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Electrochemical oxidation of 2-substituted piperidines as a key step towards the synthesis of hydroxylated γ-amino acids

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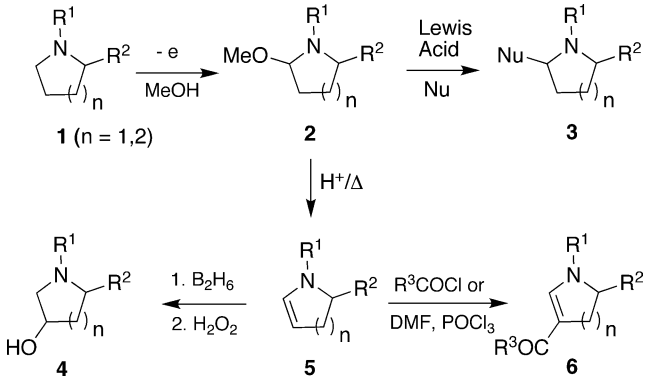
Abstract—2-Substituted piperidines containing different oxygenated side chain functionalities were investigated in the electrochemical, anodic methoxylation. Surprisingly, the configuration of the side chain has a strong influence on the outcome of the electrochemical oxidation. Subsequent elimination of methanol from the oxidation products leads to N-protected eneamides, which upon ozonolysis can be converted to N,N-bisprotected γ-amino aldehydes that are useful building blocks for further synthetic transformations.

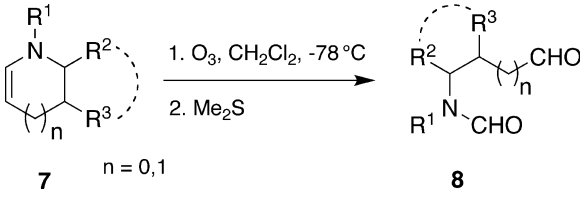
Electroorganic reactions have developed into important tools in organic synthesis.[1] In particular, the anodic oxidation of electron deficient amine derivatives such as amides,[2] sulfonamides,[3] amidophosphates[3b] and carbamates[4] is a reliable method for introducing a methoxy group in the α-position to nitrogen. One important feature of this reaction is that oxidation of 2-substituted piperidines and pyrrolidines **1** takes place regioselectively at the lesser substituted side to give rise to **2**.[4a,5]

The α-methoxylated amides or carbamates are versatile intermediates for further functionalization in α- and β-positions to nitrogen. For example, treatment with Lewis acids generates *N*-acyliminium ions, which can be trapped to yield **3** with a broad variety of nucleophiles (amidoalkylation).[6] Furthermore, elimination of methanol under acidic or thermolytic conditions leads to enamides or enecarbamates **5**,[7] which can be reacted with diborane to **4**, introducing a hydroxyl group in β-position[7b,8], or can be acylated at the β-position giving rise to **6**[7b,9] (Scheme 1).

Previously, we have shown that enecarbamates **7** (R^2, R^3 = alkyl) open a pathway to β- and γ-amino aldehydes **8**, which can be converted into the corresponding amino acids (Scheme 2)[10] being useful building blocks in peptide synthesis.[11]



Scheme 1. α-Methoxylation as a key step towards functionalized pyrrolidines and piperidines.



Scheme 2. Synthesis of β- and γ-amino aldehydes.

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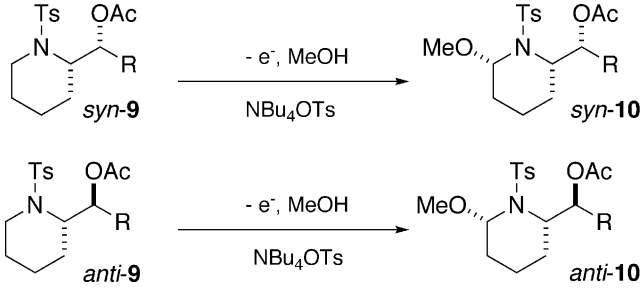
Despite the great potential value of the anodic methoxylation of nitrogen heterocycles, only few applications of this methodology at an advanced stage of a synthetic route towards complex compounds have been reported.[8b,12] In context with our ongoing studies towards the synthesis of polyhydroxylated γ-amino acids we were interested in determining the scope and limitation of the anodic methoxylation reaction of 2-substituted piperidines with different oxygenated side chain functionalities. Among the functional groups that have been shown to be compatible are carboxylic esters,[7b,13] olefins,[12e,14] acetylenes[12a] and halogens.[15] However, substrates with hydroxyl groups or aromatic rings have a tendency to undergo condensation reactions because of their nucleophilic attack to the *N*-acyliminium intermediate or to undergo direct oxidation.[16]

