Tetrahedron Letters 51 (2010) 6082–6085

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Short and efficient access to imidazo[1,2-*a*]pyrrolo[3,2-*c*]pyridine derivatives

Vincent Gaumet [a,b,c,*], Emmanuel Moreau [a,b,c], Abbass Taleb [a], Fernand Leal [a,b,c], Johan Neyts [d], Jan Paeshuyse [d], Claire Lartigue [a,b,c], Olivier Chavignon [a,b,c], Alain Gueiffier [e], Jean-Claude Teulade [a,b,c], Jacques Métin [a], Jean-Michel Chezal [a,b,c]

[a] *UFR Pharmacie, Université Clermont 1, Université d'Auvergne, F-63001 Clermont-Ferrand, France*
[b] *Inserm, UMR 990, F-63005 Clermont-Ferrand, France*
[c] *Centre Jean Perrin, F-63011 Clermont-Ferrand, France*
[d] *Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium*
[e] *UFR Sciences et Techniques, Université François Rabelais, F-37200 Tours, France*

ARTICLE INFO

Article history:
Received 2 July 2010
Revised 6 September 2010
Accepted 10 September 2010
Available online 17 September 2010

Keywords:
Imidazo[1,2-*a*]pyridine
Imidazo[1,2-*a*]pyrrolo[3,2-*c*]pyridine
Heterocyclization
Palladium catalyst
Copper catalyst

ABSTRACT

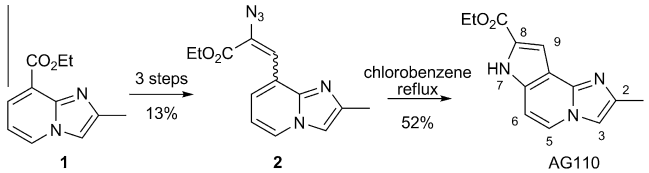
Access to N-protected or N-free imidazo[1,2-*a*]pyrrolo[3,2-*c*]pyridine derivatives as potential antiviral compounds was achieved in good yields from N-protected 7-amino-8-halo-2-methylimidazo[1,2-*a*]pyridines by catalytic coupling of terminal acetylenes under mild conditions using $[PdCl_2(PPh_3)_2]$ or $[Cu(Phen)(PPh_3)_2]NO_3$.

1. Introduction

Numerous imidazo[1,2-*a*]pyridine compounds are described in the literature, especially for their therapeutic qualities, for example, antifungal,[1–3] antibacterial,[4–8] analgesic, anti-inflammatory,[9,10] antiparasitic,[11,12] antitumoral[13–16], and antiviral activities.[17–22] These compounds also include pharmaceutical agents such as the cardiotonic olprinone[23,24] and the hypnotic zolpidem.[25,26] The reactivity of various nitrogen bridgehead systems and especially the imidazo[1,2-*a*]pyridine ring structure has been a subject of study for several years in our laboratory. Recently we focused on the synthesis of novel imidazo[1,2-*a*]pyrrolo[3,2-*c*]pyridine derivatives (IPPs).[27] The activities and mechanisms of action of these IPPs as inhibitors of the replication of pestiviruses have been evaluated. One, ethyl 2-methylimidazo[1,2-*a*]pyrrolo[2,3-*c*]pyridine-8-carboxylate (AG110), displayed a strong antiviral activity against the bovine viral diarrhea virus.[28]

A broad range of 2- or 3-substituted alkyl imidazo[1,2-*a*]pyrrolo[2,3-*c*]pyridine-8-carboxylates, including the lead compound AG110, have been prepared using the three-step procedure depicted in Scheme 1. Briefly, ethyl 2-methylimidazo[1,2-*a*]pyridine-8-carboxylate (**1**), obtained by condensation of chloroacetone with ethyl 2-aminopyridine-3-carboxylate, was converted to ethyl azidopropenoate (**2**) in three steps followed by thermal annulations to give the desired tricyclic ester in 7% overall yield.[27,29]

We extended our structure–activity relationship study to 7- and 8-substituted imidazo[1,2-*a*]pyrrolo[2,3-*c*]pyridine derivatives. To this end, we explored the short, efficient synthetic methods developed by Larock and Sonogashira for the synthesis of indole ring systems.[30,31] We assessed the heteroannulation, catalyzed by copper and palladium complexes, of N-protected 7-amino-8-haloimidazo[1,2-*a*]pyridines with either terminal or internal alkynes, and we explored the cyclization of 7-amino-8-alkyn-yl-imidazo[1,2-*a*]pyridines mediated by strong bases or catalyzed by palladium or copper complexes.



