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Substituted coumarins as ambident nucleophiles in one-pot hydrogenation/alkylation reaction

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Abstract
The regioselectivity of a one-pot hydrogenation/alkylation reaction of coumarins **1a** and **1b** with series of alkyl halides has been elucidated as a complementary work to reaction of acylation with the same coumarins. Reaction conditions have provided formation of only C-alkylation products with good to high yield. The results from the experiments are of significant importance to predict reactivity of 3-substituted coumarins in different reaction conditions.

Keywords Coumarins · Phosphonates · C-alkylation · Alkylation reaction · Tandem reactions

Introduction

Ambident nucleophilic intermediates are frequently formed during the organic reactions whenever highly functionalized substrates are modified (Savignac et al. 2003). Typically, the nucleophilic centers are C and O atoms from carbanion or enolate ion which are characterized with different reactivity depending on the complexation of the anion, the nature of the electrophile and the cation, polarity of the solvent and reaction temperature. Another concept applicable for reactivity of ambident nucleophiles is the theory of hard and soft acids and bases (HSAB) (Pearson et al. 1967; Ho 1975), where the reactive centers are characterized with their softness and hardness on the base of different experimental and theoretical parameters.

Substituted coumarins and especially their phosphorous-containing analogs are object of continuous interest in our workgroup due to the various transformations that they could perform producing analogs of important biomolecules as ketophosphonates (Petkova-Yankova et al. 2018), bisphosphonates (Petkova et al. 2009), 4,4′-biscoumarins (Koleva et al. 2018) and nitro compounds (Ilieva et al. 2012). Moreover, they still attract our interest for fundamental investigations by reason of inconstant behavior through nucleophilic addition reactions with organometallic reagents (Koleva et al. 2016), CH-acids and other nucleophilic reagents (Petkova et al. 2006). In those interactions, substituted coumarins form enolate ions which act as ambident nucleophile that could result in one of the possible products presented in Scheme 1.

Usually, the chemical reactivity of the conjugated system in the coumarin depends on the nature of the substituent in third position. In that relation, we published (Petkova et al. 2014) a comparative investigation where examples for 1,4- and 1,2-conjugate addition to three-substituted coumarins were presented and on the base of reactivity indexes as Fukui functions, electrophilicity index and atomic electrostatic potential the result of future reactions with coumarins has been proposed. The analysis from the performed quantum chemical calculations showed inconclusiveness of the prediction and strong dependence of the reaction pathway on the functional groups surrounding the conjugate structure in the coumarin. For example, 3-carboxyl, 3-alkoxycarbonyl and 3-nitrosubstituted coumarins result in higher nucleophilicity of O-center in comparison with C3-nucleophilic center, whereas 3-acetyl, 3-dialkyl phosphonic and 3-phosphonic groups induce opposite properties of the centers. Recently, a review paper presented 3-phosphonocoumarins as good acceptors in conjugate addition reactions as well as cycloaddition reaction (Koleva et al. 2019).

Most studies on alkylation of phosphonates or ambident nucleophiles have presented reactions of CH-acidic phosphonates, vinylphosphonates and acetoacetates in classical

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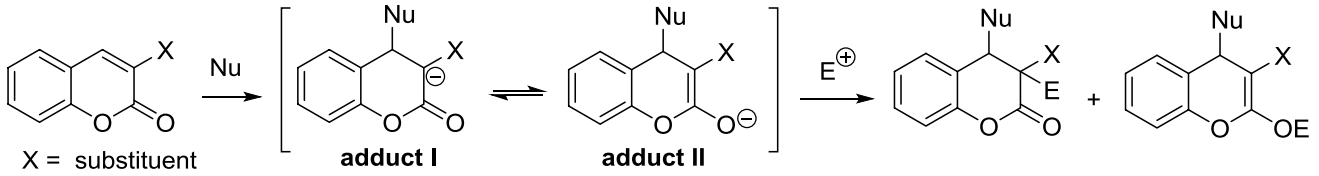


Scheme 1 Proposed reactions of 3-substituted coumarins with nucleophilic reagents

conditions of deprotonation with strong base followed by alkylation. Specific examples on the use of vinylphosphonates as Michael acceptor and ambident nucleophiles are collected in two review papers (Minammi et al. 1992; Janecki et al. 2009).

Previous research on the reactivity of three-substituted coumarins as ambident substrates in our work group was performed (Petkova et al. 2006) as a one-pot hydrogenation/acylation reaction of 3-diethylphosphonocoumarin with a series of acid anhydrides and acyl chlorides. The anion derived from the hydrogenation with $NaBH_4$ is trapped with two types of electrophiles with similar properties. The regioselectivity of the method is very high towards the formation of the C-acylation product (21–90%). The yields of the acyl derivative depend on the steric effect of the incorporated acyl group, the presence of acylation catalyst 4-dimethylaminopyridine (DMAP), the used solvent and the reaction temperature. We wanted to analyze the reactivity of the ambident nucleophile formed from several coumarin systems in the reaction with alkyl reagents as a subsequent investigation applying the conditions of the already developed method. The study displayed additional problems that need to be overcome.

