Advanced Synthesis & Catalysis

Accepted Article

Title: Reduction of Amides to Amines under Mild Conditions via Catalytic Hydrogenation of Amide Acetals and Imidates

Authors: Renat Kadyrov

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800855

Link to VoR: http://dx.doi.org/10.1002/adsc.201800855

10.1002/adsc.201800855

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Reduction of Amides to Amines under Mild Conditions via Catalytic Hydrogenation of Amide Acetals and Imidates

Renat Kadyrov[a]*

[a] Evonik Resource Efficiency GmbH, Rodenbacher Chaussee 4, 63457 Hanau-Wolfgang, Germany
e-mail renat.kadyrov@evonik.com

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

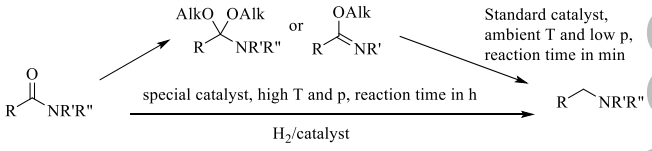
Abstract. A simple and general protocol was developed for selective conversion of amides into amines. Amides were converted into amide acetals and imido esters by O-alkylation and then hydrogenated without isolation into amines under very mild reaction conditions over standard hydrogenation catalysts. Triethyloxonium tertafluoroborate, methyl trifluoromethanesulfonate, dimethyl sulfate and ethyl chloroformate were validated as alkylating agent. The synthetic utility of this approach was demonstrated by the selective carbonyl reduction of peptide groups. Carbonyl reduction of peptide group proceeds chemoselective without racemization of the neighboring chiral center.

Keywords: Amide; Amine; Hydrogenation; Heterogeneous catalysis.

Introduction

The reduction of amides using complex aluminohydrides is one of the most frequently used methods for production of amides and often is a key step in the synthesis of natural products and pharmaceutical ingredients.[1, 2] Despite the progress made in recent years by using sodium borohydride[3] and silanes[4] as reducing agents catalytic hydrogenation remains one of the major challenges[5], as demonstrated in numerous publications over the last years. Significant improvements were achieved in recent years by employing bimetallic and homogeneous catalysts.[6] Nevertheless, the development of milder and more selective methods using commercially available heterogeneous catalysts is of significant interest for the fine chemical and pharmaceutical industries. In this respect, activation of amide is a promising strategy.[6d, 6f, 7] Recently, Huang reported the reductive alkylation of tert-amides by in situ amide activation with Tf_2O, alkylation with a Grignard reagent and reduction, particularly, with hydrogen. [8].

Very recently, we have demonstrated that hydrogenolysis of the amide acetals and imido esters proceed at very mild conditions over commercially available hydrogenation catalysts.[9] Also briefly showed that in situ generated acetals by O-alkylation with $(Et_3O)BF_4$ could be smoothly transformed into amines over 5% Pt/C. Herein we present this strategy as a general method for reduction of secondary and tertiary amides by O-alkylation and hydrogenating them directly to amines without needing the extensive isolating procedures. The primary amides were deliberately omitted, because primary amides could be straightforwardly converted into nitriles, which can be easily hydrogenated to primary amines.[5] Special attention was focused on reduction of peptide bond in amino acids presenting an alternative method for the synthesis of pseudopeptides containing CH_2-N amide bond surrogate. These types of pseudodipeptides were previously prepared from dipeptides by selective reduction of dipeptides using BH_3-THF complex[10] and phenylsilane[11]. The compounds with a reduced peptide bond represents an area of increased interest and have found importance as enzyme inhibitors, antagonists and potential agents for gene delivery.[12]



Scheme 1. Hydrogenation of amides vs. O-alkylation and hydrogenation.

Results and Discussion

Several efficient protocols for the conversion of tertiary amides into amide acetals and secondary and primary amides into imido esters are well known.[13, 14] Among them, O-alkylation of acid amides using common alkylation agents are the most attractive due to the simple alkylation procedure and high yields.

Trialkylsilyl and alkyl perfluoroalkanesulfonates[15] and trialkyloxonium salts[16] have comparable alkylation power and produce imidate salts from a broad range of amides under smooth conditions. Dialkyl sulfates O-alkylate amides in an equilibrium reaction give imidate salts.[17] The position of equilibrium depends upon the nature of the substituents - bulky and electron-withdrawing groups shift equilibrium towards the starting compounds. The alkylation at room temperature is slow and is accelerated at higher temperatures, the heating over 80 °C often led to the formation of unwanted side products. Primary and secondary amides react with alkyl chloroformates with the loss of CO_2 and formation of imidate hydrochlorides.[18]

For the reduction of non-functionalized amides (**1**, **3** and **5**) alkylation reactions were performed with Et_3OBF_4 as it was successfully used in the initial experiments described in the preliminary report.[9] Using sodium ethoxyde to liberate amide acetal hydrogenation over Pt and Pd on charcoal provided desired amines in good yields (Table 1). In the initial experiments disappointing low yields were obtained applying the same conditions for the amides **7** and **9** bearing phosphonate and ester groups. Potassium carbonate instead of the sodium alkoxide is a useful alternative for generation of free amide acetals "in situ" under milder conditions. The hydrogenation of the ethoxymethaniminium salts in the presence of K_2CO_3 provided the desired amines **8** and **10** in satisfied to good yields.

Methyl triflate is a useful and mild O-methylating agent for secondary and tertiary amides.[15c-e] As a model for secondary amides N-propylpropionamide **11** and acetanilides **13** and **15** were chosen. In initial tests the hydrogenation of the O-methyl salts in the presence of NaOMe and K_2CO_3 were disappointingly poor (10-40%). Several experiments varying the different Pt, Pd, Ru and Rh catalysts failed to improve the situation. The improvement was realized by the hydrogenation of salts without any base. The yield for N-ethyl-4-cloroaniline **16** was lower and noticeable amounts of 4-chloroaniline were detected in the reaction mixture. The reason for that could be an enhanced lability of the C-N bond of the 4-chloroanilide acetal in alcohol at slightly acidic conditions.[15c]

In order to show applicability of the alternative alkylating agents, we have revealed dimethyl sulfate and ClCOOEt as appropriate alkylating agents by reduction of lactams to cyclic amines. N-methyl pyrrolidine **18** and N-methylazepane **20** and were isolated in fair yields in hydrogenation of liberated amide acetals (using NaOMe) after O-methylation with dimethyl sulfate.

