DOI: 10.1002/ejoc.200500838

A New Three-Component Cascade Reaction to Yield 3-Spirocyclopropanated β-Lactams[‡]

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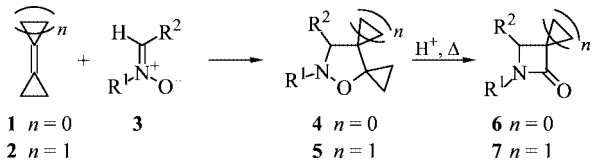
Keywords: Cascade reactions / Cycloadditions / β-Lactams / Microwaves / Small rings / Cyclopropanes

A one-pot three-component reaction for the direct conversion of certain alkylhydroxylamine hydrochlorides **8** (alkyl = benzyl, *p*-methoxybenzyl, benzhydryl, *tert*-butyl), formaldehyde (**9**) or an alkyl glyoxylate (**10**) and bicyclopropylidene (**2**) to furnish 3-spirocyclopropanated 2-azetidinones **7**, **11** has been developed. Microwave heating of mixtures of the three components in the presence of sodium acetate in ethanol for 15–120 min furnished the products **7**, **11** in 49–78 % yield (7 examples). A new protocol for the oxidative deprotection of the 3-spirocyclopropanated methyl 1-(*p*-methoxybenzyl)-2-carboxylate **11b**-Me provides the β-lactam building block **17**-Me in 90 % yield, and the latter can be reprotected and activated with an *N*-*tert*-butoxycarbonyl (Boc) group in 82 % yield.

Introduction

Not only are various β-lactams the most frequently employed kinds of antimicrobial agents,[1] but because of their inherent ring strain, β-lactams can also favorably be employed as multifunctional building blocks. In fact, every single bond in a β-lactam can undergo selective cleavage,[2] and this favors the 2-azetidinone nucleus for various applications in organic synthesis.[3] As we have recently demonstrated,[4] spirocyclopropanated β-lactams of type **7** can conveniently be employed to prepare peptide mimics incorporating the 1-(aminomethyl)cyclopropanecarboxylic acid, a β-alanine analog containing a cyclopropyl group.[5] 2-Azetidinones of type **7** are formed in high yields upon treatment of cycloadducts **5** from nitrones **3** and bicyclopropylidene (**2**) with trifluoroacetic acid.[6] This unprecedented fragmentation of 5-spirocyclopropanated isoxazolidines of types **4** and **5**[7] constitutes a versatile access to β-lactams of types **6** and **7**, yet it suffers dramatically from the long reaction times required for the formation of the unrearranged cycloadducts **4** and **5** (Scheme 1).[8]



Scheme 1. Fragmentations of the cycloadducts **4**, **5** of nitrones **3** to methylenecyclopropane (**1**) and bicyclopropylidene (**2**) under acidic conditions.

In view of the multiple beneficial effects of microwave heating on organic synthetic transformations reported in recent years,[9] we tried out the possibility of shortening the reaction times by using microwave heating during the 1,3-dipolar cycloaddition of in situ generated unstable and/or reactive nitrones[10] to bicyclopropylidene (**2**). Here we report on our first results.

Results and Discussion

When a solution of a twofold excess of *N*-benzylhydroxylamine hydrochloride (**8a**), a twofold excess of aqueous formaldehyde (8 M), a twofold excess of sodium acetate and bicyclopropylidene (**2**) in ethanol was heated in a screw-capped glass vial in a microwave reactor[11] at 100 °C, the starting material **2** had been consumed within 60 min,[12] and the 3-spirocyclopropanated 2-azetidinone **7a** was isolated in 68 % yield. Apparently, the nitrone initially formed from formaldehyde (**9**) and benzylhydroxylamine (**8**), had undergone 1,3-dipolar cycloaddition to **2**, and the resulting isoxazolidine **5a**, under the slightly acidic conditions of the hydroxylamine hydrochloride/sodium acetate buffered sys-

[‡] Cyclopropyl Building Blocks in Organic Synthesis, 122. Part 121: T. Kurahashi, A. de Meijere, *Angew. Chem.* **2005**, *114*, 8093–8096; *Angew. Chem. Int. Ed.* **2005**, *44*, 7881–7884. Part 120: T. Kurahashi, A. de Meijere, *Synlett* **2005**, 2619–2622.

