ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ

НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ
АРМЕНИЯ

Հայաստանի քիմիական հանդես 50, №3-4, 1997 Химический журнал Армении

NEW CONVENIENT METHOD FOR PREPARATION OF 2-(2-HYDROXYBENZYL)-ACETYLACETIC AND -BENZOYLACETIC ESTERS

B. SERGE KIRKIACHARIAN, JEHAD HARBALI,
ALAIN DANAN, ISABELLE SIMON

Laboratoire de Therapeutique. Faculte de Pharmacie. Universite de PARIS-SUD 5, Rue J.B. Clement - 92296 Chatenay Cedex (France)

ABSTRACT. Reduction of 3-acetyl and 3-benzoyl coumarins, performed with sodium borohydride in alcoholic solvents, lead to the corresponding 2-(2-hydroxybenzyl)-acetylacetic and -benzoylacetic esters.

INTRODUCTION

A survey of the literature indicated the lack of a convenient route for the synthesis of 2-(2-hydroxybenzyl)-acetylacetic and -benzoylacetic esters. Therefore we decided to investigate electrophilic and nucleophilic hydride reductions of the 3-substituted coumarins as synthons.

Sodium borohydride is a widely used reagent for preparation of alcohols from aldehydes and ketones. Furthermore, the reduction of conjugated carbon-carbon double bonds having at α-position an anion stabilizing group are also reported [1-4]. In the case of 3-acetyl, 3-benzoyl and 3-carbethoxy coumarins reductions performed in pyridine lead to the corresponding, 3,4-dihydroderivatives [4-6]. The 3-substituted esters of 3,4-dihydrocoumarins were also obtained by reduction with boranes [7], while their reduction with sodium borohydride in alcoholic solvents results in the formation of corresponding 2-(2-hydroxybenzyl) malonic esters [8].

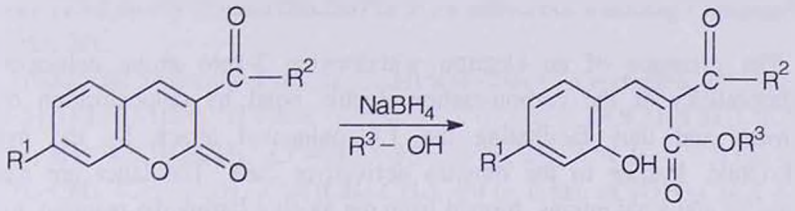
The objective of the present paper was to investigate whether the reduction of various 3-acetyl and 3-benzoyl coumarins with sodium borohydride in alcoholic solvents could lead to the desired compounds. The points of interest

being the reactivities of the ethylenic 3,4-double bond, of the ketone and the lactone groups and that of the heterocyclic system.

RESULTS

Thus, when sodium borohydride reductions in alcohols were applied to the 3-acetyl coumarins [9,10] and 3-benzoyl coumarins [11,12] **1a-d**, prepared in excellent yields via a Knœvenagel condensation, the corresponding 2-(2-hydroxybenzyl)-acetylacetic and -benzoylacetic esters **2a-f** were obtained in good yields, confirming our synthetic approach (Scheme 1).

Scheme 1



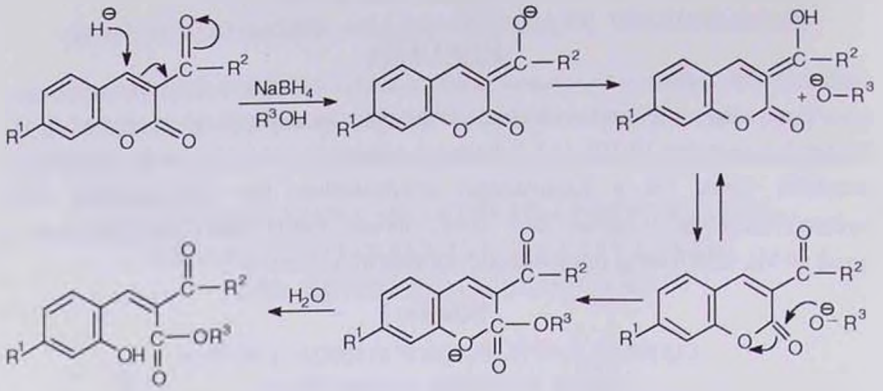
1a-d **2a-f**

Product	1a	1b	1c	1d	2a	2b	2c	2d	2e	2f
R^1	H	OCH_3	H	OCH_3	H	H	OCH_3	OCH_3	H	OCH_3
R^2	CH_3	CH_3	C_6H_5	C_6H_5	CH_3	CH_3	CH_3	CH_3	C_6H_5	C_6H_5
R^3					CH_3	C_2H_5	CH_3	C_2H_5	C_2H_5	C_2H_5

Due to the solvolysis of sodium borohydride [13,14] and to the weak reactivity of these derivatives when compared to O-ethyl coumarin 3-carboxylates (8), the addition of the reducing agent was carried our progressively and continued until disappearance of the starting compound (4-5 hours). The progress of the reaction was controlled by thin layer chromatography (TCL). All derivatives **2a-f** were purified by column chromatography over silica gel. The structures were determined by elementary analysis (C±0.31%, H±0.22%), I.R. (ν C=O at 1690 cm^{-1} and 1720 cm^{-1} attributable to ketone and ester groups) and ^{1}HMR spectroscopy.