Experimental

Materials

Characterization

Melting points were determined with a Kofler hot-stage apparatus (Department of Organic Chemistry, University of Sofia) and are uncorrected. Infrared (IR) spectra were recorded with a Specord IR 71 spectrophotometer (Department of Organic Chemistry, University of Sofia). ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were taken with a Bruker Avance DRX 250 (at 250 MHz for ^{1}H, 62.9 MHz for ^{13}C, and 101.3 MHz for ^{31}P, respectively) and a Bruker AM 300 (at 300 MHz for ^{1}H and 75.4 MHz for ^{13}C, respectively) spectrometers (Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki). Chemical shifts are given in ppm using tetramethylsilane as an internal standard in $CDCl_3$, and coupling constants are given in Hz. E.I. mass spectra were obtained at 70 eV on a VG TS-250 spectrometer (Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki). Reactions were monitored by TLC on silica gel 60 F254. Extractions were carried out with dichloromethane and the organic solutions were dried with anhydrous sodium sulfate (Na_2SO_4). The solvents were removed under reduced pressure. Column chromatography was carried out on silica gel (Merck 0.063–0.2 mm and 0.043–0.063 mm) using *n*-hexane/ethyl acetate mixtures with increasing polarity. Elemental analyses of C and H were carried out in the Laboratory of Elemental Analysis at the Department of Organic Chemistry, University of Sofia.

Chemicals

Sodium borohydride ($NaBH_4$), 4-dimethylaminopyridine (DMAP), hydrochloric acid (HCl), ammonium chloride (NH_4Cl), sodium chloride (NaCl), sodium sulfate (Na_2SO_4), methyl iodide, benzyl chloride, allyl bromide, methyl bromoacetate, ethyl bromoacetate and ethyl chloroacetate were purchased from commercial sources and were used without further purification. All organic solvents were purchased from commercial sources and were distilled according to standard methods before use. 3-Diethylphosphono-2-oxo-2*H*-1-benzopyran **1a** and ethyl 3-carboxycoumarin **1b** were prepared according to a procedure described elsewhere (Bojilova et al. 1986, 1996).

Synthesis

General method for one-pot hydrogenation/alkylation of 3-diethylphosphonocoumarin 1a with $NaBH_4$ and methyl iodide Method A: To a stirred solution of 3-diethylphosphonocoumarin **1a** (1 mmol, 0.28 g) in anhydrous pyridine (1.5 mL) at room temperature, $NaBH_4$ (1.1 mmol, 0.04 g) and DMAP (2.2 mmol. 0.26 g) were added. After 5 min, the mixture was cooled down in an ice bath and an extra DMAP (1 mmol, 0.12 g) was added followed by dropwise addition of methyl iodide (3 mmol). The reaction mixture was quenched onto 2 N HCl (10 mL) containing crushed ice after 2.5 h to give colorless crystals of alkylation product **2a** which was filtered and crystallized from *n*-hexane/diethyl ether.

Method B: To a stirred solution of 3-diethylphosphonocoumarin **1a** (1 mmol, 0.28 g) in anhydrous pyridine (1.5 mL) at room temperature, $NaBH_4$ (1.1 mmol, 0.04 g) and DMAP (1 mmol, 0.12 g) were added. After 5 min, the mixture was cooled down in an ice bath and methyl iodide (8 mmol) was added dropwise. The reaction mixture was quenched onto 2 N HCl (10 mL) containing crushed ice after 2 h to give colorless crystals of alkylation product **2a** which was filtered and crystallized from *n*-hexane/diethyl ether.

Method B_1: The procedure for Method B was used but in the absence of DMAP.

Method C: 3-Diethylphosphonocoumarin **1a** (1 mmol, 0.28 g) is hydrogenated with $NaBH_4$ (1.1 mmol, 0.04 g) in anhydrous pyridine (1.5 mL) at room temperature under stirring. After 5 min, the mixture was cooled down in an ice bath and methyl iodide (6 mmol) was added dropwise. A salt NH_4Cl (2.5 g) was added 10 min before quenching of the mixture onto 2 N HCl (10 mL) containing crushed ice. The precipitate of **2a** was filtered and crystallized from *n*-hexane/diethyl ether.

Method C_1: The procedure for Method C was used and NH_4Cl was replaced with NaCl (0.5 or 3 g).

Method D: A method similar to Method C was used and 4 mmol of methyl iodide was applied at room temperature.

Method E: This method was performed in a manner similar to Method C where 2.0 mL THF was added to the mixture after the first hour.

Method F: To a stirred solution of 3-diethylphosphonocoumarin **1a** (1 mmol, 0.28 g) in anhydrous pyridine (1.5 mL) and THF (2 mL) at room temperature, $NaBH_4$ (1.1 mmol, 0.04 g) was added. After 5 min the mixture was cooled down in an ice bath until methyl iodide (4 mmol) was added dropwise then it was allowed to warm to ambient temperature. The reaction mixture was quenched onto 2 N HCl (10 mL) containing crushed ice after 1 h to give colorless crystals of alkylation product **2a** which was filtered and crystallized from *n*-hexane/diethyl ether.

