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Synthetic Methodology

Synthesis of Polysubstituted 3-Methylisoquinolines through the 6π-Electron Cyclization/Elimination of 1-Azatrienes derived from 1,1-Dimethylhydrazine

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Abstract: A convenient one pot microwave-assisted 6π-electron cyclization/aromatization approach toward 3-methylisoquinolines is reported. The starting 1-azatriene derivatives were prepared in situ by reaction of 2-propenylbenzaldehydes with 1,1-dimethylhydrazine, which exhibited superior performance when compared with other hydrazine derivatives. Minor amounts of the related 3,4-dihydro isoquinolines were formed concomitantly with the isoquinolines, and a mechanism for their generation was proposed. The reaction conditions were optimized, and its scope and limitations were explored. In general, the transformation proceeded in moderate to good yields.

Introduction

Nitrogen heterocycles are recurrent structural motifs in important natural products as well as within biologically and technologically relevant compounds. Among them, the isoquinolines hold a central position because they are widely distributed in nature and their structural diversity and broad spectra of biological activities keeps attracting considerable attention from different perspectives. Currently, this heterocycle is considered a highly relevant privileged scaffold in fields such as medicinal and agricultural chemistry.[1]

Numerous approaches have been designed to access isoquinoline derivatives. However, new additions to the multistep synthesis armamentarium through the development of novel reagents and routes toward these heterocycles, are always welcomed, especially if readily accessible precursors are employed.

The electrocyclization reactions are powerful tools that allow the construction of ring compounds under straightforward, elegant and atom-economic conditions. Although the basic pericyclic reaction has been known for a number of years,[2] recent reviews[3] suggest that the 6π-electrocyclizations of azatrienes has comparatively fewer examples.[4]

Further, despite the group of Hibino described the general use of this methodology for the preparation of isoquinolines,[5a] there are only scattered cases involving the syntheses of the isoquinoline framework,[4d,5] and even less on natural products containing this heterocyclic framework (Figure 1).[6]

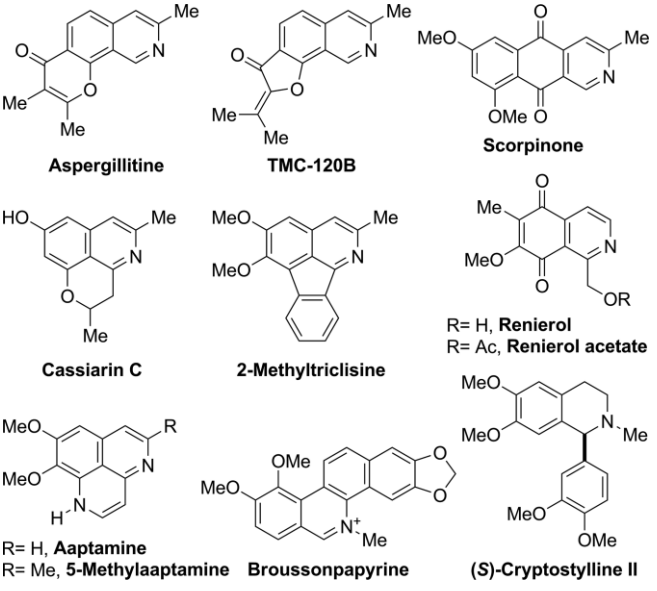

Figure 1. Chemical structures of some natural products and analogs, bearing an isoquinoline motif, which have been synthesized employing the 6π-electrocyclization reaction of 1-azatrienes.

The 3-substituted isoquinolines have recently conceited great attention; hence, considerable efforts have been made toward their synthesis and different methods have been devised for that purpose.[7]

The sequential 6π-electrocyclization/elimination of 1-azatrienes has been carried out with oximes,[8] oxime ethers[9] and oxime esters as sources of the nitrogen atom, but also and more scarcely with sulfonylimines[10] and silylimines.[11] Imines[12] and alkylimines have also been employed, but only for the 6π-electrocyclization stage.[2b,13] Surprisingly, however, despite the analogous hydrazone derivatives possess weak *N*–*N* bonds similar to those of the oxime ethers/esters, there are

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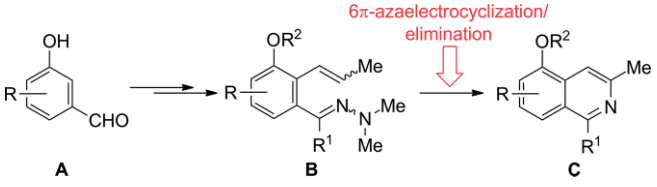
scarce and scattered examples on their use as part of 1-azatrienes involved in this kind of reactions.[14]

To the best of our knowledge, there are no precedents on the cyclization of hydrazone-derived 1-azatrienes in which one of the double bonds of the polyenic starting material belongs to an isocyclic aromatic ring. In this scenario, the need of dearomatization during the cyclization stage may favour side reactions and affect the success of the transformation.

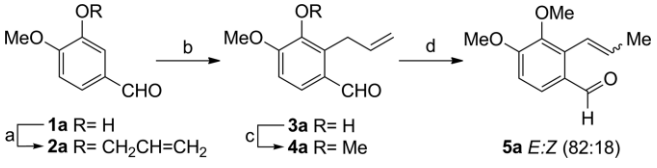
Multistep organic synthesis benefits from the availability of multiple alternatives for a given transformation. Therefore, in an effort to broaden the scope of the 6π-electron cyclization of 1-azatrienes toward polysubstituted 3-methylisoquinolines, herein we wish to report on the use of 1,1-dimethylhydrazine as a convenient and suitable nitrogen atom source for such reaction, according to the general synthetic route (**A** → **B** → **C**) outlined in Scheme 1. The scope and limitations of the transformation are also examined and discussed.



Scheme 1. Proposed general strategy toward the isoquinolines **C**.

Results and Discussion

To begin the study and in order to test the performance of different hydrazine derivatives as suitable sources of the required isoquinoline nitrogen atom, the *ortho*-propenyl benzaldehyde derivative **5a** was prepared as a model in a four-steps protocol (Scheme 2) from isovanillin (**1a**).

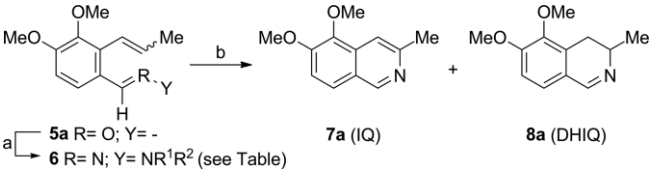


Scheme 2. *Reagents and conditions:* a) $BrCH_2CH{=}CH_2$, K_2CO_3, EtOH, reflux, 3 h (93 %); b) 1,2-$Cl_2C_6H_4$, 180 °C, 20 h (90 %); c) MeI, K_2CO_3, EtOH, reflux, 6 h (95 %); d) $RuClH(CO)(PPh_3)_3$, PhMe, 80 °C, 24 h (90 %).

To that end, **1a** was submitted to a Williamson *O*-alkylation with allyl bromide in refluxing EtOH, to which K_2CO_3 was added as base, and the resulting allyl ether **2a**, obtained in 93 % yield, was subjected to a Claisen rearrangement to afford **3a** (90 % yield). This was followed by *O*-alkylation of the free phenol with MeI/K_2CO_3 in EtOH (95 % yield) and final isomerization of the double bond of the resulting allyl derivative **4a**, promoted by catalytic amounts of $RuClH(CO)(PPh_3)_3$ in toluene at 80 °C, which afforded **5a** in 90 % yield (72 % overall yield from **1a**).

With compound **5a** in hand, the next task was to find the proper substituted hydrazine for derivatization of the model aldehyde (Table 1), in order to obtain the most suitable substrate for the cyclization. Luckily, the first attempt run with hydrazine itself, proved successful (entry 1). However, it was observed that the corresponding intermediate **6** afforded only a 29 % combined yield of isoquinoline derivatives, after heating 2 h at 180 °C in DMA, as a 1:0.45 separable mixture of the isoquinoline (IQ) **7a** and the related 3,4-dihydroisoquinoline (DHIQ) **8a**.

Table 1. Selection of the nitrogen derivatizing agent for aldehyde **5a**.[a]



Entry No.	R^1	R^2	Time [h]	Isolated yield [%] IQ[b]	DHIQ[c]	Global	IQ/DHIQ ratio
1	H	H	2	20	9	29	1:0.45
2	H	Ts	3	5	0	5	1:0
3	H	Boc	1.3	22	23	55	1:0.95
4	H	$C(O)NH_2$	1	55	38	93	1:0.7
5	H	C(O)NHPh	3	26	15	41	1:0.57
6	H	Ph	1.5	40	10	50	1:0.25
7	Ac	Ph	6	45	21	66	1:0.46
8	Ph	Ph	4	30	13	43	1:0.43
9	Me	Me	2	73	12	85	1:0.16

[a] *Reaction conditions:* a) $R^1R^2N\text{-}NH_2$, EtOH, room temp., 1–2 h; b) MW, DMA, 180 °C. [b] IQ: Isoquinoline. [c] DHIQ: 3,4-Dihydroisoquinoline.

