An Expedient Synthesis of *N*-Acceptor-Substituted 2,3-Dihydropyrrols from the Corresponding 2-Pyrrolidinones

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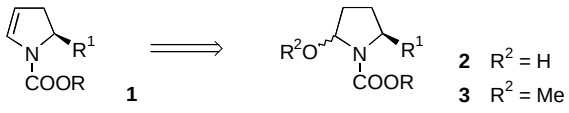
Abstract. The title compounds **1** were prepared from the corresponding *N*-acceptor substituted 2-methoxypyrrolidines **3** by elimination with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and *N*,*N*-di-*iso*-propyl ethyl amine (6 examples, 57–84% yield). The enantiomerically pure *N*-methoxycarbonyl protected elimination substrates **3aa** and **3ab** were synthesized from the L-pyroglutamic acid derived pyrrolidinones **6a** and **6b** in three steps (80–83% yield overall).

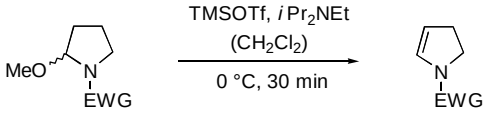
N-Alkoxycarbonyl protected chiral 2-substituted 2,3-dihydropyrrols **1** are heterocyclic olefines the synthetic potential of which has been explored only to a limited extent. There are studies on addition reactions to a proline-derived dihydropyrrol (R^1 = COOMe) and their facial diastereoselectivity [1, 2]. A 2-alkenyl substituted 2,3-dihydropyrrol was used in racemic form as an entry into biologically active *aza*-heterocycles [3]. Recent interest from our group centered on the ability of 2,3-dihydropyrrols to react as alkene components in the Paternò-Büchi reaction [4].



Scheme 1

If R^1 is a vinyl or aryl substituent the enantiomerically pure dihydropyrrols **1** can be prepared from unsubstituted *N*-alkoxycarbonyl-2,3-dihydropyrrols by an enantioselective Heck reaction [5]. If R^1 is an alkyl substituent the target compounds **1** are ideally prepared from the corresponding *N*,*O*-acetals **3** or from the lactamols **2** which may in turn be obtained either oxidatively from pyrrolidines [1, 6] or reductively from pyrrolidinones [7]. The oxidative approach has been reported to be not regioselective in some instances [8]. The proton-catalyzed [1] and the uncatalyzed [7] thermal elimination procedures which have been used to transform the *N*-alkoxycarbonyl-pyrrolidines **2** or **3** into dihydropyrrols did not prove to be well suited for small scale work in our hands. In this note we report on a new method for the conversion of chiral and achiral pyrrolidines **3** to the title compounds. In addition, we describe a reductive approach to the chiral *N*,*O*-acetals **3** (R^1 = alkyl) starting from pyroglutamic acid-derived pyrrolidinones.

It was assumed that the *N*-alkoxycarbonyl iminium ion formation with TMSOTf which has been well documented [9] can serve as an entry into the projected elimination of MeOH from **3** if it was combined with non-nucleophilic base treatment. Indeed, the reagent combination trimethylsilyl trifluoromethanesulfonate (TMSOTf) and *N*,*N*-di-*iso*-propyl ethyl amine (Hünig base) previously employed for the elimination of *O*,*O*-acetals to enol ethers [10] proved useful for the preparation of the pyrrolines **1** and **5** from the corresponding 2-methoxy pyrrolidines **3a**–**c** [11] and **4** [12] as depicted in Scheme 2.



3a	EWG = COOMe	**1a**	(83%)
3b	EWG = COOEt	**1b**	(57%)
3c	EWG = COO*t* Bu	**1c**	(65%)
4	EWG = Ts	**5**	(84%)

Scheme 2

Gratifyingly, the *N*-methoxycarbonylprotected pyrrolidine **3a** reacted particularly well and yielded the dihydropyrrol **1a** in 83% yield. Previous experiments had revealed that the *N*-methoxycarbonyl protected substrates are superior to other *N*-protected dihydropyrrols in the Paternò-Büchi reaction [13]. Upon photochemical reaction with benzaldehyde **1a** gave the corresponding oxetane in 56% yield whereas the yields with **1b** and **1c** were only 41% and 52%. The *N*-tosyl protected substrate **5** did not react at all.