One-pot hydrogenation/alkylation of 3-diethylphosphonocoumarin 1a with $NaBH_4$ and alkyl halides Method C_2: Similar to the procedure for the synthesis of **2a** 3-diethylphosphonocoumarin **1a** (1 mmol, 0.28 g), $NaBH_4$ (1.1 mmol, 0.04 g), anhydrous pyridine (1.5 mL), DMAP (2 mmol, 0.24 g) were mixed and benzyl halide (3 mmol) was added dropwise under cooling down with an ice bath. The emulsion resulting from quenching of the reaction mixture onto 2 N HCl (10 mL) containing crushed ice was extracted with dichloromethane (3×20 mL), dried with Na_2SO_4 and after solvent evaporation the product was purified by column chromatography using *n*-hexane and ethyl acetate with increasing polarity.

Method D_1: In a manner similar to Method D using 2.2 mmol DMAP.

Method D_2: Using procedure for Method D with 1 mmol DMAP.

Method D_3: Similar to the procedure for Method D where stirring was continued for 3 h.

Method E_1: Reaction was carried out as in Method E using 2 mmol of the alkyl halide. The product was purified by column chromatography.

Diethyl 3-methyl-2-oxo-3,4-dihydro-2H-chromen-3-ylphosphonate **2a**. Yields: Method A 0.08 g (27%); Method B 0.18 g (60%); Method B_1 0.24 g (80%); Method C 0.25 g (84%); Method C_1 0.24 g (81%) and 0.14 g (47%); Method D 0.15 g (50%); Method E 0.20 g (67%); Method F 0.22 g (74%), mp = 83–85 °C (*n*-hexane/diethyl ether). **IR** ($CHCl_3$): ν = 1765, 1055, 1030 cm^{-1}. **^{1}H NMR** (300 MHz) ($CDCl_3$): δ = 1.03 (t, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 1.31 (t, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 1.62 (d, 3H, PCH_3, $^3J_{HP}$ = 15.5 Hz), 3.03 (dd, 1H, 4-CH_AH_B, $^2J_{HH}$ = 16.4, $^3J_{HCCP}$ = 28.2 Hz), 3.48 (dd, 1H, 4-CH_AH_B, $^2J_{HH}$ = 16.4, $^3J_{HCCP}$ = 13.3 Hz), 3.67 (qd, 1H, $POCH_2CH_3$, $^2J_{HH}$ = 7.1, $^3J_{HCCP}$ = 10.0 Hz), 3.92 (qd, 1H, $POCH_2CH_3$, $^2J_{HH}$ = 7.1, $^3J_{HCCP}$ = 12.1 Hz), 4.09–4.19 (m, 2H, $POCH_2CH_3$), 7.02 (d, 1H, H-8, J = 7.0 Hz), 7.07–7.12 (td, 1H, H-6, J = 7.1, J = 1.2 Hz), 7.20–7.28 (m, 2H, H-5, H-7). **^{13}C NMR** (75.4 MHz) ($CDCl_3$): δ = 16.1 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 6.8 Hz), 16.3 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 6.8 Hz), 20.1 (d, PCH_3, $^2J_{CCP}$ = 4.5 Hz), 33.6 (d, C-4, $^2J_{CCP}$ = 4.5 Hz), 42.9 (d, C-3, $^1J_{CP}$ = 137.9 Hz), 63.0 (d, $POCH_2$, $^2J_{COP}$ = 6.8 Hz), 63.5 (d, $POCH_2$, $^2J_{COP}$ = 6.8 Hz), 116.1 (C-8), 120.6 (d, C-4a, $^2J_{CCP}$ = 4.8 Hz), 124.5 (C-6), 128.1 and 128.4 (C-5, C-7), 152.0 (C-8a), 167.8 (C = O, C-2). **^{31}P NMR** (101.26 MHz) ($CDCl_3$): δ = 24.26 (s). **MS**: m/z (%) = 298 $(M)^+$ (40), 161 (75), 144 (88), 138 (100), 132 (91), 111 (93), 105 (61), 82 (76), 77 (53). Found: C, 56.29; H, 6.42, requires C, 56.38; H, 6.42%.

Diethyl 2-oxo-3,4-dihydro-2H-chromen-3-ylphosphonate **3a**. mp = 65–66 °C (*n*-hexane); **IR** ($CHCl_3$): ν = 1780, 1260, 1065, 1020 cm^{-1} (Kadin 1966; Wamhoff et al. 1967; Petkova et al. 2006).