The structures of the heterocycles were assessed by NMR spectroscopic analysis. Compound **8a** displayed the diagnostic signal of the 3-methyl group as a doublet (δ = 1.40 ppm), coupled to H-3, which not unexpectedly was observed as a complex signal (δ = 3.56–3.69 ppm). On the other hand, the isoquinoline **7a** exhibited a characteristic singlet corresponding to the three hydrogens of the methyl group (δ = 2.69 ppm) and those of its heterocyclic ring (δ = 7.69 and 9.06 ppm).

Interestingly, to the best of our knowledge, 3,4-dihydroisoquinolines have not been previously reported as side products in similar cyclization reactions leading to the related isoquinolines, including those which use methoximes as source of the nitrogen atom.

This could be happened because they were not expected, were formed in minute amounts or had a very different and much higher polarity. For instance, in a typical TLC run in EtOAc/EtOH (9:1, *v*/*v*), the R_f of the isoquinolines are ≈ 0.6, whereas the R_f values of the related 3,4-dihydroisoquinolines are < 0.2. A literature search revealed only a related report by the group of Hibino, which disclosed that strong heating of an oxime derivative of 2-methoxy-6-propenyl benzaldehyde afforded the corresponding 4-methyl-4,5-dihydro benzo[*d*][1,2]-oxazepine.[4d]

Therefore, in order to rule out the possibility of formation of the analogous 4-methyl-4,5-dihydro-3λ^2-benzo[*d*][1,2]diazepine, the mass spectrum of the product was obtained; delightfully, the characteristic peak of its molecular ion $[M]^+$ at *m*/*z* = 205 confirmed its proposed identity as the 3,4-dihydroisoquinoline **8a**.

Encouraged by this result, the use of 4-toluenesulfonyl hydrazine was explored, with a frustrating outcome, since only 5 % of the expected isoquinoline was recovered, and no 3,4-

dihydroisoquinoline was observed (entry 2). Interestingly, the related *N*-sulfonylimines have been recently used in azatriene 6π-electrocyclization reactions toward 1,2-dihydropyridines.[15]

On the other hand, slightly better results were obtained employing the Boc-hydrazine derivative (entry 3), which furnished 55 % overall yield of a mixture of isoquinoline derivatives, at the expense of a high IQ/DHIQ ratio (1:0.95).

Better success was observed with the semicarbazide derived substrate, which gave 93 % yield of heterocyclic products, but still in a high IQ/DHIQ ratio (1:0.7), so that the yield of the isoquinoline was only 55 % (entry 4). Further, the performance of the related phenylsemicarbazide derivative of entry 5 was also non-satisfactory, furnishing only 41 % of isoquinoline derivatives, in a IQ/DHIQ ratio of 1:0.57.

Suspecting that thermal stability of the nitrogen derivatives could be one of the determinants of the rather poor performance of some of the candidates, the transformation was carried out with phenylhydrazine (entry 6).[16] Despite the moderate overall yield observed (50 %), the low IQ/DHIQ ratio obtained (1:0.25) prompted us to test the related reagent *N*-acetyl phenylhydrazine. A further yield improvement to 66 % (entry 7) was detected, but at the expense of an increase in the amount of the 3,4-dihydroisoquinoline side product (IQ/DHIQ = 1:0.46).

These results were encouraging but not satisfactory; therefore, the *N*-acetyl moiety was replaced by the thermally more stable *N*-phenyl motif (entry 8). However, not unexpectedly, the overall yield of heterocycles dropped to 43 %, while maintaining the IQ/DHIQ ratio essentially unchanged (1:0.43).

This meagre result was attributed to the high steric demand of the bulky phenyl substituents and suggested to experiment with 1,1-dimethylhydrazine (entry 9), the least sterically demanding 1,1-disubstituted hydrazine. Delightfully, an 85 % overall yield of isoquinoline derivatives was recorded, combined with a highly satisfactory IQ/DHIQ ratio of 1:0.16.

These experiments revealed that significant reactivity differences could be observed in the cyclization processes, depending on the nature of the substituents at the distal nitrogen atom of the hydrazone. Lyaskovskyy et al. attempted to perform the K*t*BuO-mediated hydrohydrazination of an *ortho*-alkynyl phenylhydrazone, meeting with failure. However, they found that using the analogous *N*-methyl hydrazone (prepared with $MeNH–NH_2$) afforded the expected product in moderate yield.[17] Therefore, we choose $Me_2N–NH_2$ as the most suitable hydrazine derivative for further system optimization.

Next, the selection of the most suitable reaction medium was carried out, by running the model transformation in hydrocarbon, amides, ethereal and halogenated solvents. The results, detailed in Table 2, revealed that the use of xylene was unsatisfactory (entry 1), mainly because of the poor solubility of the starting material. The overall yield of the reaction, based on 20 % of recovered starting material, was only moderate. Employing high boiling point *N*,*N*-disubstituted amides (entries 2 and 3) resulted in improved yields and good IQ/DHIQ ratios. The use of NMP gave low amounts of DHIQ, whereas the reaction run in DMA afforded cyclized products in 85 % combined yield.

Table 2. Solvent selection for the cyclization reaction of **6a**.

Entry No.	Solvent	Isolated yield [%]			IQ/DHIQ ratio
		7a (IQ)	**8a** (DHIQ)	Global	
1	Xylene[a]	53	9	62	1:0.16
2	NMP	67	3	70	1:0.04
3	$MeCONMe_2$	73	12	85	1:0.16
4	Ph_2O	74	18	92	1:0.24
5	$1,2\text{-}Cl_2C_6H_4$	68	10	78	1:0.14
6	$PhCF_3$	76	6	82	1:0.08
7	$PhCF_3$[b]	72	8	80	1:0.11

[a] Yields are based on recovered starting 1-azatriene (20 %). [b] Method B was used.

The latter result was outperformed by Ph_2O (entry 4), mainly at the expense of delivering higher amounts of DHIQ. On the other side, *ortho*-dichlorobenzene furnished 68 % yield of the IQ, similar to NMP (entry 5), whereas the reaction in $PhCF_3$ gave the highest yields of isoquinoline (76 %) and its IQ/DHIQ ratio ranked among the best.

Benzotrifluoride ($PhCF_3$) is a safe and modern replacement of hydrocarbons and chlorinated solvents, which is very suitable for microwave-assisted reactions, being also easy to recover due to its comparatively low boiling point (102 °C).[18] Taking into account its performance in the transformation and the rather difficult removability of the high boiling amides and diphenyl ether, it was chosen as the reaction solvent for further experiments.

Furthermore, two protocols were devised for the reaction. In Method A, the hydrazone was prepared in EtOH; then the solvent was removed and replaced with $PhCF_3$ to carry out the cyclization stage. In Method B, the whole hydrazonation/cyclization/aromatizing elimination sequence was performed as a one pot process in $PhCF_3$. Both alternatives proved to furnish essentially identical results (for **7a**, 76 % with Method A and 72 % using Method B; entries 6 and 7), being Method B preferred for its comparative simplicity.

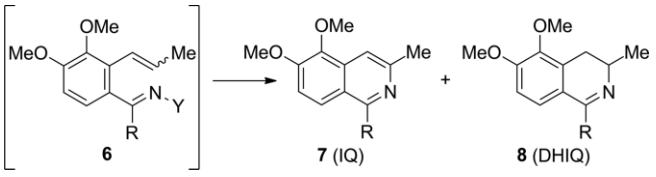
Hence, the effect of the reaction temperature on the yield of the isoquinolines and their accompanying 3,4-dihydro isoquinolines was assessed next in DMA and $PhCF_3$ employing tightly closed systems under conventional heating and employing microwaves irradiation (Table 3).

At 180 °C, $PhCF_3$ proved to be superior under both heating conditions (entries 1 vs. 4 and 2 vs. 5). Further analysis revealed that the microwaves-assisted transformations outperformed those carried out under conventional heating (entries 1 vs. 2 and 4 vs. 5), and that heating at temperatures above 180 °C resulted in diminished yields of the isoquinolines (entries 5–7). Hence, the temperature of 180 °C and microwave irradiation were judged as optimal conditions.

At this point and given the extended use methoxime derivatization for the 6π-electrocyclization of 1-azatrienes toward pyridines, isoquinolines and β-carbolines, the performances of methoxylamine and 1,1-dimethylhydrazine were compared in the model reaction, at 180 °C, in DMA and $PhCF_3$ as solvents, and running the transformations under microwave irradiation.