The extension to chiral dihydropyrrols was consequently carried out with *N*-methoxycarbonyl pyrrolidinones which bear an alkyl group adjacent to the nitrogen atom. Starting

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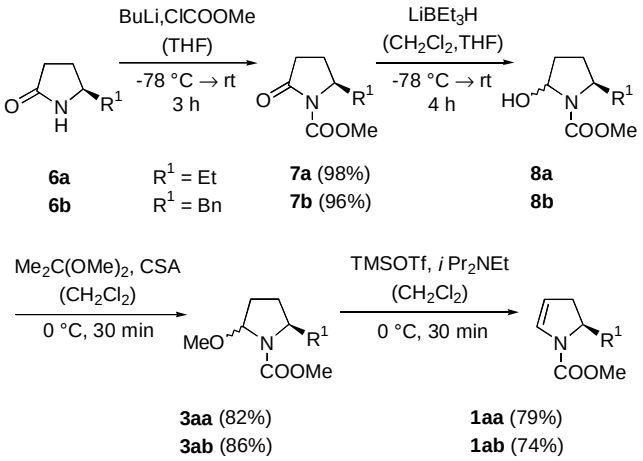
from L-pyroglutamic acid the lactams **6** can be readily prepared [14]. After protection of the nitrogen atom the reduction of the pyrrolidinones **7** was conducted with $LiEt_3BH$ following the procedure of Dieter and Sharma [7] (Scheme 3). Subsequent acetalization of the lactamols **2aa** and **2ab** to the *N*,*O*-acetals **3aa** and **3ab** proceeded best with dimethoxypropane and camphor sulfonic acid (CSA) in CH_2Cl_2 as the solvent [15]. The generality of the elimination procedure was finally demonstrated by the smooth conversion of the *N*,*O*-acetals to the corresponding dihydropyrrols **1aa** and **1ab**.



Scheme 3

In summary, the conversion of the readily available *N*-acceptorsubstituted 2-methoxypyrrolidines **3** to 2,3-dihydropyrrols **1** can be advantageously carried out with TMSOTf and *N*,*N*-di-*iso*-propyl ethyl amine. Chiral 2-methoxypyrrolidines such as **3aa** and **3ab** derived from L-pyroglutamic acid are well suited for the elimination protocol and the method described above gives ready access to the title compounds **1**. The very same procedure has recently been used to prepare a 2-nonyl substituted 2,3-dihydropyrrol which was converted to (+)-preussin [4b]. Further applications of the dihydropyrrols **1** in cycloaddition reactions are currently being investigated in our laboratories and will be reported in due course.

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Experimental

All reactions involving water sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under Ar. Chemicals and solvents for this kind of reactions were distilled from an appropriate drying agent. Common solvents (cyclohexane, ethyl acetate, pentane, *tert*-butyl methyl ether) used for chromatography were distilled prior to use. The 2-methoxypyrrolidines **3a** [1], **3b** [11b], **3c** [11c], and **4** [12] and the pyrrolidinones **6a** [14a] and **6b** [14b] were prepared as described previously. All other reagents and solvents were used as received. – IR: Nicolet 510M FT-IR. – MS: Varian CH 7. – ^1H and ^{13}C NMR: Bruker AC-300. Chemical shifts are reported relative to tetramethylsilane as an internal reference. $CDCl_3$ was used as solvent unless noted otherwise. – Elemental Analyses: Varian Elementar vario EL. – TLC: glass-backed plates (Merck 0.25 mm silica gel 60-F); eluent given in brackets, a cyclohexane (CH)/ethyl acetate (EA) or a pentane (PE)/*tert*-butyl methyl ether (TBME) mixture was used unless stated otherwise; detection by UV or by coloration with ceric ammonium molybdate (CAM). – Flash chromatography [16] (FC): Merck silica gel 60 (230-400 mesh) (50 g for 1 g of material to be separated).

N-Methoxycarbonyl-2,3-dihydropyrrol (**1a**)

Procedure A. 9.0 mmol of TMSOTf (1.96 g, 1.70 ml) was added dropwise to an ice-cooled solution of 7.5 mmol of 2-methoxypyrrolidine **3a** [1] (1.20 g) and 9.7 mmol of *N*,*N*-di-*iso*-propyl ethyl amine (1.28 g, 1.70 ml) in 20 ml of CH_2Cl_2. After 30 min the reaction was quenched by adding 40 ml of pentane. The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by flash chromatography (PE/TBME = 90/10). Yield 800 mg (83%). The analytical data for this compound were in accord with those reported in the literature [6b].