In agreement with this general trend, we also found that various piperidines having free hydroxyl substituents do not give clean methoxylation products but largely decomposed upon electrochemical oxidation. Acetate protection of the latter, however, generally gave good results (Table 1) with alkyl substituents (entries 1–3 and 6), while substrates containing phenyl groups could not be oxidized (entries 4, 5 and 7). Although we noted that the *anti*-stereoisomer of **9b** required a higher charge than the corresponding *syn*-**9b** to achieve good conversions, nevertheless, the stereochemistry of the side chain was not decisive for the success of the oxidation. Likewise, both diastereomers of the sterically more hindered **9d**, employed as a 3:1 *anti*/*syn* mixture, could be oxidized in high yields. In all cases, the methoxy group was introduced cis to the side chain.

Extending our investigation to derivatives **11** having 1,2-diacetoxylated side chains surprisingly showed a strong dependency on the relative configuration for the outcome of the electrochemical oxidation. The diastereomer **11a** having a *syn*-relationship between C-2 and C-3′ could be methoxylated in high yields[17,18] to give rise to **12a**, in which the methoxy group was again introduced exclusively cis to the side chain, most likely controlled through the trans arrangement with the tosyl group as suggested by the X-ray[19] structure of the product. Likewise, **11b** was methoxylated in good yields, however, for the first time the product **12b** was obtained as a 2:1 mixture of epimers, that is, the introduction of the methoxy group did not proceed stereoselectively any longer. In distinct contrast, **11c** and **11d**, that is, the *anti*-stereoisomers with respect to C-2 and C-3′, only gave decomposition products even upon attempts to stop the reaction at low charges (Scheme 3).

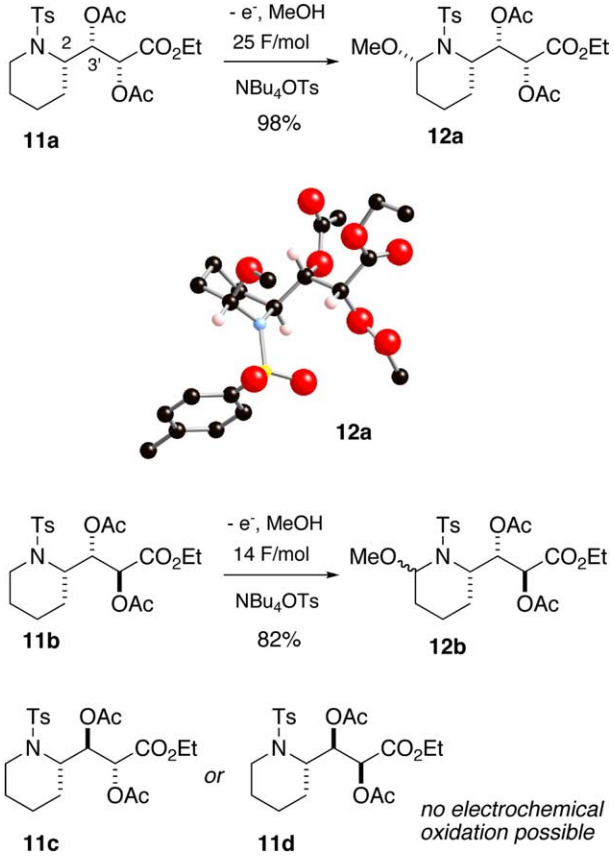
The marked role of the configuration in the propionate side chain on the success of the electrochemical oxidations is striking and not easy to rationalize. The *anti*-relationship between C-2 and C-3′ alone cannot be responsible for the failure of the methoxylation since *anti*-**9b** and *anti*-**9d** were suitable substrates (Table 1). Moreover, **13** could also be cleanly methoxylated although a high charge was necessary (75% yield of **14** along with 17% of recovered starting material,[20]) and moreover, we noted the appearance of side products at even higher currents when attempting to reach full conversion (Scheme 4).

