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REGIO- AND STEREOSELECTIVE ALKOXYCARBONYL-METHYLENATION OF PARTIALLY SATURATED HETERO-BICYCLIC COMPOUNDS: FIRST SYNTHESIS OF 2-SUBSTITUTED QUINAZOLINE-8-ACETIC ACID ESTERS

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Abstract: The three-step synthesis of 2-substituted quinazol-8-yl acetates is described, introducing a completely new method for the regio- and stereoselective alkoxycarbonylmethylenation of tetrahydroquinazolines.

The quinazolines have become a well-investigated class of heterocyclic compounds,[1] and there are many modern pharmaceuticals or agrochemicals, like

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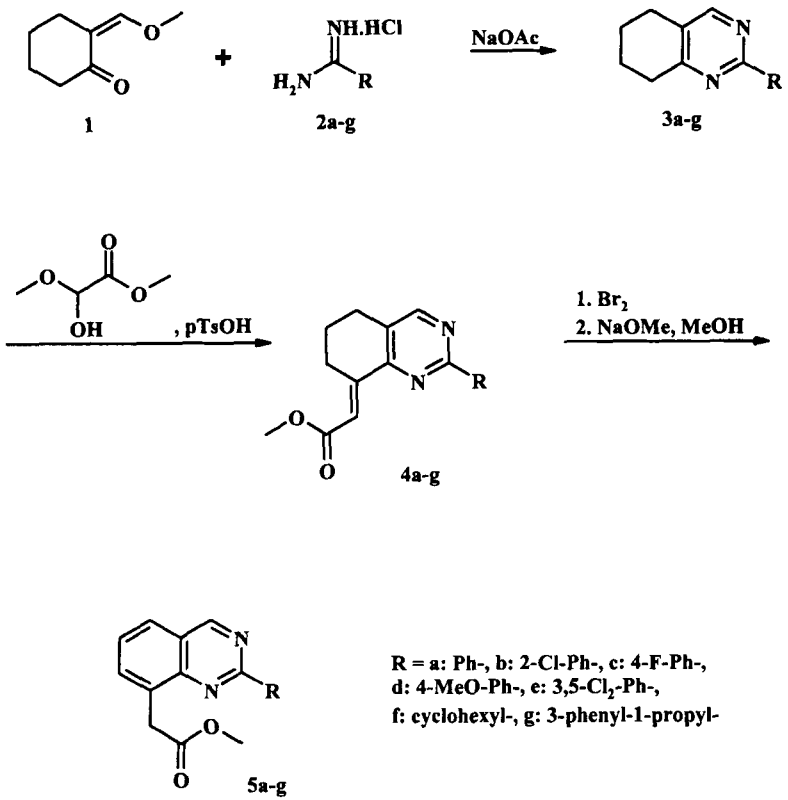
the antihypertensive vasodilator prazosin[2] and the acaricidal respiration inhibitor fenazaquin,[3] which are based on a quinazoline nucleus. But still in our days very little is known about 2,8-disubstituted derivatives, because this substitution pattern is not easy to achieve. The very few publications,[4] which report on the preparation of such compounds are limited to certain, mainly non-carbon substituents. During a synthesis program, we needed a reliable approach to 2-aryl or alkyl substituted quinazolines with an acetic acid ester function in position 8. In this paper, we present a concise approach to such compounds.

Our synthesis starts with the condensation of 2-methoxymethylenecyclohexanone (**1**)[5] with an appropriate amidine salt **2**.[6] This reaction generates in good yields 2-substituted 5,6,7,8-tetrahydroquinazolines **3**,[7] which can be transformed in an aldol-type condensation with glyoxylic acid methylester methylhemiacetal as carbonyl component to the corresponding 5,6,7,8-tetrahydroquinazol-8-ylidene acetates **4**. Hereby the C-C bond formation takes place regioselectively at ringposition 8, leading predominantly to the *E*-stereoisomers at the exocyclic C-C double bond. This is to our knowledge the first synthesis of an enoic acid ester directly from the partially saturated bicyclus.[8] So far the regioselective alkoxycarbonylmethylenation at iso- or heterocyclic ring systems had to be carried out from the corresponding cyclic ketone via Horner-Wadsworth-Emmons reaction or Peterson olefination.[9] However, there are two examples in the literature, where 8-substituted compounds are produced regioselectively in the nitrosation[10] and Vilsmeier reaction[11] of 5,6,7,8-tetrahydroquinazoline.

Finally, the saturated ring has to be aromatized to afford the desired 2-substituted quinazoline-8-acetic acid esters **5**. From several different conditions we applied to this last step in our reaction sequence, the addition of bromine to the α,β-unsaturated ester followed by a sodium methoxide mediated elimination proved to be the best method to reach the final products.



