Tetrahedron Vol. 43, No. 6, pp. 1071 to 1074, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00
Pergamon Journals Ltd.

CARBONYLATION IN BENZYL ALCOHOL. A NEW AND EASY METHOD FOR THE PREPARATION OF AROMATIC BENZYL ESTERS

ANDREAS HUTH*, ILSE BEETZ, INGRID SCHUMANN AND KRIEMHILD THIELERT

Research Laboratories of the Schering AG Berlin and Bergkamen,
Müllerstrasse 170-178, D-1000 Berlin 65, F.R.G.

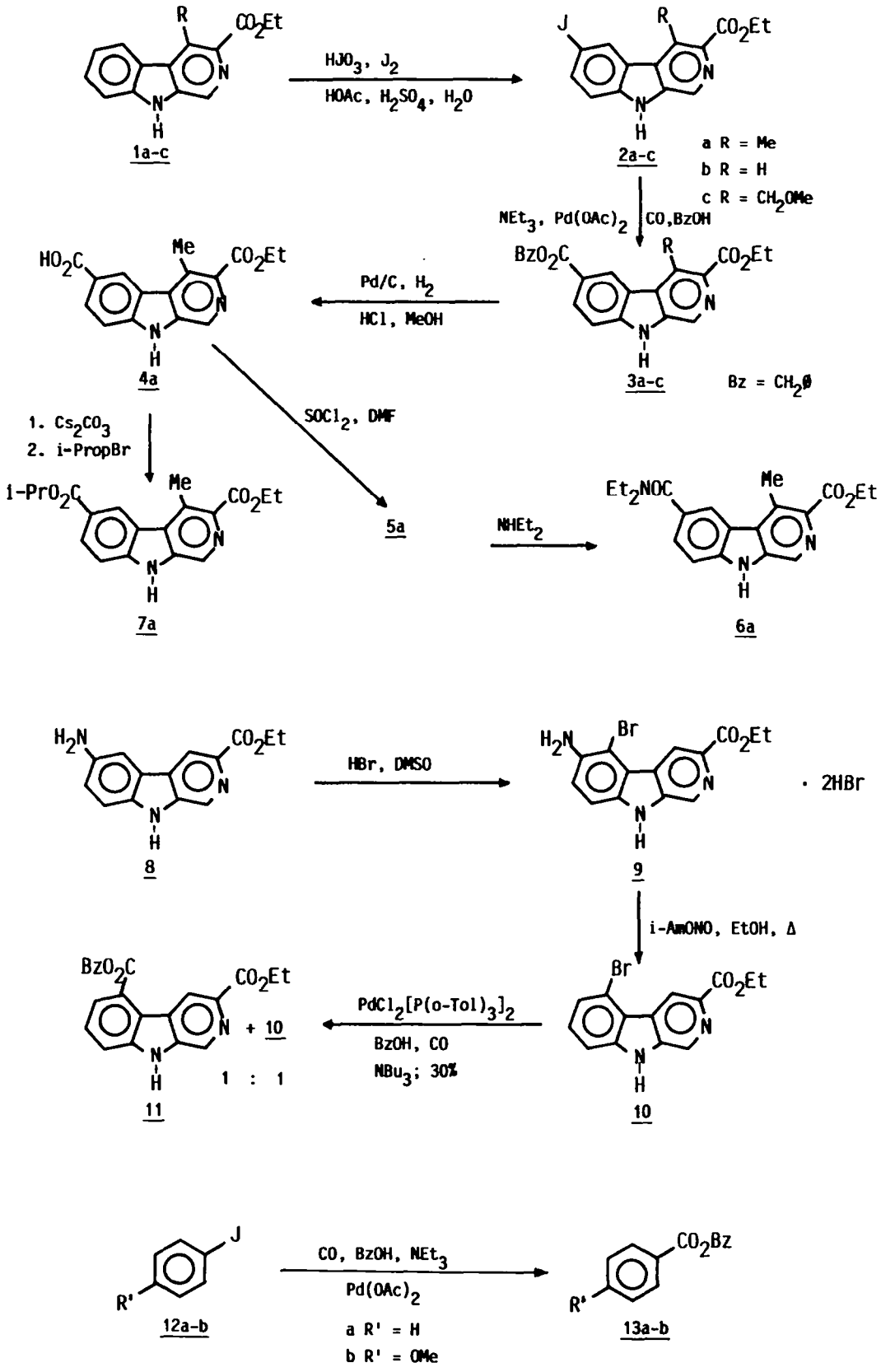
(*Received in Germany* 15 *December* 1986)

Abstract - The carbonylation of the iodides **2a-c** and **12a-b** in benzyl alcohol with carbon monoxide affords the corresponding benzyl esters **3a-c** and **13a-b** in good yields. It is shown that **3a** can be easily and selectively cleaved to the acid **4a** by catalytic hydrogenation. The acid is converted to an ester, **7a**, and an amide, **6a**.

