

A NICKELACYCLE AS PROPIONIC ACID EQUIVALENT FOR CARBON-CARBON COUPLING REACTIONS; APPLICATION TO THE SYNTHESIS OF C₂₅ STEROID CARBOXYLIC ACIDS

Bruno Schönecker^{a,+}, Dirk Walther^{b,+}, Reinald Fischer^b, Bernd Nestler^b,
Gabriele Bräunlich^b, Hermann Eibisch^a, Peter Droscher^c

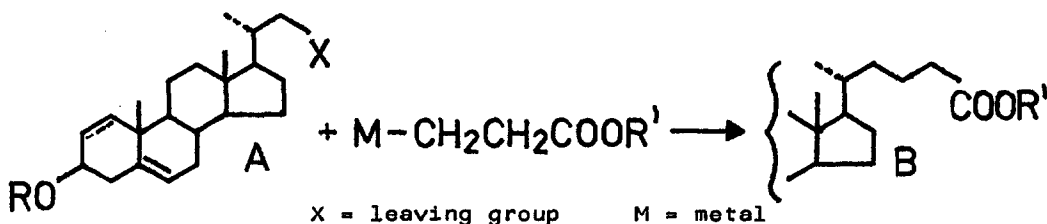
^a Central Institute of Microbiology and Experimental Therapy,
Academy of Sciences of the GDR, DDR-6900, Jena

^b Department of Chemistry, Friedrich Schiller University, DDR-6900, Jena

^c Division of Research and Development, VEB Jenapharm, DDR-6900, Jena

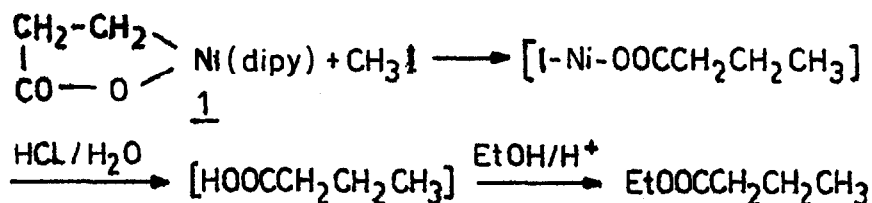
Summary: β -Substituted propionic acids are prepared in good yields by carbon-carbon coupling reaction of the nickelacycle 1 with organic iodides and anhydrous manganese(II) iodide. This new reaction is used to the synthesis of C₂₅ steroid carboxylic acids from C₂₂ steroid iodides.

In our synthetic work on vitamin-D₃ metabolites and analogs we became interested in a facile method of synthesising C₂₅ steroids with a carboxylic acid function (B), starting with the C₂₂ steroids (A) after the following scheme:



The yields of the alkylation reactions of the known propionate homo-enolate C₃ building blocks were unsatisfactory for our aim. Furthermore, the synthesis of the C₃ equivalents in some cases is cumbersome.¹ Unfortunately, the recently described zinc propionate homo-enolates, possessing a great synthetic potential, cannot be alkylated.^{2,3} Therefore, also in connection with our interest in the reactivity of nickel complexes, we have investigated the alkylation of the nickelacycle 1. This complex can be prepared from succinic anhydride and (α, α' -di-pyridyl)-(cycloocta-1,5-diene)nickel⁴ or directly from nickel acetyl-acetonate, triethyl aluminium and succinic anhydride.⁴

In a first attempt methyl iodide and 1 were heated in methanol. After acidic hydrolysis and esterification with ethanol ethyl butyrate was detected by GC.




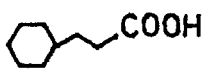




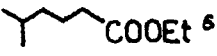

Use of methyl *p*-toluenesulfonate instead of methyl iodide provided only a small amount of ethyl butyrate.

In order to prove the generality of the alkylation reaction of 1 some other organic iodides were used (Table 1). As an example for a secondary iodide cyclohexyl iodide (2.6 mmol) in DMF (50 ml) was shaken with 1 (2.6 mmol) for 8 hours in a dry argon atmosphere. After hydrolysis with diluted hydrochloric acid the resulting 3-cyclohexyl propionic acid⁵ was isolated by extraction with ether and NaHCO₃ solution (0.55 mmol = 22% yield). We tried to increase the yield by addition of equimolar amounts of an anhydrous metal salt. With manganese(II) iodide, the yield rose to 69%. The analogous reaction of cyclohexyl bromide with MnI₂ and 1 gave only a small amount of the desired acid.

The reaction of ethyl iodide (entry 3) is remarkable in view of the nearly quantitative yield of valeric acid. This result suggests that a possible β-hydride elimination does not take place.

Iodobenzene does not react, this might be a hint to the necessity of an iodine bond to a sp³ carbon atom.

