A one-pot microwaves-mediated approach towards 3-methylisoquinolines from hydrazone-derived 1-azatrienes

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Abstract

The use of hydrazone-type 1-azatriene derivatives for the synthesis of 3-methyl isoquinolines through a one pot microwave-assisted cyclization was developed and evaluated. The 1-azatrienes were generated by reaction of 2-propenylbenzaldehydes with hydrazines. Their subsequent electrocyclization gave rise to 3-methylisoquinolines, as well as to 3-methyl-3,4-dihydroisoquinolines as reaction by-products. The reaction conditions were optimized, and its scope and limitations were explored.

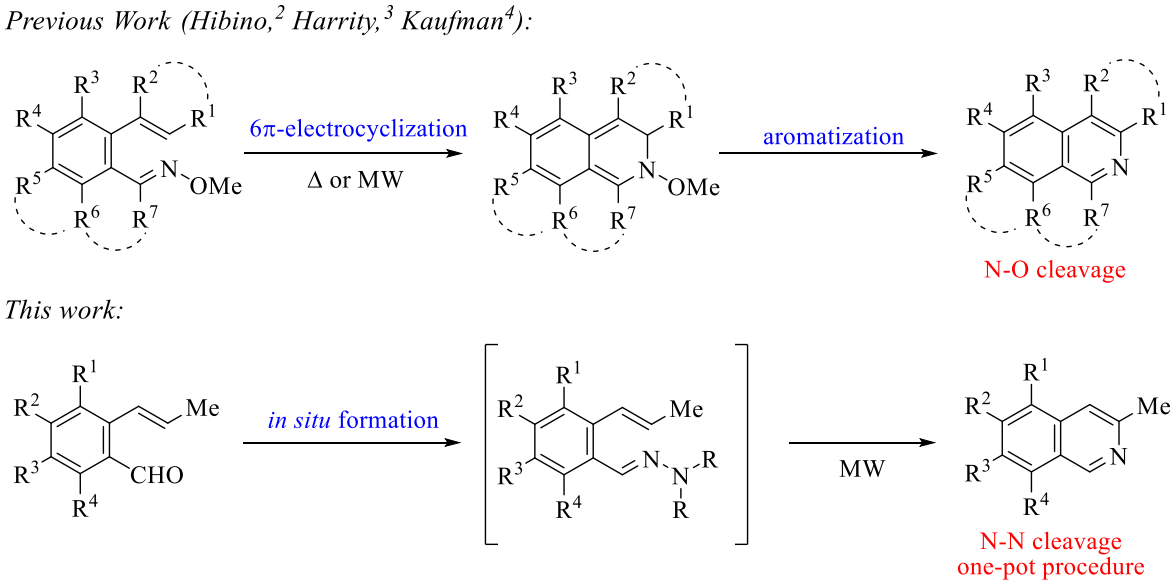
Keywords: nitrogen heterocycles, 3-methylisoquinoline synthesis, hydrazones

Introduction

The isoquinoline core is one of the most relevant scaffolds in biologically active *N*-heterocycles and natural products. Due to their structural diversity, these compounds represent an interesting challenge to the ingenuity of synthetic organic Chemists and are a constant source of inspiration for the development of new pharmacological prototypes.[1] Therefore, extensive research has focused on the development of methods for their access.

The 6π-electrocyclization of 1-azatrienes has acquired interest as a strategy to easily achieve structural complexity, since it allows the formation of heterocyclic rings under conditions of atom economy and represents an elegant approach for the synthesis of this class of structures. Usually, oximes are used in this reaction, which in a later stage of aromatization involves a N−O bond cleavage process (Scheme 1).[2, 3, 4]

