Synthesis of New Heterocyclic Derivatives of Retinoids

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Reaction of α- and β-ionones **1** and **2** with dialkylformamide/phosphorus oxychloride affords enamines **6** and **7** along with the expected chloro derivatives **4** and **5**. Reaction of **6a** with hydrazines, hydroxylamine and guanidine furnished pyrazoles, isoxazole, pyrimidine **8-10** showing the potential of these enaminones as key intermediates in the synthesis of synthetic retinoids.

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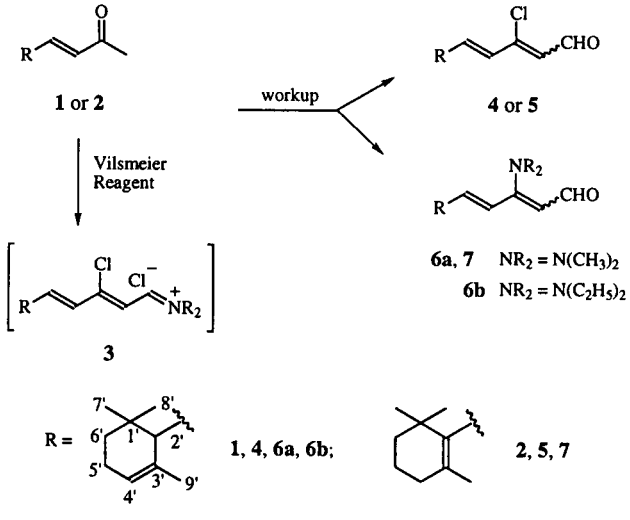
Considerable attention has been given to retinoids due to their biological activity as anti-tumor agents [1-3] as well as their interesting properties in commercially important cosmetic products. However, the use of natural retinoids has been limited because of their toxicity and poor stability [4-6]. Trying to overcome these disadvantages, the structure of vitamin A has been modified either in the cyclohexenyl ring or in the polyene side chain. The resulting synthetic retinoids have shown interesting biological activities [1,7].

Our interest in the Vilsmeier reactions and heterocyclic pharmaceuticals prompted us to study the α and β-ionones **1** and **2** in order to first functionalize and secondly cyclize them trying to form a new class of retinoid-like compounds. In fact, the Vilsmeier reagent facile attack on the α carbon of ketones is well documented [8] and gives species such as **3**, which after workup afford the corresponding β-chlorovinylaldehydes, which would have been able to cyclize by exploiting the formyl group and the chlorine.

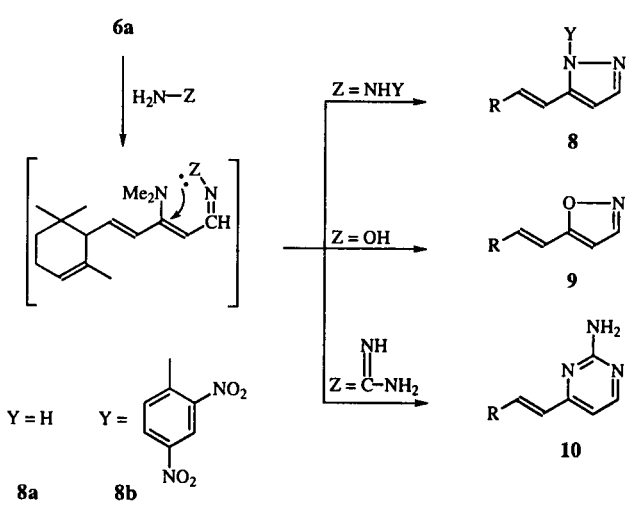
The reaction of **1** or **2** and the Vilsmeier reagent $(R_2N{=}CHCl)^+ PO_2Cl_2^-$, actually yielded derivatives **4** or **5**, which come from the expected Vilsmeier-reaction course, together with the unexpected enamines **6** and **7** (Scheme 1). Moreover, the formation of 3-dimethylamino(diethylamino)-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2,4-pentadienal **6a,b** and 3-dimethylamino-5-(2,6,6-trimethyl-1-cycloehexen-1-yl)-2,4-pentadienal **7** is unprecedented in a Vilsmeier reaction.

We, therefore, tried to cyclize derivatives **4** or **5**, but all attempts failed. We then turned our attention to the behavior of compounds **6**, supposing that the 3-dimethylamino group could act as a leaving group more readily than the chlorine atom. In fact, **6a** and **6b** displayed outstanding propensity to ring closure by bifunctional reagents as proved from the isolation of pyrazoles **8a-b**, isoxazole **9** and pyrimidine **10** in very high yields (Scheme 2). This one-pot cyclization, which involves both the formyl and the dimethylamino groups, highlights a chemical peculiarity of these enamines, which can further be exploited to obtain a new series of retinoid-like derivatives.