Table 1. Synthesis of 3-substituted propionic acids from organic iodides and (dipy)Ni(CH₂CH₂COO) (1)/MnI₂^{a)}

entry	halide	product	yield [%]
1			69
2	 (without MnI ₂)		22
3			> 90 ^b
4			88 ^c
5		no reaction	-

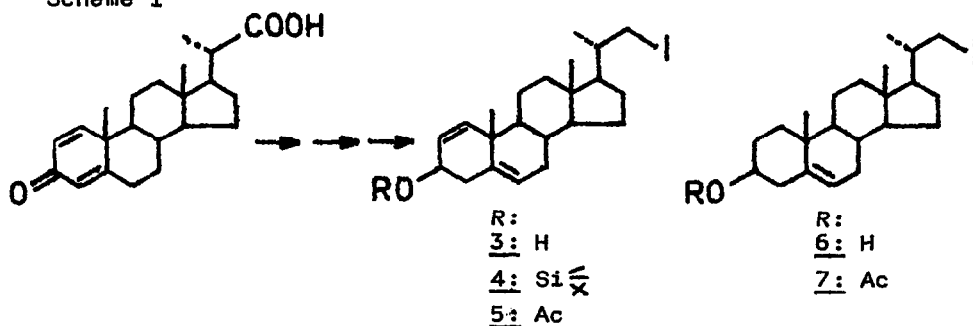
a standard conditions: equimolar amounts of R-I, 1 and MnI₂, DMF, r.t.

b GC determination

c esterification with EtOH/H₂SO₄

The steroid iodides necessary for our further investigations were prepared from the C₂₂ acid 2.⁷

Scheme 1



For the complete reaction of the steroid iodides with 1 a slight excess of 1 and MnI_2 was used. The expected acids or their methyl esters (after reaction with diazomethane) were obtained in good yields (Scheme 2 and Table 2).⁸

Interestingly, some additional functions in the steroid molecule are stable under the reaction conditions (hydroxyl or ester groups, even an allylic hydroxyl group and the silylated derivative). In contrast, the allylic acetate in compound 5 is not inert.

Scheme 2

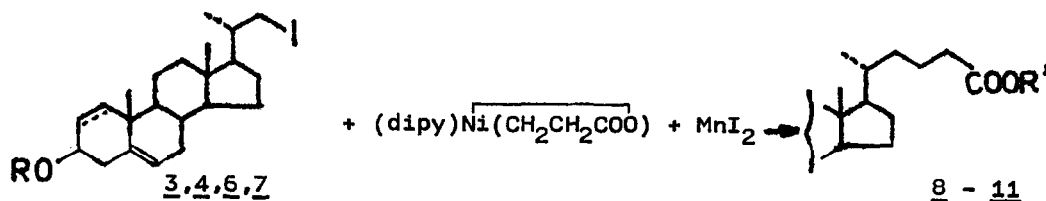


Table 2

entry	steroid iodide	mp (°C)	product	substituent		yield (%)	mp (°C)
				R	R'		
1	<u>3</u>	142-147	<u>8</u>	H, Δ^1	CH ₃	79	103-105
2	<u>4</u>	193-194	<u>9</u>	Si(CH ₃) ₂ , Δ^1	CH ₃	88	104-110
3	<u>6</u>	172-174	<u>10</u>	H	H ¹⁰	78	204-206
4	<u>7</u>	170-174	<u>11</u>	Ac	CH ₃ ¹¹	91	106-110

Unlike earlier methods¹⁰⁻¹³ C₂₅ steroid carboxylic acids are now available in a one-pot procedure from C₂₂ steroids. The compounds are useful for the preparation of 25,25-dialkyl-25-hydroxy compounds,^{12,13} intermediates for the synthesis of analogs of vitamin-D₃ metabolites with a good dissociation between calcium regulating and cell differentiation effect.¹³

REFERENCES AND NOTES

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8. Standard procedure: Steroid iodide (1-2 mmol), DMF (10-20 ml), 1 (1,6 mmol per mmol steroid), and MnI₂ (1,3 mmol per mmol steroid) were stirred at r.t. for 48 h⁹ or treated with ultrasound (cleaner) for 5 h in a dry argon atmosphere. The solvent was removed by distillation in vacuo. The residue was treated with diluted hydrochloric acid and diethyl ether. After washing the ether solution with water the steroid acid can be isolated or esterificated with CH₂N₂. Recrystallization provided pure products. ¹H-NMR of 9: (100 MHz, CDCl₃) 0,08 (s, 6H, SiCH₃), 0,68 (s, 3H, 18-H), 0,90 (s, 9H, t-Bu), 0,93 (d, J = 7 Hz, 2H, 21-H), 1,08 (s, 3H, 19-H), 3,66 (s, 3H, COOCH₃), the further downfield signals are practically identical with those of compound 4.
9. In some cases a small amount of a 20-methylene steroid, formed by elimination, could be isolated after chromatography. By using ultrasound these compounds could not be detected.
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