The results (Table 3) revealed that, under these conditions, despite requiring a longer reaction time, the 1,1-dimethyl hydrazine derivative outperformed its congener in both sol-

Table 3. Comparison of the performances of the cyclizations of methoximes and 1,1-dimethylhydrazones.[a]



Entry No.	R/Y	Solvent	Mode/ Temp. [°C]	Time [h]	Isolated yield [%] IQ	DHIQ	Total	IQ/DHIQ ratio
1	H/NMe_2	DMA	MW/180	2	73	12	85	1:0.16
2	H/NMe_2	DMA	Δ/180	3	58	11	69	1:0.20
3[b]	H/NMe_2	$PhCF_3$	MW/160	2	52	17	69	1:0.32
4[b]	H/NMe_2	$PhCF_3$	MW/180	2	72	8	80	1:0.11
5[b]	H/NMe_2	$PhCF_3$	Δ/180	3	65	17	82	1:0.26
6[b]	H/NMe_2	$PhCF_3$	Δ/200	3	64	8	72	1:0.12
7[b]	H/NMe_2	$PhCF_3$	Δ/220	3	40	12	52	1:0.30
8	H/OMe	DMA	MW/180	1	62	6	68	1:0.10
9	H/OMe	$PhCF_3$	MW/180	1	59	10	69	1:0.16
10[c]	Me/NMe_2	$PhCF_3$	MW/180	0.75	3	20	23	1:6.66
11[d]	Me/OMe	$PhCF_3$	MW/180	0.75	30	20	50	1:1.66

[a] Δ: Conventional heating (bath temperature); MW: Microwaves irradiation. [b] The reactions were carried out as one-pot procedures following Method B. [c] Starting material (10 %) was recovered. [d] Some of the 1-azatriene starting material (20 %) was recovered.

vents (entries 1 vs. 8 and 4 vs. 9, respectively), albeit at the expense of longer reaction times.

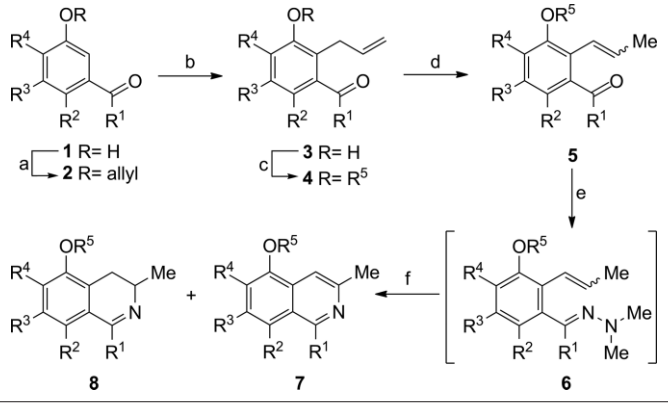
In addition, the 3,4-dihydroisoquinoline **8a** was also isolated as a minor product from the cyclization of the tested methoxime derivative (entries 8 and 9), in amounts comparable to those furnished by the related 1,1-dimethyl hydrazone **6a**. This demonstrates for the first time that 3,4-dihydroisoquinolines are also formed as by-products of the cyclization methoxime-based 1-azatrienes.

On the other hand, these experiments revealed that the methoxime largely outperformed the 1,1-dimethylhydrazone when a ketone was employed as the starting carbonyl (entries 10 and 11). However, considerable amounts of the 3,4-dihydro isoquinoline side product were produced in both cases.

Once the model reaction was fully optimized with regards to solvent, temperature and heating mode, the scope and limitations of the transformation were explored with different polysubstituted compounds.

Taking into account that naturally-occurring isoquinolines and related compounds are characterized by their oxygenated functionalities (mainly phenols and phenyl ethers),[1g] the scope of the method was probed by preparing the set of hydrazone precursors shown in Table 4, which also contains details of the outcome of their cyclization.

Table 4. Yields of the different intermediates and the isoquinoline products.[a]



Entry No.	Substitution pattern	Isolated yield [%] 2	3	4	5 (*E*/*Z*)[b]	7	8
1	$R^1 = R^2 = R^3 = H$; $R^4 = OMe$; $R^5 = Me$	93	90	95	90 (82:18)	72	8
2	$R^1 = R^2 = R^3 = R^4 = H$; $R^5 = Me$	94	36	91	89 (80:20)	57	8[c]
3	$R^1 = R^3 = R^4 = H$; $R^2 = OMe$; $R^5 = Me$	96	41	86	85 (80:20)	58	15[d]
4	$R^1 = R^2 = R^4 = H$; $R^3 = OMe$; $R^5 = Me$	84	58	97	88 (78:22)	60	12
5	$R^1 = R^2 = H$; $R^3 = R^4 = OMe$; $R^5 = Me$	91	79	91	93 (90:10)	73	13
6	$R^1 = R^2 = R^3 = R^5 = H$; $R^4 = OMe$	93	90	–	89 (78:22)	48	37
7	$R^1 = R^2 = R^3 = H$; $R^4 = OMe$; $R^5 = iPr$	–	–	–	80[e] (79:21)	65	15
8	$R^1 = R^2 = R^3 = H$; $R^4 = OMe$; $R^5 = Bn$	–	–	–	85[e] (82:18)	64	9[f]
9	$R^1 = R^2 = R^3 = H$; $R^4 = OMe$; $R^5 = MOM$	–	–	–	79[e] (80:20)	70	15
10	$R^1 = R^2 = R^3 = H$; $R^4 = OMe$; $R^5 = Ms$	–	–	–	84[e] (75:25)	60	22[g]
11	$R^1 = R^5 = Me$; $R^2 = R^3 = R^4 = H$	93	44	90	88 (84:16)	5	20[i]
12	$R^1 = R^5 = Me$; $R^2 = R^3 = H$; $R^4 = OMe$	97	87	89	95 (80:20)	3	20[h]

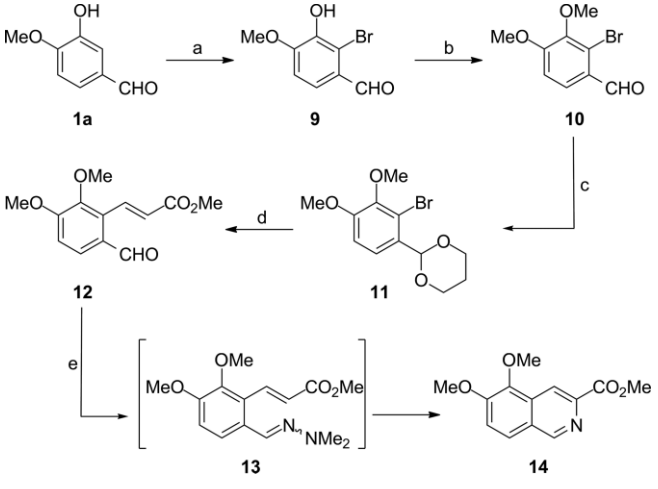
[a] *Reagents and conditions:* a) $BrCH_2CH{=}CH_2$, K_2CO_3, EtOH, Δ; b) 1,2-$Cl_2C_6H_4$, 180 °C; c) MeI, K_2CO_3, EtOH, Δ, or BnCl, K_2CO_3, KI (cat.), EtOH, Δ, or Me_2CHBr, K_2CO_3, KI (cat.), EtOH, Δ, or MOMCl, DIPEA, CH_2Cl_2, room temp., 16 h, or MsCl, pyridine, CH_2Cl_2, room temp., 2 h; d) $RuClH(CO)(PPh_3)_3$ (cat.), PhMe, 80 °C; e) $R^1R^2NNH_2$[h,i], AcOH, $PhCF_3$, room temp.; f) MW, 180 °C. [b] According to ^1H NMR integration. [c] Some starting 1-azatriene (9 %) was recovered. [d] Some starting 1-azatriene (5 %) was recovered. [e] Prepared from phenol **5f**. [f] 8-Benzyl-5-hydroxy-6-methoxy-3-methylisoquinoline (**7h′**) was also isolated in 11 % yield. [g] Compound **7f** (10 %) was also isolated. [h] The hydrazone **6** was formed according to Method A. [i] Some starting material (10 %) was recovered.

Thus, the optimized conditions were applied to similarly prepared 1-azatrienes, carrying aromatic rings functionalized with a free phenol (**6f**), as well as with different ether [Me (**6a–e**), *i*Pr (**6g**), Bn (**6h**)], acetal (MOM, **6i**) and ester moieties. It was observed that the methyl ethers of entries 1–5 gave good to very good isolated yields (57–73 %) of the expected isoquinolines, accompanied by 8–15 % of the related 3,4-dihydroisoquinolines.

On the other hand, the hydrazone derived from phenol **5f** withstood the reaction conditions (entry 6), affording a comparative higher amount of the 3,4-dihydroisoquinoline (37 %) at the expense of a moderate yield of the isoquinoline (48 %).