Diethyl 3-benzyl-2-oxo-3,4-dihydro-2H-chromen-3-ylphosphonate **2c**. Yields: Method C 0.03 g (7%); Method C_2 0.04 g (11%); Method D_1 0.17 g (45%); Method D_2 0.10 g (28%); Method D_3 0.04 g (9%), mp = 140–142 °C (*n*-hexane/diethyl ether). **IR** (CCl_4): ν = 1780, 1265, 1070, 1040 cm^{-1}. **^{1}H NMR** (250 MHz) ($CDCl_3$): δ = 0.91 (t, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 1.31 (t, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 2.91–3.31 (m, 3H, $CH_2C_6H_5$, $^2J_{HH}$ = 16.4 Hz, 4-CH_AH_B, $^2J_{HH}$ = 10.4, $^3J_{HCCP}$ = 13.7 Hz), 3.46 (m, 1H, $POCH_AH_BCH_3$), 3.76-3.94 (m, 2H, $POCH_AH_BCH_3$, 4-CH_AH_B), 4.06–4.24 (m, 2H, $POCH_2CH_3$), 6.92–7.08 (m, 2H, H-8, H-6), 7.16–7.30 (m, 2H, H-5, H-7), 7.26 (s, 5H, $CH_2C_6H_5$). **^{13}C NMR** (62.9 MHz) ($CDCl_3$): δ = 15.9 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 6.0 Hz), 16.4 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 6.0 Hz), 29.3 (d, C-4, $^2J_{CCP}$ = 4.9 Hz), 37.5 (s,

$CH_2C_6H_5$), 48.5 (d, C-3, $^1J_{CP}$ = 131.5 Hz), 63.0 (d, $POCH_2$, $^2J_{COP}$ = 7.2 Hz), 63.8 (d, $POCH_2$, $^2J_{COP}$ = 7.4 Hz), 115.9 (C-8), 120.9 (C-4a), 124.5 (C-6), 127.4 (C-4`), 128.1 (C-3`,C-5`), 128.1 (C-2`, C-6`), 128.4 (C-5), 130.9 (C-7), 135.2 (d, C-1`, $^3J_{CCCP}$ = 12.5 Hz), 151.4 (C-8a), 166.8 (C = O, C-2). **MS**: m/z (%) = 375 $(M+H)^+$ (25), 283 (82), 255 (47), 237 (59), 227 (65), 209 (48), 159 (59), 131 (55), 111 (55), 91 (93), 65 (71), 43 (62), 32 (83), 29 (99), 28 (100). Found C 64.36; H 6.11 requires C 64.17; H 6.19%.

Diethyl 3-allyl-2-oxo-3,4-dihydro-2H-chromen-3-ylphosphonate **2d**. Yields: Method C 0.14 g (43%); Method D_1 0.17 g (52%); Method D_2 0.165 g (51%); Method D_3 0.16 g (49%); Colorful oil. **IR** ($CHCl_3$): ν = 1765, 1050, 1025 cm^{-1}. **^{1}H NMR** (300 MHz) ($CDCl_3$): δ = 0.98 (td, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1, $^4J_{HP}$ = 0.5 Hz), 1.31 (td, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1, $^4J_{HP}$ = 0.5 Hz), 2.62 (dddt, 1H, $CH_AH_BCH=CH_2$, $^2J_{HH}$ = 14.0, $^3J_{HH}$ = 8.6, $^4J_{HCCP}$ = 0.8 Hz), 3.05 (dddt, 1H, $CH_AH_BCH=CH_2$, $^2J_{HH}$ = 13.9, $^3J_{HH}$ = 6.0, $^4J_{HCCP}$ = 1.4 Hz), 3.22 (dd, 2H, 4-CH_2, $^2J_{HH}$ = 17.7, $^3J_{HCCP}$ = 27.0 Hz), 3.54 (ddq, 1H, $POCH_AH_BCH_3$, $^2J_{HH}$ = 7.1, $^2J_{HH}$ = 10.1, $^3J_{HCCP}$ = 9.2 Hz), 3.86 (ddq, 1H, $POCH_AH_BCH_3$, $^2J_{HH}$ = 7.1, $^2J_{HH}$ = 10.1, $^3J_{HCCP}$ = 14.1 Hz), 4.08–4.20 (m, 2H, $POCH_2CH_3$), 5.19 (m, 2H, CH_2-$CH=CH_2$), 5.83 (m, 1H, CH_2-$CH=CH_2$), 7.02 (dd, 1H, H-8, J = 7.0, J = 0.8 Hz), 7.07–7.12 (ddd, 1H, H-6, J = 7.5, J = 1.1 Hz), 7.20–7.28 (m, 2H, H-5, H-7). **^{13}C NMR** (75.4 MHz) ($CDCl_3$): δ = 16.0 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 6.8 Hz), 16.3 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 6.8 Hz), 29.8 (s, 4-CH_2), 37.2 (s, $CH_2CH=CH_2$), 46.6 (d, C-3, $^1J_{CP}$ = 130.1 Hz), 63.0 (d, $POCH_2$, $^2J_{COP}$ = 6.8 Hz), 63.7 (d, $POCH_2$, $^2J_{COP}$ = 9.0 Hz), 116.0 (C-8), 120.6 (s, $CH_2CH=CH_2$), 120.8 (d, C-4a, $^2J_{CCP}$ = 3.2 Hz), 124.6 (C-6), 128.2 (C-5), 128.3 (C-7), 131.8 (d, $CH_2CH=CH_2$, J = 11.3 Hz), 151.7 (C-8a), 166.6 (C = O, C-2). **MS**: m/z (%) = 325 $(M+H)^+$ (25), 324 (26), 285 (39), 255 (100), 209 (94), 188 (51), 159 (58), 138 (43), 131 (67), 111 (98), 91 (53), 81 (65), 41 (68), 28 (97). Found C 59.54; H 6.50 requires C 59.26; H 6.53%.