On the basis of these results and those previously obtained (8), which proved that deuteriation takes place at the 4-position (benzyl group), Scheme 2 can be proposed to explain the mechanism of these reactions.

Scheme 2



The presence of an electron withdrawing 3-keto group enhances the electrophilicity of the carbon-carbon double bond by delocalization of the electrons and thus facilitating the 1,4-conjugated attack by the hydride nucleophile, leading to the dihydro derivatives **3a-f**. The latter are cleaved further by alkoxyde anions, formed from the alcohol during the reaction, to give the corresponding esters **2a-f**.

In the case of 3-acetyl derivatives **2a-c**, there is a keto-enol equilibrium in $CDCl_3$ at 20°C which indicates the presence of approximately 60-70% of the enolic forms. This was confirmed by acetylation of the enol **2a** which leads to the diacetylated compound.

CONCLUSION

This study indicates that it is possible to prepare in a convenient fashion and with good yields, various substituted 2-(2-hydroxybenzyl)-acetylacetic and -benzoylacetic esters, without affecting the ketone group, via the sodium borohydride reduction of appropriate coumarins.

EXPERIMENTAL PART

IR spectra were recorded on a Perkin Elmer 177 spectrophotometer and ^1H NMR spectra on a Brucker AC200 spectrometer.

Typical procedure: methyl 2-(2-hydroxybenzyl)-acetylacetate 2a. A magnetically stirred solution of 3-acetyl coumarin **1a** (1.8 *g*, 10 *mmol*) in 200 *ml* of dry methanol is cooled in an ice bath. Sodium borohydride (1.9 *g*, 50 *mmol*) is added in portions of 0.38 *g* (10 *mmol*) every hour. When TLC (CH_2Cl_2) shows

that all starting coumarin has disappeared (4-5 *hours*), 10 *ml* of water are added and the solvent is evaporated under reduced pressure (40°C). The residue is extracted with 3×50 *ml* of CH_2Cl_2; combined organic extracts are washed with water, dried with sodium sulfate and evaporated. The remaining product is purified by column chromatography on silica gel (CH_2Cl_2), Yield: 1.55 *g* (70%).

Molecular Formula: $C_{12}H_{14}O_4$ (222.2), Yield: 70%, I.R. (ν cm^{-1}): 3500-3100-1720-1680, ^{1}H NMR (δ ppm): 1.6 and 2.15 (2s, 3H, =C(OH)-**CH_3**, -CO-**CH_3**), 2.9-3.4 [m, 2H, Ar-**CH_2**-(keto and enol)], 3.75 and 3.8 [2s, 3H, -COO**CH_3** (keto and enol)], 3.9 [t, 0.3H, Ar-CH_2-**CH** (keto)], 4.1 [s, 0.7H, =C(**OH**)-CH_3 (enol)], 6.5-7.1 (m, 5H, **arom.** and Ar-**OH**).

Preparation of other products. Reductions are carried out as above in dry methanol **(2c)**, in dry ethanol **(2b, 2d)** or in an anhydrous mixture of ethanol/THF [7/3] **(2e, 2f).**

Product **2b**: Molecular Formula: $C_{13}H16O4$ (236.3), Yield: 58%, I.R. (ν cm^{-1}): 3600-3100-1720-1690, ^{1}H NMR (δ ppm): 1.2 (t, 3H, -COOCH_2-**CH_3**), 1.3 and 2.2 (2s, 3H, =C(OH)-**CH_3**, -CO-**CH_3**), 3.3-3.6 (m, 2H, Ar-**CH_2**-), 3.9 (m, 0.4H, Ar-CH_2-**CH**), 4.25 (q, 2H, -COO**CH_2**-CH_3), 4.4 (s, 0.6H, =C(**OH**)-CH_3), 4.5 (s, 1H, Ar-**OH**), 6.8-7.4 (m, 4H, **arom.**).

Product **2c**: Molecular Formula: $C_{13}H_{16}O_5$ (252.3), Yield: 67%, I.R. (ν cm^{-1}): 3600-3100-1720-1690, ^{1}H NMR (δ ppm): 1.6 and 2.15 (2s, 3H, =C(OH)-**CH_3**, CO-**CH_3**), 3.0-3.3 (m, 2H, Ar-**CH_2**-), 3.6 and 3.65 (2s, 3H, -COO**CH_3**), 3.8 (s, 3H, Ar-**OCH_3**), 3.85 (m, 0.3H, Ar-CH_2-**CH**), 4.3 (s, 0.7H, =C(**OH**)-CH_3), 6.4-7.6 (m, 4H, **arom.** and Ar-**OH**).