A similar trend was observed among the other ethers tested (entries 7 and 8), as well as with the MOM and the methanesulfonate derivatives (entries 9 and 10). However, 8-benzyl-5-hydroxy-6-methoxy-3-methylisoquinoline (**7h'**, 11 % yield) was isolated along with the benzyl ethers **7h** and **8h** and the isoquinoline **7f**, the hydrolysis product of methanesulfonate **7j**, was isolated together with the latter (10 % yield). Contrastingly however, the transformation was not satisfactory for the hydrazones derived from ketones (entries 11 and 12).

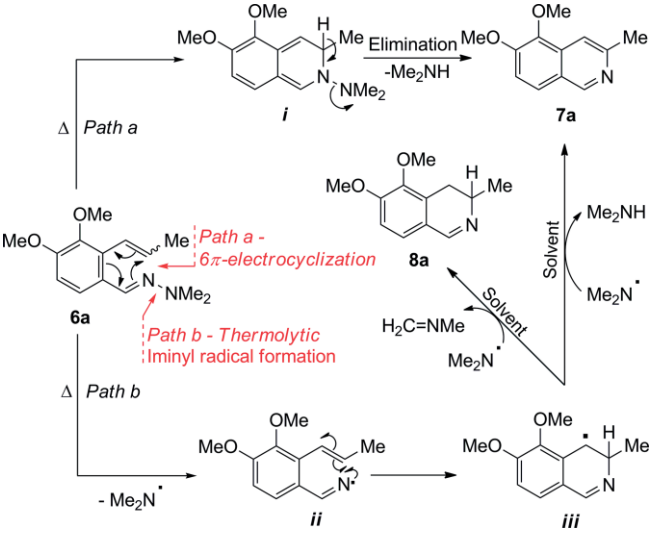
Prompted by these results, the possibility of installing a functionality other than a methyl group on C-3 was explored. To that end, isovanillin (**1a**) was subjected to a selective bromination with NBS (Scheme 3) and the resulting bromophenol **9** was *O*-methylated to furnish **10** in 75 % overall yield.[19a] Next, the formyl moiety of **10** was exposed to propane-1,3-diol and $Ce(OTf)_3$ promotion, employing $(iPrO)_3CH$ as carbonyl activator and water scavenger,[19b,19c] to afford 96 % yield of the 1,3-dioxane derivative **11**.



Scheme 3. *Reagents and conditions:* a) NBS, $CHCl_3$, reflux, 3 h (78 %); b) MeI, K_2CO_3, EtOH, reflux, 5 h (96 %); c) Propane-1,3-diol, $Ce(OTf)_3$, $(iPrO)_3CH$, hexane, room temp., overnight (96 %); d) 1. $H_2C{=}CHCO_2Me$, Et_3N, $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, DMF, 125 °C, 24 h; 2. 2 M HCl, THF, room temp., 4 h (82 %); e) 1. H_2NNMe_2, AcOH, $PhCF_3$, room temp., 5 h; 2. MW, 180 °C, 2 h (10 %).

Then, the latter was subjected to a Heck reaction with methyl acrylate, which furnished the *ortho*-formyl cinnamate **12** in 82 % yield, after mild acid hydrolysis of the protecting group.[19d] One-pot hydrazonation toward **13** and further exposure to thermal cyclization finally gave isoquinoline **14**, albeit in a rather poor 10 % yield, revealing a limitation in the scope of this reaction. This complements others previously found by the group of Hibino.[5a]

Although the exact details of the reaction mechanism remain unknown, a mechanistic picture such as that shown in Scheme 4 can be drawn on the basis of literature precedents.



Scheme 4. Proposed mechanism for the thermal cyclization of **6a** to afford the isoquinoline **7a** and the 3,4-dihydroisoquinoline **8a**.

Under the thermal conditions, the starting *ortho*-propenyl hydrazone **6a** can react along two alternate paths. In *Path a*, the 1-azatriene could undergo the expected 6π-electrocyclization process to afford the intermediate ***i***, which in turn could suffer the elimination of dimethylamine to furnish the isoquinoline **7a**. Dimethylamine has been the by-product in a cyclization/elimination sequence toward carbazoles, as well as in other aromatizations,[20] and has been detected in the reaction medium by its characteristic odour.

This reaction path is likely to involve a classical concerted mechanism, which proceeds in a disrotatory mode. The aromatic ring would ensure the initial *s-cis*-geometry of the azatriene; however, the need to dearomatize the benzenoid ring during the cyclization would turn it into a species with low reactivity, that may favour secondary reactions and conspire against high yields.

The driving force of the last stage should be aromatization, and dimethylamine is the only by-product of the reaction. This is analogous to different oxygen-based leaving groups derived from oximes, which were found to play quite similar roles at the elimination step.[5a]

In the competing *Path b*, the weak *N–N* bond could undergo homolytic cleavage to generate the iminyl radical ***ii***, which could experience an intramolecular ring closure onto the olefinic acceptor of the propenyl moiety to render the dihydropyridinyl-type radical ***iii***. In this case, *6-endo-trig* is the favoured mode of cyclization, probably because this also generates a resonance-stabilized radical.[21a] Somehow, this is conceptually reminiscent to the iminyl radical-mediated synthesis of quinoxalines by gas phase thermolysis of 1,2,5-triazapentadienes; however, the latter process seems to require more strenuous conditions (600 °C and 10^{-2} Torr) and has a lower performance.[21b,21c]

Interestingly, it was previously informed that irradiation of 2-vinylbenzaldehyde *O*-acetyloxime and (*Z*)-1-phenyl-4-hepten-1-one *O*-acetyloxime, enabled the experimental verification that iminyl radicals could evolve through cyclization to form six- or five-membered ring products, respectively, depending on the presence or absence of a phenyl group as a spacer.

In turn, the intermediate ***iii*** could interact with the aminyl radical or with the solvent and either capture H$^{\bullet}$ to afford the 3,4-dihydroisoquinoline **8a** or undergo an H-atom transfer to complete the oxidative cyclization process toward the isoquinoline **7a**.[22] In analogous embodiments, the latter transformation has also been described as a "6π-electron cyclization" process.[23]

In order to get insights into the participation of a radical mechanism, the reaction mixture containing **6a** was treated with 2,6-di-*tert*-butyl-4-methylphenol (BHT, 10 mol-%). It was observed that the presence of this free radical inhibitor affected the production the isoquinoline from 72 % to 65 % yield, whereas access to the related 3,4-dihydroisoquinoline was more drastically reduced from 8 % to 2 % yield. Further, when the semicarbazide derivative (Table 1, entry 4) was employed as starting material, the yields of the isoquinoline changed from 55 % to 24 %, whilst the yields of the 3,4-dihydroisoquinoline dropped drastically from 38 % to 8 %.

These results fully supported the hypothesis that the generation of the 3,4-dihydroisoquinolines is a result of the intervention of a radical-mediated cyclization process. On the other hand, the observed outcome of the experiment also unveiled that, to some extent, the isoquinoline may also have been produced through a radical mechanism.

Accordingly, the by-products of this path are the highly volatile Me_2NH and $H_2C{=}NMe$. The latter proved hard to be detected by GC–MS; however, the related 1,1-dimethyl-2-methylene hydrazine derivative ($H_2C{=}N{-}NMe_2$) was unequivocally observed [m/z = 72 (M^+)] in the presence of a small excess of 1,1-dimethylhydrazine.[24]

Conclusions

We have developed a convenient, efficient and atom-economical one-pot synthesis of 3-methylisoquinolines from *ortho*-formyl β-methylstyrenes, through their sequential hydrazonation with 1,1-dimethylhydrazine in $PhCF_3$, followed by a microwave-assisted cyclization and final elimination with concomitant aromatization.

The scope and limitations of the reaction were examined. It could be performed under conventional heating, but microwaves irradiation reduced substantially the reaction times, providing yields of isoquinolines similar to those obtained when the related methoximes were employed. Further, the transformation is compatible with free phenols and different ethers, as well as with MOM and methanesulfonate protecting groups.

This is the first general example involving the 6π-electron cyclization of 1-azatrienes derived from hydrazones, in which the starting polyene incorporates one double bond belonging to an homocyclic aromatic ring. The use of hydrazones enabled the development of a one-pot process, which cannot be put in place with the related methoximes, providing a simpler alternative to the latter.

In addition, this is the first report on the presence of 3,4-dihydroisoquinolines as side products, for which a mechanism of formation was proposed. Furthermore, it included the first disclosure of the generation of these heterocycles during the cyclization of the more widely used methoxime-derived 1-azatrienes.

The fact that the isoquinolines may also be produced through a radical-mediated process turns convenient to consider this transformation as a 6π-electron cyclization.

These are promising results in the field of the synthesis of isoquinolines, which suggest that the optimized reaction will find wide use in multistep syntheses of more complex molecules, as an alternative or complement to existing methodologies.

Experimental Section

General Information

All the reactions were carried out under anhydrous argon atmospheres, using oven-dried glassware and freshly distilled anhydrous solvents.