The reaction of ethyl chloroformate with δ-valerolactam **21** and ε-caprolactam **23** without solvents at 60°C yield the O-ethylvalerolactim hydrochloride[18d] and O-ethylcaprolactim hydrochloride[18b], respectively. Dissolving of the obtained solid imidate hydrochlorides in ethanol and hydrogenation without using any base provided cyclic amines with inferior (>90%) yields. By contrast, hydrogenation in the presence of K_2CO_3 delivered piperidine **22** in a lower yield (80%).

To show the potential of this method, the reduction of the peptide groups at lactams **25**, **27**, **29** as models[19] for macrocyclic peptidomimitics[20] and dipeptides **31** and **33** was studied. Amino lactones **26**, **28** and **30** were isolated in good yields after alkylation with Et_3OBF_4 and hydrogenation over Pt/C. Relatively high values of optical rotation indicates little or no racemization of the neighboring chiral center. Two equivalents of Et_3OBF_4 are necessary for alkylation of dipeptides **31** and **33**. The second equivalent of trialkyloxnium-fluorobaorates reacts with Boc-group releasing the isobutene with the formation of ethoxycarbonyl-group.[16a] Required pseudodipeptides **32** and **34** could be isolated in 70% and 61% yield, respectively. None of the diastereomeric by-products were detected by GC-MS analysis of reaction mixtures in both cases. Reduction of the carbonyl of peptide groups proceeds with high chemoselectity without affecting the neighboring chiral center.

Conclusion

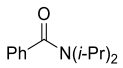
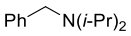
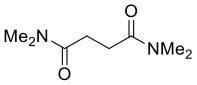
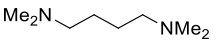
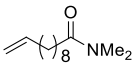
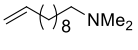
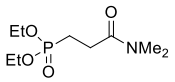
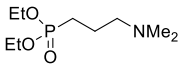
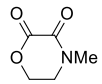
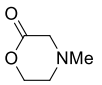
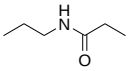
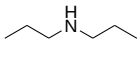
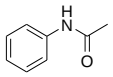
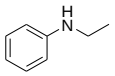
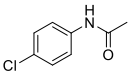
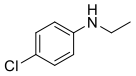
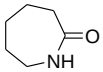
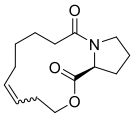
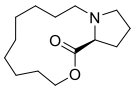
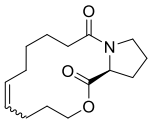
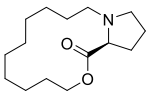
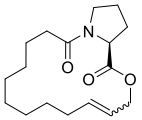
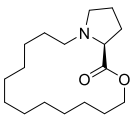
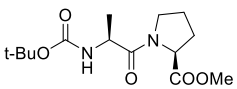
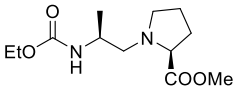
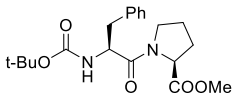
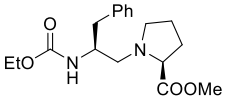
In conclusion, a simple and general protocol was developed for selective conversion of amides into amines. A variety of amides bearing light reducible functional groups were reduced into amines in practical to quantitative yields. The hydrogenations were performed at mild conditions over commercially available hydrogenation catalysts. Carbonyl reduction of peptide group proceeds chemoselective without racemization of the neighboring chiral center.

Experimental Section

In view of the moisture sensitive nature of the amide acetals, all the synthetic reactions were performed under moisture free conditions. Powder catalysts from Evonik[9] were dried at 80°C in vacuum for 4 h. Solvents and dimethyl sulfate were dried over fresh activated molecular sieves 3A. Large quantities of triethyloxonium tetrafluoroborate[21] were prepared by standard method and stored in refrigerator. Methyl triflate was prepared as described[22] and raw material was distilled off at reduced pressure(400 - 200 mbar) using efficient condenser. The pure methyl triflate (bp 98-99°C) was obtained by redistillation at atmospheric pressure using 25 cm Vigreux column. N-Propylpropionamide,[23] N,N-dimethylundec-10-enamide,[24] diethyl N,N-dimethyl-3-(diethylphosphono)propionamide,[25] 4-methyl-morpholindione-2,3,[26] N,N,N',N'-tetramethylsuccinyldiamide,[27] (2S)-pyrrolo[1,2-c][1,4]azaoxacyclotridecen-7-dione-3,13, (2S)-pyrrolo[1,2-c][1,4]azaoxacyclotetradecen-8-dione-3,14 and (2S)-pyrrolo[1,2-c][1,4]azaoxacyclohexadecen-6-dione-3,16,[19] N-[(tert-buthoxy)carbonyl]-L-alanyl-L-proline methyl ester[28] and N-[(tert-buthoxy)carbonyl]-L-phenylalanyl-L-proline methyl ester[29] were prepared according literature procedures. All other amides were purchased from commercial suppliers and used without further purification.