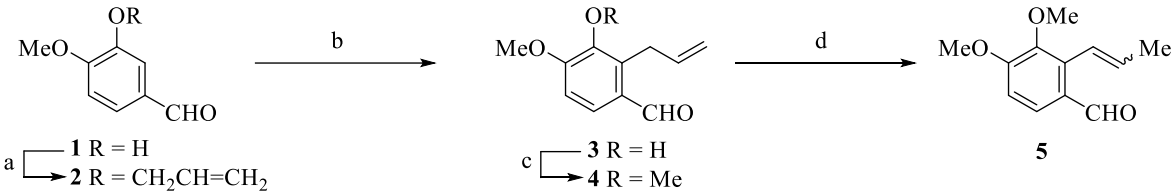
During the last decade, our research group has published results concerning the use of the 6π-electrocyclization reaction for the synthesis of polycyclic isoquinolines and analogues of natural products.[4] Based on our earlier work, we were motivated to extend these studies using hydrazone-derived 1-azatrienes involving N-N bond cleavage in order to explore a new approach to this reaction (Scheme 1).



Scheme 1. Use of 1-azatrienes in the synthesis of isoquinolines.

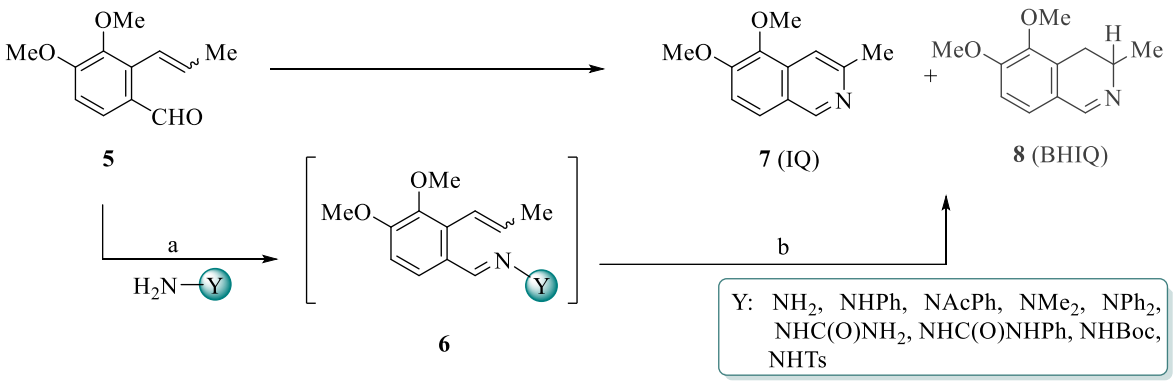
Results and Discussion

To begin the study, the *ortho*-propenylbenzaldehyde derivative **5** was synthesized using a four-steps protocol (Scheme 2) from isovanillin (**1**). Then, to rationally optimize the reaction, a screening of *N*-substituted 1-azatrienes (**6**) was performed (Scheme 3), using **5** as starting material and hydrazine derivatives (Y-NH_2). The strategy involved a first step of obtaining hydrazone-derived 1-azatrienes (**6**), followed by the change of solvent and a microwave-assisted electrocyclization reaction, all in the same reaction pot.



Scheme 2. *Reagents and conditions:* a) $BrCH_2CH=CH_2$, K_2CO_3, EtOH, reflux, 3 h (93%); b) 1,2-$Cl_2C_6H_4$, 180°C, 20 h (90%); c) MeI, K_2CO_3, EtOH, reflux, 6 h (95%); d) $RuClH(CO)(PPh_3)_3$, PhMe, 80°C, 24 h (90%, *E*:*Z* = 82:18).

It was found that the reaction invariably led to the formation of 3-methylisoquinoline (**7**, IQ) with yields between 5% and 73%, together with 3,4-dihydroisoquinoline (**8**, DHIQ) as a secondary product, with yields between 9% and 38%. The best results (yield and IQ:DHIQ ratio) were found when *N*,*N*-dimethylhydrazine (Y = NMe_2; yield = 85%; IQ:DHIQ = 1:0.16) and semicarbazide [Y = $NHC(O)NH_2$; yield = 93%; IQ:DHIQ = 1:0.7] were employed.