Due to the known high affinity of ethyl-ß-carboline-3-carboxylate for the benzodiazepine receptor[1], we became interested in preparing 5- and 6-carbonyl substituted ß-carbolines. As the total synthesis of these compounds is lengthy, we looked for a simple and direct introduction of ester- and amide groups in the A-ring of the readily accessible ß-carbolines **1a-c**. The corresponding 6-iodo compounds **2a-c** are easily prepared by analogy to the method of Wirth[2]. In the 5-position only the 5-bromo carboline **10** is available from the 6-amino derivative **8**. Treatment of **8** with hydrobromic acid and dimethyl sulfoxide (DMSO), according to the procedure of Rehse[3], affords **9**. This method works well with **8** but fails with the 4-methyl compound due to steric hindrance. Diazotization of **9** and reduction of the intermediate diazonium salt by treatment with i-amylnitrite in ethanol gives **10** in good yield.

A carbonylation seemed to be the best method to convert the above halogenated carbolines to esters and amides. We selected from among the many available carbonylation procedures[4,5] the method of Heck[6], which starts from aryl iodides and uses palladium(II)acetate as catalyst at normal pressure of carbon monoxide. We found it possible to transfer this method to carbolines. Higher boiling alcohols generally react better (ethanol < n-propanol < n-butanol). With n-butanol a partial transesterification of the 3-ester group occurs. We tried to compensate for the disadvantage of lower boiling alcohols by using the stronger catalyst $PdCl_2[P(oTol)_3]_2$ and dimethylformamide (DMF) as solvent[6]. However, the yields were not improved, because the carbonylation product and the starting material are almost identical in chromatographic behaviour and thus are difficult to separate. These unsatisfactory yields prompted us to change the alcoholic component. Isopropanol and t-butanol give only intractable mixtures, even under the improved conditions. Surprisingly, the carbonylation of **2a** with benzyl alcohol as reactant and as solvent takes place in good yield and without any transesterifaction in the 3-position. This is astonishing because, to our knowledge, this modification has not previously been used. Only the cyclization of 2-halo benzylic alcohols by carbonylation[7,8] and the use of benzyl alcohol instead of benzyl halides[9] are known. The work-up procedure is much simplified by replacing the described base tributylamine[6,7] by triethylamine.

Iodobenzene (**12a**) and 4-iodoanisole (**12b**) react in the same manner. Thus the reaction is not restricted to carbolines and seems to be general.


1a-c
HJO3, J2
HOAc, H2SO4, H2O
2a-c
a R = Me
b R = H
c R = CH2OMe
NEt3, Pd(OAc)2
CO,BzOH
3a-c
Bz = CH2Ø
Pd/C, H2
HCl, MeOH
4a
1. Cs2CO3
2. i-PropBr
SOCl2, DMF
5a
NHEt2
7a
6a
8
HBr, DMSO
9
· 2HBr
i-AmONO, EtOH, Δ
PdCl2[P(o-Tol)3]2
BzOH, CO
NBu3; 30%
10
11
1 : 1
12a-b
CO, BzOH, NEt3
Pd(OAc)2
a R' = H
b R' = OMe
13a-b

The value of this easy and simple method is obvious. One obtains benzyl esters which can be cleaved selectively to acids in the presence of other ester groups by means of catalytic hydrogenation, as shown at the example of **3a**. The acid group of **4a** can be esterified by the method of Wang[10], converting it into the cesium salt which is then alkylated by isopropyl bromide to **7a**. The also readily accessible acid chloride **5a** is transformed by diethylamine to the corresponding amide **6a**. These examples show well the synthetic scope of this method. The carbonylation is only limited by the necessity to start with an iodo compound. The 5-bromocarboline **10** yields only a 1:1 mixture of the desired product **11** and starting material **10**, even using the stronger catalyst and temperatures up to 180°C.

EXPERIMENTAL

Melting points were determined with an "Electrothermal" melting point apparatus and are not corrected. Solvents of analytical grade were used after drying over molecular sieves. Carbon monoxide (99.99% grade) was used from a small bottle obtained from Messer Griesheim. ^{1}H-NMR spectra were recorded on a Perkin Elmer R-24 A spectrometer at 60 MHz in $CDCl_3$ as solvent with TMS as internal standard. Chromatography was performed at medium pressure (up to 0.5 bar) over silica gel, 63-200 µm (Merck). Elemental analyses were carried out by our "Analytisches Kontrollabor" under the direction of Dr. Merz.