Scheme 1. AG110 synthesis.

* Corresponding author. Tel.: +33 (0)473178004.
E-mail address: vincent.gaumet@u-clermont1.fr (V. Gaumet).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.09.056

2. Results and discussion

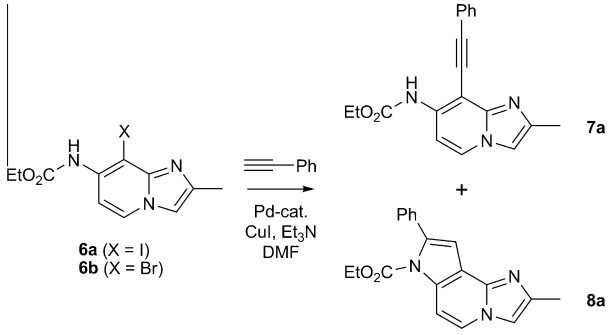
Our building blocks, 7-amino-8-bromo(or iodo)-2-methylimidazo[1,2-*a*]pyridines (**5a**, **b**), were prepared in two steps using regiospecific halogenation of 2,4-diaminopyridine followed by condensation with chloroacetone (Scheme 2). A methyl group was chosen to occupy the 2-position as it was found to give the best biological activity in our previous study.[27]

Our attempts to obtain 8- and/or 9-substituted IPPs via a one-pot heteroannulation[32–36] from **5a**, **b**, compounds containing a free amino group in position 7, failed with internal or terminal alkynes (for conditions see Ref. 37). As the failure of the annulation process could be attributed to the high nucleophilicity of the amino group, we turned our attention to N-protected 7-amino-8-halo-2-methylimidazo[1,2-*a*]pyridine derivatives. The electron-withdrawing effect of the N-protecting groups is crucial to promote the cyclization reaction. It has been demonstrated that the strong electron-withdrawing groups must be avoided because they lead to highly acidic-substituted NH groups, which can be deprotonated under the reaction conditions. The best results reported in the literature have been obtained by employing alkoxycarbonyl or trifluoroacetyl substituents.[38–42] The primary amines **5a**, **b** were thus first substituted with an ethoxycarbonyl group, and the resulting carbamates **6a**, **b** then reacted with phenylacetylene under Sonogashira conditions to give the alkynyl **7a** and/or the cyclized **8a** derivatives (Table 1). The cross-coupling reaction proved to be very sensitive to the halogen on the substrate, the iodine derivative giving the best result (Table 1, entry 1 vs entry 2). We expected similar yields with Pd(0) or Pd(II) catalysts, as Pd(0) species could be generated in situ by reduction of $[PdCl_2(PPh_3)_2]$.[33] The observed difference (Table 1, entry 2 vs entry 3) was probably because $[PdCl_2(PPh_3)_2]$ was more stable than $[Pd(PPh_3)_4]$ toward air and moisture. *ortho*-Iodo carbamate **6a** was thus totally converted into the alkenyl compound **7a** in 91% yield when $[PdCl_2(PPh_3)_2]$ was used as catalyst at room temperature (Table 1, entry 3). To promote the heteroannulation reaction, temperature was increased, but unfortunately attempts made under the same conditions at 100 °C resulted in the decomposition of starting materials (Table 1, entry 5). Heteroannulation was demonstrated to be effective only when operating at 60 °C, causing the concomitant formation of alkenyl **7a** and N-protected tricyclic **8a** compounds, respectively, in 50% and 24% yields (Table 1, entry 4).