R = a: Ph-, b: 2-Cl-Ph-, c: 4-F-Ph-, d: 4-MeO-Ph-, e: 3,5-Cl_2-Ph-, f: cyclohexyl-, g: 3-phenyl-1-propyl-

In conclusion, we found a novel possibility for the preparation of 2-substituted quinazoline-8-acetic acid esters. The fact, that acetates are transformable into

many other functionalities,[12] makes compounds **5** valuable building blocks for several different target molecules.

Experimental

General. All new compounds were characterized by standard spectroscopical and microanalytical methods. The structural confirmation of the configuration at the exocyclic double bond of compounds **4a-g** was established by NOE-experiments. ^{1}H-NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200 MHz, using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are reported in ppm downfield from the standard (δ = 0.00), coupling constants are in Hz. Melting points were determined on a Buechi 535 melting-point apparatus, column chromatography was performed on E.Merck silica gel 60 (40 - 63 mm).

2-Phenyl-5,6,7,8-tetrahydroquinazoline (**3a**). A mixture of 2-methoxymethylenecyclohexanone (**1**, 18.7 g, 0.13 mol), benzamidine hydrochloride (**2a**, 25.1 g, 0.16 mol) and sodium acetate anhydrous (13.1 g, 0.16 mol) in 250 ml ethanol is heated under reflux for 4 hours. After cooling, the reaction is poored into a 10% aqueous sodium carbonate solution and extracted three times with ethyl acetate. The combined organic layer is dried over magnesium sulfate and evaporated. The remainder is purified by column chromatography on silica gel, using hexane / ethyl acetate 15 : 85 as eluent

system. Yield: 20.4 g (97 mmol, 73 %) **3a**. Mp.: 51 - 52 °C (lit.[7] 51 - 53 °C). ^{1}H-NMR: δ = 1.76 - 2.01 (m, 4H), 2.78 (t, 2H, J = 7.0), 2.95 (t, 2H, J = 7.0), 7.42 - 7.53 (m, 3H), 8.33 - 8.47 (m, 3H).

The compounds **3b-g** are obtained analogously.

3b. ^{1}H-NMR: δ = 1.82 - 2.03 (m, 4H), 2.81 (t, 2H, J = 7.5), 2.97 (t, 2H, J = 7.0), 7.16 - 7.70 (m, 4H), 8.54 (s, 1H).

3c. ^{1}H-NMR: δ = 1.78 - 2.01 (m, 4H), 2.74 (t, 2H, J = 7.5), 2.91 (t, 2H, J = 8.0), 7.07 - 7.29 (m, 3H), 8.31 - 8.45 (m, 2H).

3d. ^{1}H-NMR: δ = 1.79 - 1.98 (m, 4H), 2.76 (t, 2H, J = 7.5), 2.92 (t, 2H, J = 7.3), 3.88 (s, 3H), 6.92 - 7.03 (m, 2H), 8.28 - 8.41 (m, 3H).

3e. ^{1}H-NMR: δ = 1.80 - 2.02 (m, 4H), 2.79 (t, 2H, J = 7.0), 2.96 (t, 2H, J = 7.5), 7.42 (t, 1H, J = 3.5), 8.27 - 8.31 (m, 2H), 8.47 (s, 1H).

3f. ^{1}H-NMR: δ = 1.20 - 2.01 (m, 15H), 2.71 (t, 2H, J = 7.5), 2.85 (t, 2H, J = 7.5), 8.33 (s, 1H).

3g. ^{1}H-NMR: δ = 1.71 - 1.96 (m, 4H), 2.03 - 2.20 (m, 2H), 2.62 - 2.98 (m, 8H), 7.11 - 7.32 (m, 5H), 8.31 (s, 1H).

Methyl (E)-(2-phenyl-5,6,7,8-tetrahydroquinazol-8-ylidene)acetate (**4a**). 7.2 g (60 mmol) of glyoxylic acid methylester methylhemiacetal, 8.4 g (40 mmol) of **3a** and 7.6 g (40 mmol) of p-toluenesulfonic acid monohydrate are taken up in 100 ml toluene, and this mixture is heated under reflux for 10 hours using a Dean-Stark water separation apparatus. Subsequently the reaction mixture is cooled, diluted

with ethyl acetate and washed twice with saturated aqueous sodium carbonate solution. The organic layer is dried over magnesium sulfate and evaporated. The remaining oil is chromatographed on silica gel (hexane / ethyl acetate, 4 : 1). Yield: 4.8 g (17 mmol, 42 %) **4a**. Mp.: 140 - 141 °C. ^{1}H-NMR: δ = 1.95 (quin, 2H, J = 3.0, 7.5), 2.87 (t, 2H, J = 7.5), 3.24 - 3.31 (m, 2H), 3.82 (s, 3H), 7.45 - 7.58 (m, 4H), 8.43 - 8.51 (m, 2H), 8.64 (s, 1H).