N-Ethoxycarbonyl-2,3-dihydropyrrol (**1b**)

Following the protocol described in procedure **A** (*vide* above) 0.65 mmol of 2-methoxypyrrolidine **3b** [11b] (112 mg) were transformed into the desired product. Purification by flash chromatography (PE/TBME = 90/10). Yield 52 mg (57%). The analytical data for this compound were in accord with those reported in the literature [6b].

N-tert-Butoxycarbonyl-2,3-dihydropyrrol (**1c**)

Following the protocol described in procedure **A** (*vide* above) 6.5 mmol of 2-methoxypyrrolidine **3c** [11c] (1.31 g) were transformed into the desired product. Purification by flash chromatography (PE/TBME = 90/10). Yield 712 mg (65%). The analytical data for this compound were in accord with those reported in the literature [6b].

N-p-Toluenesulfonyl-2,3-dihydropyrrol (**5**)

Following the protocol described in procedure **A** (*vide* above) 2.35 mmol of 2-methoxypyrrolidine **4** [12] (600 mg) were transformed into the desired product. Purification by flash chromatography (CH/EA = 95/5 → 90/10). Yield 440 mg (84%). The analytical data for this compound were in accord with those reported in the literature [12].

(S)-N-Methoxycarbonyl-5-ethyl-2-pyrrolidinone (**7a**)

Procedure B. A 1.47M solution of *n*-butyl lithium in *n*-hexane (7.5 ml, 11 mmol) was added dropwise to a cooled solution of 10 mmol of pyrrolidinone **6a** [14a] (1.13 g) in 20 ml of THF at –78 °C. The mixture was stirred for 1 h at this temperature. 14.3 mmol of methyl chloroformiate (1.35 g, 1.10 ml) were added, and the reaction mixture was allowed to warm slowly to room temperature. After 3 h it was quenched

with 15 ml of a saturated aq. NH_4Cl solution . The aqueous layer was extracted with TBME (3 × 20 ml). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (TBME). Yield 1.68 g (98%). – R_f = 0.44 (EA). – $[\alpha]_D^{25}$ = –104.9 (*c* = 1.1, $CHCl_3$). – IR (film): ν/cm^{-1} = 2965 (m), 1790 (vs, C=O), 1750 (s), 1720 (s), 1305 (m). – ^{1}H NMR (300 MHz): δ/ppm = 0.95 (t, ^3J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 1.41–2.11 (m, 4H, $C\underline{H}_2CHC\underline{H}_2$), 2.35 (ddd, ^2J = 17.8 Hz, ^3J = 9.5 Hz, ^3J = 1.6 Hz, 1H, $COCH\underline{H}$), 2.52 (ddd, ^2J = 17.8 Hz, ^3J = 9.2 Hz, ^3J = 1.7 Hz, 1H, $COC\underline{H}H$), 3.76 (s, 3H, $OC\underline{H}_3$), 4.04 (tdd, ^3J = 8.8 Hz, ^3J = 3.3 Hz, ^3J = 1.9 Hz, 1H, $C\underline{H}N$). – ^{13}C NMR (75.5 MHz): δ/ppm = 9.4 ($CH_2\underline{C}H_3$), 21.8 ($COCH_2\underline{C}H_2$), 26.1 ($CO\underline{C}H_2$), 31.2 ($\underline{C}H_2CH_3$), 53.1 ($O\underline{C}H_3$), 59.1 ($\underline{C}HN$), 152.0 ($\underline{C}OO$), 173.8 ($\underline{C}ON$). – MS (EI), *m/z* (%): 171 (10) [M$^+$], 142 (100) [M$^+$–C_2H_5], 98 (74) [$C_6H_{12}N^+$], 41 (87) [$C_2H_3N^+$]. – HRMS Calcd. for $C_8H_{13}NO_3$: 171.0895. Found: 171.0899.

$C_8H_{13}NO_3$	Calcd:	C 56.13	H 7.65	N 8.18
(171.09)	Found:	C 56.38	H 7.79	N 8.15.

