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Article

Microwave-Promoted Morita-Baylis-Hillman Reactions: Efficient Synthesis of New Monoacylglycerols (MAGs) as Potential Anti-Parasitic Compounds

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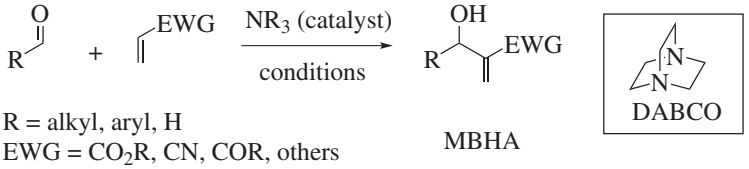
Descrevemos neste artigo, a irradiação por microondas promovendo a síntese de monoacilglicerol hidrofílico, MAG, a partir da hidrólise de um acrilato (15 min, 100%). Depois, o MAG foi transformado em adutos de Morita-Baylis-Hillman (AMBH) hidrofílicos, (54-82%, caminho 1). No caminho 2, outros AMBHs foram preparados em altos rendimentos (90-100%) e transformados em AMBH hidrofílicos em 70-90%. Durante e síntese em alta temperatura do AMBH, foi detectado por CG-EM a formação de uma indolizina inédita. Todos estes resultados estão de acordo com o novo mecanismo unificado para a reação de Morita-Baylis-Hillman. Estes novos monoacilgliceróis, bem como seus precursores sintéticos, são novos compostos antiparasitários em potencial.

In this article we describe microwave irradiation promoting the synthesis of a hydrophilic monoacylglycerol, MAG, by hydrolysis of acrylate (15 min, 100%). After, MAG was transformed in hydrophilic Morita-Baylis-Hillman adducts (MBHA), (54-82%, pathway 1). In pathway 2, the different lipophilic MBHAs were prepared in high yields (90-100%) and transformed on hydrophilic MBHA, in 70-90%. Through the high temperature synthesis of one MBHA, a unprecedented indolizine formation was detected by GC-MS,. All results are in agreement with the new unified mechanism to the Morita-Baylis-Hillman reaction. These new monoacylglycerols, as well the its synthetic precursors, are new potential antiparasitic compounds.

Keywords: Morita-Baylis-Hillman reaction, microwaves, monoacylglycerols, acrylates, potential antiparasitic

Introduction

The Morita-Baylis-Hillman reaction (MBHR) is an important way for C–C bond formation.[1,2] It involves the alkenes coupling containing electron-withdrawing groups (EWG) with aldehyde, ketones or imines, among others. Tertiary amines are used as nucleophilic catalysts on which 1,4-diazabicyclo [2.2.2]octane (DABCO) is the most widely used (Scheme 1). The Morita-Baylis-Hillman adducts (MBHA) have been extensively used as starting materials in organic synthesis for a variety of applications, many of which have biological activity.[2] An inconvenience associated with this reaction is, in several examples, the long reaction times. There are reports of reactions that, last up to 65 days.[2] However, due to the synthetic utility of these MBHA adducts, several protocols have been described to



R = alkyl, aryl, H
EWG = CO_2R, CN, COR, others

MBHA

Scheme 1. The general Morita-Baylis-Hillman reactions representation.

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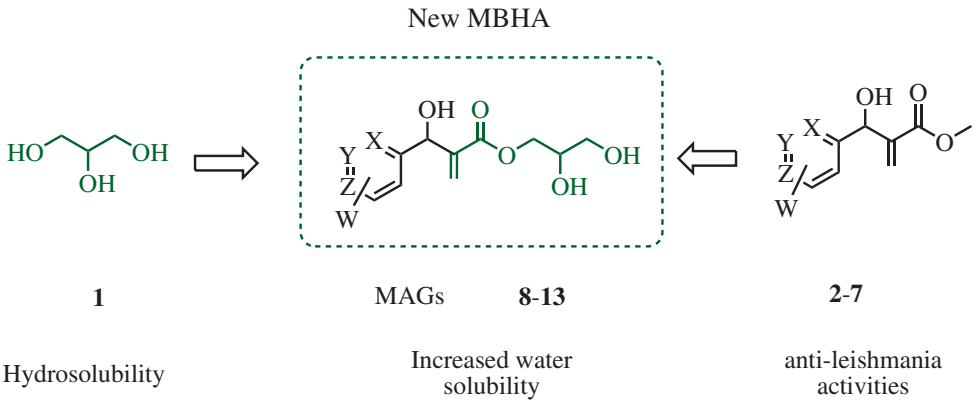


Scheme 2. 1: Glycerol; **2**, **8**: X = Y = Z = H, W = *o*-nitro; **3**, **9**: X = Y= Z = H, W = *m*-nitro; **4**, **10**: X = Y = Z = H, W = *p*-nitro; **5**, **11**: X = N, Y = Z = W = H; **6**, **12**: Y = N, X = Z = W = H; **7**, **13**: Z = N, Y = X = W = H.

improve the reaction time and yields, such as the use of ultrasound, high pressures, use of ionic liquids, change of catalyst, change of solvents, microwaves irradiation, and several other experimental protocols.[2]

Despite the fact that this reaction has already more than 40 years of existence,[1] the debate on the exact mechanism of reaction is still highlighted in the scientific community. The first catalytic cycle suggested by Hill and Isaacs[3] is still accepted, but being the rate-determining step (RDS) it remains at the center of the scientific debate. For example, the nonprotic[4] and protic[5] currently accepted mechanisms suggested by McQuade and Aggarwal respectively and corroborated by Coelho[6] have been very recently revisited by Cantillo and Kappe.[7]

