Tetrahedron 69 (2013) 6269–6274

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

A novel strategy for the synthesis of 2,6-diaryl-1,2-dihydropyridines via 6π-electrocyclization

Zoltán Vincze, Péter Nemes *

Department of Chemistry, Faculty of Veterinary Science, Szent István University, H-1400 Budapest, PO Box 2, Hungary

ARTICLE INFO

Article history:
Received 12 February 2013
Received in revised form 23 April 2013
Accepted 9 May 2013
Available online 14 May 2013

Keywords:
β-Enaminonitriles
1-Azatrienes
1,6-electrocyclizations
Pyridines
Boron trifluoride diethyl etherate

ABSTRACT

Enaminonitriles with α,β-unsaturated aldehydes in a $BF_3 \cdot OEt_2$ catalyzed reaction gave stable 1-azatrienes, which could be readily transformed to 1,2-dihydropyridines via 1,6-electrocyclizations.

1. Introduction

Polysubstituted pyridines and dihydropyridines occupy a central position in heterocyclic chemistry. Many naturally occurring and synthetic products containing the pyridine scaffold are valuable pharmaceuticals or agrochemicals, and they are also useful intermediates in preparing a large variety of interesting heterocyclic compounds.[1] Although a huge number of various approaches are known from the literature, new and efficient methods for the construction of this type of molecule attract continuous interest in contemporary organic chemistry.[2,3]

While 6π-azaelectrocyclizations are well established in the literature, few research groups apply them to the synthesis of pyridines.[4] It is envisaged that a new 1,6-electrocyclization approach to multifunctional 1,2-dihydropyridines would carry significant synthetic interest. The traditional, but not widely used, thermal 6π-electrocyclizations of 1-azatrienes likely involve a classical concerted mechanism, which proceeds in a disrotatory mode. Nevertheless, because of the low reactivity of the azatrienes and the difficulties in the preparation of the 3-*cis*-azatriene precursors, the applicability of these electrocyclizations to the synthesis of *N*-heterocycles is very limited.[5] Recently, some research groups published azaelectrocyclization approaches to 1,2-dihydropyridines starting from 1-azatrienes.[6] The reactivity of the azatrienes and the applicability in natural product synthesis were also discussed.

We have reported previously a new strategy to 1-azatrienes and 1-azapolyenes. The mesylate salts of β-enaminonitriles **1** were reacted with α,β-unsaturated aldehydes **2** to afford the iminium salts of the target compounds **3**, which underwent electrocyclization after adding TEA to the MeCN solution to afford pyrido[2,1-*a*]isoquinolines and indoloquinolizines **4**. We investigated the mechanism of the cyclization process by computational methods, and established unequivocally that the presence of the electron-withdrawing group plays a crucial role in the required (*E*)/(*Z*) isomerization step.[7] Moreover we showed that azatrienes and azatetraenes resulted in pyrimido[6,1-*a*]isoquinolines **5** with formaldehyde and primary amines in aza-annulation reactions (Scheme 1).[8]

These results prompted us to investigate the possible extension of these earlier results to the synthesis of polysubstituted pyridines and pyrimidines.

2. Results and discussion

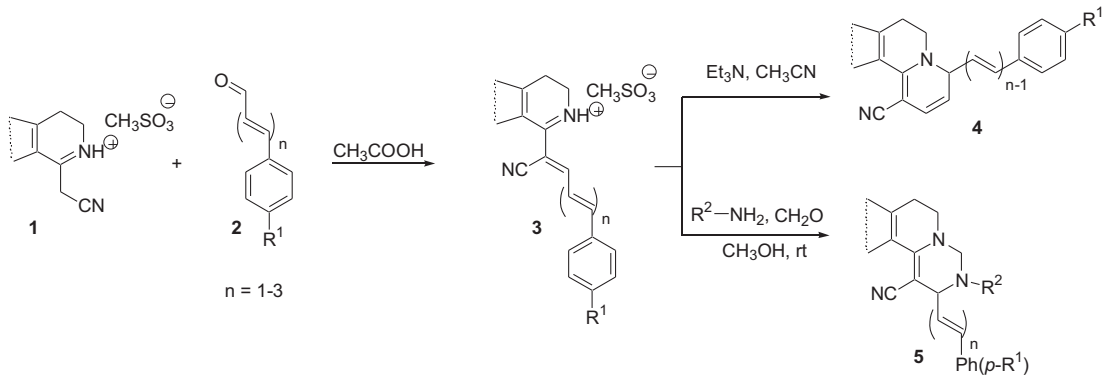
We report herein the $BF_3 \cdot OEt_2$ catalyzed formation of 1-azatrienes **10a**–**j**, starting from β-aminocrotonitriles **7a**–**d**, and their electrocyclizations to give 2,6-diaryl-3-cyano-1,2-dihydropyridines.

2.1. Synthesis and cyclization of 1-azatrienes

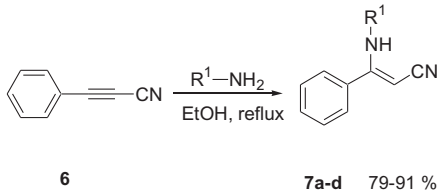
Compounds **7a**–**d** were prepared according to literature methods from phenylpropargyl nitrile (**6**) and primary amines in refluxing ethanol with good yields (Scheme 2).[9]

* Corresponding author. Tel.: +36 1 478 4176; fax: +36 1 478 4268; e-mail address: Nemes.Peter@aotk.szie.hu (P. Nemes).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.05.013

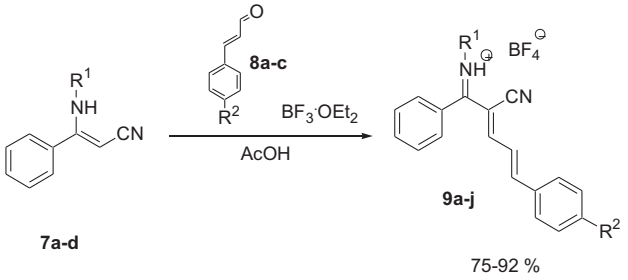


Scheme 1.