The compounds **4b-g** are obtained in an analogue manner.

4b. ^{1}H-NMR: δ = 1.96 (quin, 2H, J = 2.7, 7.5), 2.88 (t, 2H, J = 7.0), 3.21 - 3.30 (m, 2H), 3.79 (s, 3H), 7.33 - 7.82 (m, 5H), 8.69 (s, 1H).

4c. ^{1}H-NMR: δ = 1.94 (quin, 2H, J = 3.5, 7.5), 2.87 (t, 2H, J = 7.3), 3.28 (t, 2H, J = 7.5), 3.83 (s, 3H), 7.12 - 7.54 (m, 4H), 8.43 - 8.52 (m, 1H), 8.62 (s, 1H).

4d. ^{1}H-NMR: δ = 1.86 - 2.00 (m, 2H), 2.82 (t, 2H, J = 7.5), 3.27 (t, 2H, J = 7.0), 3.83 (s, 3H), 3.91 (s, 3H), 6.97 - 7.54 (m, 3H), 8.40 - 8.48 (m, 2H), 8.59 (s, 1H).

4e. ^{1}H-NMR: δ = 1.94 (quin, 2H, J = 3.3, 7.5), 2.87 (t, 2H, J = 7.3), 3.27 (t, 2H, J = 7.5), 3.86 (s, 3H), 7.42 - 7.51 (m, 2H), 8.32 - 8.37 (m, 2H), 8.62 (s, 1H).

4f. ^{1}H-NMR: δ = 1.21 - 2.05 (m, 13H), 1.79 (t, 2H, J = 7.3), 3.17 - 3.25 (m, 2H), 3.80 (s, 3H), 7.42 (t, 1H, J = 3.3), 8.49 (s, 1H).

4g. ^{1}H-NMR: δ = 1.82 - 2.27 (m, 4H), 2.65 - 3.27 (m, 8H), 3.81 (s, 3H), 7.16 - 7.42 (m, 6H), 8.48 (s, 1H).

Methyl (2-phenylquinazol-8-yl)acetate (**5a**). Bromine (1.5 g, 9.4 mmol) is added dropwise to a solution of **4a** (2.4 g, 8.5 mmol) in 40 ml ethyl acetate. After being stirred for 16 hours at room temperature, the solvent is removed at a rotary

evaporator. The residue is taken up in a solution of sodium methoxide (1.3 g, 25 mmol) in 25 ml methanol, and this mixture is heated to reflux for 6 h. After cooling, the reaction is poured into a saturated aqueous ammonium chloride solution and extracted three times with ethyl acetate. The combined organic phases are dried over magnesium sulfate and evaporated. The remainder is purified by column chromatography on silica gel (hexane / ethyl acetate 4 : 1). Yield: 1.3 g (4.7 mmol, 55 %) **5a**. Mp.: 119 °C. ^{1}H-NMR: δ = 3.75 (s, 3H), 4.32 (s, 2H), 7.49 - 7.90 (m, 6H), 8.60 - 8.68 (m, 2H), 9.47 (s, 1H).

The compounds **5b-g** are obtained analogously.

5b. ^{1}H-NMR: δ = 3.72 (s, 3H), 4.32 (s, 2H), 7.38 - 7.97 (m, 7H), 9.51 (s, 1H).

5c. ^{1}H-NMR: δ = 3.73 (s, 3H), 4.29 (s, 2H), 7.16 - 7.90 (m, 5H), 8.58 - 8.68 (m, 2H), 9.43 (s, 1H).

5d. ^{1}H-NMR: δ = 3.72 (s, 3H), 3.91 (s, 3H), 4.30 (s, 2H), 6.96 - 7.88 (m, 4H), 8.26 - 8.63 (m, 3H), 9.42 (s, 1H).

5e. ^{1}H-NMR: δ = 3.82 (s, 3H), 4.28 (s, 2H), 7.46 - 7.93 (m, 4H), 8.47 - 8.52 (m, 2H), 9.46 (s, 1H).

5f. ^{1}H-NMR: δ = 1.21 - 2.18 (m, 11H), 3.72 (s, 3H), 4.22 (s, 2H), 7.48 - 7.83 (m, 3H), 9.31 (s, 1H).

5g. ^{1}H-NMR: δ = 2.28 (quin, 2H, J = 3.3, 7.5), 2.64 - 2.81 (m, 2H), 3.18 (t, 2H, J = 7.3), 3.67 (s, 3H), 4.25 (s, 2H), 7.14 - 7.87 (m, 8H), 9.31 (s, 1H).

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