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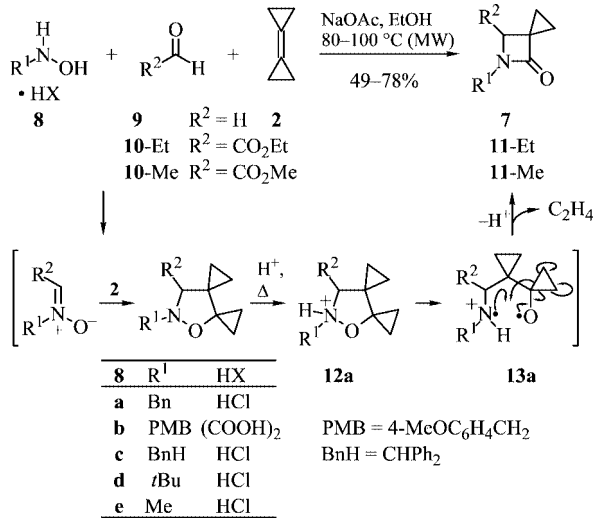
tem had fragmented via intermediates **12a**, **13a**[7b] to ethylene and the β-lactam **7a** (Scheme 2).[13]



Scheme 2. One-pot three-component reaction under microwave heating for the direct conversion of alkylhydroxylamine hydrochlorides **8**, aldehydes **9**–**10** and bicyclopropylidene (**2**) to 3-spirocyclopropanated 2-azetidinones **7** and **11**. For details see Table 1.

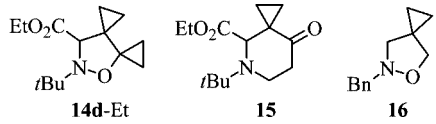
Analogously, the 3-spirocyclopropanated 2-azetidinones **7b**–**d**, **11a**-Et, **11b**-Me, **11d**-Et were obtained from the corresponding hydroxylamine hydrochlorides (or oxalate) and formaldehyde **9** or ethyl **10**-Et and methyl glyoxylate **10**-Me, respectively, in good to excellent yields (49–78%), as single products after 30–120 min reaction times in a single operation (Scheme 2 and Table 1).

Table 1. One-pot three-component reaction under microwave heating for the direct conversion of alkylhydroxylamine hydrochlorides **8**, aldehydes **9**–**10** and bicyclopropylidene (**2**) to 3-spirocyclopropanated 2-azetidinones **7** and **11** (see Scheme 2).

Starting materials	R^1	R^2	Time [min]	Temp. [°C]	Product	Yield (%)
8a + **9**	Bn	H[a]	60	100	**7a**	68
8b + **9**	PMB	H[a]	45	80	**7b**	53
8c + **9**	BnH	H[a]	30	100	**7c**	49
8d + **9**	*t*Bu	H[a]	30	80	**7d**	73
8a + **10**-Et	Bn	CO_2Et[b]	15	80	**11a**-Et	72
8d + **10**-Et	*t*Bu	CO_2Et[b]	105	80	**11d**-Et	53[c]
8b + **10**-Me	PMB	CO_2Me	120	80	**11b**-Me	78

[a] Formaldehyde was used as an aqueous solution (8 M). [b] Ethyl glyoxylate was used as a solution in toluene (50% w/w). [c] In addition, 47% of a mixture of **14d**-Et and **15** (1.3:1) was isolated.

For hydroxylamine hydrochlorides **8a** and **8c**, the reaction was also performed with paraformaldehyde instead of an aqueous solution of formaldehyde. The products **7a** and **7c** were obtained as well, but in slightly lower yields (56 and 37%, respectively). From *N*-*tert*-butylhydroxylamine hydrochloride (**8d**), ethyl glyoxylate (**10**-Et) and bicyclopropylidene (**2**), a mixture of the unfragmented *N*-*tert*-butylisoxazolidine **14d**-Et and the thermal rearrangement product,[8] the 3-spirocyclopropanated 4-oxopiperidine-2-carboxylate **15**, was isolated (44%).



With *N*-methylhydroxylamine hydrochloride, formaldehyde (**9**) and **2**, the yield of the corresponding *N*-methylazetidinone was at best 10% and with the same hydroxylamine derivative with ethyl glyoxylate (**10**-Et) and **2**, none of the corresponding azetidinone could be detected, even not in the crude reaction mixture.

