Solventless catalyzed synthesis of 2,4 bis (arylidene) -8-methyl-8-azabicyclo[3.2.1]octan-3-ones under microwave irradiation.

- **Renata Gasparova,[a,b] Didier Villemin,[a*] Nathalie Bar,[a]**

  [1] Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, INC3M, FR 3038, ENSICAEN et Université de Caen Normandie, 14050 Caen, France

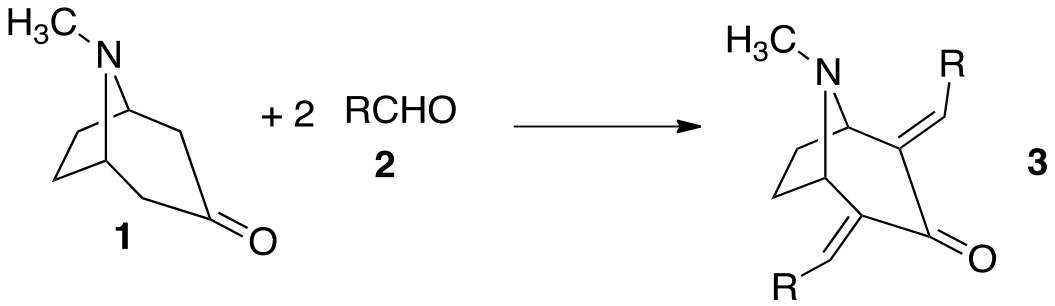
  [2] Department of Chemistry, Faculty of Natural Sciences, University of St. Cyril and Methodius, Námestie J. Herdu 2, Trnava, Slovak Republic, e-mail: renata.gasparova@ucm.sk.

- * Correspondence: didier.villemin@ensicaen.fr

Cross-conjugated dienones are very important biologically active products and in particular 3,5-bis(arylmethylidene) derivatives of cyclohexanone and piperidin-4-one display a broad spectrum of biological activities, such as androgenic, antimicrobial, 3 hypocholesterolemic, choleretic, anti-inflammatory, antimutagenic, antitumour 8 and antipyretic activities. High cytotoxicity of bis(arylmethylidene)cyclohexanones and -piperidin-4-ones against murine and human leukemia cells was documented

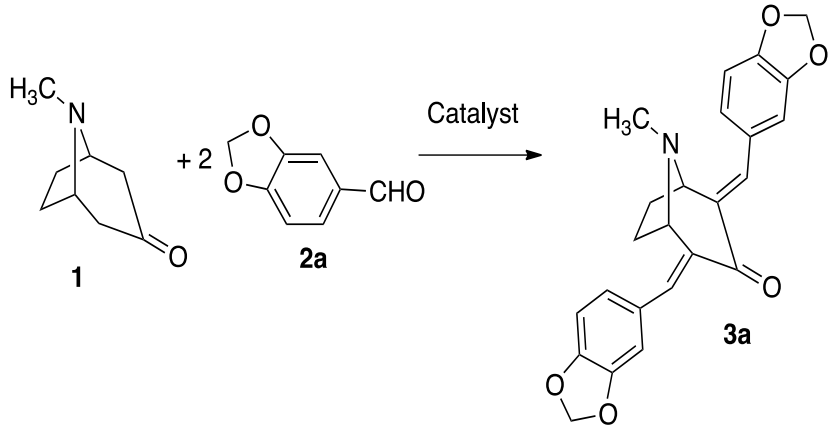
S. Z. Vatsadze, A. G. Golikov, A. P. Kriven'ko, N. V. Zyk, Chemistry of cross-conjugated dienones, *Russian Chemical Reviews* , 2008, 77 (8) 661-681; doi :10.1070/RC2008v077n08ABEH003771

Arylidene-8-methyl-8-azalbicyclo[3.2.1]octan-3-ones are also potential bioactive products, some of them were described as anticonvulsant.



- **Scheme 1** : Synthesis of 2,4-bis (arylidene)-8-methyl-8-azabicyclo[3.2.1]octan-3-ones **3** from tropinone **1** and aromatic aldehydes **2**.