Anhydrous EtOH was obtained by reaction of the AR reagent from magnesium chips and iodine, followed by distillation of the solvent from the so formed magnesium ethoxide. Anhydrous DMA, NMP and DMF were prepared by reduced-pressure distillation from BaO. Xylene was distilled from Na^0/benzophenone ketyl. 1,2-Dichlorobenzene was obtained by a 3 h reflux of the AR product over P_2O_5 and further distillation of the product under reduced pressure. The anhydrous solvents were transferred via cannula and stored under argon in dry Young ampoules containing activated 3 Å molecular sieves. All of the other solvents and reagents were used as received.

The reactions were monitored by TLC, using silica gel GF_{254} plates supported on aluminium and run in different hexane/EtOAc or EtOAc/EtOH solvent mixtures. The spots were revealed by exposure to UV light (254 and 365 nm) and spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent, followed by careful heating to improve selectivity; in selected cases, the Dragendorff reagent (Munier and Macheboeuf modification) was used.[25] The flash column chromatography was run with silica gel 60 H (particle size < 55 μm), eluting with hexane/EtOAc and EtOAc/EtOH mixtures, under positive pressure and employing gradient of solvent polarity techniques.

Equipment

The melting points were measured on an Ernst Leitz Wetzlar model 350 hot-stage microscope and are informed uncorrected.

The FT-IR spectra were acquired on a Shimadzu Prestige 21 spectrophotometer, with the samples prepared as solid dispersions in KBr disks or as thin films held between NaCl cells.

The NMR spectroscopic data were recorded in $CDCl_3$ with an FT-NMR Bruker Avance 300 spectrometer at 300.13 MHz (for ^{1}H NMR) and 75.48 MHz (^{13}C NMR). The chemical shifts are reported in ppm on the δ scale. TMS (δ = 0.0 ppm) was used as the internal standard (resonances for $CHCl_3$ in $CDCl_3$ are δ = 7.26 and 77.16 ppm for ^{1}H and ^{13}C NMR, respectively). The magnitude of the coupling constant (J) values are given in Hertz. In special cases, NOE and 2D NMR

experiments (COSY, HSQC, TOCSY and HMBC) were also employed in order to aid unequivocal signal assignment.

The GC–MS experiments were performed with a Shimadzu QP2010*Plus* instrument equipped with an AOC-20i autosampler. The high-resolution mass spectra were obtained from ICYTAC (Córdoba, Argentina) and UMYMFOR (Buenos Aires, Argentina) with Bruker MicroTOF-Q II instruments. Detection of the ions was performed in electrospray ionization, positive ion mode.

The microwave-assisted reactions were carried out in a CEM Discover microwave reactor.

General Procedures for the Sequential Hydrazine Condensation/6π-Electron Cyclization/Elimination toward Isoquinolines

Method A: A mixture of the carbonyl compound **5** (0.8 mmol), 1,1-dimethylhydrazine (64 μL, 0.85 mmol), glacial AcOH (46 μL, 0.8 mmol) and absolute EtOH (1.5 mL) was placed in a microwave tube and stirred at room temperature for 3 h. Anhydrous $MgSO_4$ (30 mg) and activated powdered 3 Å MS (30 mg) were employed for the less reactive substrates. Upon completion of the reaction, assessed by TLC analysis, the solvent was removed under reduced pressure and $PhCF_3$ (1 mL) was added. Argon was bubbled to create a suitable atmosphere and the mixture was irradiated in the microwave reactor (180 °C, ca. 250 W) in 1 h cycles until judged complete by TLC. After cooling to room temperature, the solvent was recovered by distillation, and the oily residue was purified by chromatography to afford the 3-methylisoquinoline (**7a**, **7k** and **7l**) and 3-methyl-3,4-dihydroisoquinoline (**8a**, **8k** and **8l**) products.

Method B: A mixture of the carbonyl compound **5** (0.8 mmol), 1,1-dimethylhydrazine (64 μL, 0.85 mmol) and glacial AcOH (46 μL, 0.8 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 (**7a–j**) and 3-methyl-3,4-dihydroisoquinoline (**8a–j**) products.

5,6-Dimethoxy-3-methylisoquinoline (7a):[26] Yield: 76 % (Method A); 72 % (Method B). Off-white solid, m.p.: 83–85 °C. ^{1}H NMR: δ = 2.69 (s, 3 H, Me), 3.98 (s, 3 H, OMe), 4.02 (s, 3 H, OMe), 7.29 (d, J = 9.1 Hz, 1 H, 7-H), 7.69 (br. s, 1 H, 4-H), 7.70 (d, J = 9.1 Hz, 1 H, 8-H) and 9.06 (s, 1 H, 1-H) ppm. ^{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) ppm. GC–MS: *m/z* (rel. int. %): 203 [M$^+$, 72], 188 (57), 160 (100), 145 (47), 117 (38), 89 (40) and 76 (41).

5-Methoxy-3-methylisoquinoline (7b): Yield 57 % (Method B). Light brown solid; m.p.: < 40 °C. IR (KBr): $\tilde{\nu}$ = 3057, 2935, 2837, 1589, 1429, 1465, 1330, 1282, 1199, 1003, 989, 879 and 752 cm^{-1}. ^{1}H NMR: δ = 2.70 (s, 3 H, Me), 3.98 (s, 3 H, OMe), 6.93 (d, J = 7.5 Hz, 1 H, 6-H), 7.39 (t, J = 8.0 Hz, 1 H, 7-H), 7.48 (d, J = 8.0 Hz, 1 H, 8-H), 7.82 (d, J = 0.7 Hz, 1 H, 4-H) and 9.11 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 24.4 (Me), 55.6 (OMe), 107.5 (C-6), 113.0 (C-4), 119.4 (C-8), 126.3 (C-7), 127.6 (C-8a), 129.2 (C-4a), 151.4 (C-1), 151.5 (C-3) and 154.1 (C-5) ppm. HRMS (ESI-TOF): Found *m/z*: 174.0919. $C_{11}H_{12}NO$ ([M + H]$^+$) requires *m/z*: 174.0919.

5,8-Dimethoxy-3-methylisoquinoline (7c):[26b,27] Yield: 58 % (Method B). Yellow oil. ^{1}H NMR: δ = 2.70 (s, 3 H, Me), 3.93 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 6.65 (d, J = 8.4 Hz, 1 H, 6-H), 6.82 (d, J = 8.4 Hz, 1 H, 7-H), 7.76 (br. s, 1 H, 4-H) and 9.46 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 24.5 (Me), 55.8 (OMe), 55.9 (OMe), 103.3 (C-6), 107.6 (C-7), 112.8 (C-4), 119.5 (C-4a), 130.1 (C-8a), 146.8 (C-1), 148.0 (C-5), 150.4 (C-8) and 152.3 (C-3) ppm.

5,7-Dimethoxy-3-methylisoquinoline (7d): Yield: 60 % (Method B). Brownish solid, m.p.: 52–54 °C. IR (KBr): $\tilde{\nu}$ = 2997, 2935, 2833, 1595, 1458, 1340, 1205, 1155, 1043, 999, 937 and 839 cm^{-1}. ^{1}H NMR: δ = 2.66 (s, 3 H, Me), 3.91 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 6.60 (d, J = 2.1 Hz, 1 H, 6-H), 6.75 (d, J = 2.1 Hz, 1 H, 8-H), 7.72 (br. s, 1 H, 4-H) and 9.0 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 24.2 (Me), 55.6 (OMe), 55.8 (OMe), 96.5 (C-8), 101.5 (C-6), 113.2 (C-4), 125.7 (C-8a), 128.2 (C-4a), 149.6 (C-3), 150.0 (C-1), 155.4 (C-5) and 158.4 (C-7) ppm. HRMS (ESI-TOF): Found *m/z*: 204.1025. $C_{12}H_{14}NO_2$ ([M + H]$^+$) requires *m/z*: 204.1025.

5,6,7-Trimethoxy-3-methylisoquinoline (7e): Yield: 73 % (Method B). Colorless solid, m.p.: 63–65 °C. IR (KBr): $\tilde{\nu}$ = 2987, 2945, 2833, 1595, 1489, 1307, 1244, 1103, 1039, 999, 867 and 715 cm^{-1}. ^{1}H NMR: δ = 2.66 (s, 3 H, Me), 3.97 (s, 3 H, OMe), 3.99 (s, 3 H, OMe), 4.02 (s, 3 H, OMe), 6.99 (s, 1 H, 8-H), 7.62 (s, 1 H, 4-H) and 8.98 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 24.2 (Me), 56.1 (OMe), 61.3 (OMe), 61.5 (OMe), 101.5 (C-8), 112.7 (C-4), 124.0 (C-4a), 128.5 (C-8a), 144.4 (C-7), 146.3 (C-5), 149.8 (C-1), 149.9 (C-3) and 153.2 (C-6) ppm. HRMS (ESI-TOF): Found *m/z*: 234.1119. $C_{13}H_{16}NO_3$ ([M + H]$^+$) requires *m/z*: 234.1130.

