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Synthesis of 8-R-9c-alkyl-1-aryl-2-benzyl-1-hydroxy-1,2,9b,9c-tetrahydro-5-oxa-2-aza-cyclopenta[2,3]cyclopropa[1,2-a]-naphthalene-3,4-diones and reaction thereof with acetic anhydride

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Abstract—The reaction of zinc enolates synthesized from 1-aryl-2,2-dibromoalkanones and zinc with 6-R-2-oxochromene-3-carboxylic acid N-benzylamide affords 8-R-9c-alkyl-1-aryl-2-benzyl-1-hydroxy-1,2,9b,9c-tetrahydro-5-oxa-2-aza-cyclopenta[2,3]cyclopropa-[1,2-a]naphthalene-3,4-diones. Acylation of these compounds is accompanied by an unexpected rearrangement producing a sole geometrical isomer of 4'-alkyl-5'-aryl-1'-benzyl-3,4,2',3'-tetrahydro-2,2'-dioxospiro[chroman-3,3'-pyrrol]-4-yl acetates.
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The addition of organometallic reagents formed by reacting certain metals with α,α-dibromoketones[1,2] or α,α-dihalogenocarboxylic acids[3,4] to activated olefinic compounds constitutes a route to cyclopropanes with electron accepting acylic and alkoxycarbonyl substituents. In some instances dihydrofuran derivatives are obtained, for example, upon reacting α,α-dibromo-α-phenylacetophenone with zinc and olefins.[2]

We have previously established that the reaction of brominated zinc enolates synthesized from 1-aryl-2,2-dibromoalkanones and zinc with compounds containing an activated double bond represents a general avenue to cyclopropanation of organic molecules.[5–7] In particular, it was demonstrated that brominated zinc enolates undergo facile reaction with substituted chromen-2-ones affording substituted 1a,7b-dihydrocyclopropa[c]chromen-2-ones.[7]

Hoping to gain access to new types of heterocycles annelated with a cyclopropane moiety we studied the reaction of zinc enolates 2a–e synthesized from 1-aryl-2,2-dibromoalkanones 1a–e and zinc with 2-oxochromene- and 6-bromo-2-oxochromene-3-carboxylic acid N-benzylamides 3a,b.[8] The reaction proceeds as described in Scheme 1.

In ether-ethyl acetate solvent, zinc enolates 2a–e underwent a regiospecific reaction with the electrophilic substrate 3a,b forming 4a–f (Table 1) as intermediates. Stereospecific cyclization of the intermediates 4a–f led to the formation of the cyclopropane moiety in compounds 5a–f with the aroyl and amide groups being on the same side of the cyclopropane ring. It is this fact that allowed for their interaction resulting in the annulated isomers 6a–f, which were hydrolized into 8-R-9c-alkyl-1-aryl-2-benzyl-1-hydroxy-1,2,9b,9c-tetrahydro-5-oxa-2-aza-cyclopenta[2,3]cyclopropa[1,2-a]naphthalene-3,4-diones 7a–f as the final products.

