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Clean and atom-economic synthesis of octahydroacridines: application to essential oil of citronella

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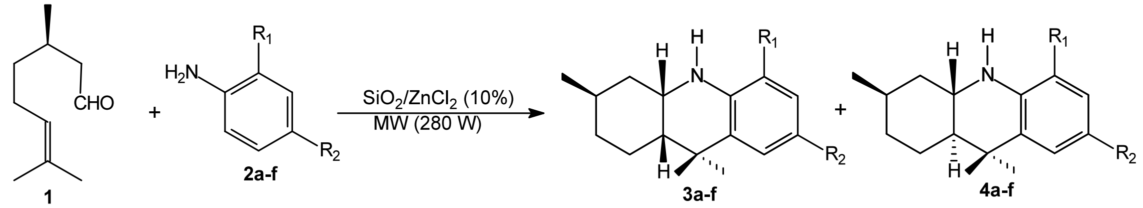
Abstract—A green and efficient method for the synthesis of octahydroacridine (OHA) has been developed by a simple one-pot hetero-Diels–Alder reaction starting from (+)-citronellal and *N*-arylamines in the presence of a solid supported catalyst ($SiO_2/ZnCl_2$), under MW irradiation and without any solvent. The method was used in the direct preparation of OHA from citronella oil in good yield.

The Lewis acid-catalyzed intramolecular reaction of *N*-arylimines with non-activated alkenes, formally a hetero-Diels–Alder reaction of a 2-azadiene, is a powerful synthetic tool for the constructing of nitrogen containing six-membered heterocycles.[1] This efficient protocol have been used during the synthesis of several substituted tetrahydroquinolines[2] and octahydroacridine (OHA) derivatives.[3] Among the OHAs derivatives, 1,2,3,4,4a,9,9a,10-octahydroacridines is a class of compounds with pharmacological interest, acting as a gastric acid secretion inhibitors.[4]

Besides the number of different methods that have been described for constructing the OHA skeleton, such as the acid-catalyzed isophorone-aniline condensation,[5] Beckmann rearrangement of oxime sulfonate,[6] catalytic hydrogenation of acridine,[7] amino-Claisen rearrangement of geranyl aniline,[8] the imine-Diels–Alder reaction catalyzed by a Lewis acid is the most atom-economic, furnishing the OHAs in high yields and, in some cases, with 100% of stereoselectivity.[3] This high atom efficient method is useful for the preparation of OHAs with a variety of substituent patterns just by choosing suitable aldehyde and aniline precursors. However, this reaction show some disadvantages, such as, the long reaction time (12 h to several days), use of low temperatures (−78°C), inert atmosphere, hazardous organic solvent and expensive Lewis acid. The use of molecular sieves[3b] and $BiCl_3$[3e] as cyclization promoters have solved some of these drawbacks, such as, allowing the reaction to be performed at room temperature or 0°C. Unfortunately, these improvements have not eliminated the use of organic solvents and longer reaction times (24 h at rt) and energy (0°C) is still demanded. These aspects are in disagreement with the clean chemistry, especially with respect to the # 5 and # 6 green chemistry principles that refer to the elimination of hazardous solvents and energy efficiency.[9]



Scheme 1.

Keywords: microwave irradiation; solvent-free reaction; octahydroacridine derivatives.

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During the last years a large number of papers have been advocating the advantages of 'MORE Chemistry' (microwave oven-induced reaction enhancement) as an effective green technique in organic synthesis.[10,11] Several reactions under MW showed dramatic increasing in yield, rate and purity of products. Of particular interest are the MW solventless reaction techniques using supported reagents.[11] This technology provides enhanced reaction rates, safety, ease of manipulation and greater selectivity. This kind of protocol have been recently used in the synthesis of several *N*-containing heterocycles.[12]

We have recently described a very simple and eco-friendly procedure for the preparation of (−)-isopulegol by cyclization of (+)-citronellal in the presence of a solid supported catalyst, under solvent-free conditions and MW irradiation.[13] We found that the reaction was clean, fast and highly selective, with results comparable to the best employed conventional methods. Herein, we describe an additional use of this protocol, involving (+)-citronellal (**1**) and amines **2** for the synthesis of 1,2,3,4,4a,9,9a,10-octahydroacridines **3** and **4**, by hetero-Diels–Alder reaction (Scheme 1, Table 2).