5-Hydroxy-6-methoxy-3-methylisoquinoline (7f): Yield: 48 % (Method B). Whitish solid, m.p.: 156–158 °C. IR (KBr): $\tilde{\nu}$ = 2991, 2937, 2839, 1624, 1595, 1489, 1332, 1271, 1114, 1062, 943, 871, 777 and 696 cm^{-1}. ^{1}H NMR: δ = 2.69 (s, 3 H, Me), 3.98 (s, 3 H, OMe), 7.26 (d, J = 8.9 Hz, 1 H, 7-H), 7.50 (d, J = 8.9 Hz, 1 H, 8-H), 7.77 (q, J = 0.7 Hz, 1 H, 4-H) and 9.05 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 24.3 (Me), 55.8 (OMe), 112.3 (C-4), 113.2 (C-7), 119.9 (C-8), 123.0 (C-8a), 127.6 (C-4a), 138.5 (C-5), 144.7 (C-6), 150.6 (C-3) and 151.5 (C-1) ppm. HRMS (ESI-TOF): Found *m/z*: 190.0861. $C_{11}H_{12}NO_2$ ([M + H]$^+$) requires *m/z*: 190.0868.

5-Isopropoxy-6-methoxy-3-methylisoquinoline (7g): Yield: 65 % (Method B). Light amber oil. IR (NaCl): $\tilde{\nu}$ = 2974, 2929, 2841, 1624, 1593, 1487, 1381, 1263, 1107, 1058, 929, 873, 777 and 692 cm^{-1}. ^{1}H NMR: δ = 1.35 (d, J = 6.2 Hz, 6 H, OCH*Me*$_2$), 2.68 (s, 3 H, Me), 3.98 (s, 3 H, OMe), 4.62 (sept, J = 6.2 Hz, 1 H, OC*H*Me$_2$), 7.28 (d, J = 9.0 Hz, 1 H, 7-H), 7.67 (d, J = 9.0 Hz, 1 H, 8-H), 7.70 (q, J = 0.7 Hz, 1 H, 4-H) and 9.04 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 22.8 (OCH*Me*$_2$), 24.6 (Me), 56.6 (OMe), 75.5 (OCHMe$_2$), 112.9 (C-4), 114.8 (C-7), 123.2 (C-8a), 124.0 (C-8), 133.8 (C-4a), 139.1 (C-5), 151.4 (C-3), 151.6 (C-1) and 151.9 (C-6) ppm. HRMS (ESI-TOF): Found *m/z*: 232.1334. $C_{14}H_{18}NO_2$ ([M + H]$^+$) requires *m/z*: 232.1338.

5-(Benzyloxy)-6-methoxy-3-methylisoquinoline (7h): Yield: 64 % (Method B). Whitish solid, m.p.: 79–81 °C. IR (KBr): $\tilde{\nu}$ = 3033, 2922, 2843, 1618, 1589, 1485, 1311, 1261, 1107, 1056, 974, 808, 732 and 696 cm^{-1}. ^{1}H NMR: δ = 2.64 (s, 3 H, Me), 4.02 (s, 3 H, OMe), 5.15 (s, 2 H, PhC*H*$_2$O), 7.31 (d, J = 9.0 Hz, 1 H, 7-H), 7.33–7.44 (m, 3 H, Ar*H*), 7.52 (dd, J = 1.7 and 8.0 Hz, 2 H, Ar*H*), 7.64 (q, J = 0.8 Hz, 1 H, 4-H), 7.71 (d, J = 9.0 Hz, 1 H, 8-H) and 9.05 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 24.5 (Me), 56.7 (OMe), 75.4 (PhCH$_2$O), 112.4 (C-4), 114.8 (C-7), 123.2 (C-8a), 124.6 (C-8), 128.2 (Ar*C*), 128.4 (Ar*C*), 128.6 (Ar*C*), 132.9 (C-4a), 137.6 (Ar*C*), 139.9 (C-5), 151.6 (C-3), 151.7 (C-1) and 151.8 (C-6) ppm. HRMS (ESI-TOF): Found *m/z*: 280.1340. $C_{18}H_{18}NO_2$ ([M + H]$^+$) requires *m/z*: 280.1338.

8-Benzyl-5-hydroxy-6-methoxy-3-methylisoquinoline (7h′): Yield 11 % (Method B). Pale brownish solid, m.p.: 159–161 °C. IR (KBr): $\tilde{\nu}$ = 3020, 2918, 2841, 1618, 1597, 1456, 1361, 1242, 1147, 1068, 958, 860, 733 and 658 cm^{-1}. ^{1}H NMR: δ = 2.66 (s, 3 H, Me), 3.96 (s, 3 H, OMe), 4.45 (s, 2 H, PhC*H*$_2$O), 7.05 (s, 1 H, 7-H), 7.13–7.29

(m, 5 H, Ar*H*), 7.66 (br. s, 1 H, 4-H) and 9.23 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 24.3 (Me), 38.1 (Ph*C*H$_2$O), 56.8 (OMe), 112.6 (C-4), 114.6 (C-7), 121.1 (C-8a), 126.4 (Ar*C*), 128.2 (C-4a), 128.6 (Ar*C*), 128.7 (Ar*C*), 130.6 (C-8), 137.0 (C-5), 140.4 (Ar*C*), 143.8 (C-6), 148.8 (C-1) and 150.7 (C-3) ppm. HRMS (ESI-TOF): Found *m/z*: 280.1326. $C_{18}H_{18}NO_2$ ([M + H]$^+$) requires *m/z*: 280.1338.

6-Methoxy-5-(methoxymethoxy)-3-methylisoquinoline (7i): Yield: 70 % (Method B). Whitish solid, m.p.: 53–55 °C. IR (KBr): $\tilde{\nu}$ = 2997, 2984, 2845, 1625, 1595, 1489, 1381, 1265, 1165, 1076, 962, 873, 779 and 696 cm^{-1}. ^{1}H NMR: δ = 2.69 (s, 3 H, Me), 3.64 (s, 3 H, OCH$_2$O*Me*), 3.99 (s, 3 H, OMe), 5.28 (s, 2 H, OC*H*$_2$OMe), 7.30 (d, *J* = 9.0 Hz, 1 H, 7-H), 7.72 (d, *J* = 9.0 Hz, 1 H, 8-H), 7.74 (q, *J* = 0.7 Hz, 1 H, 4-H) and 9.06 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 24.6 (Me), 56.6 (OMe), 57.9 (OCH$_2$O*Me*), 99.1 (O*C*H$_2$OMe), 112.3 (C-4), 114.6 (C-7), 123.2 (C-8a), 124.9 (C-8), 133.08 (C-4a), 137.9 (C-5), 151.4 (C-6), 151.7 (C-1) and 151.8 (C-3) ppm. HRMS (ESI-TOF): Found *m/z*: 234.1134. $C_{13}H_{16}NO_3$ ([M + H]$^+$) requires *m/z*: 234.1130.

6-Methoxy-3-methylisoquinolin-5-yl methanesulfonate (7j): Yield: 60 % (Method B). Whitish solid, m.p.: 156–158 °C. IR (KBr): $\tilde{\nu}$ = 3043, 3005, 2924, 2846, 1633, 1597, 1492, 1342, 1267, 1168, 1097, 985, 898, 781 and 626 cm^{-1}. ^{1}H NMR: δ = 2.71 (s, 3 H, Me), 3.43 (s, 3 H, OSO$_2$*Me*), 4.06 (s, 3 H, OMe), 7.34 (d, *J* = 9.0 Hz, 1 H, 7-H), 7.71 (q, *J* = 0.7 Hz, 1 H, 4-H), 7.90 (d, *J* = 9.0 Hz, 1 H, 8-H) and 9.09 (s, 1 H, 1-H) ppm. ^{13}C NMR: δ = 24.8 (Me), 40.0 (OSO$_2$*Me*), 56.7 (OMe), 112.0 (C-4), 113.7 (C-7), 122.8 (C-8a), 128.6 (C-8), 131.1 (C-5), 133.0 (C-4a), 151.5 (C-1), 151.8 (C-6) and 153.6 (C-3) ppm. HRMS (ESI-TOF): Found *m/z*: 268.0642. $C_{12}H_{14}NO_4S$ ([M + H]$^+$) requires *m/z*: 268.0644.

5-Methoxy-1,3-dimethylisoquinoline (7k):[28] Yield: 5 % (Method A). Amber oil. ^{1}H NMR: δ = 2.67 (s, 3 H, 3-Me), 2.92 (s, 3 H, 1-Me), 4.0 (s, 3 H, OMe), 6.95 (d, *J* = 7.7 Hz, 1 H, 6-H), 7.41 (t, *J* = 8.2 Hz, 1 H, 7-H), 7.64 (d, *J* = 8.6 Hz, 1 H, 8-H) and 7.74 (s, 1 H, 4-H) ppm. ^{13}C NMR: δ = 22.8 (1-Me), 24.5 (3-Me), 55.7 (OMe), 107.2 (C-6), 111.5 (C-4), 117.6 (C-8), 125.9 (C-7), 126.4 (C-8a), 129.4 (C-4a), 150.7 (C-3), 154.6 (C-5) and 157.5 (C-1) ppm.