7a R^1 = 2-(2-bromo-4,5-dimethoxy-phenyl)-ethyl
7b R^1 = cyclohexyl
7c R^1 = *tert*-Bu
7d R^1 = adamantyl

Scheme 2.



8a R^2 = H
8b R^2 = NO_2
8c R^2 = NMe_2

Scheme 3.

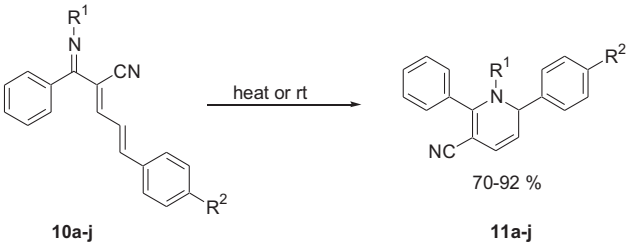
In order to prepare 1-azatrienes, first we tried to transform **7a**–**d** into the corresponding mesylate salts, according to our earlier method. These attempts, however, were unsuccessful because of the formation of a complex mixture of decomposition products. No conversion of the starting materials could be observed when we attempted to carry out the reaction of the enaminonitriles **7a**–**d** with unsaturated aldehydes in acetic acid without salt formation.

It is well known that BF_3 can activate carbonyl compounds in carbon–carbon bond forming reactions. We found that β-enaminonitriles **7a**–**d** with unsaturated aldehydes **8a**–**c** in glacial acetic acid afforded the stable tetrafluoroborate salts of 1-azatrienes **9a**–**j** in the presence $BF_3 \cdot OEt_2$ at room temperature (Table 1, Scheme 3). The salts precipitated from the reaction mixtures by adding diisopropyl ether. Although the structure elucidation of the new azatrienes was carried out in base form (**10a**–**j**) the ^{1}H NMR spectra of some salts were also registered. The presence of an N–H proton at 8.5 ppm and the strong absorption band at 1070 cm^{-1} in the IR spectra prove the tetrafluoroborate salt formation unequivocally. It can be assumed that BF_3 and water, rising from the condensation step, result in HF, which forms tetrafluoroboric acid with the excess of BF_3. The synthesis worked smoothly with enaminonitriles bearing bulky alkyl and cycloalkyl R^1 groups. Unfortunately, because of the fast polymerization of the azatrienes, the method was non utilizable for simple methyl- or ethyl-substituted enaminonitriles. In our earlier study we proved the (*E*,*E*) configurations of the double bonds for similar azatrienes by NMR (*J*-HMBC, *J*-INEPT) methods.[10] Although no such examinations were carried out to date the favored (*E*,*E*) configurations can be assumed for **9a**–**j** as well.

Table 1
Yields for the 1-azatrienes

Entry	R^1	R^2	Reaction time (h)	Yield %
9a	2-(2-Bromo-4,5-dimethoxy-phenyl)-ethyl	NO_2	4	78
9b	Cyclohexyl	H	4	85
9c	Cyclohexyl	NO_2	4	89
9d	Cyclohexyl	NMe_2	3	82
9e	*tert*-Bu	H	4	85
9f	*tert*-Bu	NO_2	4	82
9g	*tert*-Bu	NMe_2	4	75
9h	Adamantyl	H	3	92
9i	Adamantyl	NO_2	3	77
9j	Adamantyl	NMe_2	4	82

After deprotonation of the azatrienes with TEA the free bases (**10a**–**j**) cyclized readily to give **11a**–**j** 1,2-dihydropyridine derivatives in acceptable yields (Scheme 4). The first step of the process is the rate determining (*E*)→(*Z*) isomerization, which is facilitated by the electron-withdrawing CN group. The cyclizations could be followed by ^{1}H NMR spectroscopy. The appearance of the H-6 methine proton of the formed dihydropyridine ring (5.01–5.33 ppm) indicates the progress of the ring closure.



Scheme 4.

Significant reactivity differences could be observed in the cyclization processes depending on the substituent at the nitrogen atom. Compound **10a** bearing a phenethyl group cyclized at room temperature in 2 h, while the electrocyclization of the *N*-cyclohexyl derivatives **10b**–**d** required longer reaction times. The decrease of the reactivity was more striking for **10e**–**g** and **10h**–**j** with the bulky *tert*-butyl and adamantyl substituents, respectively, which gave the dihydropyridine derivatives only at elevated temperatures up to 80 °C. Moreover, a considerable effect of the C(6)-phenyl substituents on the reaction rate could also be detected. It was found that the electron donating dimethylamino group accelerated the cyclization, while the electron-withdrawing nitro group increased the reaction time (Table 2).

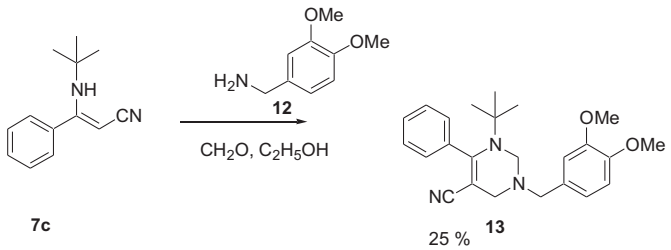
Table 2
Yields for the cyclization products

Entry	R^1	R^2	Temperature (°C)	Reaction time (h)	Yield %
11a	2-(2-Bromo-4, 5-dimethoxy-phenyl)-ethyl	NO_2	25	1	82
11b	Cyclohexyl	H	25	36	88
11c	Cyclohexyl	NO_2	25	48	92
11d	Cyclohexyl	NMe_2	25	12	90
11e	*tert*-Bu	H	60	5	84
11f	*tert*-Bu	NO_2	60	7	79
11g	*tert*-Bu	NMe_2	60	4	84
11h	Adamantyl	H	80	14	78
11i	Adamantyl	NO_2	80	24	70
11j	Adamantyl	NMe_2	80	8	71

2.2. Aza-annulations of β-aminocrotonitrile derivatives

According to earlier publications, various push–pull alkenes such as enaminones, nitroenamines or enaminonitriles with 2 mol of formaldehyde and primary amines give condensed pyrimidine derivatives in 'double' Mannich reactions.[8,11]

Although a wide scope of reaction conditions were tested, in contrast to the 1-cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, the reactivity of β-aminocrotonitriles proved to be poor. Compound **7c** and dimethoxy-phenethylamine (**12**) gave **13** tetrahydropyrimidine derivative in very low yield, but the synthesis could not be applied to other amines (Scheme 5).



