chemistry proceedings

MDPI

Proceeding Paper

Microwave Activation: Solventless Catalysed Synthesis of Cross Conjugated Dienones of Tropinone †

Renata Gasparova [1,2], Didier Villemin [1,*] and Nathalie Bar [1]

[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; renata.gasparova@ucm.sk.
* Correspondence: didier.villemin@ensicaen.fr

† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: https://ecsoc-27.sciforum.net/.

Abstract: Cross-conjugated dienones are very important biologically active products. The condensation of N-methyl-8-azabicyclo[3.2.1]-bicyclo[3.2.1]octan-3-one (tropinone) with aromatic aldehydes takes place in the presence of acidic (K10 clay, silica) or basic catalysts (alumina, KF-alumina). The best yields of (*2E*,*4E*)-2,4-bis-arylmethylene-8-methyl-8-azabicyclo[3.2.1]octan-3-ones were obtained with the K10 clay under microwave irradiation without solvent. New dienones derived from tropinone will be tested in various biological assays.

Keywords: cross-conjugated dienones; tropinone; microwave; clay catalysis; KF-alumina

Citation: Gasparova, R.; Villemin, D.; Bar, N. Microwave Activation: Solventless Catalysed Synthesis of Cross Conjugated Dienones of Tropinone. *Chem. Proc.* **2023**, *14*, x. https://doi.org/10.3390/xxxxx

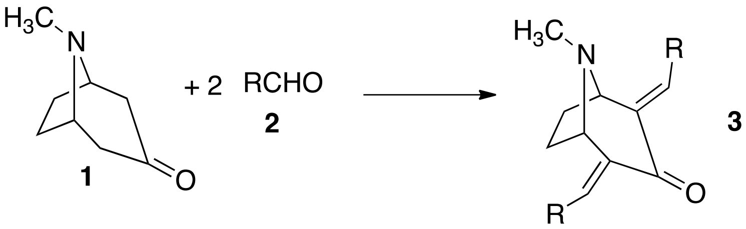
Academic Editor(s): Name

Published: 15 November 2023

1. Introduction

Cross-conjugated dienones exhibit important biologically activities [1]. Furthermore, tropane derivatives are very known class of bioactive alkaloids [2] (atropine, cocaine…).

In the course of our ongoing research on Knoevenagel condensation in dry condition under microwave activation [3], we are interested in performing condensation of tropinone **1** with aromatic aldehydes in order to prepare potentially active precursors. We described herein the solventless synthesis of 2,4-bis(arylidene)-8-methyl-8-azabicyclo [3.2.1]octan-3-ones, only some derivatives were described more than one century ago [4].



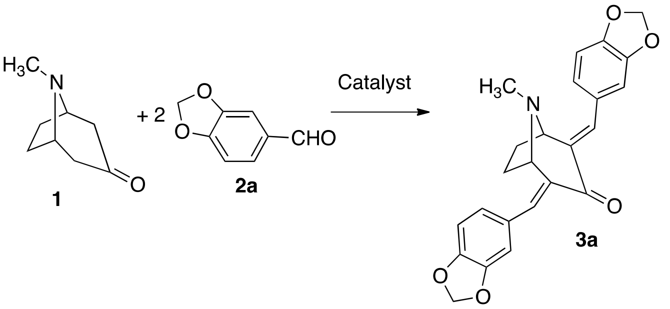
Scheme 1. Synthesis of 2,4-bis (arylidene)-8-methyl-8-azabicyclo[3.2.1]octan-3-ones **3** from tropinone **1** and aromatic aldehydes **2**.

2. Results and Dicussion

In a preliminary experiment, we have studied the reaction of condensation of tropinone with piperonal **2a** in order to optimize the experimental conditions. First, we have investigated non catalytic reaction by simply grinding the two solids at room temperature [5]. Within few minutes, an eutectic liquid (tropinone/piperonal stoichiometry: 1/1 or 1/2) was formed, but no reaction took place after ten days.