10.1002/adsc.201800855

Table 1. Isolated Yields in the Reduction of Amides.[a]

Amide		Amine		Alkylating agent	Base	Catalyst	Time[b] h	Yield, %
	**1**		**2**	$(Et_3O)BF_4$	EtONa	5% Pt/C	0.2	78
	**3**		**4**	$(Et_3O)BF_4$	EtONa	5% Pd/C	8	62
	**5**		**6**	$(Et_3O)BF_4$	EtONa	5% Pd/C 5% Pt/C	0.2 0.2	77 79
	**7**		**8**	$(Et_3O)BF_4$	K_2CO_3	5% Pd/C	3	58
	**9**		**10**	$(Et_3O)BF_4$	K_2CO_3	5% PtC	12	90
	**11**		**12**	CF_3SO_2OMe	-	5% Pt/C	0.5	96
	**13**		**14**	CF_3SO_2OMe	-	5% Pt/C	1	94
	**15**		**16**	CF_3SO_2OMe	-	5% Pt/C	0.2	62
	**17**		**18**	$(MeO)_2SO_2$	MeONa	5% Pd/C 5% Pt/C	1 0.5	65 55
	**19**		**20**	$(MeO)_2SO_2$	MeONa	5% Pd/C 5% Pt/C	0.2 0.2	58 50
	**21**		**22**	ClCOOEt	K_2CO_3 -	5% Pt/C 5% Pt/C	0.1 1	80 91
	**23**		**24**	ClCOOEt	-	5% Pt/C	2	95
	**25**		**26**	$(Et_3O)BF_4$	K_2CO_3	5% Pt/C	14[c]	75
	**27**		**28**	$(Et_3O)BF_4$	K_2CO_3	5% Pt/C	14[c]	80
	**29**		**30**	$(Et_3O)BF_4$	K_2CO_3	5% Pt/C	14[c]	59
	**31**		**32**	$(Et_3O)BF_4$	K_2CO_3	5% Pt/C	14[c]	70
	**33**		**34**	$(Et_3O)BF_4$	K_2CO_3	5% Pt/C	14[c]	61

[a] Conditions according to general procedures. [b] Time required for completeness of hydrogen uptake. [c] Stirred overnight under 40 bar hydrogen pressure.

10.1002/adsc.201800855

General Procedures for the Alkylation of Amides.

A. To the cooled in ice bath solution of amide (25 mmol) in dry CH_2Cl_2 (25 mL) triethyloxonium tetrafluoroborate (5.32 g, 28 mmol) was added at once and obtained solution was allowed to warm to ambient temperature, stirred over night and concentrated in vacuum. The residue was dissolved in dry ethanol and obtained solution used in the hydrogenation step.

B To the cooled in ice bath solution of amide (25 mmol) in dry CH_2Cl_2 (10 mL) methyl triflate (5.1 g, 31 mmol) was added drop wise, then warmed to ambient temperature, stirred for 4 h and concentrated in vacuum. The residue was dissolved in dry methanol and obtained solution used in the hydrogenation step.

C: Amide (25 mmol) and dimethyl sulfate (2.6 mL, 27 mmol) were heated under Argon at 80°C for 3 h, dissolved in dry methanol and obtained solution used in the hydrogenation step.

D: Amide (25 mmol) and ethyl chlorofomate (8 mL, 84 mmol) were heated at 60°C until CO_2 evolution cased (typically 4 h) and concentrated in vacuum. The residue was dissolved in dry ethanol and obtained solution used in the hydrogenation step.

General Procedure for Hydrogenation.

A 100 mL autoclave was charged with (0.5 mmol) of dried powder catalyst and where appropriate also 1.73 g of K_2CO_3 or 12.5 ml of 2 M ethanolic solution of EtONa, purged with nitrogen twice, a solution of iminium salt in alcohol was transferred via capillary tubing into autoclave and purged twice with hydrogen. The autoclave was pressurized with hydrogen to 40 bar and stirred at constant pressure until no hydrogen consumption was observed. Autoclave was depressurized, reaction mixture filtered through celite, solids washed with alcohol and combined filtrates concentrated on rotary evaporator. Residue was dissolved in chilled 1M hydrochloric acid (25 mL) and washed twice with diethyl ether. Diethyl ether extracts were discarded. Aqueous layer was made basic with NaOH solution and extracted with diethyl ether. Combined organic layers were dried over K_2CO_3 and concentrated on rotary evaporator. The crude product was purified by vacuum distillation or chromatography on silica gel.

E: General Procedure for Reduction of Peptide Group.

Amide (10 mmol) was alkylated according to general procedure A following by hydrogenation in 20 mL of EtOH over 0.78 g of dry 5% Pt/C and K_2CO_3 (0.69 g) at 40 bar over nigh (14 h). Autoclave was depressurized, reaction mixture filtered through celite, solids washed with alcohol and combined filtrates concentrated on rotary evaporator. Residue was treated with cold 2N NaOH solution (10 ml) and extracted with diethyl ether. Combined organic layers were dried over K_2CO_3 and concentrated on rotary evaporator. The crude product was purified by chromatography on silica gel.

N,N-Diisopropylbenzylamine **2**. According to general procedure A, the reaction of N,N-diisopropylbenzamide **1** (5.13 g, 25 mmol) and triethyloxonium tetrafluoroborate (5.32 g, 28 mmol), following by hydrogenation with 5% Pt/C (1.95 g, 2 mol%) and 12.5 ml of 2 M ethanolic solution of EtONa in 25 ml of EtOH, work up and distillation (bp 72°C/2 mbar) afforded **2** in 78% (3.73 g) yield. Spectroscopic properties of **2** matched those previously described.[30]

N,N,N',N'-Teramethyl-1,4-butanediamine **4**. According to general procedure A, the reaction of N,N,N',N'-tetramethylsuccinyldiamide **3** (4.31 g, 25 mmol) and triethyloxonium tetrafluoroborate (10.8 g, 57 mmol), following by hydrogenation with 5% Pd/C (2.12 g, 4 mol%) and 25 ml of 2 M ethanolic solution of EtONa in 40 ml of EtOH, work up and distillation (bp 75°C/40 mbar) afforded **4** in 62% (2.24 g) yield. Spectroscopic properties of **4** matched those previously described.[31]

N,N-dimethylundec-10-enamine **6**. According to general procedure A, the reaction of N,N-dimethylundec-10-enamide **5** (5.28 g, 25 mmol) and triethyloxonium tetrafluoroborate (5.32 g, 28 mmol), following by hydrogenation with 5% Pd/C (1.06 g, 2 mol%) and 12.5 ml of 2 M ethanolic solution of EtONa in 25 ml of EtOH, work up and distillation (bp 52-54°C/0.18 mbar) afforded **6** in 77% (3.80 g) yield. Spectroscopic properties of **6** matched those previously described.[32]