In our continuing search for bioactive substances[8] and in connection with our efforts towards reactivity of MBH reaction study,[9] our research group described in 2006 the molluscicidal activities of simple aromatic MBHA against *Biomphalaria glabrata* (Say) snails, intermediate schistosomiasis host.[10] In sequence, some aromatic MBHA were presented as very active compounds against the *Leishmania amazonensis* (cutaneous and mucocutaneous infections).[11] Following that work, we published the biological evaluation of aromatic MBHA against *Leishmania chagasi* (visceral infections) parasites,[12] and in 2010, we have shown that the MBHA 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile, a high anti-leishmania compound, is also a highly active compound against epimastigote and trypomastigote form of *Trypanosoma cruzi*, the parasite that causes Chagas disease.[13] In the same year, we presented an improved synthesis for sixteen MBHA and their biological evaluation against *L. amazonensis* and *L. chagasi* and we proposed, at the first time, a structure-activity relationship (SAR) analysis for this class of anti-parasitic compounds.[14]

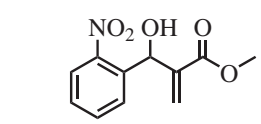
In this context we present in this article the design and two efficient synthesis of new hydrophilic **8**-**13** monoacylglycerols (MAGs)[15] (Scheme 2 and Figure 1) idealized as potential anti-parasitic compounds.

It has been reported in the literature that there is an important relationship between the hydrophilicity-lipophilicity and anti-parasitic activity of drugs, *e.g.*, it were described that increasing the solubility in water or using cationic amphiphilic drugs (CADs) tends to increase anti-leishmaniasis and anti-malarial activities.[16] The strategy presented here was based on the introduction of hydrophilic portion derived from the glycerol (**1**), as an important factor in water solubility increase of MBHA, previously described by us as anti-leishmania proprieties[14] (Figure 1). The key step in these syntheses is the MBH reaction between the commercial aldehydes **14**-**19** (Figure 2) and the corresponding acrylates **20** or **21** presented in Scheme 3. All MAGs steps preparations were promoted by microwave irradiations, a very efficient and green methodology[17] used to obtain improvement in yields and rates of organic reactions.[18]

Results and Discussion

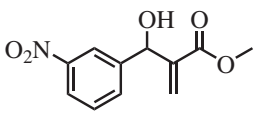
We began our experimental work on the acrylate **20** synthesis (Scheme 3). This compound was prepared by reaction between acryloyl chloride and solketal on CH_2Cl_2 at room temperature for 2 h (94%).[19] The solketal is commercial, but it could easily be prepared here in 90% yield, by heating to 60 °C of glycerol under azeotropic distillation condition, on a mixture of acetone-pentane (1:1) under *p*-toluenesulfonic acid catalysis.[19] After that, two synthetic pathways were investigated to MAGs **8**-**13** prepare (step iii and iv to pathway 1 and step v and vi to pathway 2, Scheme 3).

There are up to now, more than 280 applications to MAG **21** mainly for the polymers synthesis and other



2

logP = 2.10 ± 0.39



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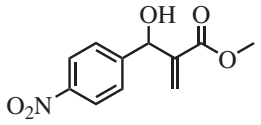

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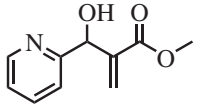
logP = 2.10 ± 0.39



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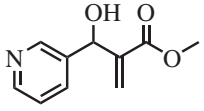
logP = 0.87 ± 0.38



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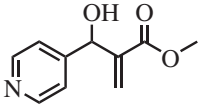
logP = 0.87 ± 0.38



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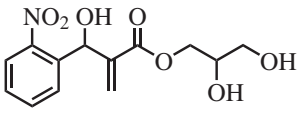
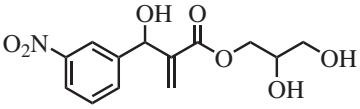
logP = 0.87 ± 0.38



8

logP = 0.63 ± 0.42



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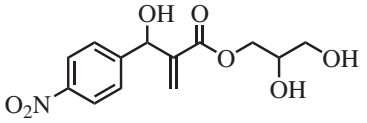
logP = 0.63 ± 0.42



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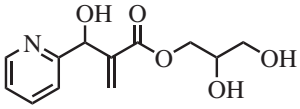
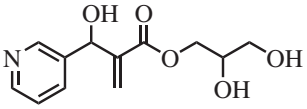
logP = 0.63 ± 0.42