The structures of compounds 7a–f were established using microanalysis, and IR and ^{1}H NMR spectroscopy.[9] The IR spectra contained signature peaks of lactam carbonyls at 1660–1665 cm^{-1}, a lactone carbonyl at 1750–1760 cm^{-1} and a broad hydroxyl band at 3250–3320 cm^{-1}. The ^{1}H NMR data featured characteristic
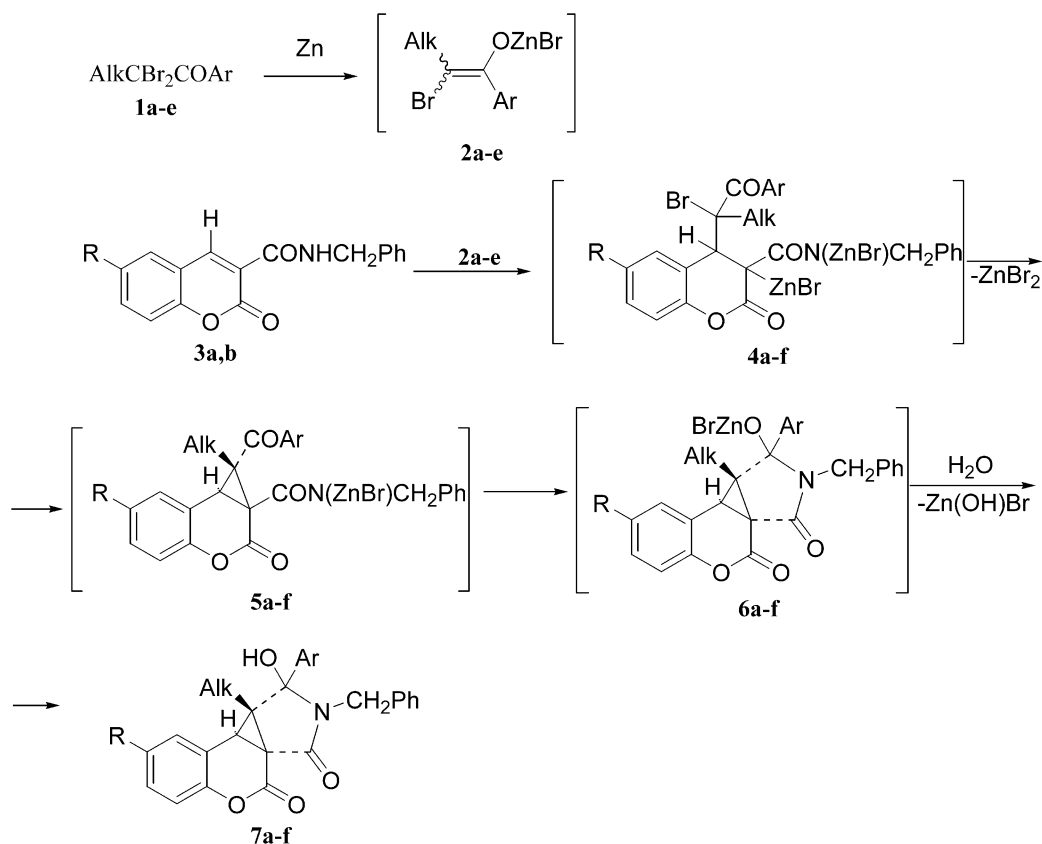
Scheme 1.

Table 1. Substituents in compounds **4**–**7**

Entry	4–7	R	Alk	Ar
1	a	H	CH_3	$4\text{-}FC_6H_4$
2	b	H	CH_3	$4\text{-}ClC_6H_4$
3	c	H	CH_3	$4\text{-}BrC_6H_4$
4	d	Br	CH_3	$4\text{-}ClC_6H_4$
5	e	Br	C_2H_5	$4\text{-}ClC_6H_4$
6	f	Br	C_2H_5	$4\text{-}BrC_6H_4$

Figure 1. 2-Benzyl-8-bromo-1-(4-bromophenyl)-9c-ethyl-1-hydroxy-1,2,9b,9c-tetrahydro-5-oxa-2-aza-cyclopenta[2,3]cyclopropa[1,2-a]naphthalene-3,4-dione **7f**.

methine (CH) proton signals at δ 3.50–3.60 ppm and two doublets at δ 3.70–3.80 and δ 4.26–4.33 ppm with a distinctive spin coupling constant ($J = 15.5$ Hz) due to the benzyl (CH_2Ph) group. To confirm the structure of these compounds we recorded the ^{13}C NMR spectrum of **7f**, 8-R-2-benzyl-1-(4-bromophenyl)-9c-ethyl-1,2,9b,9c-tetrahydro-1-hydroxy-2-aza-5-oxa-cyclopenta-[2,3]-cyclopropa[1,2-a]naphthalene-3,4-dione (Fig. 1).