Table 1. Electrochemical oxidation of piperidines **9**[17,18]

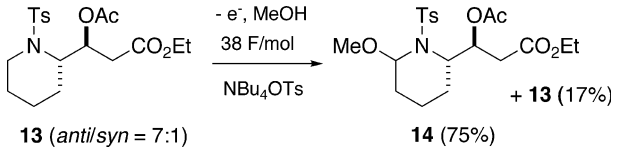


Entry	Substrate	R	*Q* (F/mol)	Yield (%)
1	**9a**	H	10.3	95
2	*syn*-**9b**	Et	5.6	62
3	*anti*-**9b**	Et	11.7	66
4	*syn*-**9c**	Ph	2–11.2[a]	0
5	*anti*-**9c**	Ph	2–9.6[a]	0
6	**9d**[b]	*i*-Pr	9.3	86
7	**9e**[b]	$(CH_2)_2Ph$	2–28[a]	0

[a] Multiple experiments.
[b] Employed as a 3:1 *anti*/*syn* mixture, the ratio was unchanged in the product.



Scheme 3. Electrochemical oxidation of diastereomeric piperidines **11**.[17,18]



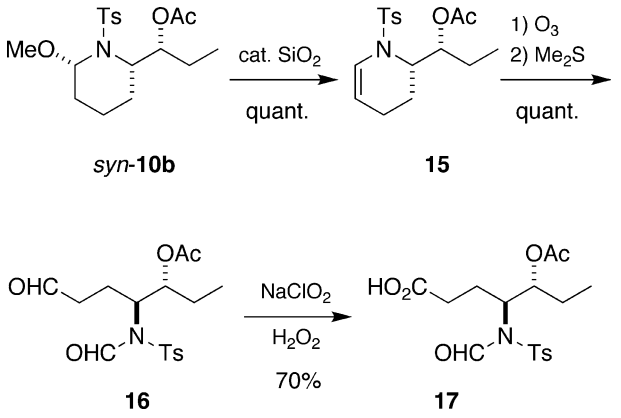
Scheme 4. Electrochemical oxidation of **13**.

The methoxylated piperidines can be readily converted via their corresponding enamdies to γ-amino aldehydes that are fully protected at nitrogen and therefore cannot undergo intramolecular amino acetal formation, normally a major obstacle to utilize this class of compounds as synthetic building blocks.

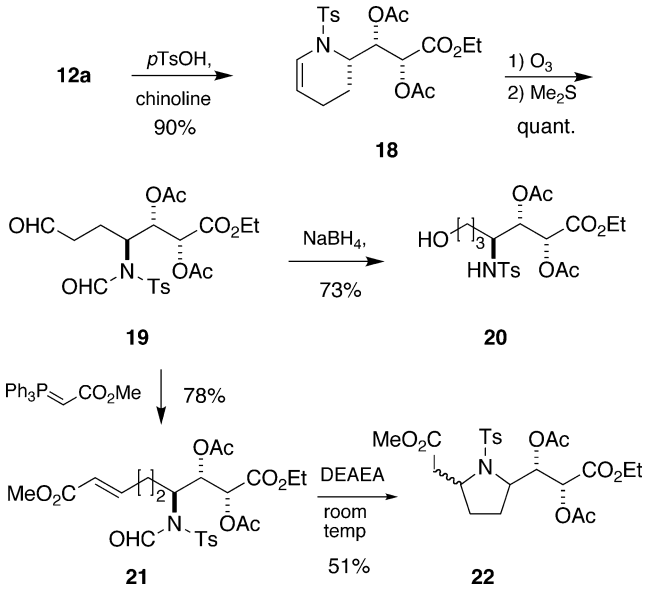
For example, **16** was obtained in quantitative yield from *syn*-**10b** upon methanol elimination induced by the treatment with silica followed by ozonolysis of the resulting **15** and reductive workup (Scheme 5). Oxidation under the conditions of Dalcanale[21] yielded the diastereomerically pure amino acid **17**.