Methyl [3-(diethoxyphosphoryl)-2-oxo-3,4-dihydro-2H-chromen]-3-acetate **2e**. Yields: Method C 0.06 g (17%); Method D_2 0.105 g (29%); Method D_3 0.09 g (25%); Method E_1 0.11 g (31%), mp = 83-85 °C (*n*-hexane/diethyl ether). **IR** (CCl_4): ν = 1770, 1755, 1255, 1050, 1025 cm^{-1}. **^{1}H NMR** (300 MHz) ($CDCl_3$): δ = 0.93 (t, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 1.30 (t, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 2.82 (dd, 1H, $CH_AH_BCOOCH_3$, $^2J_{HH}$ = 17.4, $^3J_{HCCP}$ = 5.3 Hz), 3.30–3.86 (m, 5H, 4-CH_2, $CH_AH_BCOOCH_3$, $POCH_2CH_3$), 3.70 (s, 3H, $COOCH_3$), 4.06–4.16 (m, 2H, $POCH_2CH_3$), 7.01–7.12 (m, 2H, aromatic), 7.17–7.27 (m, 2H, aromatic). **^{13}C NMR** (75.4 MHz) ($CDCl_3$): δ = 15.9 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 4.5 Hz), 16.3 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 4.5 Hz), 30.4 (d, 4-CH_2, $^2J_{CCP}$ = 6.8 Hz), 37.1 (s, CH_2COOCH_3), 45.2 (d, C-3, $^1J_{CP}$ = 131.1 Hz), 52.2 (s, $COOCH_3$), 63.5 (d, $POCH_2$, $^2J_{COP}$ = 6.8 Hz), 63.9 (d, $POCH_2$, $^2J_{COP}$ = 9.0 Hz), 116.3 (C-8), 120.5 (C-4a), 124.6 (C-6), 127.9 (C-5), 128.3 (C-7), 151.8 (C-8a), 166.5 (C = O, C-2), 170.4 (d, $COOCH_3$, $^3J_{CCCP}$ = 20.4 Hz). **MS**: m/z (%) = 356 $(M+H)^+$ (18), 283 (32), 220 (57), 188 (41), 159 (47), 138 (47), 131 (100), 111 (94), 82 (39), 32 (72), 28 (87). Found C 53.99; 6.05 requires C 53.93; H 5.94%.

Ethyl [3-(diethoxyphosphoryl)-2-oxo-3,4-dihydro-2H-chromen]-3-acetate **2f**. Yields: Method C 0.17 g (46%); Method D_1 0.10 g (27%); Method D_2 0.11 g (30%); Method D_3 0.12 g (32%), mp = 56–58 °C (*n*-hexane/diethyl ether). **IR** ($CHCl_3$): ν = 1765, 1750, 1055, 1030 cm^{-1}. **^{1}H NMR** (300 MHz) ($CDCl_3$): δ = 0.93 (t, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 1.26 (t, 3H, $COOCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 1.30 (t, 3H, $POCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 2.80 (dd, 1H, $CH_AH_BCOOC_2H_5$, $^2J_{HH}$ = 17.3, $^3J_{HCCP}$ = 5.3 Hz), 3.30–3.88 (m, 5H, 4-CH_2, $CH_AH_BCOOC_2H_5$, $POCH_2CH_3$), 4.07–4.19 (m, 4H, $COOCH_2CH_3$, $POCH_2CH_3$), 7.01–7.11 (m, 2H, H-8, H-6), 7.17-7.27 (m, 2H, H-5, H-7). **^{13}C NMR** (75.4 MHz) ($CDCl_3$): δ = 14.1 ($COOCH_2CH_3$), 15.9 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 6.8 Hz), 16.3 (d, CH_3CH_2OP, $^3J_{CCOP}$ = 4.5 Hz), 30.4 (d, 4-CH_2, $^2J_{CCP}$ = 6.8 Hz), 37.1 (s, $CH_2COOCH_2CH_3$), 45.2 (d, C-3, $^1J_{CP}$ = 131.1 Hz), 61.3 (s, $CH_2COOCH_2CH_3$), 63.5 (d, $POCH_2$, $^2J_{COP}$ = 6.8 Hz), 63.9 (d, $POCH_2$, $^2J_{COP}$ = 9.0 Hz), 116.3 (C-8), 120.6 (C-4a), 124.5 (C-6), 127.9 (C-5), 128.2 (C-7), 151.8 (C-8a), 166.8 (C = O, C-2), 169.9 (d, $COOCH_2CH_3$, $^3J_{CCCP}$ = 18.1 Hz). **MS**: m/z (%) = 371 $(M+H)^+$ (17), 325 (26), 283 (66), 234 (58), 188 (60), 160 (60), 138 (43), 131 (72), 111 (80), 82 (41), 32 (74), 29 (90), 28 (100). Found C 55.21; H 6.09 required C 55.14; H 6.26%,

Compound 3,4-dihydrocoumarin **3a** was also isolated with the corresponding yields as shown in Table 2.