Assignment of the ^1H NMR spectra was carried out using 2D COSY and ROESY homonuclear experiments and the ^{13}C spectrum was interpreted using a combination of 2D HETCOLOR and 2D HMBC methods. The ^{13}C NMR spectrum of this compound was in full correspondence with its structure. In particular, resonances at δ 33.22, 36.76 and 41.55 ppm due to C^{9b}, C^{3a} and C^{9c}, respectively, were observed, indicative of the presence of the cyclopropane moiety. The spatial configuration of the cyclopropane moiety was established on the basis
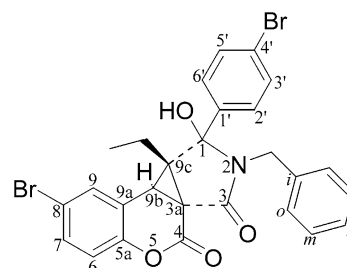
of a 2D ROESY analysis and measurements of the stationary Overhauser effect in a 1D differential NOE experiment. The spectrum lacked the low-field carbon signal of the carbonyl of the aroyl moiety at δ 195 ppm while featuring a resonance at δ 92.06 ppm due to the sp^3 C^1 carbon in the annulated isomer of **7f**. Cross-peaks between the C^1 carbon and the H^{9b},

Table 2. Substituents in compounds **7**–**9**

Entry	7–9	R	Alk	Ar
1	a	H	CH_3	$4\text{-}FC_6H_4$
2	b	H	CH_3	$4\text{-}ClC_6H_4$
3	c	H	CH_3	$4\text{-}BrC_6H_4$
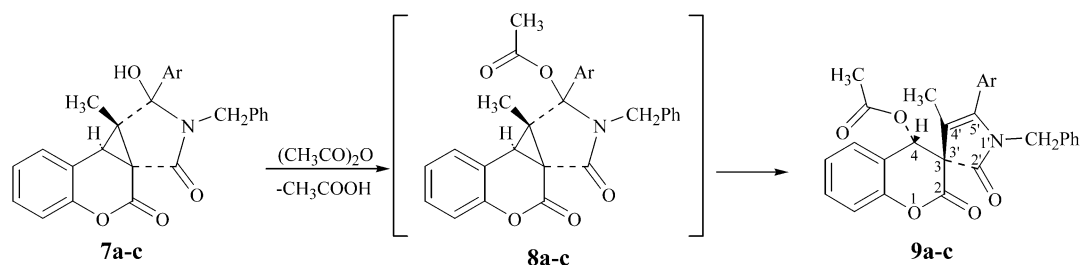
Scheme 2.

OH and NCH_2 protons in the 2D HMBC map also upheld the existence of the isolated compounds in the annulated form.

As the next step we studied the acylation of **7a–c** (Table 2) using acetic anhydride.[10] It appeared that this reaction took place by means of a rearrangement resulting in the formation of the spirocompounds 4′-alkyl-5′-aryl-1′-benzyl-3,4,2′,3′-tetrahydro-2,2′-dioxo-spiro[chroman-3,3′-pyrrol]-4-yl acetates **9a–c** according to Scheme 2.

Apparently, the first step in the reaction is the acylation of the hydroxyl groups in substrates **7a–c** to intermediates **8a–c**, which undergo subsequent rearrangement with cyclopropane ring opening and acyl group transfer to the C^4 atom of the chroman ring, thus affording the final products **9a–c**. The structures of **9a–c** were established using microanalysis, IR, ^1H and ^{13}C NMR spectroscopy.[11] The IR spectra featured signature peaks of the lactam carbonyl at 1710 cm^{-1} and of the ester and lactone carbonyls at 1755–1760 cm^{-1}. In the ^1H NMR spectra, characteristic singlets at δ 1.43–1.53, δ 1.99–2.09 and δ 6.40–6.56 ppm due to the methyl protons and the proton at position 4 of the chroman ring were observed, respectively, as well as an AB-system with a geminal coupling constant, $^2J = 15.5$ Hz, for the inequivalent protons of the benzyl group at δ 4.22–4.62 ppm. The presence of only one set of signals in the ^1H NMR spectra indicated that the reaction products represented a sole geometric isomer.