As these uncyclized and cyclized isomers were difficult to separate by column chromatography, and in order to improve yields of tricyclic compounds, we prepared IPPs in an integrated process comprising two basic steps: (i) preparation of the alkynyl derivative by the palladium-catalyzed cross-coupling reaction with terminal alkynes via a Sonogashira reaction[43] using the conditions reported in Table 1, entry 3, followed by (ii) intramolecular cyclization of NH to the triple bond.

First, **7a** was heated with sodium ethoxide in ethanol at 60 °C (Scheme 3). 8-Phenyl-2-methylimidazo[1,2-*a*]pyrrolo[3,2-*c*]pyridine **10a** was obtained in 22% yield with a concomitant formation of the deprotected alkynyl compound **9** and starting material **7a** in 53% and 8% yields, respectively. As before, decomposition was observed above 100 °C.

Table 1
Selected results of screening for optimal conditions[a]



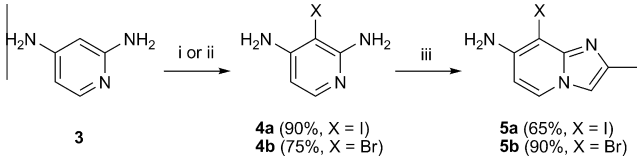
Entry	X	Pd-cat.	Temp (°C)	Recovery[b] (%)	Yield[b] (%)	
				6a, **b**	**7a**	**8a**
1	Br	$[Pd(PPh_3)_4]$	25	55	1	1
2	I	$[Pd(PPh_3)_4]$	25	—	68	—
3	I	$[PdCl_2(PPh_3)_2]$	25	3	91	—
4	I	$[PdCl_2(PPh_3)_2]$	60	—	50	24
5	I	$[PdCl_2(PPh_3)_2]$	100	—	—	—

[a] Reaction conditions: **6a**, **b** (1.0 mmol), phenylacetylene (1.2 mmol), Pd catalyst (2 mol %), CuI (20 mol %), Et_3N (3 mmol), DMF (20 mL) under argon (1 atm) for 2 d.
[b] Isolated yield.

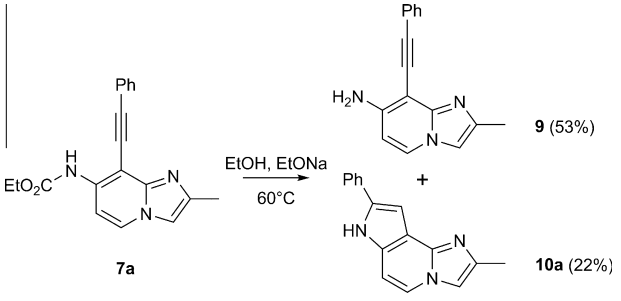
Based on these disappointing results and in accordance with the literature,[44] we examined the Lewis acid-catalyzed cyclization in 1,2-dichloroethane at 65 °C of *N*-7-ethoxycarbonylamino-8-alkynyl derivatives. This reaction gave the corresponding N-protected tricycle compounds **8a–d** in moderate yields (Table 2, entry 4). Alternatively, compounds **8a–d** could be easily converted to the free NH derivatives **10a–d** by the use of tetrabutylammonium fluoride with similar yields (Table 2, entry 5).

We next set out to prepare products **10a–d** in a one-step procedure from **6a** via a copper-catalyzed coupling-cyclization-deprotection process already described for indole synthesis.[45] Unfortunately, compound **6a** was rapidly decomposed to resinous products in the course of the reaction. By contrast, replacement of the ethoxycarbonyl moiety by trifluoroacetyl group, giving **11** (Table 2, entry 2), provided the expected compounds **10a–d** (Table 2, entry 6) in acceptable yields under the same conditions used for **6a**. Using this last method, compounds **10a–d** were obtained from **5a** with a substantial improvement in the overall yields compared with the three-step procedures involving alkynyl intermediates **7a–d** (16–36% vs 4–15%).