Scheme 3. *Reagents and conditions:* a) EtOH, rt, 1-2 h; b) MW, DMA, 180°C, 2 h.

To further study the transformation, the electrocyclization step was monitored by ^{1}H NMR. Thus, the 1-azatriene **6a** [Y = NHC(O)NH_2] was dissolved in DMSO-d_6 and heated to 140°C and 180°C (Figures 1 and 2).

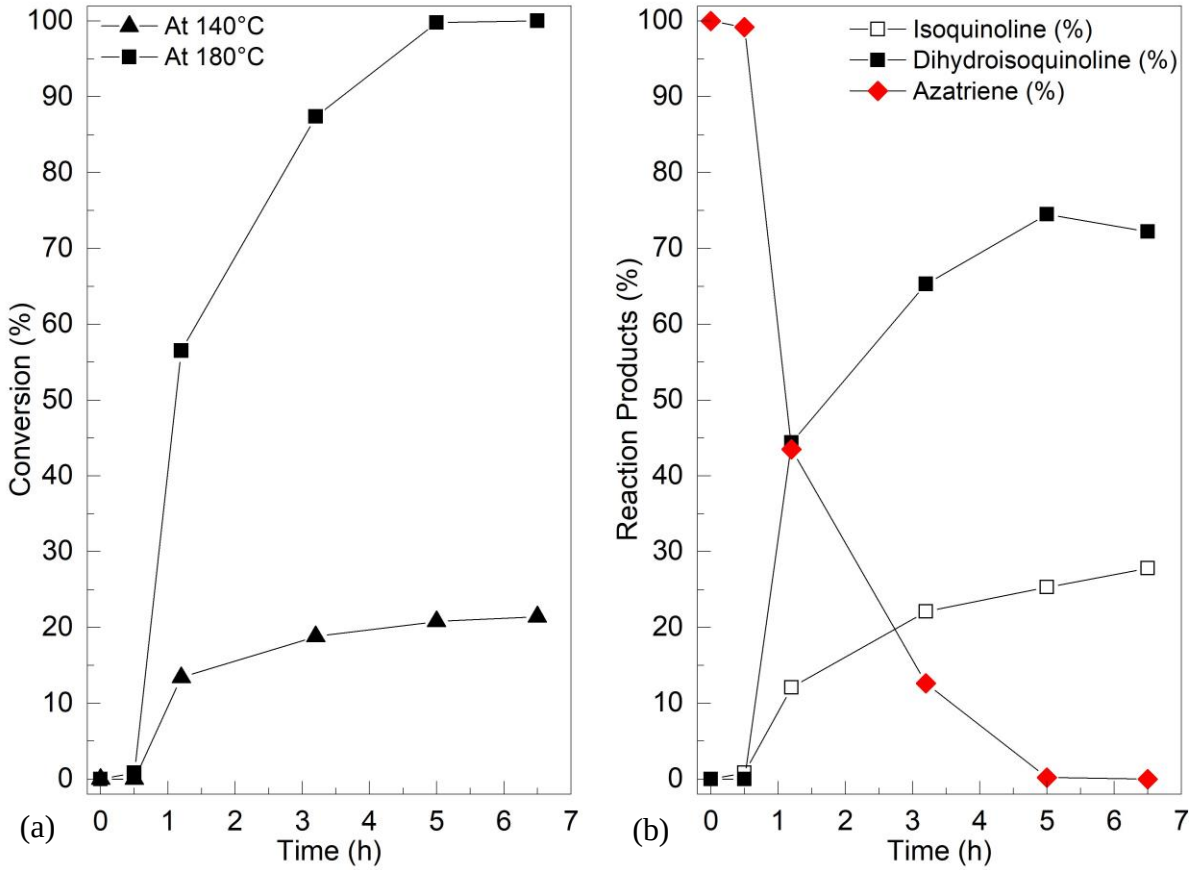


Figure 1. ^{1}H NMR, analyses of the reaction. Compound **6a** (0.16 M) was employed in DMSO-d_6 at 140°C and 180°C in a sealed NMR tube under argon. a) Influence of the reaction temperature on the electrocyclization of the 1-azatriene (140°C *vs* 180°C); b) Transformation of the 1-azatriene at 180°C.