To confirm the structures of products **9a–c**, we studied compound **9b** by ^1H and ^{13}C NMR with and without proton decoupling to determine the $^nJ_{C-H}$ values. Proton and carbon resonance assignments were aided by 2D NOESY and HSQC. NOESY spectra were also used to establish the stereoconfiguration of **9b**. Spectral analysis allowed us to elucidate the spatial arrangement of the pyrrole spirocycle with respect to the pyran by utilizing the dependence of the vicinal spin coupling constants, $^{13}C-^1H$ ($^3J_{CH}$) of the H^4 proton and the $C^{2'}$, $C^{4'}$ carbons about a dihedral angle θ. The corresponding constants could be unequivocally determined from the ^{13}C spectra without proton decoupling. In the spectrum of **9b**, the signal of the $C^{2'}$ carbon represented a doublet of triplets while for $C^{4'}$ it was a quartet of doublets with the doublet splitting caused by the interaction with the H^4 proton: $^3J_{C^{2'}-H^4} = 5.2$ Hz, $^3J_{C^{4'}-H^4} = 2.4$ Hz. Considering only the most energetically favourable six-membered ring conformation, the measured constants suggest that

the H^4 proton and the $C^{2'}$ carbon were in pseudo-axial positions, that is trans to each other, while the H^4 and $C^{4'}$ atoms were cis. This conclusion was borne out by the 2D NOESY spectra which featured a cross-peak between the H^4 protons and the methyl group at $C^{4'}$, thus confirming their proximity.

Acknowledgements

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8. General procedure for synthesizing compounds **7**: The 1-aryl-2,2-dibromoalkanone (0.03 mol) was added to fine zinc chips (4 g) and diethyl ether (8 ml) and ethyl acetate (10 ml). The mixture was initially heated to start a spontaneous reaction. After the reaction was complete, the mixture was boiled for 15 min, cooled, and was decanted off the zinc into a different flask. This was followed by the addition of compounds **3a,b** (0.01 mol), boiling for 30–40 min, cooling, and hydrolyzing with acetic acid. The reaction products were extracted, the solvent was evaporated, and the residue was recrystallized from acetone or methanol. Ratios of not less than 2:1 between the 1-aryl-2,2-dibromoalkanone and compounds **3a,b** were found to be necessary for the reaction to take place.
9. Spectral and analytical data for compounds **7**.
   Compound **7a**: Yield: 57%; mp 218–219 °C. IR: $\nu = 1665$, 1755, 3310 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 0.51 (s, 3H, CH_3), 3.59 (s, 1H, CH), 3.80 (d, 1H, NCH_2, $J = 15.5$ Hz), 4.27 (d, 1H, NCH_2, $J = 15.5$ Hz), 6.87–7.78 (m, 14H, C_6H_4, C_6H_5, 4-FC_6H_4, OH). Microanalysis:

$C_{26}H_{20}FNO_4$ (429.4): calcd, %: C 72.72, H 4.69; found, %: C 72.63, H 4.61.

Compound **7b**: Yield: 56%; mp 228–229 °C. IR: $v = 1665$, 1750, 3200 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 0.51 (s, 3H, CH_3), 3.60 (s, 1H, CH), 3.80 (d, 1H, NCH_2, $J = 15.5$ Hz), 4.27 (d, 1H, NCH_2, $J = 15.5$ Hz), 6.92–7.78 (m, 14H, C_6H_4, C_6H_5, 4-ClC_6H_4, OH). Microanalysis: $C_{26}H_{20}ClNO_4$ (445.5): calcd, %: C 70.03, H 4.52; found, %: C 69.90, H 4.43.