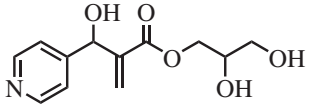
11

logP = –0.60 ± 0.42



12

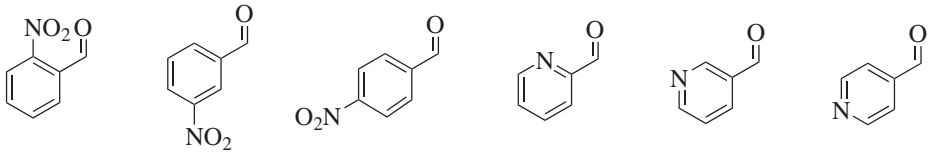
logP = –0.60 ± 0.42



13

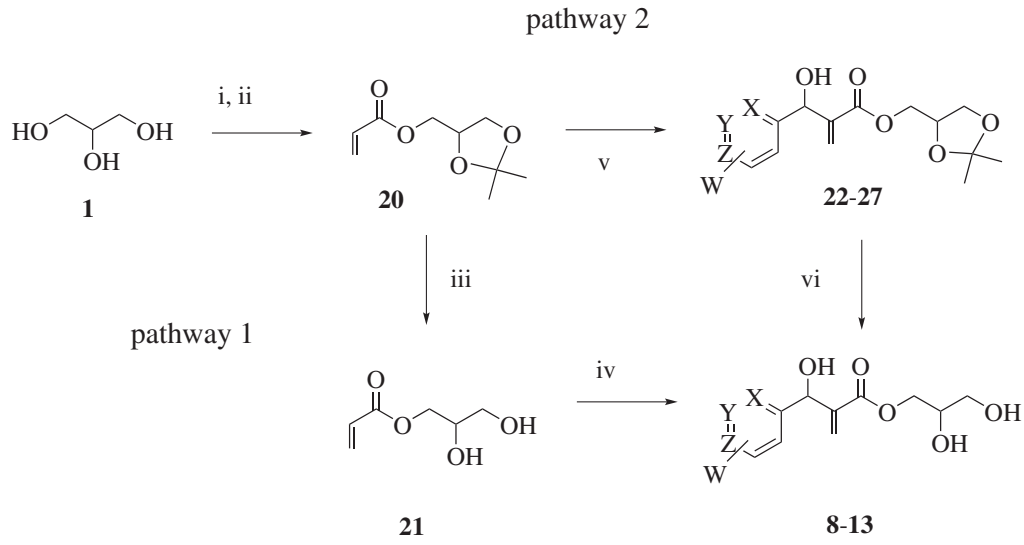
logP = –0.60 ± 0.42

Figure 1. logP values were calculated *in silico* using the Pharma-algorithms®; help available from http://pharma-algorithms.com.



14 **15** **16** **17** **18** **19**

Figure 2. Commercial aldehydes **14**-**19** used in this article, that were also used in our previous comunications.[11,12,14]



Scheme 3. i) Glycerol/acetone-pentane (1:1), 60 °C, azeotropic distillation, 24 h, 95%; ii) solketal, 1.2 equiv. acryloyl chloride, CH_2Cl_2, TEA, 94%; iii) acrylate **20**, amberlyst 15, CH_3OH, MW, 60 °C, 15 min, 100%; iv) aldehydes **14**-**19**, acrylate **21**, 1 equiv. DABCO, conditions in Table 2, 54-82%; v) aldehydes **14**-**19**, acrylate **20**, 1 equiv. DABCO, conditions in Table 3, 90-100%; vi) MBHA **22**-**27**, condition in Table 4, 70-90%. **22**, **8**: X = Y = Z = H, W = *o*-nitro; **23**, **9**: X = Y= Z = H, W = *m*-nitro; **24**, **10**: X = Y = Z = H, W = *p*-nitro; **25**, **11**: X = N, Y = Z = W = H; **26**, **12**: Y = N, X = Z = W = H; **27**, **13**: Z = N, Y = X = W = H.

macromolecules as nanoparticles.[20] However, even that acrylates **20** and **21** are described, surprisingly, in the best of our knowledge, only in 2008, Shi and co-workers[21] described a first procedure to MAG **21** synthesis directly from the acrylate **20**. Moreover, due to high water solubility of **21** it is important the development of an experimental protocol to **20**→**21** transformation using no large amount of water or other very high boiling point polar solvent, aiming to simplify this reaction isolation. Then, the development of a more efficient technology to minimize this problem is also an important point in this present article. First, to screen the suitable reaction conditions using only water quantity for the hydrolysis reaction of **20** in MAG acrylate **21** can occur (step iii, Scheme 3), we investigated many protocols as the use of PPTS/ $CHCl_3$/ r.t. (24 h, no reaction),[22] TsOH/ toluene/ 80 °C (24 h, no reaction),[23] TsOH/ CH_3OH/ r.t. (3 h, 34%),[23] $CHCl_3$/ $FeCl_3.SiO_2$/ r.t (6h, 33%),[24] HCl (catalytic)/ toluene/ r.t. (24 h, 16%),[25] montmorillonite KSF/ $CHCl_3$/ 60 °C (3 days, no reaction),[26] montimorillonite K10/ acetone/ 60 °C (24 h, 51%)[26] and amberlite IRA-120/ ethanol/78 °C (24 h, 12%).[26] In Fact, these previous results to detach this transformation difficulty appears a simple chemical processing.

After, we evaluated the use of acetic acid 10%, under 60 °C (entry 1, Table 1, 10%).[21] However, when this reaction was carried out with addition of catalytic amount of BHT as anti polymerizing compound we observed a very large increase in the reaction yield (entry 2, Table 1, 92%). However, the use of amberlyst 15 in methanol at room temperature produced **21** in high yields (entry 3, Table 1, 97%).[27] Very gratifying, we discover that the **21** yield increased when the reaction was conducted in methanol under microwave irradiation for 15 min without the addition of any anti polymerization reagent. After that irradiation, a simple filtration to remove the resin and evaporation of methanol was necessary to obtained pure **21** in 100% yields (entry 4, Table 1).

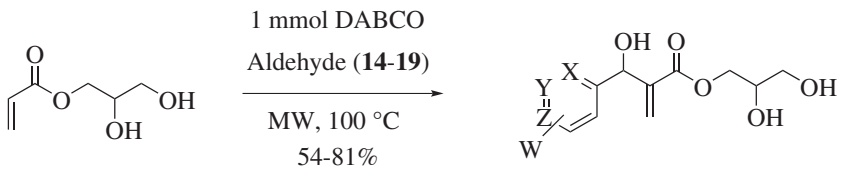
Table 1. Conditions and results to MAG **21** preparation (Scheme 3, pathway 1, step iii)

entry	Condition	time	Yields / (%)*
1	Acetic acid 10%, 60 °C	48 h	10
2	Acetic acid 10%, 0.01 equiv. BHT, 60 °C	24 h	92
3	Amberlyst 15, CH_3OH, r.t.	4 h	97
4	Amberlyst 15, CH_3OH, MW, 60 °C	15 min	100

*Isolated pure products. The compounds purities were evaluated from GC-MS analysis.

Continuing on the pathway 1, several conditions have been evaluated on MBH reaction between the MAG acrylate **21** and aldehyde **14**-**19**, modifying solvents (protic and nonprotic), temperature, using the microwave irradiation, trying to convert **21** to MBHA **8**-**13** (step iv, Scheme 3). Again, the experimental protocol development to **21**→**8**-**13** transformation without the use of large amount of water or other very high boiling point polar solvent, aiming to simplify the isolation of these reactions, especially for the more hydrophilic adducts **11**, **12** and **13** (see the calculated values of logP in Figure 1). In Table 2 we present our best results for these steps iv.