Ethyl(6-iodo-4-methyl-ß-carboline)-3-carboxylate (**2a**)

A mixture of 10.2 g (40.2 mmol) of **1a**[11] in 80 ml of glacial acetic acid with 1.9 ml of water, 0.5 ml of sulfuric acid, 1.38 g (7.84 mmol) of iodic acid (Fluka) and 3.5 g (13.8 mmol) of iodine (Merck) were stirred 3 h at 80°C. After cooling, the mixture was poured into 50 ml of water and 50 ml of ethanol. The precipitate was isolated by filtration. The filter cake was suspended in 600 ml of ethyl acetate and extracted with 300 ml of 1N aqueous NaOH. The organic layer was washed once with water, dried, filtered and evaporated. The residue was treated with a small amount of ethyl acetate and isolated by filtration, affording 9.0 g (59%) of **2a**, m.p. 245-250°C. ($C_{15}H_{13}JN_2O_2$; 380.17; requires: C 47.39, H 3.45, N 7.37; found: C 47.66, H 3,54, N 7.53).

Analogously were obtained:

2b (64%) m.p. 310-315°C (pyridine). ($C_{14}H_{11}JN_2O_2$; 366.15; requires: C 45.92, H 3.03, N 7.65; found: C 45.36, H 3.02, N 7.52).

2c (57%) m.p. 250°C (triturated with ethanol). ($C_{16}H_{15}JN_2O_3$; 410.20; requires: C 46.87, H 3.68, N 6.83; found: C 46.71, H 3.82, N 7.06).

Ethyl(5-bromo-ß-carboline-3-carboxylate) (**10**)

A solution of 2.8 g (11 mmol) of **8**[11] in 210 ml of dimethyl sulfoxide was treated dropwise at room temperature with 140 ml of hydrobromic acid (48 %, Riedel de Haen). Subsequently the mixture was cooled and the precipitate was isolated by filtration. The filter cake was recrystallized from methanol/diisopropyl ether (DIP) to afford 4.5 g (87%) of **9**, m.p. 350°C ($C_{14}H_{12}BrN_3O_2 \cdot 2\,HBr$; 496.02; requires: C 33.90, H 2.84, N 8.47, Br 48.33; found: C 33.49, H 2.86, N 8.16, Br 48.20). This material was suspended in 280 ml of absolute ethanol and treated with 8.8 ml (66 mmol) of i-amylnitrite (Riedel de Haen). After stirring for 1 h at 60-80°C the solvent was evaporated. The residue was triturated with a small amount of ethanol and filtered; 3.05 g (96%) of **10** were obtained, m.p. 305-310°C. ($C_{14}H_{11}N_2O_2Br$; 319.16; requires: C 52.66, H 3.45, N 8.77, Br 25.08; found: C 53.04, H 3.69, N 8.65, Br 24.88).

Ethyl(6-benzyloxycarbonyl-4-methyl-ß-carboline-3-carboxylate) (**3a**)

A mixture of 760 mg (2 mmol) of **2a** and 0.5 ml (7 mmol) of triethylamine (Merck) in 10 ml of benzyl alcohol (Riedel de Haen) was warmed to 80°C under an atmosphere of carbon monoxide (slowly bubbling from a balloon through the solution). Then 30 mg (0.13 mmol) of palladium(II)-acetate (EGA-Chemie) were added and the temperature was raised to 110-120°C for 7 h, always continuing the bubbling of CO. After dilution with ethyl acetate the palladium was filtered off

and the filtrate was evaporated in vacuum. The residue was dissolved in methylene chloride and washed successively with aqueous sodium carbonate and water. The organic layer was dried, filtered and evaporated. The residue was recrystallized from ethanol/water to afford 510 mg (63%) of **3a**, m.p. 213-214°C. ($C_{23}H_{20}N_2O_4 \cdot 0.3\ H_2O$; 393.83; requires: C 70.15, H 5.27, N 7.11; found: C 70.28, H 5.33, N 7.13).

Analogously were prepared:

3b (74%) m.p. 265-272°C (DMF). ($C_{22}H_{18}N_2O_4$; 374.38; requires: C 70.58, H 4.85, N 7.48; found: C 70.40, H 4.89, N 7.51).

3c (64%) m.p. 155-156°C (ethyl acetate/DIP). ($C_{24}H_{22}N_2O_5$; 418.43; requires: C 68.89, H 5.30, N 6.70; found: C 68.85, H 5.63, N 7.15).