Diethyl 3-(N,N-dimethylamino)propylphosphonate **8**. According to general procedure A, N,N-dimethyl-3-(diethylphosphono)propionamide **7** (5.28 g, 25 mmol) was alkylated with triethyloxonium tetrafluoroborate (5.32 g, 28 mmol) and hydrogenated over 5% Pd/C (1.06 g, 2 mol%) and K_2CO_3 (1.73 g) in 25 ml of EtOH. Aqueous solution was extracted 6 times with ethyl acetate, combined organic layers were dried and evaporated. Distillation in vacuum (bp = 72-73°C/0.08 mbar) afforded **8** in 58% (3.85 g) yield. ^{1}H NMR ($CDCl_3$) δ 4.08 – 3.97 (m, 4H), 2.25 (t, *J* = 6.7, 2H), 2.15 (s, 6H), 1.74 – 1.65 (m, 4H), 1.25 (t, *J* = 7.1, 6H). ^{13}C NMR ($CDCl_3$) δ 61.40 (d, *J* = 6.5), 59.81 (d, *J* = 17.9), 45.27 (s), 23.79 (s), 22.85 (s), 20.61 (d, *J* = 4.7), 16.44 (d, *J* = 6.0). MS (EI) m/z 213 (M^+), 208, 150, 125, 97, 84, 72, 58. ^{1}H NMR spectrum of **8** matched that previously described.[33]

4-Methyl-2-morpholinone **10**. According to general procedure A, the reaction of 4-methyl-morpholindione-2,3 **9** (3.23 g, 25 mmol) and triethyloxonium tetrafluoroborate (5.32 g, 28 mmol), following by hydrogenation over 5% Pd/C (1.06 g, 2 mol%) and K_2CO_3 (1.73 g) in 25 ml of EtOH, work up and distillation (bp 70°C/3 mbar) afforded **10** in 90% (2.59 g) yield. Spectroscopic properties of **10** matched those previously described.[34]

Dipropylamine **12**. According to general procedure B, the reaction of N-propylpropionamide **11** (2.88 g, 25 mmol) and methyl triflate (5.1 g, 31 mmol), following by hydrogenation over 5% Pt/C (1.95 g, 2 mol%), work up and distillation (bp 105-106°C) afforded **12** in 96% (2.43 g) yield. Spectroscopic properties of **12** matched those previously described.[35]

N-Ethylaniline **14**. According to general procedure B, the reaction of acetanilide **13** (3.38 g, 25 mmol) and methyl triflate (5.1 g, 31 mmol), following by hydrogenation over 5% Pt/C (1.95 g, 2 mol%) in MeOH (25 ml), work up and distillation (bp 81°C/10 mbar) afforded **6** in 94% (2.85 g) yield. Spectroscopic properties of **14** matched those previously described.[36]

N-Ethyl-4-chloroaniline **16**. According to general procedure B, the reaction of 4'-chloroacetanilide **15** (4.24 g, 25 mmol) and methyl triflate (5.1 g, 31 mmol), following by hydrogenation over 5% Pt/C (1.95 g, 2 mol%) in MeOH (25 ml), work up and distillation (bp 68°C/0.5 mbar) afforded **16** in 62% (2.41 g) yield. Spectroscopic properties of **16** matched those previously described.[37]

N-Methylpyrrolidine **18**. According to general procedure C, N-methylpyrrolidone **17** (2.48 g, 25 mmol) was alkylated with dimethyl sulfate (2.6 mL, 27 mmol) and hydrogenated in 25 ml of MeOH over 5% Pd/C (1.06 g, 2 mol%) in presence 12.5 ml of 2 M methanolic solution of MeONa, combined filtrates after removing of Pt/C were treated with 1M hydrochloric acid (25 mL) and MeOH evaporated in

vacuum. Aqueous residue was washed twice with diethyl ether. Diethyl ether extracts were discarded. Aqueous layer was made basic with NaOH solution and extracted with diethyl ether. Combined organic layers were dried over K_2CO_3 and treated with 2M HCl in diethyl ether. Precipitated product was filtered, washed with diethyl ether and dried affording **18**·HCl in 65% (1.98 g) yield. ^{1}H NMR ($CDCl_3$) δ 12.12 (s, 1H), δ 3.68 (td, *J* = 10.5, 5.4 Hz, 2H), 2.90 – 2.85 (m, 2H), 2.84 (d, J = 5.0 Hz, 3H), 2.19 – 2.03 (m, 4H). ^{13}C δ 55.22, 40.79, 23.67. Hydrochloride was treated with 25% sodium hydroxide solution, separated organic layer was distilled over K_2CO_3, obtaining **18**. Spectroscopic properties of **18** matched those previously described.[38]

N-Methylazepane **20**. According to general procedure C, the reaction of N-methylcaprolactam **19** (3.18 g, 25 mmol) and dimethyl sulfate (2.6 mL, 27 mmol), following by hydrogenation with 5% Pd/C (1.06 g, 2 mol%) and 12.5 ml of 2 M methanolic solution of MeONa in 25 ml of MeOH, work up and distillation (bp 86-87°C/190 mbar) afforded **20** in 55% (1.56 g) yield. Spectroscopic properties of **20** matched those previously described.[3g]

Piperidine **22**. Piperodone-2 **21** (2.5 g, 25 mmol) was alkylated according to general procedure D with ethyl chlorofomate (8 mL, 84 mmol) and hydrogenated in 25 ml of EtOH over 5% Pd/C (0.98 g, 1 mol%), combined filtrates after removing of Pt/C were treated with 1M hydrochloric acid (25 mL) and EtOH evaporated in vacuum. Aqueous residue was washed twice with diethyl ether. Diethyl ether extracts were discarded. Aqueous layer was made basic with NaOH solution and extracted with diethyl ether. Combined organic layers were dried over K_2CO_3 and treated with 2M HCl (12.5 mL) in diethyl ether. Precipitated product was filtered, washed with diethyl ether and dried affording **22**·HCl in 91% (2.77 g) yield. Spectroscopic properties of **22** matched those previously described.[39]

