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An efficient synthesis of warfarin acetals on montmorillonite clay K-10 with microwaves

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The microwave promoted reaction of warfarin with methanol, or ethanol, in the presence of montmorillonite clay K-10 as a catalyst, affords the corresponding acetals, 2-methoxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-c]chromen-5-one (**2**) and 2-ethoxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-c]chromen-5-one (**3**), respectively, in good yields.

Keywords: warfarin, cyclic acetals, montmorillonite K-10, microwaves.

INTRODUCTION

Coumarins occupy a special place in the realm of natural and synthetic organic chemistry owing to their useful and diverse biological activities such as molluscicid,[1] anthelmintic, hypnotic, insecticidal[2] and anticoagulant properties.[3] Some of the derivatives can also serve as fluorescence brighteners.[4] These compounds can also be used for the synthesis of other products as furocoumarins, chromones, coumarones and 2-acylresorcinols.[5]

In continuation of our investigations in the field of the synthesis of coumarin derivatives, the synthesis of heterocyclic condensed 4-hydroxycoumarin derivatives is described herein. In the previous syntheses of a warfarin cyclic acetal, as a blood anticoagulant,[6,7] Lewis acids were used as catalysts (zinc chloride, iron(III)chloride).

There is a number of methods available for the synthesis of acetals. Usually, the synthesis of acetals is carried out with catalysis by a strong proton acid, such as sulfuric acid,[8,9] phosphoric or methanesulfonic acid[10] or by Lewis acids. These methods are not entirely satisfactory, owing to drawbacks such as low yield, long reaction times, corrosive properties of catalysts and difficult work-up.

Montmorillonite clay has been used as a catalyst for a number of organic reactions and offers several advantages over classical acids: strong acidity, non-corrosive properties, cheapness, mild reaction conditions, high yields and selectivity and the ease of set-up and work-up.[11]

Montmorillonite K-10 clay has been used as an efficient catalyst for the formation of acetals in the preparation of a variety of multifunctional organic molecules. It is an inexpensive non-toxic powder, which can be easily filtered from the reaction mixture and may be reused.

In the last few years, a growing interest has been shown in the use of microwave heating in organic synthesis[12] ("MORE" chemistry = Microwave Oven-induced Reaction). The use of such non-conventional reaction conditions reveal the following features: (i) a reduction in the usual thermal degradation and/or better selectivity[13] and (ii) for some reactions, especially under heterogeneous conditions,[14] there seems to be a marked rate enhancement compared to conventional heating.

Microwave heating has been used for a variety of organic reactions and has found application in rapid and efficient syntheses of organic compounds.[15] More recently, the emphasis has shifted in favour of microwaves-assisted methods under solvent-free conditions,[16] which have a special appeal as they provide an opportunity to work with open vessels, thus avoiding the risk of the development of high pressure.

New results on the activation of organic compounds adsorbed on inorganic solids (dry organic reactions), are described in this paper. Generally the "dry" organic reactions were performed at room or mild temperature conditions (60–80 ºC). The poor thermal diffusion of the inorganic solids (clay, silica, and alumina) was an obstacle for the homogeneous thermal activation of these types of reaction. Inorganic solids (clay, silica, and alumina) do not absorb microwaves at 2450 MHz and therefore are not an obstacle for the transmission of microwaves. In "dry" reactions, hydroxyl groups, water, organic solvents or organic compounds present on the surface of these inorganic solids strongly absorb the microwaves and these species are thereby activated.

RESULTS AND DISCUSSION

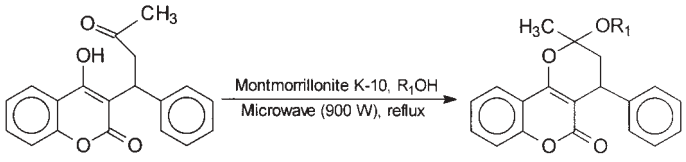
An easy and efficient procedure for the microwave promoted synthesis of the cyclic acetals 2-methoxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-c]chromen-5-one (**2**) and 2-ethoxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-c]chromen-5-one (**3**) in good yields from 4-hydroxy-3-(3-oxo-1-phenylbutyl)-chromen-2-one (**1**) catalyzed by montmorillonite clay K-10 (Scheme 1) is reported here.

In pharmacology, warfarin is one of the most important blood anticoagulants but the cyclic acetals **2** or **3**, are even better anticoagulants than warfarin.

Generally speaking, on the basis of the results obtained as shown in Scheme 1, the microwave promoted intra-cyclodehydration reaction of warfarin with methanol, or ethanol, to the corresponding acetals **2** or **3**, in the presence of montmorillonite clay K-10 as a catalyst is a better choice than the conventional methods in term of reaction temperature, reaction time and yield.

In the case of microwave heating, it appears that, unlike conventional heating, the bulk temperature is no longer representative of the reaction conditions. Secondly, a substantial increase in the yields and a decrease in the reaction times were observed in comparison with the usual conventional methods. The acetals are easily extractable in good

yields from the support. The only products observed under the employed conditions were the cyclic acetals **2** or **3**.



1

2 $R_1 = CH_3$

3 $R_1 = CH_2CH_3$

Derivatives	Irradiation conditions		Yield (%)		M.p. (ºC)	M.W.
	Time (min)	Temperature (ºC)	Found	Lit.[1,7]		
2 $R_1 = CH_3$	2	65	90	73	165	322
	5	65	89	73	165	322
3 $R_1 = CH_2CH_3$	2	80	67	55	176	336
	5	80	65	55	176	336

Scheme 1.