In conclusion, the foregoing results suggest that these strategies offer considerable advantages and inherent potential for the

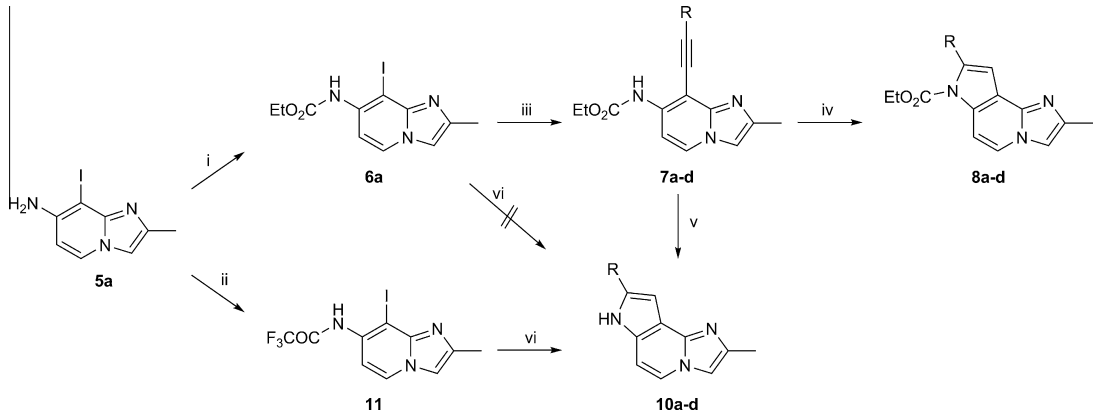


Scheme 2. Preparation of 7-amino-8-halo-2-methylimidazo[1,2-*a*]pyridines. Reagents and conditions: (i) for **4a**: HIO_4, I_2, AcOH, H_2O, H_2SO_4, 55 °C; (ii) for **4b**: Br_2, AcOH, rt; (iii) chloracetone, EtOH, 65 °C.



Scheme 3. Heteroannulation of **7a** with a strong base.

Table 2
Efficient routes for the synthesis of novel IPP derivatives



Entry	Conditions	Substrate	R	Product	Yield[a] (%)
1	(i) Ethyl chloroformate, $NaHCO_3$, DMAP,CH_2Cl_2, rt, 20 h	**5a**	—	**6a**	44
2	(ii) TFAA, pyridine, CH_2Cl_2, rt, 15 h	**5a**	—	**11**	64
3	(iii) Terminal alkyne, $[PdCl_2(PPh_3)_2]$, CuI, Et_3N, DMF, rt, 2 d	**6a**	C_6H_5	**7a**	91
			p-$CH_3OC_6H_4$	**7b**	25
			p-FC_6H_4	**7c**	70
			n-Bu	**7d**	61
4	(iv) $Cu(OAc)_2$, 1,2-dichloroethane, 65 °C	**7a**	C_6H_5	**8a**	56
		7b	p-$CH_3OC_6H_4$	**8b**	17
		7c	p-FC_6H_4	**8c**	44
		7d	n-Bu	**8d**	40
5	(v) $(n\text{-Bu})_4NF$, THF, reflux, 1 d	**7a**	C_6H_5	**10a**	36
		7b	p-$CH_3OC_6H_4$	**10b**	35
		7c	p-FC_6H_4	**10c**	43
		7d	n-Bu	**10d**	55
6	(vi) Terminal alkyne, $[Cu(phen)(PPh_3)_2]NO_3$, K_3PO_4, DMF, 115 °C, 2 d	**11**	C_6H_5	**10a**	56
			p-$CH_3OC_6H_4$	**10b**	37
			p-FC_6H_4	**10c**	25
			n-Bu	**10d**	40

[a] Isolated yield.

construction of the more complex 7-and/or 8- substituted IPPs. The present method is efficient and offers considerable versatility with respect to the range of imidazo[1,2-*a*]pyridine derivatives and alkynes that can be employed. However, the N-protecting group must be chosen carefully for the reaction to succeed.

Supplementary data

Supplementary data (a complete description of experimental details and product characterizations) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.056.