Compound **7c**: Yield: 47%; mp 248–250 °C. IR: $v = 1660$, 1750, 3250 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 0.52 (s, 3H, CH_3), 3.60 (s, 1H, CH), 3.80 (d, 1H, NCH_2, $J = 15.5$ Hz), 4.28 (d, 1H, NCH_2, $J = 15.5$ Hz), 6.86–7.70 (m, 14H, C_6H_4, C_6H_5, 4-BrC_6H_4, OH). Microanalysis: $C_{26}H_{20}BrNO_4$ (490.3): calcd, %: C 63.69; H 4.11; found, %: C 63.75, H 4.19.

Compound **7d**: Yield: 52%; mp 221–223 °C. IR: $v = 1665$, 1760, 3320 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6–CCl_4, 1:3) δ: 0.61 (s, 3H, CH_3), 3.50 (s, 1H, CH), 3.75 (d, 1H, NCH_2, $J = 15.5$ Hz), 4.33 (d, 1H, CH_2, $J = 15.5$ Hz), 6.86–7.80 (m, 13H, C_6H_3, C_6H_5, 4-ClC_6H_4, OH). Microanalysis: $C_{26}H_{19}BrClNO_4$ (524.8): calcd, %: C 59.51, H 3.65; found, %: C 59.42, H 3.60.

Compound **7e**: Yield: 46%; mp 222–223 °C. IR: $v = 1665$, 1760, 3300 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6–CCl_4, 1:3) δ: 0.60 (t, 3H, CH_3, $J = 7.5$ Hz), 0.77 (m, 1H, CH_2), 1.17 (m, 1H, CH_2), 3.51 (s, 1H, CH), 3.70 (d, 1H, NCH_2, $J = 15.5$ Hz), 4.27 (d, 1H, NCH_2, $J = 15.5$ Hz), 6.90–7.90 (m, 13H, C_6H_3, C_6H_5, 4-ClC_6H_4, OH). Microanalysis: $C_{27}H_{21}BrClNO_4$ (538.8): calcd, %: C 60.19; H 3.93; found, %: C 60.28, H 3.85.

Compound **7f**: Yield: 50%; mp 207–208 °C. IR: $v = 1665$, 1760, 3300 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 0.54 (t, 3H, CH_3, $J = 7.3$ Hz), 0.71 (dq, 1H, CH_2, $J = 14.6$, 7.3 Hz), 1.09 (dq, 1H, CH_2, $J = 14.6$, 7.3 Hz), 3.60 (s, 1H, H^{9b}), 3.72 (d, 1H, NCH_2, $J = 15.5$ Hz), 4.26 (d, 1H, NCH_2, $J = 15.5$ Hz), 6.89 (dd, 1H, H^6, $J = 8.4$, 2.4 Hz), 7.10 (d, 1H, H^6, $J = 8.8$ Hz), 7.16–7.27 (m, 5H, $CH_2C_6H_5$), 7.23 (s, 1H, OH), 7.55 (dd, 1H, H^7, $J = 8.8$, 2.5 Hz), 7.62 (dd, 1H, $H^{5'}$, $J = 8.4$, 2.0 Hz), 7.67 (dd, 1H, $H^{3'}$, $J = 8.4$, 2.0 Hz), 7.80 (dd, 1H, $H^{2'}$, $J = 8.4$, 2.4 Hz), 7.92 (d, 1H, H^9, $J = 2.5$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.74 (CH_3), 17.76 (CH_2), 33.22 (C^{9b}), 36.76 (C^{3a}), 41.55 (C^{9c}), 42.66 (NCH_2), 92.06 (C^1), 116.31 (C^8), 118.74 (C^6), 118.99 (C^{9a}), 122.10 ($C^{4'}$), 126.70 (C_p), 127.51 (C_o), 127.59 ($C^{6'}$), 128.01 (C_m), 129.38 ($C^{2'}$), 131.43 ($C^{3'}$), 131.67 ($C^{5'}$), 131.67 (C^9),

131.94 (C^7), 137.60 (C_i), 139.09 ($C^{1'}$), 149.20 (C^{5a}), 159.28 (C^4), 165.87 (C^3). Microanalysis: $C_{27}H_{21}Br_2NO_4$ (583.3): calcd, %: C 55.60, H 3.63; found, %: C 55.47, H 3.54.