(S)-N-Methoxycarbonyl-5-benzyl-2-pyrrolidinone (**7b**)

Following the protocol described in procedure **B** (*vide* above) 1.40 mmol of 2-pyrrolidinone **6b** [14b] (245 mg) were transformed into the desired product. Purification by flash chromatography (PE/TBME = 40/60). Yield 313 mg (96%). – R_f = 0.38 (TBME). – $[\alpha]_D^{25}$ = –87.1 (*c* = 7.9, $CHCl_3$). – IR (film): ν/cm^{-1} = 2955 (m), 1715 (vs, C=O), 1750 (s), 1790 (vs), 1305 (m). – ^{1}H NMR (300 MHz): δ/ppm = 1.92–1.99 (m, 1H, $CH_2C\underline{H}HCHN$), 2.06–2.14 (m, 1H, $CH_2CH\underline{H}CHN$), 2.36–2.44 (m, 2H, $COC\underline{H}_2$), 2.88 (dd, ^2J = 13.4 Hz, ^3J = 8.5 Hz, 1H, $CH\underline{H}Ph$), 3.23 (dd, ^2J = 13.4 Hz, ^3J = 3.6 Hz, 1H, $C\underline{H}HPh$), 4.55 (tdd, ^3J = 8.5 Hz, ^3J = 3.6 Hz, ^3J = 1.6 Hz, 1H, $C\underline{H}N$), 7.28–7.44 (m, 5H, arom. H). – ^{13}C NMR (75.5 MHz): δ/ppm = 21.8 ($COCH_2\underline{C}H_2$), 31.0 ($CO\underline{C}H_2$), 39.2 ($\underline{C}H_2C_{ar}$), 53.4 ($O\underline{C}H_3$), 58.9 ($\underline{C}HN$), 127.0 ($\underline{C}_{ar}$), 129.4 (2 C, $\underline{C}_{ar}$), 128.6 (2C, $\underline{C}_{ar}$), 136.8 ($CH_2\underline{C}_{ar}$), 152.2 ($\underline{C}OO$), 173.7 ($\underline{C}ON$). – MS (EI), *m/z* (%): 233 (11) [M$^+$], 142 (100) [M$^+$– C_7H_7], 98 (56) [$C_6H_{12}N^+$], 91 (35) [$C_7H_7^+$].

$C_{13}H_{15}NO_3$	Calcd:	C 66.94	H 6.48	N 6.00
(233.26)	Found:	C 67.09	H 6.57	N 6.11.

(2RS,5S)-N-Methoxycarbonyl-5-ethyl-2-methoxypyrrolidine (**3aa**)

Procedure C. A 1.0M solution of $LiEt_3BH$ in THF (1.4 ml, 1.4 mmol) was added dropwise to a cooled solution of 1.32 mmol of 2-pyrrolidinone **7a** (149 mg) in 15 ml of CH_2Cl_2 at –78 °C. The reaction mixture was allowed to reach 0 °C, and it was subsequently stirred for 4 h at this temperature. A 1M NaOH solution (2.0 ml, 2.0 mmol) and 1.0 ml of a 35% H_2O_2 solution were added successively. The organic layer was separated and filtered through a Celite pad.

The solution so received was cooled to 0 °C. 8.2 mmol of 2,2-dimethoxypropane (850 mg, 1.0 ml) and 0.1 mmol of camphor sulfonic acid (CSA) (25 mg) were added. After 30 min 10 ml of a saturated aq. $NaHCO_3$ solution was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were filtered through a Celite pad and concentrated *in vacuo*. The diastereomeric mixture of **3aa** was used without further purification for the transformation to 2,3-dihydropyrrolidine **7a**. Yield 139 mg (82 %). – R_f = 0.21/0.26 (PE/TBME = 80/20).

(2RS,5S)-N-Methoxycarbonyl-5-benzyl-2-methoxypyrrolidine (**3ab**)

Following the protocol described in procedure **C** (*vide* above) 1.18 mmol 2-pyrrolidinone **7b** (275 mg) were transformed into the desired product. Yield 253 mg (86 %). – R_f = 0.58/0.60 (TBME).