Our initial efforts were made towards the determination of the optimum conditions to perform the protocol. Thus, we chose aniline, **2a** ($R_1=R_2=H$) to establish the best conditions for the hetero-Diels–Alder reaction with citronellal (**1**) (Scheme 1, Table 1).

We examined the reaction time, amount of $SiO_2/ZnCl_2$ (10%) and MW power.[14,15] It was found that using $SiO_2/ZnCl_2$ (0.120 g) under 280 W (Method A, Table 1), the reaction proceeded slowly, with 65 and 70% yield after irradiation for 0.5 and 2 min, respectively (Table 1, entries 1 and 2). However, irradiation for 3 min led to the desired OHAs **3a** and **4a** in excellent yield (Table 1, entry 3). The use of 0.060 g of $SiO_2/ZnCl_2$ furnished only 50% yield of OHAs, while 0.180 g of the catalytic system has not significantly increased the OHAs yields. When the same protocol was performed at reduced MW power, it was observed incomplete consumption of the starting materials. At higher MW power there has been no significant increasing in yields and decomposition of reagents and products was observed.

Table 1. Optimization of the reaction time of citronellal (**1**) with aniline **2a** ($R_1=R_2=H$) under MW or conventional heating

Entry	Method[a]	Reaction time (min)	Yield (%)
1	A	0.5	65
2	A	2	70
3	A	3	78
4	B	3	33
5	B	5	37
6	B	30	48
7	B	80	79

[a] Method A: The experiments were performed at 280 W. Method B: The reaction mixture was heated at 40–45°C using an oil bath.[15]

When the mixture of citronellal (**1**) and aniline **2a** was submitted to cyclization under MW (10 min) or room temperature for 24 h in the absence of supported catalyst, no reaction took place in all conditions tested. By using only SiO_2, reaction occurs smoothly to afford traces of **3a**+**4a** (detected by GC).

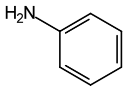
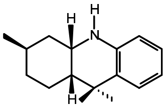
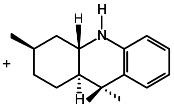
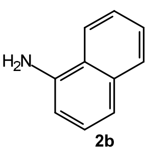
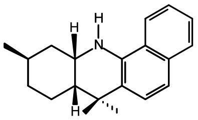
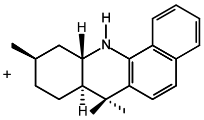
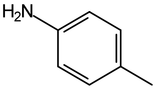
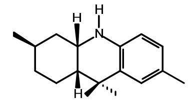
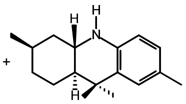
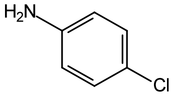
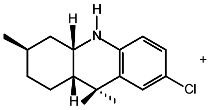
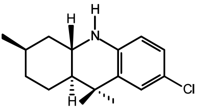
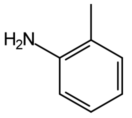
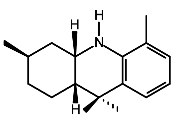
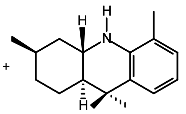
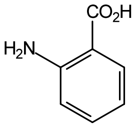
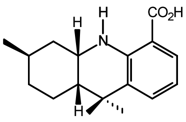
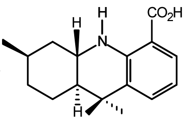
In order to check the possibility of intervention of specific (non purely thermal) microwave effects, the reaction with $SiO_2/ZnCl_2$, 10% was also examined using a pre-heated oil-bath for the same time and final temperature (40–45°C), as measured at the end of exposure during the MW-assisted synthesis (Method B, Table 1). However, the products were obtained only in poor yield (33%) after 3 min and with incomplete consumption of the starting materials (entry 4, Table 1). It was observed that 80 min were required to achieve **3a**+**4a** in the same yield that obtained after 3 min under MW. Additionally, we found that the microwave-assisted reactions are more efficient, more convenient and cleaner.

Although most experiments were performed in a 1.0 mmol scale, these reactions can also be performed with higher amount of reagents (up to 10 mmol) with comparable yields.