Table 2. Results of the MBHA synthesis **8**-**13** from step iv in Scheme 3



21 **8**-**13**

entry	Aldehyde	MBHA	Solvent	time / min	Yields / (%)
1	14	8	CH_3CN	10	68
2	15	9	CH_3CN	10	65
3	16	10	CH_3CN	10	54
4	17	11	CH_3CN	10	82
5	18	12	CH_3CN	10	81
6	19	13	CH_3CN	10	80

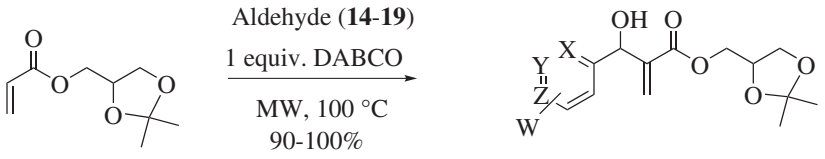
***8**: X = Y = Z = H, W = *o*-nitro; **9**: X = Y= Z = H, W = *m*-nitro; **10**: X = Y = Z = H, W = *p*-nitro; **11**: X = N, Y = Z = W = H; **12**: Y = N, X = Z = W = H; **13**: Z = N, Y = X = W = H.

In the pathway 2, the results of MBH reaction between the less hydrophilic acrylate **20** and the aldehyde **14**-**19** (step v, Scheme 3) were more efficient when they obtained from step iv from pathway 1, considering both reactions under microwave irradiations, producing the lipophilic MBHA **22**-**27** in high yields (step v, 90%-100% yields, Table 3). Again a complete study of different conditions was evaluated and we present in Table 3 the best results obtained for each evaluated adduct in this step. In this case, use of water or high boiling point polar solvent media does not minimize the reaction yield, since they are more lipophilic compounds.

We can point out that depending on the aldehydes used in the MBH reaction can be obtained good yields in both protic[4,6] or aprotic[5,6] media, confirming that slight changes in reaction conditions can change the RDS of these reactions and then, there are not, up to now, a clear general relationship between substrates-solvents-yields-rate, which corroborates the unified mechanism proposed by Cantilo and Kappe for this exquisite reaction.[7]

Completing the pathway 2 (step vi, Scheme 3), the synthesis of adducts **8**-**13** from intermediates **22**-**27** was first performed using the same methodology used on MAG **21** preparation (step iii, Scheme 3). However, surprisingly these transformations were inefficient, showing low yield (Table 4, entry 1). Since we observed no byproducts from this condition we have increased temperature (entry 2, Table 4). However, we obtained low yield and, in this case, byproduct. We believed that the origin of the principal byproduct could be the result from Michael reaction between the Methanol (a nucleophilic solvent) on 4-position of acrylate moiety from

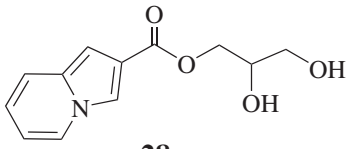
Table 3. Results of the intermediates **22**-**27** preparations from the step v, presented in Scheme 3



20 **22**-**27**

entry	MBHA	Aldehyde	Solvent	time / min	Yields / (%)
1	22	14	DMF	10	100
2	23	15	CH_3CN	10	90
3	24	16	DMF/H_2O*	10	90
4	25	17	CH_3CN	10	98
5	26	18	DMF/H_2O*	10	95
6	27	19	DMF/H_2O*	10	90

*9:1 mixture of DMF/water; **22**: X = Y = Z = H, W = *o*-nitro; **23**: X = Y= Z = H, W = *m*-nitro; **24**: X = Y = Z = H, W = *p*-nitro; **25**: X = N, Y = Z = W = H; **26**: Y = N, X = Z = W = H; **27** = Z = N,Y = X = W = H.



28

m/z = 235 [M$^+$] *m/z* = 144 (100%)

m/z = 162 (85%) *m/z* = 116 (75%)

Figure 3. Indolizines **28**, proposed as principal byproduct and characterized thought the expected fragmentations obtained by GC-MS.

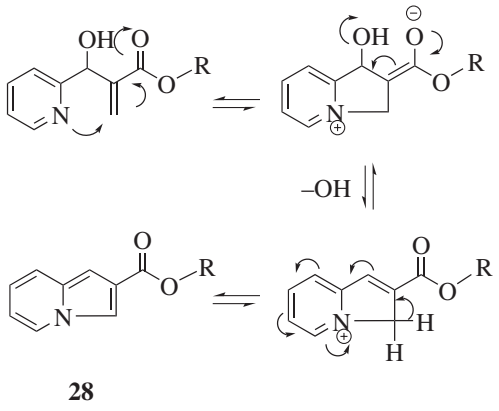
adduct **27** before or along with adduct **13** production. Another hypothesis suggested by us was the possibility of MBH reaction reversibility using high temperature, according to the unified mechanism proposed by Cantillo and Kappe.[7] Based on these hypothesis we first investigated the solvent change using *t*-butanol, which is less nucleophilic than methanol, not changing microwave irradiation temperature. In fact, this solvent change was efficient, producing the new hydrophilic adduct **13** in good yield and no byproducts was obtained (entry 3, Table 4). Continuing, this methodology was high efficient to MAGs **8**, **9** and **10** preparations from MBHA **22**, **23** and **24** (entries 4, 5 and 6, Table 4; step vi in Scheme 3). In fact, Cantillo and Kappe described that the MBH reaction between acrylates and nitroarylaldehyde are less susceptible to reversibility even when high temperatures are used (until 107 °C the reaction is exergonic).[7]

Reaction at 100 ℃ of *t*-butanol on MBH adducts **25** (entry 7, Table 4), which presented a 2-piridinyl moiety, lead to formation of two products, observed by TLC. A more polar product was isolated on 58% yield and characterized as the pure MAG **11** (entry 7, Table 4). The CGMS analysis of the less polar product indicated that this supposed product by TLC were in fact a more complex mixture of products that were not possible to be isolated. However, in the largest proportion byproduct (43% in this mixture) was proposed to be the unpublished indolizine **28** (Figure 3). Since this molecule could not be purified by flash chromatography, no NMR data could were obtained and **28** preparation was based on the CGMS data. This compound showed all the characteristic fragmentations (*m/z*) of the indolizine[28] and also all the expected fragmentations showed in Figure 3, that no doubt characterizes the molecule **28**. In fact, is already well established in the literature that indolizines are synthesized at high temperatures.[29] We presented in Scheme 4 a short proposal of mechanism reaction for the **28** formation.