(S)-N-Methoxycarbonyl-5-ethyl-2,3-dihydropyrrole (**1aa**)

Following the protocol described in procedure **A** (*vide infra*) 1.08 mmol of 2-methoxypyrrolidine **3aa** (139 mg) were transformed into the desired product. Purification by flash chromatography (PE/TBME = 90/10). Yield 132 mg (79 %). – R_f = 0.39 (PE/TBME = 80/20). – $[\alpha]_D^{25}$ = –145.7 (*c* = 1.6, $CHCl_3$). – IR (film): ν/cm^{-1} = 2960 (m), 1705 (s, C=O), 1450 (m), 1380 (m). – ^{1}H NMR (300 MHz): δ/ppm = 0.84 (t, ^3J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 1.58–1.61 (m, 2 H, $C\underline{H}_2CH_3$), 2.26 (d, ^2J = 15.8 Hz, 1H, $NCHC\underline{H}H$), 2.79 (dd, ^2J = 15.8 Hz, ^3J = 1.2 Hz, 1H, $NCHCH\underline{H}$), 3.70 (s, 1H, $OC\underline{H}_3$), 4.08–4.12 (m, 1H, $NC\underline{H}CH_2$), 4.91–4.94 (m, 1H, $NCHC\underline{H}$), 6.44–6.56 (m, 1H, $NC\underline{H}CH$). – ^{13}C NMR (75.5 MHz): δ/ppm = 8.5 ($CH_2C\underline{H}_3$), 26.5 ($C\underline{H}_2CH_3$), 34.2 ($N\underline{C}HCH_2$), 52.2 ($O\underline{C}H_3$), 58.4 ($NCH\underline{C}H_2$), 107.2 ($NCH\underline{C}H$), 128.8 ($N\underline{C}HCH$), ^{13}C signal for $\underline{C}O$ was not observed. – MS (EI), *m/z* (%): 155 (39) [M$^+$], 126 (100) [M$^+$– CH_2CH_3], 67 (45) [$C_4H_5N^+$]. – HRMS Calcd. for $C_8H_{13}NO_2$: 155.0946. Found: 155.0961.

(S)-N-Methoxycarbonyl-5-benzyl-2,3-dihydropyrrole (**1ab**)

Following the protocol described in procedure **A** (*vide* above) 1.01 mmol of 2-methoxypyrrolidine **3ab** (253 mg) were transformed into the desired product. Purification by flash chromatography (PE/TBME = 90/10). Yield 163 mg (74%). – R_f = 0.35 (PE/TBME = 80/20). – $[\alpha]_D^{25}$ = –73.5 (*c* = 0.4, $CHCl_3$). – IR (film): ν/cm^{-1} = 2955 (m), 1700 (vs, C=O), 1450 (m), 1385 (m). – ^{1}H NMR (300 MHz): δ/ppm = 2.33 (d, ^2J = 15.8 Hz, 1H, $CHCHCH\underline{H}$), 2.66 (dd, ^2J = 13.1 Hz, ^3J = 9.1 Hz), 3.10 (d, ^2J = 15.8 Hz, 1H, $CHCHC\underline{H}H$), 3.75 (s, 3H, $O\underline{C}H_3$), 4.31–4.43 (m, 1H, $N\underline{C}HCH_2$), 4.86–4.95 (m, 1H, $NCHC\underline{H}$), 6.44–6.57 (m, 1H, $NC\underline{H}CH$), 7.18–7.31 (m, 5H, arom. $\underline{H}$). – ^{13}C NMR (75.5 MHz): δ/ppm = 33.7 ($CHCH\underline{C}H_2$), 39.2 ($\underline{C}HCH_2C_{ar}$), 52.3 ($O\underline{C}H_3$), 58.4 ($\underline{C}H_2C_{ar}$), 107.1 ($NCH\underline{C}H$), 126.3 ($\underline{C}_{ar}$), 128.3 (2 C, $\underline{C}_{ar}$), 128.5 ($N\underline{C}HCH$), 129.5 (2 C, $\underline{C}_{ar}$), 137.7 ($CH_2\underline{C}_{ar}$), ^{13}C signal for $\underline{C}O$ was not observed. – MS (EI), *m/z* (%): 217 (11) [M$^+$], 126 (100) [M$^+$– C_7H_7], 91 (51) [$C_7H_7^+$].

$C_{13}H_{15}NO_2$	Calcd:	C 71.87	H 6.96	N 6.45
(217.26)	Found:	C 72.03	H 7.06	N 6.67.

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