References and notes

1. Yu, L.; Lopez, A.; Anaflous, A.; El-Bali, B.; Hamal, A.; Ericson, E.; Heisler, L. E.; McQuibban, A.; Giaever, G.; Nislow, C.; Boone, C.; Brown, G. W.; Bellaoui, M. *PLoS Genet.* **2008**, *4*, e1000284. doi:10.1371/journal.pgen.1000284.
2. Kaplancikli, Z. A.; Turan-Zitouni, G.; Özdemr, A.; Revial, G. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 866–870.
3. Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *Eur. J. Med. Chem.* **1991**, *26*, 13–18.
4. East, S. P.; White, C. B.; Barker, O.; Barker, S.; Bennett, J.; Brown, D.; Boyd, E. A.; Brennan, C.; Chowdhury, C.; Collins, I.; Convers-Reignier, E.; Dymock, B. W.; Fletcher, R.; Haydon, D. J.; Gardiner, M.; Hatcher, S.; Ingram, P.; Lancett, P.; Mortenson, P.; Papadopoulos, K.; Smee, C.; Thomaides-Brears, H. B.; Tye, H.; Workman, J.; Czaplewski, L. G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 894–899.
5. Shah, V.; Kansagara, N.; Godhasra, J.; Patel, M. *Int. J. Chem. Sci.* **2008**, *6*, 1826–1831.
6. Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170–1176.
7. Revanker, G. R.; Matthews, T. R.; Robins, R. K. *J. Med. Chem.* **1975**, *18*, 1253–1255.
8. Anaflous, A.; Benchat, N.; Mimouni, M.; Abouricha, S.; Ben-Hadda, T.; El-Bali, B.; Hakkou, A.; Hacht, B. *Lett. Drug Des. Disc.* **2004**, *1*, 224–229.
9. Lacerda, R. B.; de Lima, C. K. F.; da Silva, L. L.; Romeiro, N. C.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Bioorg. Med. Chem.* **2009**, *17*, 74–84.
10. Sacchi, A.; Laneri, S.; Arena, F.; Luraschi, E.; Attignente, E.; Arnico, M. D.; Berrino, L.; Rossi, F. *Eur. J. Med. Chem.* **1997**, *32*, 677–682.
11. Scribner, A.; Dennis, R.; Lee, S.; Ouvry, G.; Perrey, D.; Fisher, M.; Wyvratt, M.; Leavitt, P.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thompson, D.; Schmatz, D.; Biftu, T. *Eur. J. Med. Chem.* **2008**, *43*, 1123–1151.
12. Scribner, A.; Dennis, R.; Hong, J.; Lee, S.; McIntyre, D.; Perrey, D.; Feng, D.; Fisher, M.; Wyvratt, M.; Leavitt, M.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thompson, D.; Schmatz, D.; Biftu, T. *Eur. J. Med. Chem.* **2007**, *42*, 1334–1357.
13. Sato, Y.; Onozaki, Y.; Sugimoto, T.; Kurihara, H.; Kamijo, K.; Kadowaki, C.; Tsujino, T.; Watanabe, A.; Otsuki, S.; Mitsuya, M.; Iida, M.; Haze, K.; Machida, T.; Nakatsuru, Y.; Komatani, H.; Kotani, H.; Iwasawa, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4673–4678.
14. Huq, F.; Abdullah, A.; Beale, P. *Int. J. Cancer Res.* **2006**, *2*, 367–375.
15. Byth, K. F.; Geh, C.; Forder, C. L.; Oakes, S. E.; Thomas, A. P. *Mol. Cancer Ther.* **2006**, *5*, 655–664.
16. Jaramillo, C.; De Diego, J. E.; Hamdouchi, C.; Collins, E.; Keyser, H.; Sanchez-Martinez, C.; Del Prado, M.; Norman, B.; Brooks, H. B.; Watkins, S. A.; Spencer, C. D.; Dempsey, J. A.; Anderson, B. D.; Campbell, R. M.; Leggett, T.; Patel, B.; Schultz, R. M.; Espinosa, J.; Vieth, M.; Zhang, F.; Timm, D. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6095–6099.
17. Gudmundsson, K. S.; Boggs, S. D.; Catalano, J. G.; Svolto, A.; Spaltenstein, A.; Thomson, M.; Wheelan, P.; Jenkinson, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6399–6403.
18. Gudmundsson, K. S.; Johns, B. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2735–2739.
19. Veron, J.-B.; Allouchi, H.; Enguehard-Gueiffier, C.; Snoeck, R.; Andrei, G.; De Clercq, E.; Gueiffier, A. *Bioorg. Med. Chem.* **2008**, *16*, 9536–9545.
20. Veron, J.-B.; Enguehard-Gueiffier, C.; Snoeck, R.; Andrei, G.; De Clercq, E.; Gueiffier, A. *Bioorg. Med. Chem.* **2007**, *15*, 7209–7219.