In previous experiments it was found that the complete conversion of azatriene **6a** is favored at 180°C, whilst at 140°C only a 21% conversion was found (Figure 1a). In

addition to isoquinoline **7**, the formation of **8** was also observed to take place at 140°C. Monitoring the reaction at 180°C revealed that DMSO-d_6 favors the formation of **8**, since a higher proportion of **8** was found than of **7** (Figure 1b). Unfortunately, no reaction intermediates were observed.

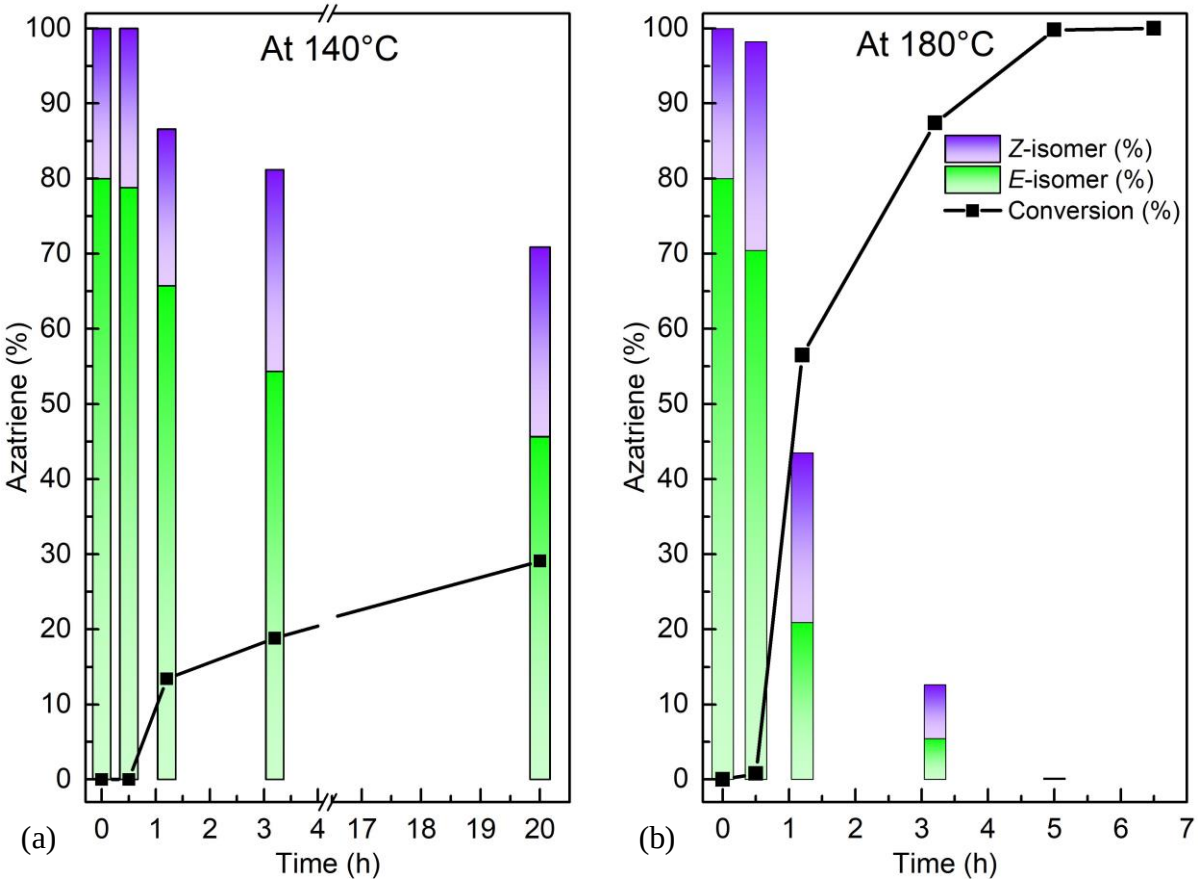
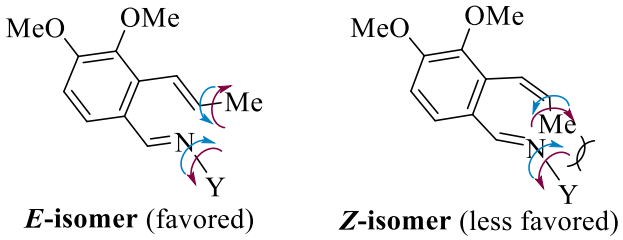