Scheme 5.

3. Conclusions

It was demonstrated that simple aryl substituted β-aminocroto nitriles with α,β-unsaturated aldehydes afforded 1-azatrienes at room temperature in $BF_3 \cdot OEt_2$ catalyzed reactions. The products could be transformed into *N*-alkyl-2,6-diaryl-3-cyano-1,2-dihydropyridine derivatives in a 6π-electrocyclization sequence. The new strategy can serve as an attractive synthetic route to 1,2-dihydropyridines.

4. Experimental section

4.1. General

The structure and the purity of the final products as free bases were confirmed by ^1H, ^{13}C NMR, IR, and microanalysis. NMR spectra were recorded on a Varian Unity 300 (300 MHz) spectrometer, in $CDCl_3$ solutions. Chemical shifts (δ) are expressed in parts per million (ppm) relative to the internal standard TMS. IR spectra were recorded on a Perkin Elmer 1600 FT IR spectrometer. The microanalysis was carried out on a Heraeus Micro Rapid CHN. Melting points were measured with a Büchi SMP-20 apparatus and are uncorrected. Column chromatography was conducted with Merck Kieselgel 60 (0.063–0.200 mm). Analytical TLC was carried out on precoated plates (Merck silica gel 60, F_{254}). Solvents were dried and freshly distilled according to the common practice.

4.2. General Procedure for the synthesis of 1-azatrienes (10a–j)

The α,β-unsaturated aldehydes (**8a**–**c**) (3.0 mmol) and $BF_3 \cdot OEt_2$ (6 mmol, 852 mg, 0.740 mL) were added to a solution of β-enaminonitriles (**7a**–**d**) (2.0 mmol) in glacial acetic acid (6 mL). The mixture was stirred at room temperature for 3–4 h until the reaction was complete. The solution was then poured into diisopropyl ether (30 mL), the precipitated tetrafluoroborate salt was filtered, and washed with diethyl ether. The solid was dissolved in CH_2Cl_2 (10 mL) and the solution was washed with saturated $NaHCO_3$ (2×10 mL) with water (1×10 mL), dried over Na_2SO_4 and then evaporated. After evaporation the crude base was obtained.

*4.2.1. 2-{[2-(2-Bromo-4,5-dimethoxy-phenyl)-ethylimino]-phenyl-methyl}-5-(4-nitro-phenyl)-penta-2,4-dienenitrile (**10a**).* Recrystallization of the crude product (EtOAc) gave **10a** (989 mg, 78%) as a yellow solid, mp 79 °C; R_f (hexane/EtOAc 5:1) 0.51. Found: C, 61.77; H, 4.53; N, 7.65. $C_{28}H_{24}BrN_3O_4$ requires C, 61.55; H, 4.43; N, 7.69%; ν_{max} (KBr) 3429, 2938, 1561, 1298, 1005 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.19 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NO_2)), 7.59 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NO_2)), 7.41–7.24 (5H, m, Ph), 6.91 (1H, s, H-3′), 6.85 (1H, d, *J* 15.3 Hz, H-3), 6.80 (1H, s, H-6′), 6.76 (1H, dd, *J* 11.4, 15.3 Hz, H-4), 6.55 (1H, d, *J* 11.4 Hz, H-5), 3.86 (3H, s, O*Me*), 3.82 (3H, s, O*Me*), 3.58 (2H, t, *J* 6.6 Hz, N–*CH*$_2$–CH_2-Ph(OMe)$_2$), 3.04 (2H, t, *J* 6.6 Hz, N–CH_2–*CH*$_2$–Ph(OMe)$_2$); δ_C (75 MHz, $CDCl_3$) 165.4, 148.3, 148.0, 141.5, 140.7, 133.4, 131.3, 129.5, 129.1, 128.6, 128.4, 128.3, 127.7, 124.4, 120.6, 115.6, 115.4, 114.7, 114.4, 56.4, 56.3, 54.0, 37.0.

*4.2.2. 2-(Cyclohexylimino-phenyl-methyl)-5-phenyl-penta-2,4-dienenitrile (**10b**).* Recrystallization of the crude product (EtOAc-hexane) gave **10b** (727 mg, 85%) as a yellow solid, mp 108 °C; R_f (hexane/EtOAc 5:1) 0.56. Found: C, 84.55; H, 7.00; N, 8.37. $C_{24}H_{24}N_2$ requires C, 84.67; H, 7.11; N, 8.23%; ν_{max} (KBr) 3432, 2937, 1561, 1294, 1014 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.48–7.38 (5H, m, Ph), 7.35–7.32 (3H, m, Ph), 7.24 (1H, dd, *J* 11.9, 16.0 Hz, H-4), 7.12–7.11 (2H, m, Ph), 6.83 (1H, d, *J* 16.0 Hz, H-3), 6.60 (1H, d, *J* 11.9, H-5), 3.14–3.08 (1H, m, C_6H_{11}), 1.72–0.98 (10H, m, C_6H_{11}); δ_C (75 MHz, $CDCl_3$) 162.2, 148.7, 143.6, 135.7, 134.7, 130.1, 129.2, 129.1, 129.0, 127.9, 127.7, 124.8, 118.5, 116.1, 61.9, 33.9, 25.8, 24.3.