As expected, the MAG **11** could be prepared in good yield without byproducts formations by decreasing the temperature at 60 ºC (entry 8, Table 4). Then, it is clear that in lower temperature the addition of less nucleophilic *t*-butanol solvent on **25** do not occurs and also the formation of indolizines was not observed.

It is important to detach that both reactions with adducts presenting 3-pyridinyl (**26**) and 4-pyridinyl (**27**) moieties give best yields than the reaction with the **25** adduct (in the same experimental condition, compare the entries 3, 7 and 10, Table 4). This experimental observation also confirms what has been discussed here about 2-N participation.

Finally, we believe that the best conversions to **8**, **9** and **10** MAGs preparations compared with the conversions in MAGs **11**, **12** and **13** syntheses can be also explained by the possibility of reversibility to the MBH reaction in both protic and nonprotic media as proposed by Cantilo and Kappe. [7]



28

Scheme 4. A proposal mechanism of reaction to **28** formation. R = $CH_2CH(OH)\ CH_2OH$.

Table 4. Results of the MBHA **8**-**13** synthesis from step vi, presented in Scheme 3

entry	MBHA	Solvent	T / °C	time /min	Yields / (%)
1	13	CH_3OH	60	60	< 10
2	13	CH_3OH	100	15	< 10*
3	13	*t*-butanol	100	15	70
4	8	*t*-butanol	100	15	90
5	9	*t*-butanol	100	15	90
6	10	*t*-butanol	100	15	90
7	11	*t*-butanol	100	15	58**
8	11	*t*-butanol	60	90	70
9	12	*t*-butanol	60	60	40
10	12	*t*-butanol	100	15	70

*Byproducts were observed from chromatography, no identified.
Purified MAG **11 by chromatography.

Conclusions

In summary we report in this article two efficient, facile and quick synthesis of six new hydrophilic MBHA

8-**13** on high yield (pathway 2, 67-90% two steps-yields and pathway 1, 54-82% two steps-yields, Scheme 3) from solketal acrylate **20**. We also report a new very efficient and quick synthesis of MAG **20** from **21** (100% yield), using resin and microwave irradiation for 15 min. All steps starting from acrylate **20** were performed under microwave irradiation methodology. An advantage of pathway 2 is that we can also produce a new more lipophilic MBHA **22**-**27** in high yields (90-100% one step from acrylate **20**, step v, Scheme 3). The bioactivities evaluations of these new **8**-**13** hydrophilic MAGs and also the new hydrophobic MBHA **22**-**27** will continue with this present article.

Experimental

General

All commercially available reagents and solvent were obtained from commercial providers and used without further purification. Reactions were monitored by TLC using silica gel 60 UV254 Macherey-Nagel pre-coated silica gel plates; detection was by means of a UV lamp. Flash column chromatography was performed on 300-400 mesh silica gel. Organic layers were dried over anhydrous $MgSO_4$ or Na_2SO_4 prior to evaporation on a rotary evaporator. Reactions requiring microwave irradiation were performed in a microwave reactor CEM® model system Discover benchmate with temperature monitored by built-in infrared sensor. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Mercury Spectra AC 20 spectrometer (200 MHz for ^{1}H, 50 MHz for ^{13}C) for adducts **22**-**27** together with the acrylates **20** and **21** acrylates and Bruker DPX300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C) for the adducts **8**-**13**. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) for ^{1}H, and $CDCl_3$ (δ 77.0 ppm) for ^{13}C. FTIR spectra were recorded on a Shimadzu spectrophotometer model IRPrestige-21 in KBr pellets. MS data were measured with a Shimadzu GCMS-QP2010 mass spectrometer. High resolution mass spectra were determined using a MicroTOF Ic Bruker Daltonics spectrometer®. Solketal were prepared in this work as described in Results and Discussion section and characterized in accordance with the commercial compounds physical data.

*(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl acrylate (**20**)* [21]

The reaction was performed using solketal 6 g (0.045 mols) which was left under stirring at 0 °C with 80 mL of dichloromethane (CH_2Cl_2) and 7 mL of TEA in a closed system. After 5 min, a solution containing 20 mL of CH_2Cl_2 and 4.8 mL of acryloyl chloride was slowly added. The reaction mixture kept under magnetic stirring for 1 h at room temperature. Then the isolation was done by adding the reaction mixture a solution of sodium bicarbonate $NaHCO_3$ 10% and the product was extracted by the organic phase (CH_2Cl_2), which, in turn, was dried with sodium sulfate anhydrous Na_2SO_4 and concentrated under reduced pressure where it was obtained a 94% isolated yield. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.38 (s, 3H), 1.41 (s, 3H), 3.71-4.41 (m, 5H), 5.84 (dd, 1H, *J* 10.2/1.6 Hz), 6.13 (dd, 1H, *J* 17.2/10.2 Hz), 6.43 (dd, 1H, *J* 17.2/1.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.3, 30.6, 68.7, 70.2, 77.5, 113.8, 131.9, 135.4, 169.8.