Scheme 1



Scheme 2



Support for the assigned structures **4-10** comes from the elemental analysis, spectral data and from their chemical transformations. In particular, the signal at 9.30 ppm in the ^1H nmr and the doublet at 190 ppm (J = 166.7 Hz) in the total coupling ^{13}C nmr of componds **6** unequivocally confirm the presence of an aldehyde which can only be in the position assigned.

In conclusion, once more the Vilsmeier reaction has proven to be a reaction of choice to obtain unexpected results. In this case, this one-pot reaction opens up new possibilities for the synthesis of stable enaminones, which, in turn, could be very useful key intermediates to synthesize promising heterocyclic derivatives.

Further studies are underway in order to broaden the applicability of this reaction to other α,β-unsaturated ketones.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. The ir spectra were recorded in chloroform or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AC 300 (300 MHz, ^1H; 75 MHz, ^{13}C) or a Varian Gemini 200 (200 MHz, ^1H; 50 MHz, ^{13}C) spectrometers in deuteriochloroform solutions with tetramethylsilane as the internal standard (δ = 0). The purity of all compounds was checked by thin-layer chromatography on silica gel 60-F-254 pre-coated plates and the spots were located in uv light or by vanillin in sulfuric acid. Elemental analyses were performed on a Carlo Erba 1106 Elemental Analyzer in the Microanalysis Laboratory in our Institute.

Preparation of Compounds **4-7**.

General Procedure.

Phosphorus oxychloride (50.0 mmoles, 4.57 ml) was added dropwise, during 15 minutes at 0°, to 3.87 ml of *N,N*-dimethylformamide in a two-necked flask protected from atmospheric moisture and efficiently stirred with a magnetic bar. A solution of **1** or **2** (25.0 mmoles) in 3 ml of dimethylformamide was added dropwise into the above Vilsmeier reagent cooled at -20°. The reaction mixture was allowed to stir while the temperature rose to 0° during 45 minutes, then poured onto crushed ice. The aqueous layer was separated, alkalinized for **6** and **7** or neutralized for **4** and **5** with a diluted solution of sodium hydroxide and allowed to stand overnight at room temperature. The resulting water-oil mixture was extracted with chloroform, and the combined organic layers dried over magnesium sulphate and evaporated to give an oil which solidified on standing for **6a** or which was chromatographed for **6b** and **7**.

3-Chloro-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2,4-pentadienal **4**.

By use of the general procedure, the reaction of the Vilsmeier reagent with **1** at -20 to 0°, after neutralization of the aqueous layer with a diluted solution of sodium hydroxide, provided a mixture from which compounds **4** were separated as a colorless oil by column chromatography on silica gel eluting with toluene (12% yield); ir (film): ν 2900, 2840, 1665, 1615, 1575, 1160 cm^{-1}; ^1H nmr (200 MHz): δ 0.90 (6H, s, CH_3), 1.20 (1H, m, H-5'), 1.45 (1H, m, H-5'), 1.60 (3H, s, CH_3), 2.02 (2H, m, H-4'), 2.35 (1H, d, H-1', J = 9.20 Hz), 5.50 (1H, m, H-3'), 6.12 (1H, d, H-2, J = 7.89 Hz), 6.25 (1H, d, ethene, J = 10.52 Hz), 6.60 (1H, dd, ethene, J = 9.20 Hz and J = 10.52 Hz), 10.20 (1H, d, CHO, J = 7.89 Hz); ^{13}C nmr (50 MHz): δ 23.4 (C-9'), 23.5 (C-5'), 27.3 (C-7'), 28.3 (C-8'), 31.7 (C-4'), 33.0 (C-6'), 54.9 (C-1'), 123.1 (C-3'), 125.7 (C-2), 128.8 (ethene), 132.4 (C-2'), 146.0 (ethene), 148.0 (C-3), 192.0 (CHO).

Anal. Calcd. for $C_{14}H_{19}OCl$: C, 70.4; H, 8.0; Cl, 14.8. Found: C, 70.2; H, 8.1; Cl, 14.6.

3-Chloro-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal **5**.