*4.2.3. 2-(Cyclohexylimino-phenyl-methyl)-5-(4-nitro-phenyl)-penta-2,4-dienenitrile (**10c**).* Recrystallization of the crude product (EtOAc) gave **10c** (686 mg, 89%) as an orange solid, mp 170 °C; R_f (hexane/EtOAc 5:1) 0.45. Found: C, 74.69; H, 5.90; N, 11.02. $C_{24}H_{23}N_3O_2$ requires C, 74.78; H, 6.01; N, 10.90%; ν_{max} (KBr) 3441, 2937, 1593, 1519, 1342, 1014 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.18 (2H, d, *J* 8.4 Hz, *Ph*(*p*-NO_2)), 7.60 (2H, d, *J* 8.4 Hz, *Ph*(*p*-NO_2)), 7.52–7.48 (3H, m, Ph), 7.35 (1H, dd, *J* 11.2, 15.4 Hz, H-4), 7.15–7.11 (2H, m, Ph), 6.85 (1H, d, *J* 15.3 Hz, H-3), 6.75 (1H, d, *J* 11.2, H-5), 3.13–3.07 (1H, m,

C_6H_{11}), 1.68–0.94 (10H, m, C_6H_{11}); δ_C (75 MHz, $CDCl_3$) 161.9, 148.2, 147.2, 141.7, 140.1, 134.2, 129.4, 129.2, 128.6, 128.3, 127.7, 124.4, 121.3, 115.6, 62,1, 33.8, 25.7, 24.3.

*4.2.4. 2-(Cyclohexylimino-phenyl-methyl)-5-(4-dimethylamino-phenyl)-penta-2,4-dienenitrile (**10d**).* Recrystallization of the crude product (EtOAc) gave **10d** (628 mg, 82%) as a red solid, mp 124 °C; R_f (hexane/EtOAc 5:1) 0.41. Found: C, 81.35; H, 7.60; N, 11.05. $C_{26}H_{29}N_3$ requires C, 81.42; H, 7.62; N, 10.96%; ν_{max} (KBr) 3439, 2926, 1591, 1565, 1165 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.56–7.45 (3H, m, Ph), 7.36 (2H, d, *J* 8.6 Hz, *Ph*(*p*-NMe_2)), 7.29 (1H, dd, *J* 11.1, 15.3 Hz, H-4), 7.13–7.05 (2H, m, Ph), 6.74 (1H, d, *J* 15.3 Hz, H-3), 6.71 (1H, d, *J* 11.1, H-5), 6.63 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NMe_2)), 3.03 (6H, s, Ph(*p*-N*Me*$_2$)), 2.95–2.93 (1H, m, C_6H_{11}), 1.65–0.93 (10H, m, C_6H_{11}); δ_C (75 MHz, $CDCl_3$) 162.6, 151.7, 150.2, 144.7, 135.2, 129.8, 128.9, 127.8, 123.7, 120.2, 117.0, 114.5, 112.1, 61.7, 40.3, 33.9, 25.8, 24.5.

*4.2.5. 2-(tert-Butylimino-phenyl-methyl)-5-phenyl-penta-2,4-dienenitrile (**10e**).* Recrystallization of the crude product (EtOAc/hexane) gave **10e** (534 mg, 85%) as a yellow solid, mp 125 °C; R_f (hexane/EtOAc 5:1) 0.45. Found: C, 84.00; H, 6.95; N, 9.02. $C_{22}H_{22}N_2$ requires C, 84.04; H, 7.05; N, 8.91%; ν_{max} (KBr) 3442, 2969, 1605, 1576 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.50–7.40 (5H, m, Ph), 7.37–7.32 (3H, m, Ph), 7.26 (1H, dd, *J* 11.3, 15.5 Hz, H-4), 7.17–7.13 (2H, m, Ph), 6.75 (1H, d, *J* 15.5 Hz, H-3), 6.54 (1H, d, *J* 11.3, H-5), 1.12 (9H, s, ^tBu–N); δ_C (75 MHz, $CDCl_3$) 160.4, 147.8, 143.3, 137.1, 135.7, 130.0, 129.1, 129.0, 128.5, 128.4, 127.9, 121.0, 116.2, 58.1, 31.5.

*4.2.6. 2-(tert-Butylimino-phenyl-methyl)-5-(4-nitro-phenyl)-penta-2,4-dienenitrile (**10f**).* Recrystallization of the crude product (EtOAc) gave **10f** (510 mg, 71%) as an orange solid, mp 128 °C; R_f (hexane/EtOAc 5:1) 0.39. Found: C, 73.33; H, 5.99; N, 11.42. $C_{22}H_{21}N_3O_2$ requires C, 73.52; H, 5.89; N, 11.69%; ν_{max} (KBr) 3424, 2930, 1595, 1513, 1346 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.19 (2H, d, *J* 8.3 Hz, *Ph*(*p*-NO_2)), 7.60 (2H, d, *J* 8.3 Hz, *Ph*(*p*-NO_2)), 7.59–7.47 (3H, m, Ph), 7.35 (1H, dd, *J* 11.4, 15.5 Hz, H-4), 7.16–7.11 (2H, m, Ph), 6.80 (1H, d, *J* 15.4 Hz, H-3), 6.56 (1H, d, *J* 11.4, H-5), 1.19 (9H, s, ^tBu–N); δ_C (75 MHz, $CDCl_3$) 160.1, 148.2, 146.2, 141.8, 139.8, 136.7, 129.2, 128.8, 128.6, 128.5, 128.3, 124.4, 123.8, 115.7, 58.4, 31.4.

*4.2.7. 2-(tert-Butylimino-phenyl-methyl)-5-(4-dimethylamino-phenyl)-penta-2,4-dienenitrile (**10g**).* Recrystallization of the crude product (EtOAc) gave **10g** (536 mg, 75%) as a red solid, mp 97 °C; R_f (hexane/EtOAc 5:1) 0.54. Found: C, 80.60; H, 7.69; N, 11.80. $C_{24}H_{27}N_3$ requires C, 80.63; H, 7.61; N, 11.75%; ν_{max} (KBr) 3424, 2928, 1600, 1559, 1350 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.45–7.39 (3H, m, Ph), 7.35 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NMe_2)), 7.15–7.11 (2H, m, Ph), 7.08 (1H, dd, *J* 11.4, 15.2 Hz, H-4), 6.65 (1H, d, *J* 15.2 Hz, H-3), 6.60 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NMe_2)), 6.52 (1H, d, *J* 11.4 Hz, H-5), 3.00 (6H, s, Ph(*p*-N*Me*$_2$)), 1.11 (9H, s, ^tBu–N); δ_C (75 MHz, $CDCl_3$) 160.8, 151.7, 149.2, 144.3, 137.6, 129.7, 128.7, 128.6, 128.3, 123.8, 120.3, 117.4, 117.0, 112.1, 57.7, 40.3, 31.6.