*Synthesis of 2,3-dihydroxypropyl acrylate (**21**)*[21]

It was produced using 186 mg (1 mmol) of the corresponding acrylate **20**, 5 mL of methanol and 100 mg of resin Amberlyst 15 that were placed in a 10 mL glass microwave tube with magnetic stirrer. The reaction tube was placed inside the cavity of a CEM Discover benchmate and irradiated at 60 °C for 15 min. After the reaction completes, the reaction mixture brought to room temperature and was directly filtered using methanol and concentrated in a rotary evaporator. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.39-4.71(m, 7H), 5.86(dd, 1H, *J* 10.4/1.6 Hz), 6.13 (dd, 1H, *J* 17.2/10.4 Hz), 6.43 (dd, 1H, *J* 17.2/1.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 67.2, 69.2, 74.0, 131.8, 135.8, 170.6.

*A typical procedure for synthesis of **22**-**27** (Scheme 3)*

The corresponding aldehydes (1,5 mmol), 186 mg (1 mmol) of acrylate **20**, DABCO (1 equiv.) and 5 mL of appropriate solvent were placed in a 10 mL glass microwave tube with magnetic stirrer. The reaction tube was placed inside the cavity of a CEM Discover® benchmate and irradiated at 100 °C for 10 min. After the reaction completes, the reaction mixture brought to room temperature where the solvent used were extracted from the reaction medium and the product was isolated from the crude reaction by column chromatography through silica gel, using AcOEt:hexane as solvent at a ratio of 3:7 to the adducts **22**, **23** and **24** and 7:3 to the adducts **25**, **26** and **27**. The reaction products were concentrated under reduced pressure and characterized by NMR, IR and mass spectroscopy.

*(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl[2-(hydroxy(2-nitrophenyl)methyl)] acrylate (**22**)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31 (s, 3H), 1.38 (s, 3H), 3.60-4.34 (m, 6H), 5.70 (d, 1H, *J* 5.8 Hz), 6.20 (s, 1H), 6.38 (s, 1H), 7.45 (m, 1H), 7.63 (t, 1H, *J* 7.8 Hz), 7.75 (d, 1H, *J* 8.0 Hz), 7.94 (d, 1H, *J* 8.0 Hz); ^{13}C NMR ($CDCl_3$,

50 MHz): δ 29.1, 30.5, 69.5, 70.0, 71.1, 77.2, 113.8, 128.5, 130.9, 132.6, 132.8, 137.5, 140.3, 144.8, 152.1, 169.4; IR (KBr) ν_{max}/cm^{-1}: 3433, 2989, 2939, 2889, 1724, 1527, 1350, 1157, 1053; ESI-HRMS (*m/z*) calc. for $C_{16}H_{19}NO_7$ [(M+H)$^+$] 338.1195, found 338.1233.

*(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl[2-(hydroxyl(3-nitrophenyl)]methyl) acrylate (**23**)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.34 (s, 3H), 1.40 (d, 3H, *J* 4.0 Hz), 3.65-4.37 (m, 6H), 5.67 (d, 1H, *J* 4.6 Hz), 6.01 (d, 1H, *J* 5.2 Hz), 6.47 (s, 1H), 7.52 (t, 1H, *J* 7.8 Hz), 7.75 (d, 1H, *J* 7.6 Hz), 8.15 (d, 1H, *J* 8.0 Hz), 8.27 (s, 1H); ^{13}C NMR ($CDCl_3$ 50 MHz): δ 29.1, 30.6, 69.1, 69.9, 75.9, 77.2, 113.8, 125.7, 126.6, 131.4, 133.2, 136.8, 145.1, 147.9, 152.2, 169.4; IR (KBr) ν_{max}/cm^{-1}: 3437, 2989, 2935, 2889, 1716, 1531, 1350, 1157, 1053; ESI-HRMS (*m/z*) calc. for $C_{16}H_{19}NO_7$ [(M+H)$^+$] 338.1195, found 338.1239.

*(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl[2-(hydroxyl(4-nitrophenyl)methyl)] acrylate (**24**)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31 (s, 3H), 1.36 (d, 3H, *J* 4.0 Hz), 3.62-4.33 (m, 5H), 4.44 (sl, 1H), 5.64 (d, 1H, *J* 4.2 Hz), 5.97 (d, 1H, *J* 4.8 Hz), 6.41 (s, 1H), 7.55 (d, 2H, *J* 8.4 Hz), 8.15 (d, 2H, *J* 8.6 Hz); ^{13}C NMR ($CDCl_3$ 50 MHz): δ 29.1, 30.6, 70.0, 69.9, 75.5, 77.2, 113.8, 127.4, 131.2, 131.5, 145.3, 151.2, 153.2, 169.4; IR (KBr) ν_{max}/cm^{-1}: 3410, 3213, 2985, 2935, 2897, 1716, 1519, 1350, 1157, 1056; ESI-HRMS (*m/z*) calc. for $C_{16}H_{19}NO_7$ [(M+H)$^+$] 338.1195, found 338.1229.

*(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl[2-(hydroxy(pyridin-2-yl)methyl)] acrylate (**25**)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30 (s, 3H), 1.36 (d, 3H, *J* 3.8 Hz), 3.59-4.28 (m, 5H), 4.98 (sl, 1H), 5.59 (s, 1H), 5.97 (s, 1H), 6.38 (s, 1H), 7.18 (m, 1H), 7.40 (d, 1H, *J* 8.0 Hz), 7.65 (td, 1H, *J* 7.6/1.6 Hz), 8.49 (dd, 1H, *J* 4.8/1.0 Hz); ^{13}C NMR ($CDCl_3$ 50 MHz): δ 29.2, 30.6, 68.7, 70.2, 76.0, 77.2, 113.7, 125.2, 126.6, 131.5, 140.8, 145.4, 152.1, 163.4, 169.8; IR (KBr) ν_{max}/cm^{-1}: 3421, 2985, 2939, 2889, 1720, 1157, 1053; ESI-HRMS (*m/z*) calc. for $C_{15}H_{19}NO_5$ [(M+H)$^+$] 294.1296, found 294.1335.