Hexamethyleneimine **24**. According to general procedure C, the reaction of ε-caprolacatam **23** (2.83 g, 25 mmol) and ethyl chlorofomate (8 mL, 84 mmol), following by hydrogenation over 5% Pt/C (1.95 g, 2 mol%) in EtOH (25 ml), work up and distillation afforded **24** (bp 68°C/95 mbar) in 95% (2.36 g) yield. Spectroscopic properties of **24** matched those previously described.[40]

(2S)-Pyrrolo[1,2-c][1,4]azaoxacyclotridecanone-3 **26**. According to general procedure E, the reaction of (2S)-pyrrolo[1,2-c][1,4]azaoxacyclotridecen-7-dione-3,13 **25** (251 mg, 1 mmol) and triethyloxonium tetrafluoroborate (0.21 g, 1.1 mmol), following by hydrogenation over 5% Pt/C (78 mg) and K_2CO_3 (138 mg) in 5 ml of EtOH, after work up and silica gel chromatography using EA/hexane (1:5) as eluent afforded **26** (Rf 0.36) as colorless syrup in 75% (182 mg) yield. ^{1}H NMR ($CDCl_3$) δ 4.17 (ddd, *J* = 10.7, 7.1, 3.4 Hz, 1H), 4.07 (ddd, *J* = 10.9, 7.6, 3.3 Hz, 1H), 3.24 – 3.18 (m, 1H), 3.15 (t, *J* = 6.9 Hz, 1H), 2.86 (dt, *J* = 12.0, 7.4 Hz, 1H), 2.37 (dt, *J* = 11.7, 5.7 Hz, 1H), 2.24 (dd, *J* = 16.3, 8.4 Hz, 1H), 1.98–1.83 (m, 3H), 1.77–1.11 (m, 15H). ^{13}C NMR δ 174.94, 66.86, 64.32, 54.57, 54.26, 28.96, 27.04, 26.85, 25.35, 25.05, 25.02, 24.10, 23.79, 23.29; MS (EI) m/z 239 (M^+), 195, 152, 110, 83; HRMS (EI) calc. for $C_{14}H_{25}NO_2$: 239.18798, found 239.18790; α_D^{22}= -27.2 (c 0.86, $CHCl_3$).

(2S)-Pyrrolo[1,2-c][1,4]azaoxacyclotetradecanone-3 **28**. According to general procedure E, the reaction of (2S)-pyrrolo[1,2-c][1,4]azaoxacyclotetradecen-8-dione-3,14 **27** (1.33 g, 5 mmol) and triethyloxonium tetrafluoroborate (1.14 g, 6 mmol), following by hydrogenation over 5% Pt/C (390 mg) and K_2CO_3 (345 mg) in 10 ml of EtOH, after work up and silica gel chromatography using EA/hexane (1:5) as eluent afforded **28** (Rf 0.31) as colorless syrup in 80% (1.02 g) yield. ^{1}H NMR ($CDCl_3$) δ 4.20–4.08 (m, 2H), 3.15 (td, *J* = 8.4, 2.9 Hz, 1H), 3.06 (dd, *J* = 8.2, 6.6 Hz, 1H), 2.83–2.73 (m, 1H), 2.22–2.11 (m, 2H), 2.05–1.07 (m, 21H), ^{13}C NMR δ 174.52, 66.93, 63.97, 53.37, 53.37, 28.95, 27.94, 25.77, 25.70, 25.04, 24.72, 24.02, 23.98, 23.17, 22.84; MS (EI) m/z 253 (M^+), 209, 166, 110, 83; HRMS (EI) calc. for $C_{15}H_{27}NO_2$: 253.20363, found 253.20346; α_D^{22}= -35.2 (c 1.01, $CHCl_3$).

(2S)-Pyrrolo[1,2-c][1,4]azaoxacyclohexadecanone-3 **30**. According to general procedure E, the reaction of (2S)-pyrrolo[1,2-c][1,4]azaoxacyclohexadecen-6-dione-3,16 **25** (1.47 g, 5 mmol) and triethyloxonium tetrafluoroborate (1.15 g, 6 mmol), following by hydrogenation over 5% Pt/C (390 mg) and K_2CO_3 (345 mg) in 10 ml of EtOH, after work up and silica gel chromatography using EA/hexane (1:5) as eluent afforded **26** (Rf 0.29) as colorless syrup in 59% (0.83 g) yield. ^{1}H NMR ($CDCl_3$) δ 4.22 (ddd, *J* = 10.9, *J* = 7.1, *J* = 4.9, 1H), 4.00 (ddd, *J* = 10.8, *J* = 6.1, *J* = 4.7, 1H), 3.13 (dd, *J* = 8.5, *J* = 5.4, 1H), 3.09 (td, *J* = 8.3, *J* = 3.5, 1H), 2.61 (ddd, *J* = 11.6, *J* = 10.0, *J* = 6.0, 1H), 2.37 (ddd, *J* = 11.5, *J* = 9.8, *J* = 5.3, 1H), 2.32 (q, *J* = 8.0, 1H), 1.98-2.05 (m, 1H), 1.84-1.91 (m, 2H), 1.71-1.77 (m, 1H), 1.57-1.62 (m, 2H), 1.18-1.48 (m, 18H); ^{13}C δ 174.72, 66.06, 64.40, 54.92, 53.55, 29.28, 28.58, 27.22, 26.75, 26.64, 26.55, 26.12, 25.79, 25.64, 25.53, 25.05, 23.18; MS (EI) m/z 281 (M^+), 237, 194, 110, 83; MS ESI-TOF $C_{17}H_{32}NO_2$ $(M+H)^+$ calc. 282.24276 found 282.24266. α_D^{23}= -39.0 (*c* 1.04, $CHCl_3$).