*4.2.8. 2-[(Adamantan-1-ylimino)-phenyl-methyl]-5-phenyl-penta-2,4-dienenitrile (**10h**).* Recrystallization of the crude product (EtOAc) gave **10h** (721 mg, 92%) as a yellow solid, mp 155 °C; R_f (hexane/EtOAc 5:1) 0.52. Found: C, 85.65; H, 6.99; N, 7.33. $C_{28}H_{28}N_2$ requires C, 85.67; H, 7.19; N, 7.14%; ν_{max} (KBr) 3440, 2900, 1685, 1576 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.49–7.40 (5H, m, Ph), 7.36–7.30 (3H, m, Ph), 7.26 (1H, dd, *J* 11.4, 15.4 Hz, H-4), 7.15–7.13 (2H, m, Ph), 6.73 (1H, d, *J* 15.4 Hz, H-3), 6.53 (1H, d, *J* 11.4 Hz, H-5), 2.03 (3H, br s, $C_{10}H_{15}$), 1.68–1.60 (6H, m, $C_{10}H_{15}$), 1.55–1.48 (6H, m, $C_{10}H_{15}$); δ_C (75 MHz, $CDCl_3$) 159.7, 147.7, 143.2, 137.6, 135.8, 130.0, 129.1, 128.9, 128.5, 128.3, 127.9, 121.3, 116.3, 59.3, 44.2, 36.5, 29.8.

*4.2.9. 2-[(Adamantan-1-ylimino)-phenyl-methyl]-5-(4-nitro-phenyl)-penta-2,4-dienenitrile (**10i**).* Recrystallization of the crude product (EtOAc) gave **10i** (674 mg, 77%) as an orange solid, mp 173 °C; R_f (hexane/EtOAc 5:1) 0.28. Found: C, 76.99; H, 6.40; N, 9.73. $C_{28}H_{27}N_3O_2$ requires C, 76.86; H, 6.22; N, 9.60%; ν_{max} (KBr) 3428, 2923, 1656, 1512 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.18 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NO_2)), 7.58 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NO_2)), 7.47–7.38 (5H, m, Ph), 7.14 (1H, dd, *J* 11.2, 15.4 Hz, H-4), 6.77 (1H, d, *J* 15.4 Hz, H-3), 6.54 (1H, d, *J* 11.2 Hz, H-5), 1.94 (3H, br s, $C_{10}H_{15}$), 1.66–1.60 (6H, m, $C_{10}H_{15}$), 1.57–1.47 (6H, m, $C_{10}H_{15}$); δ_C (75 MHz, $CDCl_3$) 159.4, 148.2, 146.1, 146.0, 141.8, 139.7, 137.2, 129.1, 128.8, 128.5, 128.4, 128.3, 124.4, 115.8, 59.6, 44.1, 36.5, 29.8.

*4.2.10. 2-[(Adamantan-1-ylimino)-phenyl-methyl]-5-(4-dimethylamino-phenyl)-penta-2,4-dienenitrile (**10j**).* Recrystalliz ation of the crude product (EtOAc) gave **10j** (714 mg, 82%) as a red solid, mp 158 °C; R_f (hexane/EtOAc 5:1) 0.23. Found: C, 82.66; H, 7.68; N, 9.77. $C_{30}H_{33}N_3$ requires C, 82.72; H, 7.64; N, 9.65%; ν_{max} (KBr) 3442, 2902, 1592, 1561 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.42–7.35 (3H, m, Ph), 7.32 (2H, d, *J* 8.9 Hz, *Ph*(*p*-NMe_2)), 7.15–7.14 (2H, m, Ph), 7.08 (1H, dd, *J* 11.4, 15.6 Hz, H-4), 6.68 (1H, d, *J* 15.6 Hz, H-3), 6.62 (2H, d, *J* 8.9 Hz, *Ph*(*p*-NMe_2)), 6.52 (1H, d, *J* 11.4 Hz, H-5), 3.01 (6H, s, Ph(*p*-N*Me*$_2$)), 1.94 (3H, br s, $C_{10}H_{15}$), 1.78–1.65 (6H, m, $C_{10}H_{15}$), 1.58–1.48 (6H, m, $C_{10}H_{15}$); δ_C (75 MHz, $CDCl_3$) 160.2, 151.7, 149.0, 144.2, 138.1, 129.7, 128.7, 128.5, 128.2, 123.9, 120.4, 117.6, 117.1, 112.2, 58.9, 44.3, 40.3, 36.6, 29.9.

4.3. General procedure for the cyclization (11a–j)

The free base of the 1-azatriene (**10a**–**j**) was dissolved (1 mmol) in acetonitrile (10 mL), and stirred at the appropriate temperature (Table 2) until the starting material consumed. The solvent was removed under reduced pressure, and the residue dissolved in CH_2Cl_2 (10 mL). The CH_2Cl_2 solution was washed with water (2×5 mL), dried over Na_2SO_4, and then evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using EtOAc/hexane as eluent.