*(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl[2(hydroxyl(pyridin-3-yl)methyl)] acrylate (**26**)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32 (s, 1H), 1.38 (d, 1H, *J* 3.2 Hz), 3.58-4.33 (m, 6H), 5.59 (s, 1H), 6.02 (d, 1H, *J* 3.4 Hz), 6.43 (s, 1H), 7.25 (dd, 1H, *J* 8.0/5.0 Hz), 7.72 (d, 1H, *J* 8.0 Hz), 8.38 (d, 1H, *J* 4.6 Hz), 8.47 (d, 1H, *J* 2.0 Hz); ^{13}C NMR ($CDCl_3$ 50 MHz): δ 29.1, 30.6, 69.9, 70.0, 74.3, 77.2, 113.8, 127.4, 130.7, 141.5, 145.4, 152.3, 152.5, 169.4; IR (KBr) ν_{max}/cm^{-1}: 3124, 2989, 2877, 1716, 1145, 1060; ESI-HRMS (*m/z*) calc. for $C_{15}H_{19}NO_5$ [(M+H)$^+$] 294.1296, found 294.1337.

*(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl[2-(hydroxyl(pyridin-4-yl)methyl)] acrylate (**27**)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.34 (s, 3H), 1.39 (d, 3H, *J* 4.2 Hz), 3.63-4.35 (m, 6H), 5.55 (s, 1H), 5.96 (d, 1H, *J* 4.6 Hz), 6.44 (s, 1H), 7.33 (d, 2H, *J* 6 Hz), 8.46 (d, 2H, *J* 4.8); ^{13}C NMR ($CDCl_3$ 50 MHz): δ 29.1, 30.6, 69.0, 69.9, 75.5, 77.2, 113.8, 125.5, 131.6, 145.0, 153.4, 155.1, 169.4; IR (KBr) ν_{max}/cm^{-1}: 3140, 2989, 2877, 1716, 1141, 1056; ESI-HRMS (*m/z*) calc. for $C_{15}H_{19}NO_5$ [(M+H)$^+$] 294.1296, found 294,1337.

*A typical procedure for synthesis of MAGs **8**-**13** from step iv (Scheme 3)*

The corresponding aldehydes (1.5 mmol), 146 mg (1 mmol) of acrylate **21**, DABCO (1 equiv.) and 5 mL of acetonitrile (CH_3CN) were placed in a 10 mL glass microwave tube with magnetic stirrer. The reaction tube was placed inside the cavity of a CEM Discover benchmate and irradiated at 100 °C for 10 min. After the reaction completes, the reaction mixture brought to room temperature where the CH_3CN was extracted from the reaction medium and the product was isolated from the crude reaction by column chromatography through silica gel, using AcOEt:hexane as solvent at a ratio of 8:2 to the adducts **8**, **9** and **10** and using MeOH:AcOEt as solvent at a ratio of 1:9 to the adducts **11**, **12** and **13**. The reaction products were concentrated under reduced pressure and characterized by NMR, IR and mass spectroscopy.

*A typical procedure for synthesis of MAGs **8**-**13** from step vi (Scheme 3)*

The corresponding MBHA **22**-**27** (1.0 mmol), 5.0 mL of *t*-butanol and 100 mg of resin Amberlyst 15 were placed in a 10 mL glass microwave tube with magnetic stirrer. The reaction tube was placed inside the cavity of a CEM Discover® benchmate and irradiated at 100 °C for 15 min (except for the adduct **25** which was irradiated at 60 °C for 90 min to get to **11**). After the reaction completes, the reaction mixture brought to room temperature and was directly filtered using methanol as solvent and concentrated under reduced pressure. The reaction products were isolated from the crude reaction by column chromatography through silica gel using AcOEt:hexane as solvent at a ratio of 8:2 to the adducts **8**, **9** and **10** and using MeOH:AcOEt as solvent at a ratio of 1:9 to the adducts **11**, **12** and **13**. The reaction products were concentrated under reduced pressure and compared by TLC with those obtained in the step iv.

*The MAGs **8**-**13** spectroscopic data*

*2,3-Dihydroxypropyl[2-(hydroxyl(2-nitrophenyl)methyl)] acrylate (**8**)*

^{1}H NMR (MeOD, 300 MHz): δ 3.35 (s, 3H), 3.46-3.55 (m, 2H), 3.79-3.86 (m, 1H), 4.13-4.23 (m, 2H), 5.72-5.74 (m, 1H), 6.26 (s, 1H), 6.37 (s, 1H), 7.48-7.54 (m, 1H), 7.66-7.72 (m, 1H), 7.77 (d, 1H, *J* 7.8 Hz), 7.94 (d, 1H, *J* 8.1 Hz); ^{13}C NMR (MeOH, 75 MHz): δ 64.2, 67.0, 67.6, 71.1, 124.5, 126.4, 129.3, 129.8, 134.3, 138.4, 144.2, 167.1; IR (KBr) ν_{max}/cm^{-1}: 3383, 1712, 1527, 1350, 1265, 1157, 1120, 1045; ESI-HRMS (*m/z*) calc. for $C_{13}H_{15}NO_7$ [(M+Na)$^+$] 320.0746, found 320.0748.