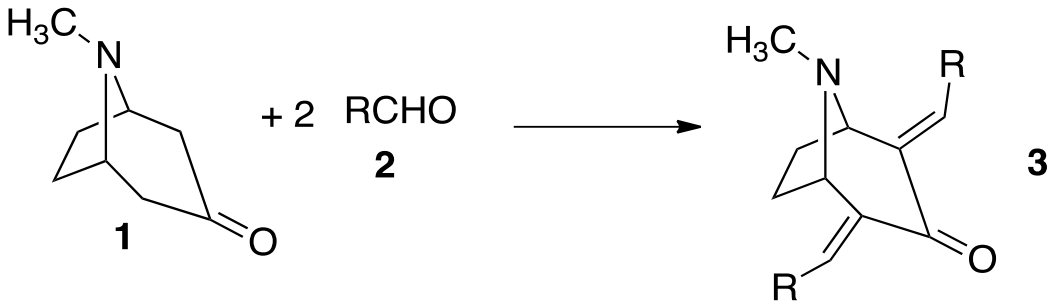
In a preliminary experiment, we have studied the reaction of condensation of tropinone with piperonal in order to optimize the experimental condition



Catalysts	RT	Microwave		
Piperidine		partial reaction		
Neutral alumina	no reaction	**Catalysts**	**RT**	**Microwave**
		Piperidine		partial reaction
		Neutral alumina	no reaction	partial reaction
KF on alumina	reaction	**KF on alumina**	reaction	reaction and byproducts
Silica	no reaction	**Silica**	no reaction	partial reaction
K10	complete after 3 days	**K10**	complete after 3 days	complete within 4 min

A. Ben Alloum, B. Labiad ,D. Villemin, Application of microwave heating techniques for dry organic
B. reactions. *J. Chem. Soc. Chem. Commun.*, 1989, 386-387; doi: 10.1039/C39890000386.

We have chosen to conduct the condensations of tropinone with K10 clay, under microwave irradiation with other aromatic aldehydes both in a stoichiometry 1/2 . The products were eluted with acetonitrile and purified by flash chromatography on silica column. The monocondensation products can be isolated in very small amount as oil and the bicondensation products are recovered as crystallized solids



Aldehydes : piperonal **2a,** benzaldehyde **2b,** 2,4-dichlorobenzaldehyde **2c,** 2,4,6-trimethoxybenzaldehyde **2d,** 3-phenoxybenzaldehyde **2e,** furaldehyde **2f,** cinnamaldehyde **2g**

All products have been characterized by ^{1}H and ^{13}C NMR, elemental analysis and ESI mass spectroscopy. The stereochemistry of double bonds (*2E,4E*) were attributed by NOE experiments according to the method described7 for the nortropinone derivatives.

Aldehyde		Yield (%)	mp (mp lit.)	Mol formula	Found (required)%	
					C	H
2a	benzaldehyde	77	152 (153)	$C_{22}H_{21}NO$	83.63(83.78)	6.76(6.71)
2b	2,4-dichlorobenzaldehyde	88	222	$C_{22}H_{17}NOCl_4$	58.10(58.31)	3.75(3.78)
2c	2,4,6-trimethoxybenzaldehyde	85	215	$C_{28}H_{33}NO_7$	67.75(67.86)	6.82(6.71)
2d	piperonal	96	214 (214)	$C_{24}H_{21}NO_5$	71.37(71.45)	5.34(5.25)
2e	3-phenoxybenzaldehyde	92	114	$C_{34}H_{29}NO_3$	81.83(81.74)	5.95(5.85)
2f	furaldehyde	81	145	$C_{18}H_{17}NO_3$	73.17(73.20)	5.86(5.80)
2g	cinnaldehyde	98	149	$C_{26}H_{25}NO$	84.95(84.98)	6.90(6.86)

Conclusion

New (2,4-bis-arylidene)-8-methyl-8-azabicyclo[3.2.1]octan-3-ones can be conveniently prepared by the reaction of tropinone with various aromatic aldehydes without solvent on K10 clay under microwave irradiation.

New dienones derived from tropinones will be tested in various biological assays