5,6-Dimethoxy-1,3-dimethylisoquinoline (7l):[26b,28a] Yield: 3 % (Method A). Pinkish oil. ^{1}H NMR: δ = 2.65 (s, 3 H, 3-Me), 2.89 (s, 3 H, 1-Me), 3.96 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 7.26 (d, *J* = 9.2 Hz, 1 H, 7-H), 7.59 (s, 1 H, 4-H) and 7.84 (dd, *J* = 1.0 and 9.2 Hz, 1 H, 8-H) ppm. ^{13}C NMR: δ = 22.5 (1-Me), 24.7 (3-Me), 56.6 (OMe), 61.2 (OMe), 110.8 (C-4), 114.0 (C-7), 121.9 (C-8a), 122.6 (C-8), 132.8 (C-4a), 141.5 (C-5), 150.6 (C-3), 151.3 (C-6) and 157.9 (C-1) ppm.

5,6-Dimethoxy-3-methyl-3,4-dihydroisoquinoline (8a):[26b] Yield: 6 % (Method A); 8 % (Method B). Amber oil. ^{1}H NMR: δ = 1.40 (d, *J* = 6.8 Hz, 3 H, Me), 2.39 (dd, *J* = 11.8 and 16.5 Hz, 1 H, 4-H$_A$), 2.97 (dd, *J* = 5.7 and 16.5 Hz, 1 H, 4-H$_B$), 3.56–3.69 (m, 1 H, 3-H), 3.80 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 6.80 (d, *J* = 8.2 Hz, 1 H, 7-H), 7.05 (d, *J* = 8.2 Hz, 1 H, 8-H) and 8.21 (d, *J* = 2.6 Hz, 1 H, 1-H) ppm. ^{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) ppm. GC–MS: *m/z* (rel. int. %): 205 [M$^+$, 85], 190 (100), 175 (13), 146 (13), 117 (6), 91 (13) and 77 (12).

5-Methoxy-3-methyl-3,4-dihydroisoquinoline (8b): Yield 8 % (Method B). Amber brown oil. IR (NaCl): $\tilde{\nu}$ = 3001, 2960, 2837, 1633, 1573, 1469, 1315, 1261, 1112, 1045, 966, 777 and 666 cm^{-1}. ^{1}H NMR: δ = 1.41 (d, *J* = 6.8 Hz, 3 H, Me), 2.32 (dd, *J* = 12.1 and 16.8 Hz, 1 H, 4-H$_A$), 2.95 (dd, *J* = 6.3 and 16.8 Hz, 1 H, 4-H$_B$), 3.59–3.73 (m, 1 H, 3-H), 3.85 (s, 3 H, OMe), 6.93 (d, *J* = 7.5 Hz, 1 H, 8-H), 6.94 (d, *J* = 8.0 Hz, 1 H, 6-H), 7.26 (t, *J* = 8.0 Hz, 1 H, 7-H), and 8.28 (d, *J* = 2.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 22.1 (Me), 25.5 (C-4), 52.3 (C-3), 55.7 (OMe), 113.3 (C-6), 119.8 (C-8), 124.4 (C-4a), 127.5 (C-7), 129.0 (C-8a), 156.0 (C-5) and 159.3 (C-1) ppm. HRMS (ESI-TOF): Found *m/z*: 176.1076. $C_{11}H_{14}NO$ ([M + H]$^+$) requires *m/z*: 176.1075.

5,8-Dimethoxy-3-methyl-3,4-dihydroisoquinoline (8c):[26b] Yield: 15 % (Method B). Light amber oil. ^{1}H NMR: δ = 1.40 (d, *J* = 6.8 Hz, 3 H, Me), 2.25 (dd, *J* = 12.5 and 16.8 Hz, 1 H, 4-H$_A$), 2.90 (dd, *J* = 5.9 and 16.8 Hz, 1 H, 4-H$_B$), 3.50–3.64 (m, 1 H, 3-H), 3.80 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 6.72 (d, *J* = 8.9 Hz, 1 H, 6-H), 6.88 (d, *J* = 8.9 Hz, 1 H, 7-H) and 8.67 (d, *J* = 2.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 22.1 (Me), 25.9 (C-4), 51.6 (C-3), 56.0 (OMe), 56.2 (OMe), 109.1 (C-6), 114.1 (C-7), 117.8 (C-8a), 126.5 (C-4a), 149.9 (C-5), 151.6 (C-8) and 154.8 (C-1) ppm.

5,7-Dimethoxy-3-methyl-3,4-dihydroisoquinoline (8d): Yield: 12 % (Method B). Amber oil. IR (NaCl): $\tilde{\nu}$ = 2956, 2920, 2848, 1598, 1595, 1458, 1319, 1203, 1151, 1049, 908 and 839 cm^{-1}. ^{1}H NMR: δ = 1.40 (d, *J* = 6.8 Hz, 3 H, Me), 2.25 (dd, *J* = 12.2 and 16.5 Hz, 1 H, 4-H$_A$), 2.86 (dd, *J* = 6.2 and 16.5 Hz, 1 H, 4-H$_B$), 3.59–3.69 (m, 1 H, 3-H), 3.82 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 6.46 (d, *J* = 2.1 Hz, 1 H, 6-H), 6.86 (d, *J* = 2.1 Hz, 1 H, 8-H) and 8.23 (d, *J* = 2.8 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 22.2 (Me), 25.1 (C-4), 52.8 (C-3), 55.7 (2 × OMe), 101.4 (C-8), 103.2 (C-6), 117.0 (C-4a), 129.2 (C-8a), 157.7 (C-5), 159.2 (C-1) and 159.7 (C-7) ppm. HRMS (ESI-TOF): Found *m/z*: 206.1167. $C_{12}H_{16}NO_2$ ([M + H]$^+$) requires *m/z*: 206.1181.

5,6,7-Trimethoxy-3-methyl-3,4-dihydroisoquinoline (8e): Yield: 13 % (Method B). Amber oil. IR (NaCl): $\tilde{\nu}$ = 2962, 2929, 2846, 1598, 1573, 1415, 1330, 1244, 1120, 1031, 991 and 831 cm^{-1}. ^{1}H NMR: δ = 1.40 (d, *J* = 6.8 Hz, 3 H, Me), 2.32 (dd, *J* = 12.1 and 16.5 Hz, 1 H, 4-H$_A$), 2.87 (dd, *J* = 5.8 and 16.5 Hz, 1 H, 4-H$_B$), 3.55–3.70 (m, 1 H, 3-H), 3.85 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 6.66 (s, 1 H, 8-H) and 8.20 (d, *J* = 2.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 22.9 (Me), 25.7 (C-4), 52.2 (C-3), 56.3 (OMe), 61.0 (OMe), 61.1 (OMe), 107.1 (C-8), 122.5 (C-8a), 123.8 (C-4a), 145.0 (C-6), 150.5 (C-5), 152.4 (C-7) and 158.7 (C-1) ppm. HRMS (ESI-TOF): Found *m/z*: 236.1290. $C_{13}H_{18}NO_3$ ([M + H]$^+$) requires *m/z*: 236.1287.

5-Hydroxy-6-Methoxy-3-methyl-3,4-dihydroisoquinoline (8f): Yield: 37 % (Method B). Light brown solid, m.p.: 146–148 °C. IR (KBr): $\tilde{\nu}$ = 3110, 2964, 2854, 1608, 1578, 1490, 1332, 1273, 1138, 1089, 947, 837 and 788 cm^{-1}. ^{1}H NMR: δ = 1.40 (d, *J* = 6.8 Hz, 3 H, Me), 2.40 (dd, *J* = 11.5 and 16.5 Hz, 1 H, 4-H$_A$), 2.98 (dd, *J* = 6.0 and 16.5 Hz, 1 H, 4-H$_B$), 3.61–3.73 (m, 1 H, 3-H), 3.92 (s, 3 H, OMe), 5.26 (br. s, 1 H, OH), 6.76 (d, *J* = 8.2 Hz, 1 H, 7-H), 6.87 (d, *J* = 8.2 Hz, 1 H, 8-H) and 8.23 (d, *J* = 2.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 21.6 (Me), 25.9 (C-4), 51.4 (C-3), 56.1 (OMe), 108.3 (C-7), 120.8 (C-8), 121.7 (C-4a), 122.1 (C-8a), 142.3 (C-5), 149.5 (C-6) and 159.5 (C-1) ppm. HRMS (ESI-TOF): Found *m/z*: 192.1012. $C_{11}H_{14}NO_2$ ([M + H]$^+$) requires *m/z*: 192.1025.