13a (62%) ^{1}H-NMR identical with Aldrich Library of NMR spectra Vol. 2 (2), 281 D.

13b (44%) NMR: δ_H 3.8 (3H, s); 5.3 (2H, s); 7.3 (5H, s); 6.85, 8.0 (4H, ABqu. J = 9 Hz).

Ethyl(4-methyl-ß-carboline-6-carbonic acid-3-carboxylate) (**4a**)

A solution of 1.6 g (4.1 mmol) of **3a** in 150 ml of methanol and 10 ml of 1N hydrochloric acid with 1.4 g of palladium/charcoal (10%) was hydrogenated for 1 h at room temperature and 1 bar. After removal of the catalyst by filtration and evaporation of the filtrate, the residue was stirred with a small amount of ethanol. The precipitate was filtered off and 1.15 g (83%) of **4a** m.p. 328-329°C were obtained. ($C_{16}H_{14}N_2O_4 \cdot H_2O$, HCl; 352.77; requires: C 54.48, H 4.86, N 7.94, Cl 10.05; found: C 54.55, H 4.93, N 8.02, Cl 9.88).

Ethyl(6-isopropoxycarbonyl-4-methyl-ß-carboline-3-carboxylate) (**7a**)

To a suspension of 1.15 g (3.4 mmol) of **4a** in 75 ml of ethanol and 30 ml of water were added 1.68 g (5.16 mmol) of cesium carbonate (Merck). The mixture was stirred 1 h at 80°C, after which time all material had been dissolved. After evaporation the residue was dried over phosphorous pentoxide and dissolved in 72 ml DMF and treated with 566 mg (4.6 mmol) of isopropyl bromide (Merck). The mixture was stirred 1 h at 70°C and then evaporated. The residue was dissolved in 150 ml of ethyl acetate and washed successively with aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was separated, dried, filtered and evaporated. Recrystallization of the residue twice from ethyl acetate and hexane afforded 433 mg (37%) of **7a** m.p. 193-194°C. ($C_{19}H_{20}N_2O_4$; 340.38; requires: C 67.04, H 5.92, N 8.23; found: C 67.10, H 5.86, N 8.28).

Ethyl(6-diethylaminocarbonyl-4-methyl-ß-carboline-3-carboxylate) (**6a**)

A mixture of 200 mg (0.6 mmol) of **4a** in 10 ml of thionyl chloride (Merck) with 1 drop of DMF was heated at reflux for 3 h. After evaporation, the crude residue was suspended in 20 ml of tetrahydrofuran and treated dropwise with 0.5 ml of diethylamine (Merck). After stirring 1 h at room temperature and evaporation, the residue was dissolved in methylene chloride and washed with water and saturated aqueous NaCl. The organic layer was dried, filtered and evaporated. The residue was purified by chromatography with methylene chloride: ethanol = 10:1. Recrystallization from ethanol/hexane afforded 210 mg (52%) of **6a** m.p. 218-220°C. ($C_{20}H_{23}N_3O_3$; 353.42; requires: C 67.97, H 6.56, N 11.89; found: C 68.09, H 6.39, N 11.73).

REFERENCES

1. C. Braestrup, M. Nielsen, E.N. Petersen and L.H. Jensen, Biochem. Pharmacol. 33 (6), 859 (1984).
2. H.O. Wirth, O. Königstein and W. Kern, Lieb. Ann. Chem. 634, 84 (1960).
3. K. Rehse, T. Fischer and R. Maybauer, Arch. Pharm. 313, 379 (1980).
4. R.F. Heck, Palladium Reagents in Org. Synth., Academic Press, Orlando 1985.
5. C. Narayama and M. Periasamy, Synth. 1985, 253.
6. A. Schönberg, I. Bartoletti and R.F. Heck, J. Org. Chem. 39, 3318 (1974).
7. M. Mori, K. Chiba, N. Inotsume and Y. Ban, Heterocycles 12, 921 (1979).
8. A. Cowell and K.J. Stille, J. Am. Chem. Soc. 102, 4193 (1980).
9. T. Imamoto, T. Kusumoto and M. Yokoyama, Bull. Chem. Soc. Jpn. 55, 643 (1982).
10. S.S. Wang, B.F. Gisin, D.P. Winter, R. Makofske, I.D. Kulesha, C.T. Tzougraki and J. Meienhofer, J. Org. Chem. 42, 1286 (1977).
11. G. Neef, U. Eder, A. Huth, D. Rahtz, R. Schmiechen and D. Seidelmann, Heterocycles 20, 1295 (1983).