By use of the above procedure, compound **5** was prepared from **2**. The product was finally separated by column chromatography on silica gel as a colorless oil (14% yield); ir (film): ν 2920, 2860, 1670, 1610, 1590, 1570, 1170 cm^{-1}; ^1H nmr (200 MHz): δ 1.10 (6H, s, CH_3), 1.50 (2H, m, H-5'), 1.62 (2H, m, H-4'), 1.80 (3H, s, CH_3), 2.10 (2H, t, H-3'), 6.12 (1H, d, H-2, J = 7.40 Hz), 6.30 (1H, d, ethene, J = 14.81 Hz), 7.15 (1H, d, ethene, J = 14.81 Hz), 10.18 (1H, d, CHO, J = 7.40 Hz); ^{13}C nmr (50 MHz): δ 19.4 (C-4'), 22.3 (C-9'), 29.4 (C-7' and C-8'), 34.0 (C-3'), 34.8 (C-6'), 40.1 (C-5'), 125.6 (C-2), 129.0 (ethene), 136.2 (C-2'), 136.5 (C-1'), 140.4 (ethene), 150.6 (C-3), 191.8 (CHO).

Anal. Calcd. for $C_{14}H_{19}OCl$: C, 70.4; H, 8.0; Cl, 14.8. Found: C, 70.3; H, 8.2; Cl, 14.5

3-Dimethylamino-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2,4-pentadienal **6a**.

By use of the general procedure, the reaction of Vilsmeier reagent with **1** at -20 to 0°, after alkalinization of the aqueous layer, was allowed to stand overnight at room temperature. The resulting water-oil mixture led to an oil which solidified on standing furnishing **6a** as an essentially pure pale yellow powder (30% yield) mp 147° from *n*-hexane: ir (potassium bromide): ν 2900, 1610, 1540, 1380, 1190, 820 cm^{-1}; uv (ethanol): λ_{max} 305 nm, ε = 52800; ^1H nmr (200 MHz): δ 0.89 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.20 (1H, m, H-5'), 1.40 (1H, m, H-5'), 1.65 (3H, s, CH_3), 2.20 (2H, m, H-4'), 2.30 (1H, d, H-1', J = 7.5 Hz), 2.90 (6H, s, N-CH_3), 5.25 (1H, d, H-2, J = 8.8 Hz), 5.50 (1H, m, H-3'), 5.95 (2H, m, ethene), 9.30 (1H, d, CHO, J = 8.8 Hz); ^{13}C nmr (75 MHz): δ 23.5 (t, CH_2), 23.6 (q, CH_3), 27.2 (q, CH_3), 28.7 (q, CH_3), 31.6 (t, CH_2), 33.0 (s, C), 40.6 (q, CH_3, J = 138.36 Hz), 55.5 (d, CH, J = 125.65 Hz), 103.8 (dd, CH, J = 22.4, 154.3 Hz), 123.1 (d, CH, J = 158.9 Hz), 123.9 (d, CH, J = 154 Hz), 132.6 (s, C), 144.7 (d, CH, J = 156.5 Hz), 166.6 (s, C), 190.3 (d, CHO, J = 166.7 Hz).

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.6; H, 10.2; N, 5.6. Found: C, 77.7; H, 10.3; N, 5.7.

3-Diethylamino-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2,4-pentadienal **6b**.

By use of the general method the resulting water-oil mixture was extracted with chloroform and the combined organic layer dried (magnesium sulfate) and evaporated to give an oil which was chromatographed on silica gel eluting with toluene and ethyl acetate. The first elution gave the unreacted α-ionone, the second elution gave **6b** (15% yield) as a thick yellow oil; ir (film): ν 2900, 1620, 1540, 1430, 1380, 1310, 1260, 1200, 1180

cm^{-1}; ^{1}H nmr (200 MHz): δ 0.90 (3H, s, CH_3), 0.94 (3H, s, CH_3), 1.16 (6H, t, CH_3, J = 7.14 Hz), 1.20 (1H, m, H-5'), 1.40 (1H, m, H-5'), 1.64 (3H, s, CH_3), 2.00 (2H, m, H-4'), 2.30 (1H, m, H-1'), 3.30 (4H, q, N-CH_2, J = 7.14 Hz), 5.28 (1H, d, H-2, J = 8.38 Hz), 5.50 (1H, m, H-3'), 5.95 (2H, m, ethene), 9.30 (1H, d, CHO, J = 8.38 Hz); ^{13}C nmr (50 MHz): δ 13.3 (NCH_2CH_3), 23.5 (C-5'), 23.6 (C-9'), 27.1 (C-7'), 28.8 (C-8'), 31.5 (C-4'), 33.1 (C-6'), 45.0 (NCH_2), 55.5 (C-1'), 103.2 (C-2), 123.1 (C-3'), 123.4 (ethene), 132.6 (C-2'), 144.6 (ethene), 165.1 (C-3), 190.6 (CHO).