Figure 2. [1]H NMR analyses of the electrocyclization reaction. Compound **6a** (0.16 M) was employed at 140°C and 180°C in a sealed NMR tube under argon. a) Variation of *E*/*Z* ratio of the 1-azatriene during the transformation at 140°C; b) Variation of *E*/*Z* ratio of the 1-azatriene during the transformation at 180°C.

During these experiments, a variation of the *E*/*Z* ratio during the reaction was detected (Figure 2). Significantly, it was observed that the *E*-isomer decreased more pronouncedly during the heating, while the *Z*-isomer appeared to be less prone to undergo the electrocyclization. The Woodward and Hoffmann rules predict that the thermal electrocyclization is allowed by a disrotatory ring closure, where the cyclization of the *Z*-isomer would be sterically disfavored (Figure 3).[5]

In order to expand the scope and the general efficiency of our methodology, the effect of the solvent on the yield of IQ and their accompanying DHIQ was assessed employing tightly closed systems under conventional heating and employing microwaves irradiation (Table). Furthermore, an oxime-derived 1-azatriene was also used for comparison purposes.

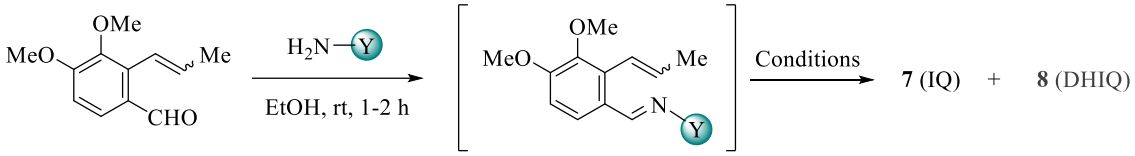


***E*-isomer** (favored) ***Z*-isomer** (less favored)

Figure 3. Disrotatory modes of electrocyclization of a hydrazone-derived.

To amplify the study, the cyclization was performed out in benzotrifluoride ($PhCF_3$), a safe and modern replacement of hydrocarbons and chlorinated solvents, which is very suitable for microwave-assisted reactions, being also easy to recover.[6]

Table. Comparison of the performances of the cyclization.



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6a Y = $NHC(O)NH_2$
6b Y = NMe_2
6c Y = OMe

Entry N°	Reaction Conditions	Y	Yield of IQ (%)	Yield of DHIQ (%)	Overall Yield (%)	IQ:DHIQ ratio
1	DMA, MW, 180°C, 1h	$NHC(O)NH_2$	55	88	93	1:0.70
2	DMA, MW, 180°C, 2h	NMe_2	73	12	85	1:0.20
3	DMA, Δ, 180°C, 3h	NMe_2	58	11	69	1:0.18
4	DMA, MW, 180°C, 1h	OMe	62	6	62	1:0.18
5	$PhCF_3$, MW, 180°C, 2h	NMe_2	76	6	82	1:0.08
6[a]	$PhCF_3$, MW, 180°C, 2h	NMe_2	72	8	80	1:0.11
7[a]	$PhCF_3$, Δ, 180°C, 3h	NMe_2	65	17	82	1:0.26
8	$PhCF_3$, MW, 180°C, 1h	OMe	59	10	69	1:0.16

[a] Without solvent change; $PhCF_3$ was used from the first stage.