When methylenecyclopropane (**1**) was employed as dipolarophile in this three-component reaction with **8a** and formaldehyde (**9**), the expected product **6a** was isolated in only 9% yield along with the spiro[cyclopropane-1,4′-isoxazolidine] **16**, which was formed along with the fragmented 5-spirocyclopropanated regioisomer, and cannot undergo acid-catalyzed fragmentative rearrangement.

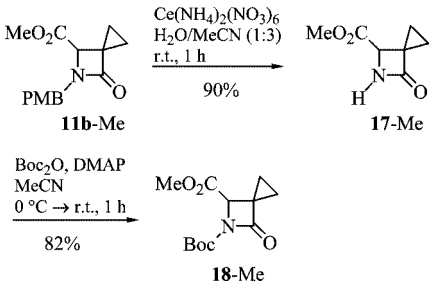
The fragmentative rearrangement of 5-spirocyclopropanated isoxazolidines **4** and **5** previously had been brought about with reasonably strong acids such as trifluoroacetic, *p*-toluenesulfonic or hydrochloric acid. To better understand why this new one-pot three-component reaction worked without any of these strong free acids present, control experiments were carried out with the isolated dispirocyclopropanated **14a**-Et. When the latter was heated with added acetic acid in acetonitrile at 70 °C overnight, none of the azetidinone **11a**-Et was detected. But heating **14a**-Et under the same conditions with benzylhydroxylamine hydrochloride did furnish **11a**-Et (59%). For the overall transformation to occur, the added sodium acetate is essential as well. An experiment with all the ingredients for the formation of **11a**-Et, except for the added sodium acetate, carried out in the microwave oven, gave no trace of product. In fact, not even the condensation of the hydroxylamine and the aldehyde to the nitrone took place.

Since this one-pot three-component sequential reaction[14] has no precedent, it is difficult to estimate the role of the microwave heating. In any case, it is remarkable that the time required for the overall reaction is never longer than 2 h, whereas with traditional heating at 45 °C the 1,3-dipolar cycloaddition of the most reactive *N*-methyl-*C*-(ethoxycarbonyl)nitrone onto bicyclopropylidene (**2**) requires 16 d, and at higher temperatures only the corresponding spirocyclopropanated piperidone derivative is formed.[15]

To demonstrate the accessibility of the unprotected **17**-Me, conditions for the removal of the *p*-methoxybenzyl group were developed, under which no trace of oxidized byproduct was found, as had previously been observed.[4]

Treatment of **11b**-Me with ceric ammonium nitrate (CAN) in aqueous acetonitrile (1:3) at room temperature did indeed furnish **17**-Me in 90% yield, and this in turn could be protected with a *t*-Boc group to yield **18**-Me (82%). The latter can serve as a building block for β-amino acid peptides incorporating 1-(aminomethyl)cyclopro-

panecarboxylic acid, as it is activated towards ring opening at the lactam bond (Scheme 3).[4]



Scheme 3. Modification of the β-lactam **11b**-Me to yield the reactive building block **18**-Me.

Experimental Section

NMR spectra were recorded with Bruker AM 250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C NMR), Varian Mercury 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C NMR), Varian Unity 300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C NMR), Varian INOVA 600 (600 MHz for ^{1}H and 150.8 MHz for ^{13}C NMR) instruments in $CDCl_3$, if not otherwise specified. Multiplicities were determined by DEPT (Distortionless Enhancement by Polarization Transfer) or APT (Attached Proton Test) measurements. Chemical shifts refer to δ_{TMS} = 0.00 according to the chemical shifts of residual $CHCl_3$ signals. IR: Bruker IFS 66 (FT-IR) spectrophotometer, measured as KBr pellets, oils between KBr plates. MS (EI, 70 eV): Finnigan MAT 95 spectrometer. M.p.: Büchi 510 capillary melting point apparatus, uncorrected values. TLC: Macherey–Nagel precoated sheets, 0.25 mm Sil G/UV$_{254}$. Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Starting materials: methylenecyclopropane (**1**),[6] bicyclopropylidene (**2**),[6] *N*-benzhydrylhydroxylamine hydrochloride (**8c**),[16] and methylglyoxylate (**10**-Me),[17] were prepared according to published procedures. All operations in anhydrous solvents were performed under an argon atmosphere in flame-dried glassware. Diethyl ether was dried by distillation from sodium benzophenone ketyl, CH_2Cl_2 and acetonitrile from P_2O_5. Commercially available *m*-chloroperbenzoic acid (*m*CPBA) was enriched according to a published procedure.[18] All other chemicals were used as commercially available. Organic extracts were dried with $MgSO_4$ or Na_2SO_4.