1-[(2S)-2-[(ethoxycarbonyl)amino]propyl]-L-proline methyl ester **32**. According to general procedure E, the reaction of N-Boc-L-Ala-L-Pro-OMe **31** (3 g, 10 mmol) and triethyloxonium tetrafluoroborate (3.80 g, 20 mmol), following by hydrogenation over 5% Pt/C (0.78 g) and K_2CO_3 (0.69 g) in 20 ml of EtOH, after work up and silica gel chromatography using EA/hexane (1:1) as eluent afforded **32** (Rf 0.25) as colorless syrup in 65% (1.68 g) yield. ^{1}H NMR ($CDCl_3$) δ 5.19 (br. s, 1H), 3.99-4.07 (m, 2H), 3.63 (s, 3H), 3.60 (q, *J*=6.4, 1H), 3.23 (dd, *J* = 8.6, *J* = 5.1, 1H), 3.09 (ddd, *J* = 8.3, *J* = 8.2, *J* = 3.9, 1H), 2.60 (dd, *J* = 12.4, *J* = 6.0, 1H), 2.50 (dd, *J* = 11.7, *J* = 5.9, 1H), 2.47 (dt, *J* = 8.9, *J* = 7.5, 1H), 2.00-2.05 (m, 1H), 1.81-1.86 (m, 2H), 1.72-1.78 (m,1H), 1.17 (t, *J* = 7.1, 3H), 1.13 (d, *J* = 6.6, 3H); ^{13}C δ 174.80, 156.28, 66.50, 60.38, 60.20, 54.44, 51.69, 46.41, 29.39, 23.83, 19.48, 14.64. MS (EI) m/z 258 (M^+), 226, 199, 142, 114; MS ESI-TOF $C_{12}H_{22}N_2O_4$ $(M+H)^+$ calc. 259.16523 found 259.16499. α_D^{22} -57.9 (c = 1.0, $CHCl_3$)

1-[(2S)-2-[(ethoxycarbonyl)amino]-3-phenylpropyl]-L-proline methyl ester **34**

According to general procedure E, the reaction of N-Boc-L-Phe-L-Pro-OMe **33** (3.87 g, 10 mmol) and triethyloxonium tetrafluoroborate (3.80 g, 20 mmol), following by hydrogenation over 5% Pt/C (0.78 g) and K_2CO_3 (0.69 g) in 20 ml of EtOH, after work up and silica gel chromatography using EA/hexane (1:1) as eluent afforded **34** (Rf 0.40) as colorless syrup in 1.84 g (55%) yield. ^{1}H NMR ($CDCl_3$) δ 7.20 (t, *J* = 7.6, 2H), 7.12 (t, *J* = 7.8, 3H), 5.46 (br. s, 1H), 4.07 (dq, *J* = 10.6, *J* = 7.2, 1H), 4.02 (dq, *J* = 10.6, *J* = 7.1, 1H), 3.75 (br. m, 1H), 3.61 (s, 3H), 3.18 (br. m, 1H), 3.07 (br. m, 1H), 3.03 (td, *J* = 7.9, *J* = 3.4, 1H),2.58 (dd, *J* = 13.5, *J* = 7.8, 1H), 2.52 (t, *J* = 11.3, 1H), 2.40 (dd, *J* = 12.1, *J* = 3.85, 1H), 2.21 (br. m, 1H), 1.98-2.04 (m, 1H), 1.98-2.04 (m, 1H), 1.66-1.72 (m, 2H), 1.18 (t, *J* = 7.2, 3H); ^{13}C δ 174.71, 156.84, 138.20, 129.48, 128.29, 126.25, 65.51, 60.54, 56.79, 53.04, 51.81, 51.44, 39.48 , 29.21, 23.43, 14.69; MS (EI) m/z 334 (M^+), 302, 275, 142, 114; MS ESI-TOF $C_{18}H_{26}N_2O_4$ $(M+H)^+$ calc. 335.19653 found 335.19616; α_D^{22} -53.7 (c = 1.0, $CHCl_3$).

Acknowledgements

Author gratefully acknowledge Dr. Konrad Möbus for helpful discussions. Author also thank Ralf Jantke and Stephan Weidlich for assistance with hydrogenation experiments.

References

[1] For monographs, see: a) N. G. Gaylord, *Reduction with Complex Metyl Hydrides*, Interscience, New York, 1956; b) *Reduction Techniques and Applications in Organic Synthesis* (Ed.: R. L. Augustine) Marcel Dekker, New York, 1968; c) A. Hajos, *Complex Hydrides in Organic Synthesis*, Elsevier, New York, 1979; d) M. Hudlicky, *Reductions in Organic Chemistry*, Vols. 1 and 2, Ellis Horwood, Chichester, 1984; e) J. Seyden-Penne, *Reductions by Alumino and Borohydrides in Organic Synthesis*, *2nd ed*., Wiley, New York, 1997; f) B. Wünsch, C. Geiger in *Science of Synthesis*, *Vol 40a* (Eds.: D. Enders, E. Schaumann) Thieme, Stuttgart, 2009, pp. 23-64.

[2] J. Magano, J. R. Dunetz, *Org. Process Res. Dev*. **2012**, *16*, 1156−1184.