5-Isopropoxy-6-methoxy-3-methyl-3,4-dihydroisoquinoline (8g): Yield: 15 % (Method B). Amber oil. IR (NaCl): $\tilde{\nu}$ = 2970, 2926, 2843, 1625, 1570, 1487, 1379, 1274, 1109, 1089, 924 and 801 cm^{-1}. ^{1}H NMR: δ = 1.26 (d, *J* = 6.2 Hz, 3 H, OCH*Me*$_2$), 1.29 (d, *J* = 6.2 Hz, 3 H, OCH*Me*$_2$), 1.37 (d, *J* = 6.8 Hz, 3 H, Me), 2.37 (dd, *J* = 11.2 and 16.2 Hz, 1 H, 4-H$_A$), 2.96 (dd, *J* = 6.0 and 16.2 Hz, 1 H, 4-H$_B$), 3.54–3.68 (m, 1 H, 3-H), 3.87 (s, 3 H, OMe), 4.41 (sept, *J* = 6.2 Hz, 1 H, OC*H*Me$_2$), 6.79 (d, *J* = 8.2 Hz, 1 H, 7-H), 7.02 (d, *J* = 8.2 Hz, 1 H, 8-H) and 8.20 (d, *J* = 2.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 22.0 (3-Me), 22.6 (OCH*Me*$_2$), 22.7 (OCH*Me*$_2$), 27.2 (C-4), 52.2 (C-3), 55.8 (OMe), 75.0 (O*C*HMe$_2$), 109.7 (C-7), 122.5 (C-4a), 123.6 (C-8), 130.8 (C-8a), 143.5 (C-5), 155.5 (C-6) and 158.9 (C-1) ppm. HRMS (ESI-TOF): Found *m/z*: 234.1481. $C_{14}H_{20}NO_2$ ([M + H]$^+$) requires *m/z*: 234.1494.

5-(Benzyloxy)-6-methoxy-3-methyl-3,4-dihydroisoquinoline (8h): Yield 9 % (Method B). Amber oil. IR (NaCl): $\tilde{\nu}$ = 3130, 2962, 2854, 1622, 1568, 1487, 1315, 1276, 1167, 1089, 976, 805, 742 and

698 cm^{-1}. ^1H NMR: δ = 1.28 (d, J = 6.8 Hz, 3 H, Me), 2.22 (dd, J = 11.5 and 16.5 Hz, 1 H, 4-H_A), 2.79 (dd, J = 5.7 and 16.5 Hz, 1 H, 4-H_B), 3.41–3.53 (m, 1 H, 3-H), 3.92 (s, 3 H, OMe), 4.99 (s, 2 H, PhCH_2O), 6.83 (d, J = 8.2 Hz, 1 H, 7-H), 7.05 (d, J = 8.2 Hz, 1 H, 8-H), 7.32–7.44 (m, 5 H, Ar*H*) and 8.18 (d, J = 2.8 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 21.9 (Me), 26.7 (C-4), 52.0 (C-3), 55.9 (OMe), 74.9 (PhCH_2O), 109.8 (C-7), 122.5 (C-8a), 124.2 (C-8), 128.3 (Ar*C*), 128.5 (Ar*C*), 128.7 (Ar*C*), 130.6 (C-4a), 137.4 (Ar*C*), 144.2 (C-5), 155.3 (C-6) and 159.8 (C-1) ppm. HRMS (ESI-TOF): Found m/z: 282.1494. $C_{18}H_{20}NO_2$ ([M + H]$^+$) requires m/z: 282.1494.

6-Methoxy-5-(methoxymethoxy)-3-methyl-3,4-dihydroisoquinoline (8i): Yield: 15 % (Method B). Amber oil. IR (NaCl): $\tilde{\nu}$ = 2960, 2926, 2843, 1624, 1570, 1489, 1273, 1157, 1068, 960 and 804 cm^{-1}. ^1H NMR: δ = 1.39 (d, J = 6.8 Hz, 3 H, Me), 2.43 (dd, J = 11.5 and 16.5 Hz, 1 H, 4-H_A), 3.02 (dd, J = 5.8 and 16.5 Hz, 1 H, 4-H_B), 3.57 (s, 3 H, OCH$_2$O*Me*), 3.55–3.71 (m, 1 H, 3-H), 3.88 (s, 3 H, OMe), 5.07 (d, J = 6.0 Hz, 1 H, OCH_2OMe), 5.10 (d, J = 6.0 Hz, 1 H, OCH_2OMe), 6.81 (d, J = 8.2 Hz, 1 H, 7-H), 7.06 (d, J = 8.2 Hz, 1 H, 8-H) and 8.21 (d, J = 2.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 22.0 (Me), 27.0 (C-4), 52.1 (C-3), 55.9 (OMe), 57.6 (OCH$_2$O*Me*), 98.8 (OCH$_2$OMe), 109.8 (C-7), 122.5 (C-8a), 124.4 (C-8), 130.5 (C-4a), 142.7 (C-5), 154.7 (C-6) and 158.7 (C-1) ppm. HRMS (ESI-TOF): Found m/z: 236.1285. $C_{13}H_{18}NO_3$ ([M + H]$^+$) requires m/z: 236.1287.

6-Methoxy-3-methyl-3,4-dihydroisoquinolin-5-yl methanesulfonate (8j): Yield: 22 % (Method B). Amber oil. IR (NaCl): $\tilde{\nu}$ = 3015, 2927, 2846, 1625, 1568, 1494, 1359, 1282, 1174, 1080, 972, 852, 736 and 692 cm^{-1}. ^1H NMR: δ = 1.39 (d, J = 6.9 Hz, 3 H, Me), 2.53 (dd, J = 11.3 and 16.7 Hz, 1 H, 4-H_A), 3.03 (dd, J = 5.8 and 16.7 Hz, 1 H, 4-H_B), 3.32 (s, 3 H, OSO$_2$*Me*), 3.63–3.74 (m, 1 H, 3-H), 3.93 (s, 3 H, OMe), 6.89 (d, J = 8.3 Hz, 1 H, 7-H), 7.23 (d, J = 8.3 Hz, 1 H, 8-H) and 8.24 (d, J = 2.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 21.7 (Me), 27.3 (C-4), 39.8 (OSO$_2$*Me*), 51.7 (C-3), 56.2 (OMe), 110.2 (C-7), 122.7 (C-8a), 127.2 (C-8), 132.6 (C-4a), 136.1 (C-5), 153.9 (C-6) and 157.8 (C-1) ppm. HRMS (ESI-TOF): Found m/z: 270.0786. $C_{12}H_{16}NO_4S$ ([M + H]$^+$) requires m/z: 270.0800.

5-Methoxy-1,3-dimethyl-3,4-dihydroisoquinoline (8k):[29] Yield: 20 % (Method A). Amber brown oil. ^1H NMR: δ = 1.39 (d, J = 6.8 Hz, 3 H, 3-Me), 2.23 (dd, J = 12.7 and 16.5 Hz, 1 H, 4-H_A), 2.38 (d, J = 2.1 Hz, 3 H, 1-Me), 2.94 (dd, J = 5.6 and 16.5 Hz, 1 H, 4-H_B), 3.41–3.53 (m, 1 H, 3-H), 3.85 (s, 3 H, OMe), 6.95 (d, J = 8.0 Hz, 1 H, 6-H), 7.13 (d, J = 7.6 Hz, 1 H, 8-H) and 7.25 (t, J = 8.0 Hz, 1 H, 7-H) ppm. ^{13}C NMR: δ = 22.4 (3-Me), 23.8 (1-Me), 26.1 (C-4), 51.6 (C-3), 55.7 (OMe), 112.6 (C-6), 117.9 (C-8), 125.8 (C-4a), 127.0 (C-7), 130.2 (C-8a), 156.0 (C-5) and 163.5 (C-1) ppm.

5,6-Dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline (8l):[26b] Yield: 20 % (Method A). Amber brown oil. ^1H NMR: δ = 1.38 (d, J = 6.8 Hz, 3 H, 3-Me), 2.31 (dd, J = 12.1 and 16.1 Hz, 1 H, 4-H_A), 2.36 (d, J = 1.9 Hz, 3 H, 1-Me), 2.97 (dd, J = 5.3 and 16.1 Hz, 1 H, 4-H_B), 3.41–3.56 (m, 1 H, 3-H), 3.80 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 6.79 (d, J = 8.5 Hz, 1 H, 7-H) and 7.26 (d, J = 8.5 Hz, 1 H, 8-H) ppm. ^{13}C NMR: δ = 22.3 (3-Me), 23.4 (1-Me), 27.1 (C-4), 51.6 (C-3), 55.8 (OMe), 60.7 (OMe), 109.4 (C-7), 122.2 (C-8), 123.5 (C-8a), 13.4 (C-4a), 145.4 (C-5), 154.6 (C-6) and 163.1 (C-1) ppm.

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