21. Gueiffier, A.; Mavel, S.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J.-C.; Witvrouw, M.; Balzarini, J.; De Clercq, E.; Chapat, J.-P. *J. Med. Chem.* **1998**, *41*, 5108–5112.
22. Gueiffier, A.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J.-C.; Kerbal, A.; Essassi, E. M.; Debouzy, J.-C.; Witvrouw, M.; Blache, Y.; Balzarini, J.; De Clercq, E.; Chapat, J.-P. *J. Med. Chem.* **1996**, *39*, 2856–2859.
23. Ueda, T.; Mizushige, K. *Curr. Vasc. Pharmacol.* **2006**, *4*, 1–7.
24. Adachi, H.; Kamata, S.; Kodama, K.; Nagakura, T. *Eur. J. Pharmacol.* **2000**, *396*, 43–47.
25. Monti, J. M.; Warren Spence, D.; Pandi-Perumal, S. R.; Langer, S. Z.; Hardeland, R. *Clin. Med.: Ther.* **2009**, *1*, 123–140.
26. Swainston Harrison, T.; Keating, G. M. *CNS Drugs* **2005**, *19*, 65–89.
27. Chezal, J.-M.; Paeshuyse, J.; Gaumet, V.; Canitrot, D.; Maisonial, A.; Lartigue, C.; Gueiffier, A.; Moreau, E.; Teulade, J.-C.; Chavignon, O.; Neyts, J. *Eur. J. Med. Chem.* **2010**, *45*, 2044–2047.
28. Paeshuyse, J.; Chezal, J.-M.; Froeyen, M.; Leyssen, P.; Dutartre, H.; Vrancken, R.; Canard, B.; Letellier, C.; Li, T.; Mittendorfer, H.; Koenen, F.; Kerkhofs, P.; De Clercq, E.; Herdewijn, P.; Puerstinger, G.; Gueiffier, A.; Chavignon, O.; Teulade, J.-C.; Neyts, J. *J. Virol.* **2007**, *81*, 11046–11053.
29. Chezal, J.-M.; Moreau, E.; Delmas, G.; Gueiffier, A.; Blache, Y.; Grassy, G.; Lartigue, C.; Chavignon, O.; Teulade, J.-C. *J. Org. Chem.* **2001**, *66*, 6576–6584.
30. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.
31. Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680.
32. Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690.
33. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662.
34. Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129–4132.
35. Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 627–630.
36. Chouzier, S.; Gruber, M.; Djakovitch, L. *J. Mol. Catal. A: Chem.* **2004**, *212*, 43–52.
37. Alkynes used: dimethylacetylenedicarboxylate, trimethylsilylacetylene and phenylacetylene. Three conditions tested: $[Pd(dppf)Cl_2]$, Na_2CO_3, LiCl, DMF, 100 °C (for details see Ref. 35); $[Pd(OAc)_2]$, PPh_3, LiCl, K_2CO_3, DMF, 100 °C (for details see Ref. 33): $[PdCl(hp)_3Cu]_2$, Et_3N, DMF, 100 °C (for details see Ref. 36).
38. Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 1845–1847.
39. Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823–1828.
40. Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772–6780.
41. Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915–3918.
42. Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529–534.
43. Sonogashira, K.; Ohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.
44. Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136.
45. Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843–3846.