Product **2d**: Molecular Formula: $C_{14}H_{18}O_5$ (266.3), Yield: 62%, I.R. (ν cm-1): 3600-3100-1715-1690, ^{1}H NMR (δ ppm): 1.2 (t, 3H, -COOCH_2-**CH_3**), 2.2 (s, 3H, -CO-**CH_3**), 3.2 (m, 2H, Ar-**CH_2**-CH), 3.7 (s, 3H, Ar-**OCH_3**), 3.9 (m, 1H, Ar-CH_2-**CH**), 4.25 (q, 2H, -COO**CH_2**-CH_3), 5.4 (s, 1H, Ar-**OH**), 6.7-7.5 (m, 3H, **arom.**).

Product **2e**: Molecular Formula: $C_{18}H_{18}O_4$ (298.3), Yield: 56%, I.R. (ν cm^{-1}): 3600-3100-1715-1690, ^{1}H NMR (δ ppm): 1.3 (t, 3H, -COOCH_2-**CH_3**), 3.25 (d, 2H, Ar-**CH_2**-CH), 3.8 (q, 2H, -COO**CH_2**-CH_3), 4.0 (t, 1H, Ar-CH_2-**CH**), 6.8-7.6 (m, 10H, **arom.** and Ar-**OH**).

Product **2f**: Molecular Formula: $C_{19}H_{20}O_5$ (252.3), Yield: 54%, I.R. (ν cm^{-1}): 3600-3100-1720-1690, ^{1}H NMR (δ ppm): 1.1 (t, 3H, -COOCH_2-**CH_3**), 3.0 (d, 2H, Ar-**CH_2**-CH), 3.85 (s, 3H, Ar-**OCH_3**), 3.95 (q, 2H, -COO**CH_2**-CH_3), 4.2 (t, 1H, Ar-CH_2-**CH**), 5.4 (s, 1H, Ar-**OH**), 6.4-7.6 (m, 8H, **arom.**).

2-(2-ՕՔՍԻԲԵՆԶԻԼ)ԱՑԵՏԻԼՔԱՑԱԽԱԹԹՈՒՆԵՐԻ ԵՎ -ԲԵՆԶՈՒԼՔԱՑԱԽԱԹԹՈՒՆԵՐԻ ԵԹԵՐՆԵՐԻ ՍՏԱՑՄԱՆ ՆՈՐ ՀԱՐՄԱՐ ԵՂԱՆԱԿ

Ս. ԿԻՐԿԱՇԱՐՅԱՆ, Ջ. ԽԱՐԲԱԼԻ, Ա. ԴԱՆԱՆ և Ի. ՍԻՄՈՆ

Սպիրտային լուծիչներում 3-ացետիլ- և 3-բենզոիլ կումարինները նատրիումի բորհիդրիդով վերականգնելու միջոցով ստացվել են համապատասխան 2-(2-օքսիբենզիլ)ացետիլքացախաթթվական և -բենզոիլքացախաթթվական եթերները:

НОВЫЙ УДОБНЫЙ МЕТОД ПОЛУЧЕНИЯ 2-(2-ОКСИБЕНЗИЛ)-АЦЕТИЛУКСУСНЫХ И -БЕНЗОИЛУКСУСНЫХ ЭФИРОВ

С. КИРКИАШАРЯН, Дж. ХАРБАЛИ, А. ДАНАН и И. СИМОН

Восстановлением 3-ацетил- и 3-бензоилкумаринов с помощью боргидрида натрия в спиртовых растворителях получены соответствующие 2-(2-оксибензил)-ацетилуксусные и -бензоилуксусные эфиры.

REFERENCES

1. *Johnson M.R., Rickborn B.* – J. Org. Chem. (1970), 35, 1041.
2. *Iqbal K., Jackson W.R.* – J. Chem. Soc. (1968), 616.
3. *Schauble J.H., Walter G.J., Morin J.G.* – J. Org. Chem. (1974), 39, 755.
4. *Kadin S.B.* – J. Org. Chem. (1966), 31, 620.
5. *Wamhoff H., Schorn G., Korte F.* – Chem. Ber. (1967), 100, 1296.
6. *Wamhoff H., Korte F.* – Chem. Ber. (1968), 101, 772.
7. *Kirkiacharian B.S., Danan A.* – Synthesis (1986), 383.
8. *Kirkiacharian B.S., Brion J.D., Billet D.* – C.R. Acad. Sci. Ser.II (1982), 294, 181.
9. *Knœvenagel E.* – Ber. Dtsch. Chem. Ges. (1898), 31, 732.
10. *Knœvenagel E., Arnot R.* – Ber. Dtsch. Chem. Ges. (1904), 37, 4496.
11. *Dean F.M., Robertson A., Whalley W.B.* – J. Chem. Soc. (1950), 900.
12. *Woods L.L.* – Trans. Kansas Acad. Sci. (1965), 68, 302.
13. *Brown H.C., Ichikawa K.* – J. Amer. Chem. Soc. (1965), 83, 2748.
14. *Brown H.C., Mead E.J., Subba Rao B.C.* – J. Amer. Chem. Soc. (1955), 77, 6209.