10. General procedure for synthesizing compounds **9**: 8-R-9*c*-alkyl-1-aryl-2-benzyl-1-hydroxy-1,2,9*b*,9*c*-tetrahydro-5-oxa-2-aza-cyclopenta[2,3]cyclopropa[1,2-*a*]naphthalene-3,4-dione (0.005 mol) was boiled with excess acetic anhydride and three drops of *n*-tributylamine for 3 h followed by evaporation of the acetic acid formed and unreacted acetic anhydride. The residue was dissolved in boiling benzene and salted out with petroleum ether. After precipitation the reaction product was recrystallized from ethyl acetate. Acetylation did not proceed and starting material was recovered when the reaction was carried out at room temperature.

11. Spectral and analytical data for compounds **9**.
Compound **9a**: Yield: 51%; mp 142–144 °C. IR: $v = 1710$, 1760 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 1.44 (s, 3H, CH_3), 2.02 (s, 3H, CH_3COO), 4.23 (d, 1H, NCH_2, $J = 15.5$ Hz), 4.51 (d, 1H, NCH_2, $J = 15.5$ Hz), 6.43 (s, 1H, C^4H), 6.65–7.25 (m, 13H, C_6H_4, C_6H_5, 4-FC_6H_4). Microanalysis: $C_{28}H_{22}FNO_5$ (471.5): calcd, %: C 71.33, H 4.70, N 2.97; found, %: C 71.18, H 4.59, N 2.85.

Compound **9b**: Yield: 57%; mp 177–178 °C. IR: $v = 1710$, 1755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.53 (s, 3H, CH_3), 2.09 (s, 3H, CH_3COO), 4.36 (d, 1H, NCH_2, $J = 15.5$ Hz), 4.62 (d, 1H, NCH_2, $J = 15.5$ Hz), 6.56 (s, 1H, C^4H), 6.88 (m, 2H, H_m-Ph), 6.94 (d, 2H, H_m-4-ClC_6H_4, $J = 8.5$ Hz), 7.17 (m, 4H), 7.21–7.27 (m, 2H), 7.30 (d, 2H, H_o-4-ClC_6H_4, $J = 8.5$ Hz), 7.42 (ddd, 1H, H^6, $J = 8.3$, 6.5, 2.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.88 (CH_3), 20.48 (CH_3CO), 44.63 (NCH_2), 61.10 (C^3), 67.80 (C^4), 111.77 ($C^{4'}$), 116.58 (C^8), 119.42 (C^{4a}), 125.14 (C^6), 126.64 (C^5), 127.32 (C_o-Ph), 127.35 (C_i-4-ClC_6H_4), 127.39 (C_p-Ph), 128.40 (C_m-Ph), 128.78 (C_m-4-ClC_6H_4), 130.64 (C^7), 130.87 (C_o-4-ClC_6H_4), 135.46 (C_p-4-ClC_6H_4), 136.40 (C_i-Ph), 141.65 ($C^{5'}$), 150.49 (C^{8a}), 162.09 (C^2), 169.57 (COO), 170.65 ($C^{2'}$). Microanalysis: $C_{28}H_{22}ClNO_5$ (487.9): calcd, %: C 68.92, H 4.54, N 2.87; found, %: C 68.80, H 4.40, N 2.74.

Compound **9c**: Yield: 59%; mp 165–166 °C. IR: $v = 1710$, 1755 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 1.43 (s, 3H, CH_3), 1.99 (s, 3H, CH_3COO), 4.22 (d, 1H, NCH_2, $J = 15.5$ Hz), 4.50 (d, 1H, NCH_2, $J = 15.5$ Hz), 6.40 (s, 1H, C^4H), 6.65–7.40 (m, 13H, C_6H_4, C_6H_5, 4-BrC_6H_4). Microanalysis: $C_{28}H_{22}BrNO_5$ (532.4): calcd, %: C 63.17, H 4.17, N 2.63; found, %: C 63.01, H 4.08, N 2.49.