Anal. Calcd. for $C_{18}H_{29}NO$: C, 78.5; H, 10.6; N, 5.1. Found: C, 78.4; H, 10.5, N, 5.1.

3-Dimethylamino-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal **7**.

By use of the above procedure, the oil was chromatographed on silica gel (30 g) eluting with toluene, toluene-ethyl acetate (1:1), ethyl acetate and ethanol. The first elution (toluene) gave the unreacted β-ionone, the second and third elution gave a product which is still under investigation and finally the last elution (ethanol) gave **7** (25% yield) as pale yellow needles, mp 85° from *n*-hexane; ir (potassium bromide): ν 2900, 1610, 1540, 1375, 1185, 820 cm^{-1}; uv (ethanol): λ_{max} 307 nm, ε = 29200; ^{1}H nmr (200 MHz): δ 1.02 (6H, s, CH_3), 1.48 (2H, m, H-5'), 1.60 (2H, m, H-4'), 1.74 (3H, s, CH_3), 2.02 (2H, t, H-3'), 2.97 (6H, s, N-CH_3), 5.26 (1H, d, H-2, J = 9.30 Hz), 5.92 (1H, d, ethene, J = 16.28 Hz), 6.48 (1H, dd, ethene, J = 16.28 Hz), 9.38 (1H, d, CHO, J = 9.30); ^{13}C nmr (50 MHz): δ 19.5 (C-4'), 22.2 (C-9'), 29.3 (C-7' and C-8'), 33.5 (C-3'), 34.6 (C-6'), 39.9 (C-5'), 40.8 (C-N), 104.0 (C-2), 125.0 (ethene), 132.85 (C-2'), 136.9 (C-1'), 140.8 (ethene), 167.1 (C-3), 190.3 (CHO).

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.6; H, 10.2; N, 5.6. Found: C, 77.7; H, 10.4; N, 5.7.

5-(2,6,6-Trimethyl-2-cyclohexen-1-yl)ethenyl-1*H*-pyrazole **8a**.

A solution of 0.25 g (1 mmole) of **6a**, 1 ml of hydrazine hydrate (20 mmoles) in 10 ml of ethanol was allowed to stand at -10°. The resulting oil, purified by chromatography on silica gel (toluene/ethyl acetate 1:1), gave **8a** in 85% yield as a thick oil; ir (film): ν 3200, 2915, 1650, 1560, 1500, 1380, 1360 cm^{-1}; ^{1}H nmr (200 MHz): δ 0.86 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.22 (1H, m, H-5'), 1.45 (1H, m, H-5'), 1.62 (3H, s, CH_3), 2.05 (2H, m, H-4'), 2.28 (1H, d, H-1', J = 9.80 Hz), 5.48 (1H, m, H-3'), 6.05 (1H, dd, ethene, J = 15.68 Hz and J = 9.80 Hz), 6.32 (1H, d, H-4, J = 2.03 Hz), 6.38 (1H, d, ethene, J = 15.68 Hz), 7.51 (1H, d, H-3, J = 2.03 Hz), 14.4 (1H, s, NH); ^{13}C nmr (50 MHz): δ 23.5, 23.6, 27.4, 28.3, 32.0, 33.0, 55.3, 102.6, 121.2, 121.9, 134.1, 134.4, 135.1, 146.7.

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.7; H, 9.3; N, 12.9. Found: C, 77.4; H, 9.1; N, 13.0.

1-(2,4-Dinitrophenyl)-5-[(2,6,6-trimethyl-2-cyclohexen-1-yl)-ethenyl]-1*H*-pyrazole **8b**.

A solution of 0.25 g (1 mmole) of **6a** and 2,4-dinitrophenylhydrazine [0.2 g (1 mmole) in ethanol/sulfuric acid] in 10 ml of ethanol was allowed to stand at -10°. The resulting yellow crystals were **8b** already pure in 81% yield, mp 116-117° from ethanol; (potassium bromide): ν 3100, 2900, 2860, 1610, 1530, 1450, 1390, 1350 cm^{-1}; ^{1}H nmr (200 MHz): δ 0.86 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.22 (1H, m, H-5'), 1.42 (1H, m, H-5'), 1.58 (3H, s, CH_3), 2.05 (2H, m, H-4'), 2.20 (1H, d, H-1', J = 8.6 Hz), 5.48 (1H, m, H-3'), 6.12 (2H, m, ethene), 6.54 (1H, d, H-4, J = 2.15 Hz), 7.68 (1H, d, H-3, J = 2.15 Hz), [7.75 (1H, d), 8.56 (1H, dd), 8.85 (1H, d) arom-H]; ^{13}C nmr (50 MHz): δ 23.4, 23.5, 27.3, 28.3, 31.8, 33.2, 55.4, 105.9, 116.9, 121.6, 122.8, 127.7, 130.3, 133.0, 138.1, 139.8, 143.1, 143.4, 146.0, 147.0.