In conclusion, a simpler and mild method for the intracyclodehydration of 4-hydroxy-3-(3-oxo-1-phenylbutyl)-chromen-2-one (**1**) to the corresponding acetals 2-methoxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-c]chromen-5-one (**2**) or 2-ethoxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-c]chromen-5-one (**3**) on a clay surface using microwave irradiation has been demonstrated.

EXPERIMENTAL

General. Melting points were recorded on Kofler-hot plate apparatus and are uncorrected. Microanalysis of carbon and hydrogen was carried out with a Carlo Erba 1106 microanalyser. IR spectra were run on a Perkin-Elmer Grating Spectrophotometer Model 137 and Model 197. NMR spectra were recorded on a Varian FT 80 A and 200 "Gemini" spectrometer (^1H at 80 and ^{13}C at 200 MHz, $CDCl_3$), using TMS as the internal standard. The chemical shifts are given in δ ppm, and the coupling constants *J* in Hz. Abbreviations: *s*-singlet, *d*-doublet, *t*-triplet, *q*-quartet, *m*-multiplet and *b*-broad. Mass spectroscopic analyses were carried out on a MAT 44S and Finnigen MAT 8230 instruments. A Sears Kenmore household microwave oven operating at 2450 MHz was used at its full power, 900 W, for all the experiments. The products were identified by comparison of their mp., IR and NMR spectra with those of authentic samples.

Typical procedure

Warfarin (1.0 g, 0.003 mol) was dissolved in a small amount of dry methanol, or ethanol (10 ml) and adsorbed on montmorillonite K-10 (450 mg, 45 % weight amount). The reaction vessel was placed inside the microwave oven and irradiated (900 W) for 2-5 min. The progress of the reaction was monitored by TLC. The reaction mixture had to have dissolved prior to filtration and washing with dry methanol (2 × 15 ml) or ethanol. The solvent was removed under reduced pressure to afford the crude product. The crude product was purified by crystallization from methanol.

2-Methoxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-c]chromen-5-one (**2**) as white needles, yield 0.82 g (90 %), mp. 165–166 ºC, IR (KBr) ν_{max}/cm^{-1}: 1708, 1625, 1611, 1493, 1379, 1142,

1102, 1054, 730, 690. ^{1}H-NMR ($CDCl_3$): 1.47 (3H, *s*, CH_3) 2.25-2.32 (2H, AB*q*, C-3, *J* = 14.2 Hz, *J* = 7.3 Hz, *J* = 5.4 Hz), 3.17 (3H, *s*, OCH_3), 4.15 (H, *dd*, C-4, *J* = 7.3 Hz, *J* = 5.4 Hz), 7.13–7.17 (3H, *m*, Ar), 7.43–7.58 (5H, *m*, C-8, C-9, C-7, Ar), 7.66 (H, *dd*, C-10, *J* = 7.8, *J* = 1.6 Hz,). ^{13}C($CDCl_3$): 23.41 (CH_3), 38,99 (C-3), 42.18 (C-4), 48.83 (CH_3O), 102.29 (C-2), 105.95 (C-4a), 161.04 (C-5), 161.99 (C-10b). MS = $[M^+$+1]323, M^+ 322, M^+–15 (CH_3, 100 %) 307, M^+ – 31 (OCH_3) 291. Anal. Calcd. for ($C_{20}H_{18}O_4$): C, 74.52, H, 5.63, Found C, 74.43 H, 5.49.

2-Ethoxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-pyrano[3,2-c]chromen-5-one (**3**), as white needles, yield 0.59g (67 %) mp. 174–176 ºC, IR (KBr) ν_{max}/cm^{-1}: 1710, 1629, 1607, 1490, 1377, 1142, 1102, 1054, 730, 690. ^{1}H-NMR ($CDCl_3$): 1.45 (3H, *s*, CH_3), 1.15 (3H, *t*, CH_3, *J* = 7.15 Hz), 2.23–2.54 (2H, AB*q*, C-3, *J* = 14.5 Hz, *J* = 7.5 Hz, *J* = 5.5 Hz, *J* = 0.85 Hz), 3.37 (2H, *q*, OCH_2, *J* = 7.15Hz), 4.13 (H, *dd*, C-4, *J* = 5.5 Hz, *J* = 7.5 Hz), 7.13–7.16 (3H, *m*, Ar), 7.43–7.56 (5H, *m*, C-8, C-9, C-7, Ar) 7.61 (H, *dd*, C-10, *J* = 7,8 *J* = 1.6 Hz). ^{13}C ($CDCl_3$): 15.61 (CH_3), 25.01 (CH_3), 38.99 (C-3), 57.41 (CH_2O), 42.38 (C-4), 102.79 (C-2), 105.55 (C-4a), 160.54 (C-5), 162.19 (C-10b). MS = $[M^+ + 1]$ 337, M^+ 336, $M^+ – 15$ (CH_3 100 %) 321, $M^+ – 45$ (OCH_2CH_3) 291. Anal. Calcd. for ($C_{21}H_{20}O_4$): C, 75.00, H, 6.00, Found C, 75.24 H, 6.26.

ИЗВОД

СИНТЕЗА ВАРФАРИН АЦЕТАЛА НА МОНТМОРИЈОНИТ ГЛИНИ K-10 ПОД ДЕЈСТВОМ МИКРОТАЛАСНОГ ЗРАЧЕЊА

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Реакцијом варфарина са апсолутним метанолом (или етанолом) под дејством микроталасног зрачења и у присуству монтморијонит глине K-10 као катализатора, добијају се ацетали: 2-метокси-2-метил-4-фенил-3,4-дихидро-2*H*-пирано[3,2-c]хромен-5-он (**2**) или 2-етокси-2-метил-4-фенил-3,4-дихидро-2*H*-пирано[3,2-c]хромен-5-он (**3**) у добрим приносима.

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