For all the studied anilines **2a**–**f**, we observed the formation of a *cis* and *trans* mixture of OHAs (determined by ^1H NMR), easily separable by column chromatography, with the more polar isomer showing the *trans*-configuration.[8] Surprising, and in contrast to hetero-Diels–Alder reactions involving *N*-arylimines and non-activated alkenes under organic solvent, *p*-toluidine **2c**, *o*-toluidine **2e** and *o*-aminebenzoic acid **2f** furnished the OHAs selectively. Thus, **3c** and **4c** were prepared in 75% yield, with a **3c**:**4c** ratio of 1.8:1 from **2c** (entry 3, Table 2), while **3f** and **4f** were obtained in 92% yield, with a **3f**:**4f** ratio of 3:1, starting from **2f** (entry 6, Table 2). On the other hand, **2e** reacted with citronellal to furnish **3e** and **4e** in 83% yield and larger amount of the *trans* isomer (**3e**:**4e** ratio = 1:2, entry 5, Table 2). According to the conventional reactional conditions, increasing in stereoselectivity could be reached only by using lower temperatures (−78°C, 0°C),[3] by increasing the aldehyde steric hindrance at position 3,[3a,c] or by coordinating a $Cr(CO)_3$ group to the aromatic ring in the *N*-arylimine precursor.[3b]

Due to our interest in synthetic use of the essential oil of citronella (*Cymbopogon nardus* (L) Rendle) and their constituents as renewable raw-material font, we tried to use our best catalytic system ($SiO_2/ZnCl_2$, 10%) in the direct *N*-arylimino-Diels–Alder reaction with the crude citronella oil.[16] The major component of the essential oil of citronella, extracted from the plant grew in southern Brazil (Três Passos-RS), was found to be (+)-*R*-citronellal (40–51%).[17] Thus, when a mixture of *o*-toluidine **2e** and the essential oil of citronella was submitted to MW irradiation for 5 min under 280 W in the presence of $SiO_2/ZnCl_2$, 10% (0.120 g), OHAs **3e** and **4e** were obtained in 79% yield, together with unreacted geraniol, citronellol, geranyl acetate, and others minor constituents of the starting oil, that were

Table 2. Synthesis of octahydroacridine derivatives

Entry	Arilamine	Product[a]	Reaction Time (min)[b]	Yield (%)	Ratio[c] (*cis* : *trans*)
1	 **2a**	 **3a** +  **4a**	3	78	1 : 1
2	 **2b**	 **3b** +  **4b**	3	87	1 : 1
3	 **2c**	 **3c** +  **4c**	3	75	1.8 : 1
4	 **2d**	 **3d** +  **4d**	1	85	1 : 1
5	 **2e**	 **3e** +  **4e**	5	83	1 : 2
6	 **2f**	 **3f** +  **4f**	3	92	3 : 1

[a] The power of the MW oven was calibrated at 280W.[18]

[b] The reaction progress was followed by TLC.

[c] Determined by ^{1}H NMR of the crude reaction mixture and compared after purification.

recovered (detected by GC). The isomeric ratio of **3e** and **4e** was the same that one observed for the reaction with citronellal, being the *trans* isomer **4e** the major product (entry 5, Table 2).

In conclusion, several octahydroacridines could be prepared directly by treatment of citronellal and amines under solid-supported acid catalysis and solvent-free MW assisted intramolecular hetero-Diels–Alder reaction. This eco-friendly protocol can be successfully applied to the synthesis of OHAs from crude citronella oil, avoiding the necessity for separation of citronellal. This method consists in low consumption of solvent, short reaction time, mild reaction conditions, excellent yields and simplicity, with non-aqueous work-up.