One-pot hydrogenation/alkylation of ethyl 3-carboxycoumarin 1b with $NaBH_4$ and methyl iodide Method: To a stirred solution of ethyl 3-carboxycoumarin **1b** (1 mmol) in dry pyridine (1.5 mL), $NaBH_4$ (1.1 mmol, 0.04 g) was added. The stirring continued for 5 min at room temperature and the mixture was cooled down in an ice bath. Methyl iodide (8 mmol) was dropped in three portions for 10 min and after 2 h the reaction mixture was quenched onto 2 N HCl (10 mL) containing crushed ice. The resulted emulsion was extracted with dichloromethane (3 × 20 mL), dried with Na_2SO_4 and after solvent evaporation the product was purified by column chromatography using *n*-hexane and ethyl acetate with increasing polarity.

Ethyl 3-methyl-2-oxo-3,4-dihydro-2H-chromen-3-carboxylate **2b**. Yields: 0.17 g (73%). Colorless oil. **IR** (CCl_4): ν = 1795, 1755 cm^{-1}. **^{1}H NMR** (300 MHz) ($CDCl_3$): δ = 1.00 (t, 3H, $COOCH_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 1.63 (s, 3H, CH_3-3), 2.98 (d, 1H, CH_A-4 $^2J_{HH}$ = 15.9 Hz), 3.37 (d, 1H, CH_B-4 $^2J_{HH}$ = 15.9 Hz), 3.94–4.14 (m, 2H, $COOCH_2$), 7.04–7.28 (m, 4H, aromatic). **^{13}C NMR** (75.4 MHz) ($CDCl_3$): δ = 13.7

(s, CH_3-3), 20.8 (s, $COOCH_2CH_3$), 35.4 (s, CH_2-4), 49.5 (s, C-3), 62.1 (s, $COOCH_2$), 116.5 (C-8), 121.3 (C-4a), 124.6 (C-6), 128.2 (C-7), 128.7 (C-5), 151.5 (C-8a), 168.2 (C=O, C2), 170.6 ($COOC_2H_5$). **MS**: m/z (%) = 235 $(M+H)^+$ (10), 219 (23), 173 (25), 161 (78), 131 (44), 105 (56), 91 (31), 78 (43), 39 (41), 29 (87), 28 (100), 27 (64). Found C 66.60; H 6.07 required C 66.66; H 6.02%.

Ethyl 2-oxo-3,4-dihydro-2H-chromen-3-carboxylate **3b**. mp = 53–54 °C (n-hexane/ethyl acetate) (Kirkiacharian et al. 1986).

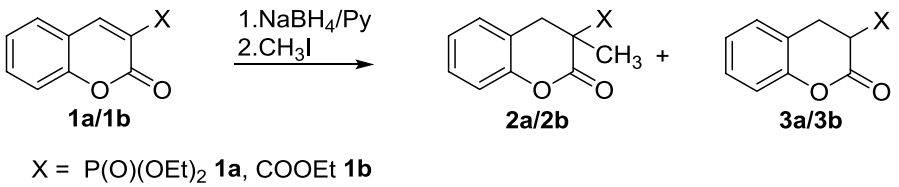
Results and discussion

Organophosphorus compounds have been successfully applied as building blocks under different reaction conditions. Acylation and alkylation reaction to beta-phosphonoacetates are a useful method for modification (Vieth et al. 1997) and synthesis of varied biologically active phosphonates (Savignac and Bogdan 2003). Thus, the conditions of one-pot hydrogenation/acylation were applied in reactions with alkyl halides and two coumarin compounds 3-diethylphosphonocoumarin **1a** and ethyl coumarin-3-carboxylate **1b**. The regioselectivity and the stereoselectivity of the studied reaction are of great interest for us to understand the behavior of the in situ generated nucleophile from the coumarin system and to control the reactivity for further functionalization. The outcome from the experiments was also of significant importance to validate the theoretical predictions on the reactivity of 3-substituted coumarins under different reaction conditions.

In the present work, several factors were discussed that could impact the reactivity of the ambident nucleophile derived from a coumarin system (Scheme 1). The principle of hard and soft acid and bases characterized the carbon center as soft (**adduct I**) and oxygen center as hard (**adduct II**). However, the electronic effect of the substituents on the coumarin should be accounted due to their influence on the local reactivity of the centers (Petkova et al. 2014). Substituents could favor the localization of the negative charge in the adduct on the carbon center which could direct the mechanism to bimolecular substitution.

Preliminary investigations were carried out with methyl iodide as alkyl halide. The small steric effect of the methyl group was the reason to use this halide as a model compound. The best reaction conditions for the acylation reaction (Table 1, entry 1) were found by applying 4-dimethylaminopyridine (DMAP) in the reaction mixture, thus resulting in the isolation of the corresponding C-alkylated product-3-methyl-3-diethylphosphono-2-oxochroman **2a**. It was expected that the reaction conditions have to be optimized due to the different chemical properties of alkyl halide in comparison with anhydrides and acyl chlorides. The essential reason was the low yield for the product **2a**.