In a second time, we have chosen to explore the abilities of various catalysts of different acid-base properties (Table 1). The progress of the reactions was monitored by TLC.

The progress of the reactions was monitored by TLC [6]. Firstly, we have performed the condensation of tropinone and piperonal in the presence of few drops of piperidine, as a base, but unfortunately, an incomplete condensation took place even under microwave irradiation.



Scheme 2. catalysed condensation of tropinone with piperonal.

Table 1. Catalysts and experimental conditions for condensation of tropinone **1** with piperonal **2a**.

Catalysts	RT conditions	Microwave
Piperidine	Very partialreaction	partial reaction
Neutral alumina	no reaction	partial reaction
KF on alumina	reaction	reaction with by-products
Silica	no reaction	partial reaction
K10	complete after 3 days	complete within 4 min

Next, we have focussed on several solid catalysts, two with basic properties such as alumina and KF on alumina and two with acidic properties, such as silica and K10 clay. With neutral alumina (Woelm 2087), a poorly basic catalyst, no reaction was observed at room temperature whereas the reaction took place under microwave irradiation but ungratifyingly, the reaction was not completed. 6 With the very basic catalyst KF on alumina, the solid became rapidly yellow, even at room temperature. Nevertheless, in the case of alumina/KF (and unlike alumina), the products remain adsorbed on the support and are very difficult to recover using a solvent. Moreover, by-products were detected under microwave irradiation.

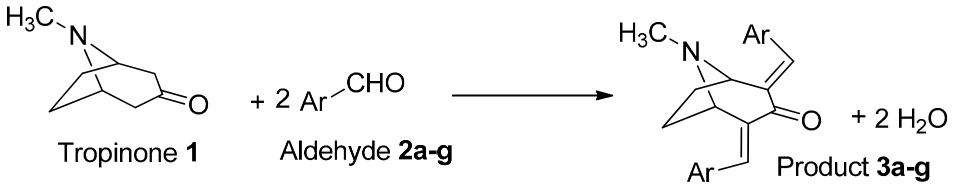
With silica, a poorly acidic catalyst, no reaction was observed at room temperature after 24 h. With the more acidic clay K10 the reaction occurred, and the reaction was completed after more than 3 days, but under microwave irradiation (50 W, 4 min, 2450 MHz) the condensation was very rapid and efficient.

It is worth mentioning that with piperonal, under basic or acidic conditions, the bicondensation product was accompanied by only a small amount of the monocondensation product. By varying the stoichiometry of the reactants, it was not possible to prepare pure monocondensation product whereas the bicondensation product can be obtained with an excellent purity with an excess of piperonal (piperonal/tropinone equal or superior to 2).

Based on these results and by taking into consideration both the purity of the product and yield of the reaction, we have chosen to conduct the condensations of tropinone with K10 clay, under microwave irradiation to recover using a solvent. Moreover, by-products were detected under microwave irradiation. with other aromatic aldehydes ~~both~~ in a stoichiometry 1/1. 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. In one case, the monocondensation product was obtained in significant amount with the hindered 2,6-dichlorobenzaldehyde.

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*) was attributed by NOE experiments according to the method described [7] for the nortropinone derivatives. The products of condensation are reported in Table 2.

Table 2. Condensation products **3a–g** obtained from tropinone **1** and aromatic aldehydes with K10 clay under microwave irradiation (2450 MHz, 4 min, 50 W).



Product	Aldehyde	Yield (%)	mp (mp lit.)	Mol Formula	Found (required) %	
					C	H
2a	piperonal	96	214	$C_{24}H_{21}NO_5$	71.37 (71.45)	5.34 (5.25)
2b	benzaldehyde	77	152 (153^4)	$C_{22}H_{21}NO$	83.63 (83.78)	6.76 (6.71)
2c	2,4-dichlorobenzaldehyde	88	222	$C_{22}H_{17}NOCl_4$	58.10 (58.31)	3.75 (3.78)
2d	2,4,6-trimethoxybenzaldehyde	85	215	$C_{28}H_{33}NO_7$	67.75 (67.86)	6.82 (6.71)
2e	3-phenoxybenzaldehyde	92	114	$C_{34}H_{29}NO_3$	81.83 (81.74)	5.95 (5.85)
2f	furaldehyde	81	145 (145^4)	$C_{18}H17NO_3$	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)

3. Conclusions

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.