Synthesis of *N*-(*p*-Methoxybenzyl)hydroxylamine Oxalate (8b): To a solution of *N*-(*p*-methoxybenzyl)-*C*-cyanonitrone (4.70 g, 25.0 mmol) in MeOH (125 mL) was added $NH_2OH{\cdot}HCl$ (8.7 g, 125 mmol). After stirring for 2 h at 60 °C, the resulting mixture was cooled to room temp., methanol was evaporated in vacuo, and $CHCl_3$ (100 mL) was added. The mixture containing some undissolved solids was filtered through a pad of Celite. The filtrate was concentrated, and the residue was partitioned with $CHCl_3$ (150 mL) and a satd. solution of $NaHCO_3$ (150 mL). The acqueous layer was extracted with $CHCl_3$ (2×70 mL), and the combined extracts were washed with satd. solution of NaCl (150 mL), dried ($MgSO_4$) and filtered. To the filtrate was added a solution of oxalic acid (3.15 g, 250.0 mmol) in 25 mL of methanol, and the resulting suspension was evaporated to dryness. The solid obtained was triturated with ether/pentane, and collected by suction. After drying in vacuo, analytically pure **8b** (4.84 g, 80%) was obtained as a yellowish solid, m.p. 145 °C. IR (KBr): $\tilde{\nu}$ = 3424 cm^{-1}, 2932, 2837, 1721, 1612, 1515, 1454, 1306, 1253, 826, 710. ^{1}H NMR (250 MHz, CD_3OD): δ = 3.85 (s, 3 H), 4.35 (s, 2 H), 7.01–7.05 (m, 2 H), 743–7.47 (m, 2 H). ^{13}C NMR (62.9 MHz): δ = 56.0 (CH_3), 56.4 (CH_2), 115.7 (2 CH), 122.1 (C), 133.6 (2 CH), 162.1 (C), 165.5 (2 C). $C_{10}H_{13}NO_6$ (243.22): C 49.38, H 5.39, N 5.76; found C 49.13, H 5.61, N 5.90.

One-Pot Three-Component Synthesis of β-Lactams 7a–d and 11a,b,d. General Procedure (GP) 1: A solution of the hydroxylamine salt (2 equiv.), the aldehyde (2 equiv.), bicycloproppylidene (**2**) (1 equiv.), and NaOAc (2 equiv.) in ethanol was sealed in a screw-capped vial for the microwave apparatus and heated at the indicated temperature for the indicated time. After cooling down to room temperature, the solution was concentrated under reduced pressure. An equal amount each of water and ethyl acetate was added, and the two phases were separated. The water phase was made basic with $NaHCO_3$ (satd. solution) and extracted three times with ethyl acetate. The combined organic layers were then washed with brine and dried with Na_2SO_4.

5-Benzyl-5-azaspiro[2.3]hexan-4-one (7a): Column chromatography (R_f = 0.10, 45 g of silica gel, 12×3 cm column, hexane/Et_2O, 2:1) of the residue obtained from the hydroxylamine **8a** (0.638 g, 4.00 mmol), formaldehyde (**9**) solution (8.0 M) in water (0.250 mL, 2.00 mmol), bicyclopropylidene (**2**) (0.190 mL, 2.00 mmol), and NaOAc (0.328 g, 4.00 mmol) in 1.75 mL of ethanol according to GP1 (100 °C, 60 min) gave the product **7a** (0.255 g, 68%) as a yellow oil. IR (film): $\tilde{\nu}$ = 3064 cm^{-1}, 3004, 2890, 1751, 1496, 1455, 1395, 1354. ^{1}H NMR (250 MHz): δ = 0.92–0.97 (m, 2 H, cPr-H), 1.18–1.23 (m, 2 H, cPr-H), 3.33 (s, 2 H, CH_2), 4.47 (s, 2 H, CH_2), 7.17–7.39 (m, 5 H, Ar-H). ^{13}C NMR (62.9 MHz): δ = 7.6 (2 CH_2), 32.1 (C), 46.3 (CH_2), 48.1 (CH_2), 127.6 (CH), 128.1 (2 CH), 128.7 (2 CH), 136.0 (C), 172.6 (C). MS (EI): *m*/*z* (%) = 187 (44), 131 (10), 91 (100), 54 (21). $C_{12}H_{13}NO$ (187.24): C 76.98, H 7.00, N 7.48; found C 76.83, H 7.13, N 7.25.