*2,3-Dihydroxypropyl[2-(hydroxyl(3-nitrophenyl)methyl)] acrylate (**9**)*

^{1}H NMR (MeOD, 300 MHz): δ 3.35 (s, 2H), 3.49 (d, 2H, *J* 5.4 Hz), 3.75-3.83 (m, 1H), 4.07 (ddd, 1H, *J* 11.4/6.0/4.2 Hz), 4.17 (ddd, 1H, *J* 11.4/4.5/3.0 Hz), 5.70 (s, 1H), 6.13 (dd, 1H, *J* 2.1/1.5 Hz), 6.46 (dd, 1H, *J* 2.4/1.2 Hz), 7.56 (t, 1H, *J* 8.1 Hz), 7.77-7.81 (m, 1H), 8.13 (ddd, 1H, *J* 8.1/2.1/0.9 Hz), 8.26 (t, 1H, *J* 1.8 Hz); ^{13}C NMR (MeOH, 75 MHz): δ 64.1, 67.0, 71.1, 72.2, 123.0, 123.5, 126.5, 130.6, 134.6, 144.3, 146.4, 149.7, 167.0; IR (KBr) ν_{max}/cm^{-1}: 3375, 1708, 1527, 1350, 1273, 1157, 1095, 1049; ESI-HRMS (*m/z*) calc. for $C_{13}H_{15}NO_7$ [(M+Na)$^+$] 320.0746, found 320.0749.

*2,3-Dihydroxypropyl[2-(hydroxyl(4-nitrophenyl)methyl)] acrylate (**10**)*

^{1}H NMR (MeOD, 300 MHz): δ 3.35 (s, 2H), 3.47-3.51 (m, 3H), 3.75-3.82 (m, 1H), 4.04-4.21 (m, 2H), 5.69 (s, 1H), 6.10 (dd, 1H, *J* 2.1/1.5 Hz), 6.44 (dd, 1H, *J* 2.1/0.9 Hz), 7.63 (d, 2H, *J* 9.0 Hz), 8.19 (d, 2H, *J* 9.0 Hz); ^{13}C NMR (MeOH, 75 MHz): δ 64.1, 67.0, 71.1, 72.3, 124.5, 126.6, 129.3, 138.4, 144.2, 148.9, 167.0; IR (KBr) ν_{max}/cm^{-1}: 3375, 1708, 1519, 1350, 1269, 1157, 1111, 1049; ESI-HRMS (*m/z*) calc. for $C_{13}H_{15}NO_7$ [(M+Na)$^+$] 320.0746, found 320.0749.

*2,3-Dihydroxypropyl[2-(hydroxy(pyridin-2-yl)methyl)] acrylate (**11**)*

^{1}H NMR (MeOD, 300 MHz): δ 3.349 (s, 2H), 3.470-3.670 (m, 3H), 3.750-3.825 (m, 1H), 4.08 (ddd, 1H, *J* 11.4/9.0/6.0 Hz), 4,17 (ddd, 1H, *J* 11.4/7.5/4.5 Hz), 5.66 (s, 1H), 5.98 (d, 1H, *J* 0.6 Hz), 6.43 (d, 1H, *J* 0.9 Hz), 7.31 (ddd, 1H, *J* 7.5/5.1/1.2 Hz), 7.56 (d, 1H, *J* 8.1 Hz), 7.82 (td, 1H, *J* 7.8/1.8 Hz), 8.46 (ddd, 1H, *J* 5.1/1.8/0.9 Hz); ^{13}C NMR (MeOH, 75 MHz): δ 64.1, 67.0, 71.1, 73.9, 123.2, 124.2, 127.1, 138.8, 143.8, 149.47, 162.5, 167.3; IR (KBr) ν_{max}/cm^{-1}: 3383, 1712, 1269, 1161, 1111, 1049; ESI-HRMS (*m/z*) calc. for $C_{12}H_{15}NO_5$ [(M+H)$^+$] 254.0983, found 254.1021.

*2,3-Dihydroxypropyl[2-(hydroxyl(pyridin-3-yl)methyl)] acrylate (**12**)*

^{1}H NMR (MeOD, 300 MHz): δ 3.35 (s, 2H), 3.47-3.67 (m, 3H), 3.75-3.83 (m, 1H), 4.07 (ddd, 1H, *J* 11.4/6.0/4.2 Hz), 4.17 (ddd, 1H, *J* 11.4/4.5/2.4 Hz), 5.64 (s, 1H), 6.15 (s, 1H), 6.46 (d, 1H, *J* 1.2 Hz), 7.40 (ddd, 1H, *J* 7.8/4.8/0.6 Hz), 7.84 (dt, 1H, *J* 8.1/1.8 Hz), 8.43 (dd, 1H, *J* 4.8/1.5 Hz), 8.56 (d, 1H, *J* 1.8 Hz); ^{13}C NMR (MeOH, 75 MHz): δ 64.1, 67.0, 70.9, 71.1, 125.1, 126.2, 137.0, 140.3, 144.1, 149.2, 149.4, 167.0; IR (KBr) ν_{max}/cm^{-1}: 3348, 1716, 1265, 1157, 1118, 1029; ESI-HRMS (*m/z*) calc. for $C_{12}H_{15}NO_5$ [(M+H)$^+$] 254.0983, found 254.1023.

*2,3-Dihydroxypropyl[2-(hydroxyl(pyridin-4-yl)methyl)] acrylate (**13**)*

^{1}H NMR (MeOD, 300 MHz): δ 3.35 (s, 3H), 3.49-3.60 (m, 2H), 3.77-3.83 (m, 1H), 4.06-4.21 (m, 2H), 5.61 (s, 1H), 6.08 (dd, 1H. *J* 2.5/1.0 Hz), 6.45 (dd, 1H, *J* 2.0/1.0 Hz), 7.47 (d, 2H, *J* 6.5 Hz), 8.47 (dd, 2H, *J* 4.5/1.5 Hz); ^{13}C NMR (MeOH, 75 MHz): δ 64.1, 64.6, 71.1, 71.8, 123.7, 127.0, 143.9, 150.0, 167.0; IR (KBr) ν_{max}/cm^{-1}: 3363, 1716, 1269, 1161, 1115, 1053; ESI-HRMS (*m/z*) calc. for $C_{12}H_{15}NO_5$ [(M+H)$^+$] 254.0983, found 254.1027.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as a PDF file.

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