[3] a) S. Hanada, E. Tsutsumi, Y. Motoyama, H. Nagashima, *J. Am. Chem. Soc*. **2009**, *131*, 15032–15040; b) S. Das, D. Addis, S. Zhou, K. Junge, M. Beller, *J. Am. Chem. Soc*. **2010**, *132*, 1770–1771; c) S. Das, D. Addis, K. Junge, M. Beller, *Chem. Eur. J*. **2011**, *17*, 12186–12192; d) S. Das, B. Wendt, K. Mçller, K. Junge, M. Beller, *Angew. Chem*. **2012**, *124*, 1-5; *Angew. Chem. Int. Ed*. **2012**, *51*, 1-5; e) Y. Li, J. A. Molina de La Torre, K. Grabow, U. Bentrup, K. Junge, S. Zhou, A. Brückner, M. Beller, *Angew. Chem*. **2013**, *125*, 11791–11794; *Angew. Chem. Int. Ed*. **2013**, *52*, 11577–11580; g) J. T. Reeves, Z. Tan, M. A. Marsini, Z. S. Han, Y. Xu, D. C. Reeves, H. Lee, B. Z. Lu, C. H. Senanayake *Adv. Synth. Catal*. **2013**, *355*, 47–52; f) S. Pisiewicz, K. Junge, M. Beller, *Eur. J. Inorg. Chem*. **2014**, 2345–2349; h) E. Blondiaux, T. Cantat, *Chem. Commun*., **2014**, *50*, 9349-9352; i) N. Sakai, M. Takeoka, T. Kumaki, H. Asano, T. Konakahara, Y. Ogiwara, *Tetrahedron Letters* **2015**, *56*, 6448–6451; j) D. Mukherjee, S. Shirase, K. Mashima, J. Okuda, *Angew. Chem. Int. Ed*. **2016**, *55*, 13326 –13329; F. Tinnis, A. Volkov, T. Slagbrand, H. Adolfsson, *Angew. Chem*. **2016**, *128*, 4638–4642; *Angew. Chem. Int. Ed*. **2016**, *55*, 4562 – 4566.

[4] S.-H. Xianga, J. Xua, H.-Q. Yuana, P.-Q. Huang, *Synlett* **2010**, 1829-1832.

[5] S. Nishimura, Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis, Willey, N.Y., **2001**, pp. 406-411.

[6] a) G. Beamson, A. J. Papworth, C. Philipps, A. M. Smith, R. Whyman, *Adv. Synth. Catal*. **2010**, *352*, 869-883; b) M. Stein , B. Breit, *Angew. Chem*. **2013**, *125*, 2287-2290; *Angew. Chem. Int. Ed.* **2013**, *52*, 2231–2234; c) J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinski, W. Leitner, A. M. Z. Slawin, D. J. Cole-Hamilton, *Chem. Eur. J*. **2013**, *19*, 11039-11050; d) M.-L. Yuan, J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *ACS Catal*. **2016**, *6*, 3665–3669; e) J. R. Cabrero-Antonino, E. Alberico, K. Junge, H. Junge, M. Beller, *Chem. Sci*. **2016**, *7*, 3432–3442; f) M.-L. Yuan, J.-H. Xie, Q.-L. Zhou, *ChemCatChem* **2016**, *8*, 3036-3040; g) T. Mitsudome, K. Miyagawa, Z. Maeno, T. Mizugaki, K. Jitsukawa, J. Yamasaki, Y. Kitagawa, K. Kaneda, *Angew. Chem*. **2017** *129*, 9509-9513, *Angew. Chem. Int. Ed*. **2017**, *56*, 9381-9385.

[7] a) V. Pace, W. Holzer, B. Olofsson, *Adv. Synth. Catal*. **2014**, *356*, 3697–3736; b) A. Volkov, F. Tinnis, T. Slagbrand, P. Trillo, H. Adolfsson, *Chem. Soc. Rev*. **2016**, *45*, 6685-6697.

[8] a) K.-J. Xiao, Y. Wang, Y.-H. Huang, X.-G. Wang, P.-Q. Huang, *J. Org. Chem*. **2013**, *78*, 8305–8311; b) H.-Q. Deng, X.-Y. Qian, Y.-X. Li, J.-F. Zheng, L. Xie, P.-Q. Huang, *Org. Chem. Front*. **2014**, *1*, 258-266.

[9] R. Kadyrov, *ChemCatChem* **2018**, *10*, 170-172.

[10] a) R. W. Roeske, F. L. Weitl, K. U. Prasad, R. M. Thompson, *J. Org. Chem.* **1976**, *41*, 1260−1261; b) M. Cushman, Y.-I. Oh, *J. Org. Chem*. **1991**, *56*, 4161−4167; c) K. Adachi, E. Tsuru, E. Banjyo, M. Doe, K. Shibata, T. Yamashita, *Synthesis* **1998**, 1623-1626; d) G. G. Xu, Y. Zhang, A. Y. Mercedes-Camacho, F. A. Etzkorn, *Biochemistry* **2011**, *50*, 9545−9550.

[11] S. Das, Y. Li, L.-Q. Lu, K. Junge, M. Beller, *Chem. Eur. J*. **2016**, *22*, 7050–7053.

[12] For a review, see: M. Zivec, Z. Jakopin, S. Gobec, *Curr. Med. Chem*. **2009**, *16*, 2289−2304.

[13] a) W. Kantlehner, *Adv. Org. Chem.*, **1979**, **9**, 181-268; b) G. Simchen in Methoden Org. Chem. (Houben-Weyl), Band E5/1, (Ed.: J. Falbe) Thieme, Stuttgart, 1985 pp. 3-192; c) W. Kantlehner in Comprehensive Organic Synthesis, Vol 6 (Eds: B. M. Trost and I. Fleming), Pergamon, Oxford, 1991, pp. 487-599.

[14] a) R. Roger, D. G. Neilson, *Chem. Rev*., **1961**, *61*, 179-209; b) D. G. Neilson, in The Chemistry of Amidines and Imidates (Ed.: S. Patai), John Wiley & Sons, London, 1975, pp. 385-489; c) H. Pielartzik, B. Irmisch-Pielartzik, T. Eicher in Methoden Org. Chem. (Houben-Weyl), 1985, E5/1, pp. 812-831; d) N. Nakajima, M. Ubukata in Science of Synthesis Vol. 22. Thieme; Stuttgart; 2005, pp. 343-360.

