.; Napolitano, H. B.; Oliveira, C. M. A.; Kato, L.; Silva, C. C.; Menezes, D.; Vannier-Santos, M. A. *Monatsh. Chem.* **2007**, *138*, 111–119; (d) Cunha, S.; Silva, V. C.; Napolitano, H. B.; Lariucci, C.; Vencato, I. *J. Braz. Chem. Soc.* **2003**, *14*, 107–112; (e) Cunha, S.; Rodovalho, W.; Azevedo, N.; Mendonça, M. O.; Lariucci, C.; Vencato, I. *J. Braz. Chem. Soc.* **2002**, *13*, 629–634; (f) Cunha, S.; Kascheres, A. *J. Braz. Chem. Soc.* **2001**, *12*, 481–484.
16. For reviews see: (a) Lue, P.; Greenhill, J. V. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1997; Vol. 67, pp 207–343; (b) Kuckländer, V. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1994; pp 525–639. Part 1; (c) Elliott, M. C.; Wood, J. L.; Wordingham, S. V. *Trends Heterocycl. Chem.* **2005**, *10*, 73–95; (d) Ferraz, H. M.; Gonçalo, E. R. S. *Quim. Nova* **2007**, *30*, 957–964; (e) Cheng, Y.; Huang, Z. T.;

Wang, M.-X. *Curr. Org. Chem.* **2004**, *8*, 325–351; (f) Ferraz, H. M. C.; Pereira, F. L. C. *Quim. Nova* **2004**, *27*, 89–95; (g) Negri, G.; Kascheres, C.; Kascheres, A. J. *J. Heterocycl. Chem.* **2004**, *41*, 461–491; (h) Kascheres, C. *J. Braz. Chem. Soc.* **2003**, *14*, 945–969; (i) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463–8480; (j) Kostyuk, A. N.; Volochnyuk, D. M.; Sibgatulin, D. A. *Synthesis* **2008**, 161–184; (k) Michael, J. P.; Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; M. Krause, R. W.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979–988.

17. (a) Cleary, T.; Rawalpally, T.; Kennedy, N.; Chavez, F. *Tetrahedron Lett.* **2010**, *51*, 1533–1536; (b) Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 425–427; (c) Khan, K. M.; Mughal, U. R.; Khan, M. T. H.; Ullah, Z.; Perveen, S.; Choudhary, M. I. *Bioorg. Med. Chem.* **2006**, *14*, 6027–6033.
18. (a) Cunha, S.; Costa, M. B.; Napolitano, H. B.; Lauriucci, C.; Vecanto, I. *Tetrahedron* **2001**, *57*, 1671–1675; (b) Cunha, S.; Lima, B. R.; Souza, A. R. *Tetrahedron Lett.* **2002**, *43*, 49–52; (c) Cunha, S.; Rodrigues, M. T., Jr.; Silva, C. C.; Napolitano, H. B.; Vencato, I.; Lariucci, C. *Tetrahedron* **2005**, *61*, 10536–10540; (d) Cunha, S.; Rodrigues, M. T., Jr. *Tetrahedron Lett.* **2006**, *47*, 6955–6956; (e) Cunha, S.; Macedo, F. C.; Costa, G. A. N.; Neves, D. C.; Souza Neta, L. C.; Vecanto, I.; Sabino, J. R.; Lauriucci, C. *J. Braz. Chem. Soc.* **2009**, *20*, 327–634.
19. (a) For reviews see: *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: Amsterdam, 2001; (b) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373–8397; (c) Bothwell, J. M.; Krabbe, S. W.; Mohan, R. S. *Chem. Soc. Rev.* **2011**, *40*, 4649–4707; (d) *Bismuth-mediated Organic Reactions*; Ollevier, T., Ed.; Springer: Heideberg; 2012.
20. (a) Worayuthakarn, R.; Nealmongkol, P.; Ruchirawat, S.; Thasana, N. *Tetrahedron* **2012**, *68*, 2864–2875; (b) Worayuthakarn, R.; Thasana, N.; Nealmongkol, P.; Ruchirawat, S. *Org. Lett.* **2006**, *8*, 5845–5848.