Table 1 One-pot hydrogenation/alkylation of 3-diethylphosphonocoumarin **1a** with $NaBH_4$ and methyl iodide



Entry	Method	**1a**: CH_3I: DMAP	Solvent	Time [hours]	Temp [°C]	Yield [%], **2a**
1	A	1: 3: 2.2[a]	pyridine	2.5	0	27
2	B	1: 8: 1	pyridine	2	0	60
3	B_1	1: 8: -	pyridine	2	0	80
4	C	1: 6/-[b]	pyridine	1	0	84
5	C_1	1: 6/-[b]	pyridine	1	0	81
6	C_1	1: 6/-[b]	pyridine	1	0	47
7	D	1: 4/-	pyridine	1.5	r.t.	50
8	E	1: 6/-[c]	pyridine/THF	2	0	67
9	F	1: 4/-	pyridine/THF	1	r.t.	74

[a]DMAP was added in two portions—1.2 mmol before the addition of $NaBH_4$ and 1 mmol after that

[b]Salting out the product with NH_4Cl (Method C) or NaCl (Method C1) 10 min before quenching the mixture

[c]A solvent THF (2.0 mL) was added on the first hour of the reaction

The results from the reactions of hydrogenation/alkylation of 3-diethylphosphonocoumarin **1a** with methyl iodide are presented in Table 1.

As can be seen from Table 1, the yield of the C-product increases three times when a large excess of methyl iodide was dropped to the reaction mixture (Table 1, entry 2) or particularly in absence of DMAP (Table 1, entry 3). A significant detail for the yield improvement is the addition of the methyl iodide in portions in the first 10 min of the alkylation. The quantity of methyl iodide was optimized in Methods C and D (Table 1, entry 4 and 7), but the reduction of the halide to 4 mmol resulted in an increase of 3,4-dihydrocoumarin **3a**. The best conditions for alkylation of the nucleophilic adduct was found by applying Method C1 (Table 1, entry 5 and 6) where the product was salted out with ammonium or sodium chlorides 10 min before quenching the reaction mixture. The ammonium salt had a better impact on the product separation and isolation. The yield of the C-alkylated product was also affected by the addition of tetrahydrofuran (THF) as a second solvent (Table 1, entry 8). In Method F (Table 1, entry 9), the one-pot reaction was carried out with 4 mmol of methyl iodide in a mixed solvent pyridine/THF deriving **2a** in a very good yield (74%).

The reaction of hydrogenation/alkylation of ethyl coumarin-3-carboxylate **1b** with methyl iodide was accomplished and used for comparison with coumarin **1a**. The ester functional group resembles steric hindrance of the phosphonic group as well as the influence on the stabilization and enolization (Scheme 1) of the carbanion after the hydrogenation step to the lactone carbonyl group as well as the substituent. However, from the performed alkylation reaction the C-alkylated product **2b** was isolated with yield of 73% for 2 h. Compounds of this type were synthesized previously from 3-carbethoxy-3,4-dihydrocoumarin using t-BuOK as base under inert atmosphere for 8 h (Mitra et al. 1980).

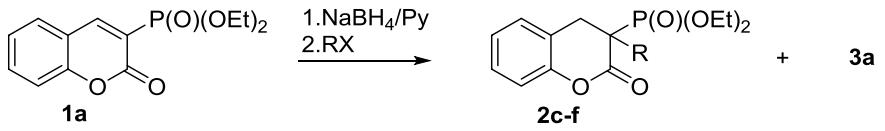
The one-pot hydrogenation/alkylation was performed with several alkyl halides—benzyl chloride, allyl bromide, methyl bromoacetate, ethyl bromoacetate and ethyl chloroacetate. In all these reactions, the yield of C-alkylated product depended strongly on the reaction conditions and was lower (7–52%) comparing to the results with methyl iodide. The data from these investigations are shown in Table 2. The principal distinction from methyl iodide is the higher temperature at which the alkylation takes place. Only in case of ethyl bromoacetate (Table 2, entry 14) the optimized reaction conditions for the alkylation with methyl iodide led to higher yield of the alkylated product comparing with reactions at room temperature. The reaction with benzyl chloride is an example where the yield of the C-alkylated product depended on the used amount of DMAP. Appling the conditions of Method D_3 (Table 2, entry 5), the product was isolated only with 9% yield, while in Method D_1 (Table 2, entry 3) the yield increased to 45%. The general observation on the process of the alkylation reaction is that the usage of DMAP is recommended when sterically hindered reagent is applied. This common conclusion is frequently a reason to apply that catalyst (Höfle et al. 1978; Scriven 1983).

Regarding the alkyl halides used in the current study (Tables 1 and 2), the alkylation was accomplished with primary halides which could suggest bimolecular nucleophilic substitution with the exception of the reactions with benzyl chloride and allyl bromide where monomolecular mechanism could be preferred due to the stabilization of the positive charge on the electrophile. In general, alkyl halides are characterized with soft carbon center therefore the favored product from the studied reaction is the C-alkylation product as all the results presented. The other aspect of the application of alkyl halides is the electronegativity of the leaving group. When hardens of the leaving group increases (I < Br < Cl) the carbon center in the alkyl reagent becomes harder which could favor the O-alkylation. In our case, the same effect lowers the yield of the C-product when benzyl chloride and ethyl chloroacetate (Table 2, entry1, 18 and 19) were used. Methyl iodide is the softest reagent in the series, thus, the alkylation of the carbon center dominates over the oxygen center. Comparing the highest yields of the C-product obtained with all alkyl halides, it can be seen that there is a step of decrease of about 30%. The product **2a** was isolated in 84%, whereas products **2c** and **2d** (allyl and benzyl) were obtained in about 50% and in the case of esters of acetic acid, **2e** and **2f**, only about 30%.