*4.3.1. 1-[2-(2-Bromo-4,5-dimethoxy-phenyl)-ethyl]-6-(4-nitro-phenyl)-2-phenyl-1,6-dihydropyridine-3-carbonitrile (**11a**).* Recrystallization of the crude product (EtOAc) gave **11a** (520 mg, 82%) as a pale yellow solid, mp 123 °C; R_f (hexane/EtOAc 5:1) 0.67. Found: C, 61.43; H, 4.42; N, 7.89. $C_{28}H_{24}BrN_3O_4$ requires C, 61.55; H, 4.43; N, 7.69%; ν_{max} (KBr) 3450, 2203, 1629, 1513, 1340 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.27 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NO_2)), 7.63 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NO_2)), 7.46–7.30 (3H, m, Ph), 7.14–7.09 (2H, m, Ph), 6.89 (1H, s, H-3′), 6.34 (1H, s, H-6′), 6.15 (1H, d, *J* 8.1 Hz, H-4), 5.28 (1H, dd, *J* 5.9, 8.1 Hz, H-5), 5.23 (1H, d, *J* 5.9 Hz, H-6), 3.82 (s, 3H, O*Me*), 3.73 (3H, s, O*Me*), 3.50–3.44 (1H, m, N–CH_2^a–CH_2–Ph$(OMe)_2$), 3.08–3.03 (1H, m, N–CH_2^b–CH_2–Ph$(OMe)_2$), 2.72–2.68 (2H, m, N–CH_2–CH_2–Ph$(OMe)_2$); δ_C (75 MHz, $CDCl_3$) 157.7, 149.3, 148.9, 148.7, 148.2, 132.9, 130.5, 129.2, 128.6, 127.5, 124.7, 123.2, 120.9, 115.7, 114.5, 114.0, 113.6, 82.0, 62.0, 56.4, 56.2, 35.5.

*4.3.2. 1-Cyclohexyl-2,6-diphenyl-1,6-dihydropyridine-3-carbonitrile (**11b**).* Recrystallization of the crude product (EtOAc/hexane) gave **11b** (299 mg, 88%) as a pale yellow solid, mp 141 °C; R_f (hexane/EtOAc 5:1) 0.72. Found: C, 84.39; H, 6.99; N, 8.22. $C_{24}H_{24}N_2$ requires C, 84.67; H, 7.11; N, 8.23%; ν_{max} (KBr) 3428, 2925, 2193, 1525, 1500 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.55–7.15 (10H, m, Ph), 6.10 (1H, d, *J* 9.0 Hz, H-4), 5.40 (1H, dd, *J* 6.4, 9.0 Hz, H-5), 5.33 (1H, d, *J* 6.4 Hz, H-6), 3.56–3.28 (1H, m, C_6H_{11}), 1.62–0.91 (10H, m, C_6H_{11}); δ_C (75 MHz, $CDCl_3$) 157.9, 145.0, 134.6, 130.5, 129.1, 129.0, 128.9, 127.9, 125.6, 122.3, 121.8, 115.4, 84.4, 61.7, 55.9, 33.5, 32.4, 25.9, 25.3.

*4.3.3. 1-Cyclohexyl-6-(4-nitro-phenyl)-2-phenyl-1,6-dihydropyridine-3-carbonitrile (**11c**).* Recrystallization of the crude product (EtOAc) gave **11c** (354 mg, 92%) as a yellow solid, mp

209 °C; R_f (hexane/EtOAc 5:1) 0.76. Found: C, 74.85; H, 5.93; N, 10.99. $C_{24}H_{23}N_3O_2$ requires C, 74.78; H, 6.01; N, 10.90%; ν_{max} (KBr) 3424, 2930, 2194, 1519, 1490, 1344 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.22 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NO_2)), 7.61 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NO_2)), 7.56–7.39 (5H, m, Ph), 6.17 (1H, d, *J* 8.7 Hz, H-4), 5.41 (1H, dd, *J* 6.5, 8.7 Hz, H-5), 5.33 (1H, d, *J* 6.5 Hz, H-6), 3.38–3.30 (1H, m, C_6H_{11}), 1.68–0.94 (10H, m, C_6H_{11}); δ_C (75 MHz, $CDCl_3$) 157.8, 151.3, 147.6, 133.9, 130.9, 129.3, 128.9, 126.5, 124.4, 123.8, 121.0, 113.8, 85.4, 61.8, 55.2, 33.3, 32.6, 25.8, 25.2.

*4.3.4. 1-Cyclohexyl-6-(4-dimethylamino-phenyl)-2-phenyl-1,6-dihydropyridine-3-carbonitrile (**11d**).* Recrystallization of the crude product (EtOAc) gave **11d** (345 mg, 90%) as an orange solid, mp 158 °C; R_f (hexane/EtOAc 5:1) 0.54. Found: C, 81.45; H, 7.51; N, 11.04. $C_{26}H_{29}N_3$ requires C, 81.42; H, 7.62; N, 10.96%; ν_{max} (KBr) 3428, 2930, 2192, 1611, 1519, 1435 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.55–7.40 (5H, m, Ph), 7.30 (2H, d, *J* 8.7 Hz, Ph(*p*-NMe_2)), 6.72 (2H, d, *J* 8.7 Hz, Ph(*p*-NMe_2)), 6.09 (1H, d, *J* 9.1 Hz, H-4), 5.35 (1H, dd, *J* 6.4, 9.1 Hz, H-5), 5.08 (1H, d, *J* 6.4 Hz, H-6), 3.28–3.11 (1H, m, C_6H_{11}), 2.96 (6H, s, Ph(*p*-NMe_2)), 1.70–0.98 (10H, m, C_6H_{11}); δ_C (75 MHz, $CDCl_3$) 157.7, 150.4, 134.9, 133.1, 130.2, 129.0, 126.8, 122.1, 121.6, 120.2, 116.0, 112.8, 84.0, 61.7, 55.5, 40.7, 33.7, 32.4, 25.9, 25.4.

*4.3.5. 1-tert-Butyl-2,6-diphenyl-1,6-dihydropyridine-3-carbonitrile (**11e**).* Recrystallization of the crude product (EtOAc/hexane) gave **11e** (264 mg, 84%) as a pale yellow solid, mp 128 °C; R_f (hexane/EtOAc 5:1) 0.59. Found: C, 83.87; H, 6.89; N, 9.24. $C_{22}H_{22}N_2$ requires C, 84.04; H, 7.05; N, 8.91%; ν_{max} (KBr) 3429, 2963, 1511, 1488, 1184 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.62–7.30 (10H, m, Ph), 6.41 (1H, d, *J* 8.4 Hz, H-4), 5.70 (1H, dd, *J* 6.6, 8.4 Hz, H-5), 5.33 (1H, d, *J* 6.6 Hz, H-6), 1.12 (9H, s, ^tBu–N); δ_C (75 MHz, $CDCl_3$) 155.6, 141.1, 138.2, 129.7, 129.1, 128.4, 128.0, 127.7, 127.4, 124.4, 120.9, 119.5, 95.4, 61.9, 55.3, 32.4.