4. Experimental

The reactions were conducted with the monomode resonance cavity Prolabo Synthewave 402 (2450 MHz) piloted by a microcomputer. ^{1}H and ^{13}C NMR (reference from internal Me_4Si) were recorded on a Brucker AC 250 instrument from solution in $CDCl_3$ with TMS as the internal reference. FT IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. Elemental analyses were recorded on a CE Instrument NA 2500. Melting points were determined with a Kofler bench. KF on alumina was prepared according to the litterature.

General procedure for the preparation of (2E,4E)-2,4-bis-benzo[1,3]dioxol-5-ylmethylene-8-methyl-8-aza-bicyclo[3.2. 1]octan-3-one. In a typical experiment, a mixture of 8-methyl-8-aza-bicyclo [3.2.1]octan-3-one (600 mg, 4.3 mmol) and piperonal (1.3 g, 8.6 mmol) was ground and a liquid was obtained. The liquid was adsorbed on clay K10 (2 g) and the solid mixture was irradiated at 50 W for 4 min. The yellow solid was extracted with acetonitrile (3 X 20 mL). After evaporation of solvent, the residue was chromatographied on silica with AcOEt - n-hexane (30:70) and then with pure AcOEt.

(2E,4E)-2,4-bis-benzo[1,3]dioxol-5-ylmethylene-8-methyl-8-aza-bicyclo[3.2.1]octan-3-one. Yellow solid, was recrystallized in ethyl acetate. (mp = 214 °C; lit 214 °C). $C_{24}H_{21}NO_5$; IR = 1680 cm^{-1} (νCO). PMR: δ = 1.50–1.55 (m, 4H, CH_2-CH_2); 2.30 (s, 3H, N-CH_3); 3.50 (m, 2H, 2xCH-N); 6.0 (s, 4H, 2X-O-CH_2-O-); 6.90–7.0 (m, 6H, 2X 3Harom).

Author Contributions: Conceptualization, D.V.; investigation, R.G.; writing—review and editing, D.V., N.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors thanks Karine Jarsalé for mass spectrometry spectra.

Conflicts of Interest: The authors declare no conflict of interest.

References and notes

1. Vatsadze, S.Z.; Golikov, A.G.E.; Kriven'ko, A.P.; Zyk, N.V.E. Chemistry of cross-conjugated dienones. *Russ. Chem. Rev.* **2008**, *77*, 661–681.
2. Fodor, G. *Chemistry of the Alkaloids*; Chapter 15; Pelletier, S.W., Ed.; Van Nostrand-Reinhold: Princeton, NJ, USA, 1970.
3. Alloum, A.B.; Labiad, B.; Villemin, D. Application of microwave heating techniques for dry organic reactions. *J. Chem. Soc. Chem. Commun.* **1989**, 7, 386–387.
4. Willstäter, R. Ueber Dibenzaltropinone. *Berichte Der Dtsch. Chem. Ges.* **1897**, *30*, 731–736.
5. Tanaka, K.; Toda, F.J.C.R. Solvent-free organic synthesis. *Chem. Rev.* **2000**, *100*, 1025.
6. Villemin, D.; Jullien, A.; Bar, N. Optimisation of Solvent Free Parallel Synthesis under Microwaves: synthesis of new arylacrylonitriles. *Green Chem.* **2003**, *5*, 467.
7. Jung, D.I.; Park, C.S.; Kim, Y.H.; Lee, D.H.; Lee, Y.G.; Park, Y.M.; Choi, S.K. Synthesis of 2,4-disubstituted nortropinone derivative by aldol condensation. *Synth. Commun.* **2001**, *31*, 3255.