The DMAP catalyst is not frequently used reagent for alkylation reactions with carbanions and ambident nucleophiles. Its advantage is the ability to form ammonium salts as intermediate that act as a carrier for the electrophile to the reaction center (Höfle et al. 1978; Scriven 1983; Sakakura et al. 2007). It could be assumed that acyl group is converted to softer reagent than the anhydride in the ammonium salt which directed the reaction path to the soft nucleophilic center. Probably in case of alkyl reagents, the application of DMAP changes the nucleophilic substitution by decreasing the hardness of the alkylating agent too (Table 2). A similar strategy was applied previously by Palomo et al. in reaction of carbonyl compounds with electron-deficient allylic halides (Gomez-Bengoa et al. 2011). The best example for the one-pot reaction is the alkylation with benzyl chloride, but the same influence is observed for the other alkyl halides (Table 2, entry 3, 7 and 11).

The preferred organic solvent for the one-pot reactions is pyridine. It is a polar solvent appropriate for nucleophilic substitution; however, addition of THF also influences the formation of C-alkylation product (Table 1, entry 8 and Table 2, entry 13). Probably, the THF changes the cation solvation which could enhance the reactivity of the nucleophile (**adduct I**).

Table 2 One-pot hydrogenation/alkylation of 3-phosphonocoumarin **1a** with $NaBH_4$ and alkyl halides in pyridine



R = CH_2Ph, CH_2-CH=CH_2, CH_2COOMe, CH_2COOEt

Entry	Method	RX	**1a**: RX: DMAP	Time [hours]	Temp [°C]	Yields, %	
						2c-f	**3a**
1	C	$C_6H_5CH_2Cl$	1: 6: -	1	0	7	65
2	C_2		1: 3: 2	15	0	11	77
3	D_1		1: 3: 2.2	3	r.t.	45	28
4	D_2		1: 3: 1	3	r.t.	28	30
5	D_3		1: 3: -	3	r.t.	9	51
6	C	$BrCH_2CH=CH_2$	1: 6: -	1	0	43	18
7	D_1		1: 4: 2.2	3	r.t.	52	18
8	D_2		1: 4: 1	3	r.t.	51	11
9	D_3		1: 4: -	3	r.t.	49	12
10	C	$BrCH_2COOCH_3$	1: 6: -	1	0	17	46
11	D_2		1: 3: 1	3	r.t.	29	33
12	D_3		1: 3: -	3	r.t.	25	33
13	E_1		1: 2: -[a]	1	r.t.	31	25
14	C	$BrCH_2COOC_2H_5$	1: 6: -	1	0	46	24
15	D_1		1: 3: 2	3	r.t.	27	37
16	D_2		1: 3: 1	3	r.t.	30	26
17	D_3		1: 3: -	3	r.t.	32	40
18	C	$ClCH_2COOC_2H_5$	1: 6: -	1	0	16	67
19	D_3		1: 3: -	3	r.t.	15	63

[a]The reaction was carried out in a mixed solvent of pyridine and THF

Further analysis of the results and the steric factors of the alkylating reagents should give an explanation for the different yields of C-alkylated products. The lower yields with all halides (Table 2) are due to the steric hindrance of the alkyl group.

Spectroscopic data

The structures of the prepared 3-alkyl-3-diethylphosphono-2-oxochromans **2a**, **c-f** and 3-methyl-3-ethoxycaroxyl-2-oxochroman **2b** were characterized by their analytical and spectroscopic data (IR, ^{1}H- and ^{13}C-NMR). Protons from the methylene group at fourth position in the lactone ring appeared separately as doublets of doublets in the interval of $\delta = 2.91–3.88$ ppm. The geminal coupling constants were with values between 10.4 and 17.7 Hz, whereas the coupling constants with the closer phosphorous atom were between $^3J_{HCCP} = 13.3$-28.2 Hz. In the carbon spectra, the chemical shift for C-3 carbon atom was in the interval $\delta = 42.9–48.5$ ppm and the expected large phosphorous–carbon coupling constants were observed (130.1–137.9 Hz).

Conclusions

In summary, the current study presented a one-pot hydrogenation/alkylation reaction of coumarins **1a** and **1b** with series of alkyl halides using in situ generated carbanion from coumarin system. The optimized reaction conditions are specified with high regioselectivity for the C-alkylation product. Several factors determined the yields of the products **2** from which reactivity of the carbanion, nature of the electrophile, reaction solvent and temperature were discussed. In general, suitable reaction conditions for the preparation of only the C-products were provided by comparative investigations on the one-pot reactions of acylation and alkylation of three-substituted coumarins.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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