Likewise, **12a** yielded the amino aldehyde **19** that could be further reduced to the amino alcohol **20** or elongated by a Wittig olefination to **21**. The protecting group combination N,N-formyl-tosyl proved to be stable under neutral and acidic conditions, while under basic conditions loss of the formyl group occurred followed by immediate condensation reactions leading to decomposition of the compounds occurred. Also, removal of the N-formyl group from **21**, which can be achieved with amines such as diethylaminoethyleneamine (DEAEA), resulted in the immediate cyclization to give rise to **22** (Scheme 6).

In conclusion, piperidines with a variety of acetoxylated side chains in the 2-position could be electrochemically α-methoxylated at C-6. Surprisingly, a strong influence of the configuration in the side chain on the outcome of the oxidation was observed, in spite of the considerable distance of the side chain to the reaction centre. The resulting methoxylated piperidines can be converted to acyclic γ-aminoaldehydes, doubly protected at nitrogen, which allows their utilization in further transformations leading to γ-amino-α,β-dihydroxylated esters,



Scheme 5. Synthesis of γ-amino acid **17**.



Scheme 6. Conversion of **12a** to γ-amino-α,β-dihydroxylated esters **20** and **21**.

which have been recognized as important constituents in natural products.[22]

Acknowledgements

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17. Representative procedure for the electrochemical oxidation: 2.02 g (4.43 mmol, 1.0 equiv) **11a** and 0.92 g (2.22 mmol, 0.5 equiv) NBu_4OTs in methanol (150 ml) were electrolyzed at 15 °C (graphite electrodes, 10.0 V; 0.25 A). The starting material was consumed completely (NMR control) after 11 h. The mixture was concentrated, and the residue purified through a short silica plug to give 2.1 g (98%) pure **12a** (colorless oil), which could be recrystallized from diethylether to obtain crystals suitable for X-ray analysis.
18. Selected analytical data: *syn*-**10b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.89 (t, $J = 7.3$ Hz, 3H), 1.12–1.35 (m, 3H), 1.37–1.55 (m, 1H), 1.56–1.85 (m, 4H), 2.08 (s, 3H), 2.43 (s, 3H), 3.27 (s, 3H), 4.04–4.16 (m, 1H), 4.93–5.03 (m, 1H), 5.30–5.43 (m, 1H), 7.30 (d, $J = 7.9$ Hz, 2H), 7.71 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 8.15 (CH_3), 14.03 (CH_2), 21.26 (CH_3), 21.43 (CH_3), 24.52 (CH_2), 24.78 (CH_2), 30.07 (CH_2), 54.24 (CH), 55.82 (CH_3), 74.08 (CH), 84.83 (CH), 126.93 (CH), 129.68, (CH), 138.76 (C_{quat}), 143.08 (C_{quat}), 170.77 (C_{quat}); MS (DCI(NH_3)); *m*/*z* (%): 387 (9) [$M+NH_4^+$], 338 (100) [(MH^+–CH_3OH)]; $C_{18}H_{27}NO_5S$ (369.5): calcd C, 58.51; H, 7.37; N, 3.79; found: C, 58.66; H, 7.36; N, 3.77. Compound **12a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, $J = 8.2$ Hz, 2H), 7.54 (d, $J = 8.2$ Hz, 2H), 6.22 (d, $J = 10.8$ Hz, 1H), 5.60 (s, 1H), 5.25 (m, 1H), 4.51 (m, 1H), 4.46–4.34 (m, 2H), 3.76 (s, 3H), 2.67 (s, 3H), 2.50 (s, 3H), 2.29 (s, 3H), 2.01–1.90 (m, 2H), 1.72 (br d, $J = 14.3$ Hz, 1H), 1.51 (t, $J = 7.4$ Hz, 3H), 1.49–1.40 (m, 1H), 1.33–1.00 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 170.41 (C_{quat}), 169.44 (C_{quat}), 168.41 (C_{quat}), 143.70 (C_{quat}), 137.59 (C_{quat}), 129.94 (CH), 126.86 (CH), 85.26 (CH_3), 70.11 (CH), 69.54 (CH), 61.68 (CH_2), 56.22 (CH), 50.84 (CH), 29.38 (CH_2), 22.65 (CH_2), 21.55 (CH_3), 20.63 (rel. int. 2; CH_3), 13.94 (CH_3), 13.10 (CH_2); MS (CI pos NH_3): *m*/*z* (%) 503 (32) [$M+NH_4^+$], 454 (38) [M^+–OCH_3], 300 (100) [MH^+–$TolSO_2$–OCH_3]; $C_{22}H_{31}NO_9S$ (485.6): calcd C, 54.42; H, 6.44; N, 2.88; found: C, 54.21; H, 6.42; N, 2.84. Compound **20**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 5.59 (d, $J = 9.5$ Hz, 1H), 5.23 (d, $J = 2.5$ Hz, 1H), 5.19 (dd, $J = 7.0$, 2.5 Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.75–3.70 (m, 1H), 3.62–3.58 (m, 1H), 3.49–3.46 (m, 1H), 2.43 (s, 3H), 2.20 (s, 3H), 1.99 (s, 3H), 1.61 (br s, 1H), 1.52–1.41 (m, 4H, 5-H), 1.24 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 170.02 (C_{quat}), 169.86 (C_{quat}), 167.36 (C_{quat}), 143.69 (C_{quat}), 137.86 (C_{quat}), 129.81 (CH), 127.12 (CH), 72.30 (CH), 71.04 (CH), 62.18 (CH_2), 61.98 (CH_2), 52.59 (CH), 27.83 (CH_2), 27.16 (CH_2), 21.55 (CH_3), 20.59 (CH_3), 20.50 (CH_3), 14.00 (CH_3). IR (KBr): ν 3855, 3539, 3504, 3456, 3407, 3308, 3025, 2924, 2853, 2361, 2342, 1763, 1746 cm^{-1}; MS (DCI(NH_3)): *m*/*z* (%) 477 (100) [$M+NH_4^+$]; $C_{20}H_{29}NO_9S$ (459.5): calcd C, 52.30; H, 6.36; N, 3.05; found: C, 52.01; H, 6.41; N, 2.93. Compound **21**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.11 (s, 1H), 7.90–7.63 (m, 2H), 7.48–7.31 (m, 2H), 6.70–6.40 (m, 1H), 6.21–5.84 (m, 1H), 5.68–4.78 (m, 3H), 4.23–4.06 (m, 2H), 3.71 (s, 3H), 2.48 (s, 3H), 2.27–2.08 (m, 4H), 2.08 (s, 3H), 1.94–1.68 (m, 3H), 1.26 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 169.96 (C_{quat}), 169.26 (C_{quat}), 166.95 (C_{quat}), 166.50 (C_{quat}), 162.02 (CH), 146.34 (C_{quat}), 138.00–138.85 (C_{quat}), 130.61 (CH), 127.66 (CH), 121.86 (CH), 70.70 (br, CH), 61.96 (CH_2), 54.50 (br, CH), 51.40 (CH_3), 39.05 (br, CH_2), 27.30 (br, CH_2), 21.61 (CH_3), 20.55 (CH_3), 20.46 (CH_3), 13.94 (CH_3); $C_{24}H_{31}NO_{11}S$ (541.6): calcd C, 53.22; H, 5.77; N, 2.59; found: C, 52.95; H, 5.86; N, 2.54.
19. Details on the X-ray structure of **12a** can be obtained from the Cambridge Crystallographic Data Centre (CCDC 296457).
20. Compounds **13** and **14** could not be separated from each other, thus, making the stereochemical analysis of **14** not possible.
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