[15] a) H. Emde, D. Domsch, H. Feger, U. Frick, A. Götz, H. H. Hergott, K. Hofmann, W. Kober, K. Krägeloh, T. Oesterle, W. Steppan, W. West, G. Simchen, *Synthesis* **1982**, 1-26; b) P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85-126; c) R. A. McClelland, G. Patel, P. W. K. Lam, *J. Org. Chem*. **1981**, *46*, 1012-1014; d) H. Hennige, R. Kreher, J. Uhrig, *Synthesis* **1982**, 842-844; e) D. H. Hoskin, R. A. Olofson, *J. Org. Chem*. **1982**, *47*, 5222-5225.

[16] a) H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, J. Spille, *Chem. Ber*. **1956,** *89*, 2060-2079; b) J. P. Celerier, M. G. Richaud, G. Lhommet, *Synthesis* **1983**, 195-197; c) R. K. Webber, S. Metz, W. M. Moore, J. R. Connor, M. G. Currie, K.F. Fok, T. J. Hagen, D. W. Hansen, Jr., G. M. Jerome, P. T. Manning, B. S. Pitzele, M. V. Toth, M. Trivedi, M. E. Zupec, F. S. Tjoeng, *J. Med. Chem*. **1998**, *41*, 96-101; d) G. E. Keck, M.D. McLaws, T. T. Wager, *Tetrahedron* **2000**, *56*, 9875-9883; e) K. Popov, P. Somfai, *J. Org. Chem*. **2016**, *81*, 3470−3472.

[17] a) H. Bredereck, F. Effenberger, H. P. Beyerlin, *Chem. Ber*. **1964**, *97*, 3081-3087; b) H. Bredereck, W. Kantlehner, D. Schweizer, *Chem. Ber*. **1971**, *104*, 3475-3485.

[18] a) H. Bredereck, F. Effenberger, G. Simchen, *Chem. Ber*. **1963**, *96*, 1350-1355; b) W. Hechelhammer DE 948973 ,1956 (Chem. Abs. 1959, 53, 6088); c) F. H. Suydam, W. E. Greth, N. R. Langerman, *J. Org. Chem.* **1969**, *34*, 292-296; d) R. Gauthier, P. Blondeau, C. Berse, D. Gravel, *Canad. J. Chem*. **1971**, *49*, 2612-2616.

[19] R. Kadyrov, *Eur. J. Chem*, **2013**, *19*, 1002–1012.

[20] a) M. J. Perez de Vega, M. I. Garcia-Aranda, R. Gonzalez-Muniz, *Med. Res. Rev.* **2011**, *31*, 677–715; b) A. D. Pehere, X. Zhang, A. D. Abell, *Aust. J. Chem*. **2017**, *70*, 138-151.

[21] H. Meerwein, *Org. Syntheses*, **1966**, *46*, 113-4.

[22] N. V. Ignat'ev, P. Barthen, A. Kucheryna, H. Willner, P. Sartori, *Molecules* **2012**, *17*, 5319-38.

[23] T. Gajda, A. Zwierzak, *Synthesis* **1981**, 1005-8.

[24] S. B. Coan, D. Papa, *J. Am. Chem. Soc*. **1955**, *77*, 2402-2404.

[25] a) B. R. Paatz, J. F. Falbe, F. W. A. G. K. Korte, (Shell Internationale Research Maatschappij NV, den Haag). 1965, NL 299935; b) T. K. Gazizov, M. A. Vasyanina, A. P. Pashinkin, N. P. Anoshina, Z. I. Goldfarb, A. N. Pudovik, *Zh. Obshch. Khim*. **1971**, *41*, 1957; engl 1973.

[26] G. Drefahl, M. Hartmann, A. Skurk, *Chem. Ber*. **1966**, *99*, 2716-2717.

[27] J. C. Sierra, S. G. Kehr, R. Fröhlich, G. Erker, *Eur. J. Inorg. Chem.* **2004**, 2260-2265.

[28] M. A. Fox, E. Galoppini, *J. Am. Chem. Soc*. **1997**, *119*, 5277-5285.

[29] a) S. Selvakumar, D. Sivasankaran, V. K. Singh, *Org. Biomol. Chem.*, **2009**, *7*, 3156–3162; b) M. Tullberg, M. Grotli, K. Luthman, *Tetrahedron* **2006**, *62*, 7484-7491; c) M. Cushman, Y. I. Oh, T. D. Copeland, S. Oroszlan, S. W. Snyder, *J. Org. Chem*. **1991**, *56*, 4161-7.

[30] S.-H. Xiang, J. Xu, H.-Q. Yuan, P.-Q. Huang, *Synlett* **2010**, 1829-1832

[31] J. Hoque, P. Akkapeddi, V. Yarlagadda, D. S. S. M. Uppu, P. Kumar, J. Haldar, *Langmuir* **2012**, *28*, 12225-12234.

[32] E. Paetzold, I. Jovel, G. Oehme, *J. Mol. Cat. A: Chem.* **2004**, *214*, 241-247.

[33] N. Collignon, G. Fabre, J.M. Varlet, P. Savignac, *Phosphorus Sulfur Relat. Elem.* **1981**, *10*, 81-86.

[34] T. Mitsudome, A. Noujima, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Green Chem.* **2009**, *11*, 793-797.

[35] C. J. Charles, J. Behnke, *The Aldrich Library of 13C and 1 H FT NMR Spectra*, Vol. 1, Aldrich Chemical: Milwaukee, **1993**, p. 474.

[36] D. Hollmann, S. Bähn, A. Tillack, M. Beller, *Chem. Commun.*, **2008**, 3199-3201

[37] C. S. Yi, S. Y. Yun, *Org. Lett*. **2005**, *7*, 2181-2183.

[38] a) I. Alkorta, J. Elguero, *Magn. Reson. Chem*. **2004**, *42*, 955-961; b) Ref. 17 p. 558.

[39] Ref. 17 p. 563.

[40] S. Hanada, T. Ishida, Y. Motoyama, H. Nagashima, *J. Org. Chem*. **2007**, *72*, 7551-7559

10.1002/adsc.201800855

UPDATE

Reduction of Amides to Amines under Mild Conditions via Catalytic Hydrogenation of Amide Acetals and Imidates

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Renat Kadyrov*