*4.3.6. 1-tert-Butyl-6-(4-nitro-phenyl)-2-phenyl-1,6-dihydropyridine-3-carbonitrile (**11f**).* Recrystallization of the crude product (EtOAc) gave **11f** (284 mg, 79%) as a yellow solid, mp 145 °C; R_f (hexane/EtOAc 5:1) 0.62. Found: C, 73.65; H, 6.00; N, 11.52. $C_{22}H_{21}N_3O_2$ requires C, 73.52; H, 5.89; N, 11.69%; ν_{max} (KBr) 3448, 2204, 1636, 1513, 1341 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.20 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NO_2)), 7.66 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NO_2)), 7.45–7.31 (5H, m, Ph), 6.50 (1H, d, *J* 8.6 Hz, H-4), 5.76 (1H, dd, *J* 6.5, 8.6 Hz, H-5), 5.41 (1H, d, *J* 6.5 Hz, H-6), 1.20 (9H, s, ^tBu–N); δ_C (75 MHz, $CDCl_3$) 160.8, 151.7, 149.2, 144.3, 137.6, 129.7, 128.7, 128.6, 128.3, 123.8, 120.3, 117.2, 117.0, 112.1, 57.7, 40.3, 31.6.

*4.3.7. 1-tert-Butyl-6-(4-dimethylamino-phenyl)-2-phenyl-1,6-dihydropyridine-3-carbonitrile (**11g**).* Recrystallization of the crude product (EtOAc) gave **11g** (300 mg, 84%) as an orange solid, mp 135 °C; R_f (hexane/EtOAc 5:1) 0.49. Found: C, 80.69; H, 7.49; N, 11.76. $C_{24}H_{27}N_3$ requires C, 80.63; H, 7.61; N, 11.75%; ν_{max} (KBr) 3444, 2970, 1612, 1521 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.49–7.35 (5H, m, Ph), 7.25 (2H, d, *J* 8.6 Hz, Ph(*p*-NMe_2)), 6.40 (2H, d, *J* 8.6 Hz, Ph(*p*-NMe_2)), 6.50 (1H, d, *J* 8.7 Hz, H-4), 5.66 (1H, dd, *J* 6.4, 8.7 Hz, H-5), 5.24 (1H, d, *J* 6.4 Hz, H-6), 2.94 (6H, s, Ph(*p*-N*Me*$_2$)), 1.17 (9H, s, ^tBu–N); δ_C (75 MHz, $CDCl_3$) 155.6, 149.5, 134.9, 130.8, 130.1, 129.0, 126.7, 123.2, 121.3, 120.0, 112.9, 112.2, 94.9, 61.6, 54.9, 40.7, 32.4.

*4.3.8. 1-Adamantan-1-yl-2,6-diphenyl-1,6-dihydropyridine-3-carbonitrile (**11h**).* Recrystallization of the crude product (EtOAc) gave **11h** (306 mg, 78%) as a pale yellow solid, mp 169 °C; R_f (hexane/EtOAc 5:1) 0.70. Found: C, 85.80; H, 7.09; N, 7.10. $C_{28}H_{28}N_2$ requires C, 85.67; H, 7.19; N, 7.14%; ν_{max} (KBr) 3432, 2908, 1617, 1512 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.70–7.28 (10H, m, Ph), 6.44 (1H, d, *J* 8.6 Hz, H-4), 5.71 (1H, dd, *J* 6.3, 8.6 Hz, H-5), 5.38 (1H, d, *J* 6.3 Hz, H-6), 2.00 (3H, br s, $C_{10}H_{15}$), 1.81–1.69 (6H, m, $C_{10}H_{15}$), 1.58–1.48 (6H, m, $C_{10}H_{15}$); δ_C (75 MHz, $CDCl_3$) 155.1, 140.9, 138.7, 129.9, 129.7, 128.4, 128.1, 127.8, 127.8, 124.7, 120.9, 120.0, 96.2, 63.1, 53.0, 44.9, 36.1, 30.3.

*4.3.9. 1-Adamantan-1-yl-6-(4-nitro-phenyl)-2-phenyl-1,6-dihydropyridine-3-carbonitrile (**11i**).* Recrystallization of the crude product (EtOAc) gave **11i** (306 mg, 70%) as a yellow solid, mp 208 °C; R_f (hexane/EtOAc 5:1) 0.46. Found: C, 76.75; H, 6.41; N, 9.70. $C_{28}H_{27}N_3O_2$ requires C, 76.86; H, 6.22; N, 9.60%; ν_{max} (KBr) 3440, 2908, 1617, 1518 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.16 (2H, d, *J* 8.5 Hz, *Ph*(*p*-NO_2)), 7.64 (2H, d, *J* 8.5 Hz, *Ph*(*p*-NO_2)), 7.42–7.32 (5H, m, Ph), 6.49 (1H, d, *J* 8.6 Hz, H-4), 5.74 (1H, dd, *J* 6.8, 8.6 Hz, H-5), 5.44 (1H, d, *J* 6.3 Hz, H-6), 2.00 (3H, br s, $C_{10}H_{15}$), 1.73–1.65 (6H, m, $C_{10}H_{15}$), 1.50–1.48 (6H, m, $C_{10}H_{15}$); δ_C (75 MHz, $CDCl_3$) 155.1, 148.8, 147.6, 137.9, 130.4, 129.5, 128.7, 128.3, 125.8, 123.6, 120.1, 118.8, 96.4, 63.6, 52.6, 44.9, 36.0, 30.3.