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14. The solid supported catalyst ($SiO_2/ZnCl_2$, 10%) was prepared by the following procedure: To a 100 mL beaker, silica gel 60 (9.0 g), $ZnCl_2$ (1.0 g) and water (3.0 mL) were added. The suspension was stirred for 15 min. at room temperature, dried at 80°C for 3 h and for additional 15 h at 150°C in an oven and then cooled in a desiccator.
15. **General procedure for the synthesis of octahydroacridines 3 and 4**. **Method A**: A mixture of (+)-citronellal (0.154 g; 1 mmol) and aniline (0.093 g; 1 mmol) was added to silica gel impregnated with $ZnCl_2$ (0.120 g). The whole mixture was previously stirred for 1 min and then was irradiated by microwave (Brastemp model VIP-38 Sensor Crisp operating at 2.45 GHz) at 280 W.[18] The reaction progress was followed by TLC and after 3.0 min, the reaction vessel was cooled, and the product was filtered off the silica gel by washing with ethyl acetate (10 mL). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel (SiO_2) eluting with hexane/ethyl acetate (98:2), yielding **3a** and **4a** in a 1:1 ratio (0.179 g, 78%). The spectral data were in perfect agreement with those reported in the literature.[3a,e] *cis*-**3a** (first eluted fraction): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.11 (dd, $J=7.6$ and 1.4 Hz, 1H); 6.94 (ddd, $J=8.0$, 7.5 and 1.5 Hz, 1H); 6.57 (dt, $J=7.4$ and 1.2 Hz, 1H); 6.41 (dd, $J=7.9$ and 1.1 Hz, 1H); 3.81–3.83 (m, 1H); 3.50 (br s, 1H); 1.56–1.77 (m, 5H); 1.31 (s, 3H); 1.21 (s, 3H); 1.07–1.31 (m, 3H); 0.88 (d, $J=6.3$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.1, 128.1, 126.5, 126.1, 116.2, 112.8, 46.8, 44.5, 41.2, 35.6, 34.8, 34.1, 26.1, 25.5, 23.0, 22.2. *trans*-**4a** (second eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, $J=7.6$ and 0.8 Hz, 1H); 6.94 (ddd, $J=7.6$, 7.4 and 1.2 Hz, 1H); 6.63 (dd, $J=7.6$ and 0.8 Hz, 1H); 6.41 (dd, $J=8.0$ and 0.4 Hz, 1H); 3.55 (br s, 1H); 3.05 (ddd, $J=10.4$, 10.3 and 4.0 Hz, 1H); 1.50–1.87 (m, 6H); 1.32 (s, 3H); 1.09 (s, 3H); 0.99–1.28 (m, 2H); 0.95 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 131.0, 126.4 (2C), 116.6, 113.5, 50.4, 46.9, 43.2, 35.0, 34.7, 30.8, 27.1, 26.6, 24.6, 22.2. **Method B**: The procedure aforementioned was followed using citronellal and aniline and the solvent less reaction was stirred at 41–45°C for 3–80 min.
16. **OHAs 3e and 4e from essential oil of citronella**. The procedure described above (Method A, Ref. 15) was used for the reaction of essential oil of citronella (0.460 g; 40% of citronellal, determined by GC analysis), *o*-toluidine **2e** (0.107 g; 1 mmol) and $SiO_2/ZnCl_2$ (10%) (0.120 g). The reaction mixture was irradiated at 280W for 5.0 min to yield, after purification, **3e** and **4e** in a 1:2 ratio (0.192 g; 79%). The spectral data were in perfect agreement with those reported in the literature.[3a,e] *cis*-**3e** (first eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, $J=7.6$ Hz, 1H); 6.83 (d, $J=7.2$ Hz, 1H); 6.52 (t, $J=7.6$ Hz, 1H); 3.82–3.85 (m, 1H); 3.31 (br s, 1H); 2.05 (s, 3H); 0.81–2.15 (m, 8H); 1.30 (s, 3H); 1.20 (s, 3H); 0.88 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 127.5, 127.4, 123.9, 119.2, 115.5, 46.7, 44.3, 41.3, 35.5, 34.8, 34.0, 26.4, 25.4, 22.8, 22.2, 17.4. *trans*-**4e** (second eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, $J=8.0$ Hz, 1H); 6.83 (d, $J=7.3$ Hz, 1H); 6.56 (t, $J=7.6$ Hz, 1H); 3.44 (br s, 1H); 3.06 (td, $J=10.4$ and 4.0 Hz, 1H); 2.04 (s, 3H); 0.81–2.15 (m, 8H); 1.31 (s, 3H); 1.09 (s, 3H); 0.94 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 130.4, 127.5, 124.2, 119.8, 116.0, 50.5, 46.8, 43.5, 35.0, 34.7, 30.9, 27.0, 26.8, 24.7, 22.1, 17.3.
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18. The oven powers were determined according to described by Kingston, H. M. *Introduction to Microwave Sample Preparation-Theory and Practice*; Jassie, L. B., Ed.; American Chemical Society, DC, 1988.