Anal. Calcd. for $C_{20}H_{22}N_4O_4$: C, 62.8; H, 5.8; N, 14.6. Found: C, 62.8; H, 5.7; N, 14.6.

5-(2,6,6-Trimethyl-2-cyclohexen-1-yl)ethenylisoxazole **9**.

The solution of 0.4 g (1.6 mmoles) of **6a** and hydroxylamine hydrochloride [0.5 g (7.0 mmoles) in 3 ml of water] in 30 ml of ethanol and 2 ml of a 10% water solution of sodium hydroxide was allowed to stand at room temperature 2 days. The resulting oil, purified by chromatography on silica gel (toluene/ethyl acetate 1:1), gave **9** in 85% yield as a thick oil; ir (film): ν 3100, 2900, 1640, 1570, 1449, 1370, 915, 870 cm^{-1}; ^{1}H nmr (200 MHz): δ 0.82 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.22 (1H, m, H-5'), 1.42 (1H, m, H-5'), 1.56 (3H, s, CH_3), 2.01 (2H, m, H-4'), 2.23 (1H, d, H-1', J = 9.50 Hz), 5.46 (1H, m, H-3'), 5.85 (1H, dd, ethene, J = 9.50; 15.23 Hz), 6.28 (1H, d, ethene, J = 15.23 Hz), 6.32 (1H, d, H-4, J = 2.80 Hz), 7.45 (1H, d, H-3, J = 2.80 Hz); ^{13}C nmr (50 MHz): δ 23.3 (CH_3), 24.5 (CH_2), 27.2 (CH_3), 28.4 (CH_3), 31.6 (CH_2), 32.9 (C), 55.2 (CH), 93.1 (CH), 121.1 (CH), 122.3 (CH), 133.2 (CH), 133.2 (C), 142.4 (CH), 158.01 (C).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.4; H, 8.8 N, 6.4. Found: C, 76.9; H, 8.9; N, 6.1.

6-(2,6,6-Trimethyl-2-cyclohexen-1-yl)ethenyl-2-aminopyrimidine **10**.

The solution of 0.5 g (2.0 mmoles) of **6a** and guanidine carbonate [0.36 g (2.0 mmoles) in 3 ml of water] in 30 ml of ethanol was refluxed for 48 hours. The resulting oil was extracted with chloroform. The combined extracts were dried (sodium sulfate) and evaporated to afford an oil which was purified by chromatography on silica gel (toluene/ethyl acetate 1:1), giving **10** in 85% yield as a thick oil; ir (film): ν 3300, 3180, 2900, 2860, 1680, 1560, 1450 cm^{-1}; ^{1}H nmr (200 MHz): δ 0.87 (3H, s, CH_3), 0.93 (3H, s, CH_3), 1.25 (1H, m, H-5'), 1.45 (1H, m, H-5'), 1.59 (3H, s, CH_3), 2.04 (2H, m, H-4'), 2.30 (1H, d, H-1', J = 8.98 Hz), 5.17 (2H, s, NH_2), 5.48 (1H, m, H-3'), 6.20 (1H, d, ethene, J = 8.60 Hz), 6.58 (1H, d, H-4, J = 5.26 Hz), 6.65 (1H, dd, ethene, J = 15.05, 8.60 Hz), 8.19 (1H, d, H-5, J = 5.26 Hz); ^{13}C nmr (50 MHz): δ 23.4 (CH_3), 23.6 (CH_2), 27.4 (CH_3), 28.4 (CH_3), 31.8 (CH_2), 33.1 (C), 55.1 (CH), 108.9 (CH), 122.5 (CH), 130.2 (CH), 133.3 (C), 141.6 (CH), 158.6 (CH),163.5 (C), 164.4 (C).

Anal. Calcd. for $C_{15}H_{21}N_3$: C, 74.0; H, 8.7; N, 17.3. Found: C, 73.8; H, 8.6; N, 17.0.

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