*4.3.10. 1-Adamantan-1-yl-6-(4-dimethylamino-phenyl)-2-phenyl-1,6-dihydropyridine-3-carbonitrile (**11j**).* Recrystallization of the crude product (EtOAc) gave **11j** (309 mg, 71%) as an orange solid, mp 200 °C; R_f (hexane/EtOAc 5:1) 0.45. Found: C, 82.50; H, 7.58; N, 9.41. $C_{30}H_{33}N_3$ requires C, 82.72; H, 7.64; N, 9.65%; ν_{max} (KBr) 3447, 2902, 1611, 1521 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.52–7.38 (5H, m, Ph), 7.29 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NMe_2)), 6.70 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NMe_2)), 6.38 (1H, d, *J* 8.6 Hz, H-4), 5.67 (1H, dd, *J* 6.5, 8.6 Hz, H-5), 5.30 (1H, d, *J* 6.5 Hz, H-6), 2.99 (6H, s, Ph(*p*-N*Me*$_2$)), 1.99 (3H, br s, $C_{10}H_{15}$), 1.75–1.68 (6H, m, $C_{10}H_{15}$), 1.59–1.48 (6H, m, $C_{10}H_{15}$); δ_C (75 MHz, $CDCl_3$) 155.0, 150.3, 139.0, 129.5, 128.5, 128.2, 127.9, 123.8, 121.2, 120.5, 112.6, 112.1, 95.8, 62.8, 52.6, 44.3, 40.7, 36.1, 30.3.

4.4. 3-*tert*-Butyl-1-(3,4-dimethoxy-benzyl)-5-phenyl-1,2,3,6-tetrahydropyrimidine-4-carbonitrile (13)

A solution of formaldehyde (37% w/w aq solution, 0.2 mL, 3.2 mmol), 3,4-dimethoxy-benzylamine (**12**) (0.17 mL, 117 mg, 1.6 mmol), and enaminonitrile (**7e**) (320 mg, 1.6 mmol) in MeOH (5 mL) was stirred at room temperature for 10 h. The reaction mixture was concentrated under reduced pressure and the oily residue was dissolved in CH_2Cl_2 (20 mL). The solution was washed with H_2O (3×10 mL), dried over Na_2SO_4, and then evaporated. The crude product was purified by column chromatography on silica gel using EtOAc/hexane as eluent to give **13** (156 mg, 25%) as a white solid, mp 139 °C; R_f (hexane/EtOAc 5:1) 0.18. Found: C, 73.76; H, 7.40; N, 10.65. $C_{24}H_{29}N_3O_2$ requires C, 73.63; H, 7.47; N, 10.73%; ν_{max} (KBr) 3438, 2965, 2192, 1513 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.38–7.30 (5H, m, Ph), 6.92 (3H, m, *Ph*(OMe)$_2$), 3.86 (6H, s, O*Me*), 3.75 (2H, s, *CH*$_2$–Ph(OMe)$_2$), 3.52 (2H, s, H-2), 3.30 (2H, s, H-6), 0.95 (9H, s, ^tBu–N); δ_C (75 MHz, $CDCl_3$) 160.0, 149.2, 148.8, 138.6, 130.1, 129.7, 129.6, 128.2, 121.6, 120.9, 112.6, 111.1, 90.0, 66.6, 59.6, 59.1, 56.2, 54.0, 31.2.

Acknowledgements

The authors are grateful to Mrs. Vali Sz. Marjay for her technical help.

References and notes

1. (a) Bogdanowicz-Szwed, K.; Krasodomska, M. *Monatsh. Chem.* **2006**, *137*, 347; (b) Abdelrazek, F. M.; Metwally, M. H.; Kassab, N. A.; Sobhy, N. A.; Metz, P.; Jaeger, A. *J. Heterocycl. Chem.* **2010**, *47*, 348; (c) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643.
2. (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642; (b) Bagley, M. C.; Hughes, D. D.; Sabo, H. M.; Taylor, P. H.; Xiong, X. *Synlett* **2003**, 1443; (c) Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Phillips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663; (d) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. N.; Zabel, M.; König, B. *J. Org. Chem.* **2003**, *68*, 2882.

3. (a) Altuna-Urquijo, M.; Gehre, A.; Stanforth, S. P.; Tarbit, B. *Tetrahedron* **2009**, *65*, 975; (b) Shi, F.; Tu, S.; Fang, F.; Li, T. *ARKIVOC* **2005**, 137; (c) Hameed, A.; Anwar, A.; Yousaf, S.; Khan, K. M.; Basha, F. Z. *Eur. J. Chem.* **2012**, *2*, 179.
4. Tanaka, K.; Fukase, K.; Katsumura, S. *Synlett* **2011**, 2115.
5. Sydorenko, N.; Hsung, R. P.; Vera, E. L. *Org. Lett.* **2006**, *12*, 2611.
6. (a) Trujillo, J. I.; Meyers, M. J.; Anderson, D. R.; Hegde, S.; Mahoney, M. W.; Vernier, W. F.; Buchler, I. P.; Wu, K. K.; Yang, S.; Hartmann, S. J.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4657; (b) Costa, E. V.; Pinheiro, M. L. B.; Xavier, C. M.; Silva, J. R. A.; Amaral, A. C. F.; Souza, A. D. L.; Barison, A.; Campos, F. R.; Ferreira, A. G.; Machado, G. M. C.; Leon, L. L. P. *J. Nat. Prod.* **2006**, *69*, 292.
7. Vincze, Z.; Mucsi, Z.; Scheiber, P.; Nemes, P. *Eur. J. Org. Chem.* **2008**, *6*, 947.
8. Vincze, Z.; Nemes, P. *Tetrahedron* **2011**, *67*, 3380.
9. Merah, B.; Texier, F. *Bull. Soc. Chim. Fr.* **1980**, 552.
10. (a) Boros, S.; Tóth, G. A Practical Comparation of Methods for Determination of Long-range $^{n}J_{C,H}$ Coupling Constants, VIth Central European NMR Symposium & VIth Central European Bruker NMR Users Meeting, September 27–28, 2004, Linz, Austria. (b) Vogeli, U.; von Philipsborn, W. *Org. Magn. Reson.* **1975**, *7*, 617.
11. (a) Chakrabarti, S.; Srivastava, M.; Ils, H.; Junjappa, H. *Synlett* **2003**, 2369; (b) Harsányi, K.; Kiss, P.; Korbonits, D. *J. Heterocycl. Chem.* **1973**, *10*, 435.