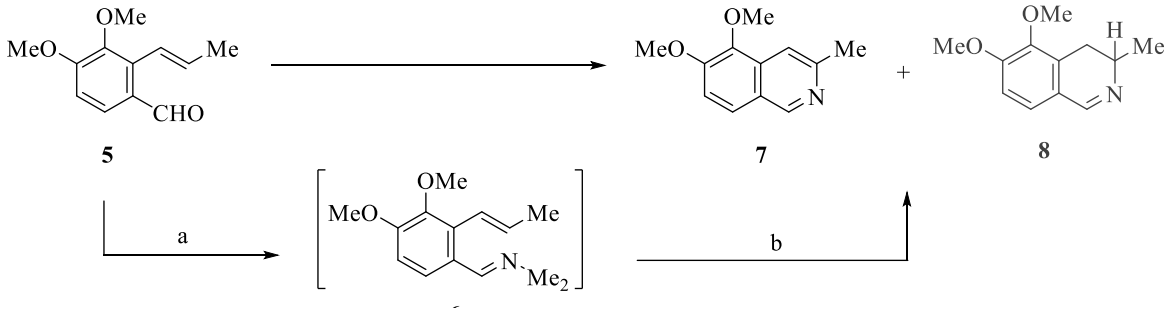
At 180°C, $PhCF_3$ proved to be superior under both heating conditions (entries 2 vs. 5 and 3 vs. 7). Further analysis revealed that the microwaves-assisted transformations outperformed those carried out under conventional heating (entries 2 vs. 3 and 5 vs. 7). Further, this solvent allowed accessing the products in a single operation where the 1-azatriene is generated *in situ* in the first stage and there is no need to change the solvent (one pot cyclization). The results of the entries 5 and 6 proved to furnish essentially identical results, being the conditions of entry 6 preferred for their comparative simplicity.

Interestingly, to date there is no report of the formation of 3,4-dihydroisoquinolines by this cyclization. Therefore, the use of a methoxime-derived azatriene was evaluated for the

sake of comparison. Notably, the DHIQ was also isolated as a minor product from the cyclization of the tested methoxime derivative, in amounts comparable to those furnished by the related 1,1-dimethyl hydrazone **6b** (entries 4 and 8).

The isomerization of 2-allylbenzaldehyde (**4**) by $RuClH(CO)(PPh_3)_3$ catalysis allowed the obtention of the *ortho*-propenylbenzaldehyde **5** in good yield and acceptable *E*:*Z* selectivity (90%, *E*:*Z* = 82:18, Scheme 2). However, treatment with sodium hydroxide in refluxing methanol, as reported by Chang *et al*.,[7] resulted in the isomerization of **4** with acceptable yield and good *E*:*Z* selectivity (80%, *E*:*Z* = 95:5 to 100:0).

The selective access to ***E*-5** enabled its use as a precursor of the electrocyclization reaction. Thus, **7** was found with 79% yield, accompanied by **8** in 15% yield. Thus, an increase of 14% in the overall performance of the transformation was noticed (Scheme 4).



Scheme 4. *Reagents and conditions:* a) Me_2N-NH_2, AcOH, $PhCF_3$, rt, 3h; b) MW, 180°C, 2h, (**5** *E*:*Z* = 80:20, **7**, 72%; **8**, 8%); (**5** *E*:*Z* = 100:0, **7**, 79%; **8**, 15%).

Experimental section

1. General experimental details

All the reactions were carried out under anhydrous argon atmospheres, using oven-dried glassware and freshly distilled anhydrous solvents. The reactions were monitored by TLC, using silica gel GF_{254} plates supported on aluminum and run in different hexane-EtOAc solvent mixtures. The chromatographic spots were detected by exposure to 254 nm UV light, and by spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent. The flash column chromatographies were run with silica gel 60 H (particle size < 55 μm), eluting with hexane-EtOAc mixtures, under positive pressure and employing gradient of solvent polarity techniques.

The nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 NMR spectrometer, at 300.13 (^{1}H) and 75.48 (^{13}C) MHz. $CDCl_3$ was used as solvent, unless otherwise noted, and the chemical shifts are informed in parts per million in the δ scale. TMS was used as the internal standard (resonances of $CHCl_3$ in $CDCl_3$: δ 7.26 and 77.0 ppm for ^{1}H and ^{13}C NMR, respectively). The GC–MS experiments were performed with a

Shimadzu QP2010*Plus* instrument equipped with an AOC-20i autosampler.

2. *General procedure for the electrocyclization of hydrazone-derived 1-azatrienes toward isoquinolines*

A mixture of the *ortho*-propenylbenzaldehyde (**5**, 0.3 mmol), 1,1-dimethylhydrazine (25 μL, 0.33 mmol) and glacial AcOH (18 μL, 0.3 mmol) in $PhCF_3$ (1 mL) was transferred to a microwave tube. Argon was bubbled, and the mixture was stirred at room temperature until TLC analysis indicated complete aldehyde consumption (approx. 3 h). Then, the vessel was irradiated (180°C, *ca*. 250 W) in the microwave reactor in 1 h cycles until completeness, as judged by TLC. After cooling to room temperature, the solvent was recovered by careful distillation under atmospheric pressure, and the oily residue was purified by chromatography to afford the 3-methylisoquinoline (**7**) and 3-methyl-3,4-dihydro-isoquinoline (**8**) products.

5,6-Dimethoxy-3-methylisoquinoline (**7a**): Yield: 72%, Off-white solid, m.p.: 83-85 °C. ^{1}H NMR δ: 2.69 (s, 3H, Me), 3.98 (s, 3H, OMe), 4.02 (s, 3H, OMe), 7.29 (d, *J* = 9.1, 1H, 7-H), 7.69 (br s, 1H, 4-H), 7.70 (d, *J* = 9.1, 1H, 8-H) and 9.06 (s, 1H, 1-H). ^{13}C NMR δ: 24.5 (Me), 56.6 (OMe), 61.2 (OMe), 112.1 (C-7), 114.8 (C-4), 123.2 (C-8a), 124.5 (C-8), 132.5 (C-4a), 141.1 (C-5), 151.7 (C-1 and C-6) and 151.8 (C-3). GC-MS *m*/*z* (rel. int. %): 203 (M^+, 72), 188 (57), 160 (100), 145 (47), 117 (38), 89 (40) and 76 (41).

5,6-Dimethoxy-3-methyl-3,4-dihydroisoquinoline (**8a**): Yield: 8%, Amber oil. ^{1}H NMR δ: 1.40 (d, *J* = 6.8, 3H, Me), 2.39 (dd, *J* = 11.8 and 16.5, 1H, 4-H_A), 2.97 (dd, *J* = 5.7 and 16.5, 1H, 4-H_B), 3.56-3.69 (m, 1H, 3-H), 3.80 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.80 (d, *J* = 8.2, 1H, 7-H), 7.05 (d, *J* = 8.2, 1H, 8-H) and 8.21 (d, *J* = 2.6, 1H, 1-H). ^{13}C NMR δ: 22.0 (Me), 26.4 (C-4), 52.0 (C-3), 55.8 (OMe), 60.7 (OMe), 109.8 (C-7), 122.5 (C-8a), 124.1 (C-8), 130.1 (C-4a), 145.6 (C-5), 155.2 (C-6) and 158.7 (C-1). GC-MS *m*/*z* (rel. int. %): 205 (M^+, 85), 190 (100), 175 (13), 146 (13), 117 (6), 91 (13) and 77 (12).

Conclusions

A synthesis of 3-methylisoquinolines by a one pot hydrazonation-6π-electrocyclization-elimination sequence, under microwave promotion in benzotrifluoride, was developed. The reaction conditions were optimized, and its scope and limitations were explored, finding that 3-methyl-3,4-dihydroisoquinolines are concomitantly produced as side products.

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