5-(4-Methoxybenzyl)-5-azaspiro[2.3]hexan-4-one (7b): Column chromatography (R_f = 0.28, 30 g of silica gel, 12×2.5 cm column, hexane/Et_2O, 3:1) of the residue obtained from the hydroxylamine **8b** (0.780 g, 3.20 mmol), formaldehyde (**9**) solution (8.0 M) in water (0.250 mL, 2.00 mmol), bicyclopropylidene (**2**) (0.190 mL, 2.00 mmol), and NaOAc (0.263 g, 3.20 mmol) in 2.50 mL of ethanol according to GP1 (80 °C, 45 min) gave the product **7b** (0.232 g, 53%) as a yellow oil. IR (KBr): $\tilde{\nu}$ = 3080 cm^{-1}, 3001, 2936, 2894, 2839, 1732, 1512, 1401. ^{1}H NMR (250 MHz): δ = 0.90–0.95 (m, 2 H, cPr-H), 1.16–1.21 (m, 2 H, cPr-H), 3.30 (s, 2 H), 3.80 (s, 3 H), 4.40 (s, 2 H), 6.85–6.91 (m, 2 H, Ar-H), 7.17–7.23 (m, 2 H, Ar-H). ^{13}C NMR (62.9 MHz): δ = 7.33 (2 CH_2), 31.8 (C), 45.6 (CH_2), 47.7 (CH_2), 55.1 (CH_3), 113.9 (2 CH), 127.8 (C), 129.2 (2 CH), 158.9 (C), 172.3 (C). MS (EI): *m*/*z* (%) = 217 (100), 186 (8), 163 (10), 121 (85), 78 (10). $C_{13}H_{15}NO_2$ (217.26): C 71.87, H 6.96, N 6.45; found C 72.07, H 7.10, N 6.30.

5-(Benzhydryl)-5-azaspiro[2.3]hexan-4-one (7c): Column chromatography (R_f = 0.18, 36 g of silica gel, 15×2.5 cm column, hexane/Et_2O, 2:1) of the residue obtained from the hydroxylamine **8c** (0.707 g, 3.00 mmol), formaldehyde (**9**) solution (8.0 M) in water (0.375 mL, 3.00 mmol), bicyclopropylidene (**2**) (0.140 mL, 1.50 mmol), and NaOAc (0.246 g, 3.00 mmol) in 2.00 mL of ethanol according to GP1 (100 °C, 30 min) gave the product **7c** (193 mg, 49%) as a colorless solid, m.p. 95–96 °C. IR (KBr): $\tilde{\nu}$ = 3080 cm^{-1}, 3060, 2962, 2892, 1888, 1745, 1597, 1581, 1494, 1446, 1384, 1364. ^{1}H NMR (250 MHz): δ = 0.93–0.98 (m, 2 H, cPr-H), 1.20–1.25 (m, 2 H, cPr-H), 3.39 (s, 2 H, CH_2), 6.25 (s, 1 H, CH), 7.02–7.28 (m, 5 H, Ar-H), 7.30–7.40 (m, 5 H, Ar-H). ^{13}C NMR (62.9 MHz): δ = 7.8 (2 CH_2), 31.4 (C), 47.4 (CH_2), 59.3 (CH), 127.6 (2 CH), 128.1 (4 CH), 128.6 (4 CH), 139.2 (2 C), 172.5 (C). MS (EI): *m*/*z* (%) = 263 (45), 186 (20), 167 (100), 165 (25), 152 (18), 91

(18). $C_{18}H_{17}NO$ (263.33): C 82.10, H 6.51, N 5.32; found C 82.12, H 6.25, N 5.16.

5-*tert*-Butyl-5-azaspiro[2.3]hexan-4-one (7d): Column chromatography (R_f = 0.19, 25 g of silica gel, 12 × 2 cm column, hexane/Et_2O, 2:1) of the residue obtained from the hydroxylamine **8d** (0.251 g, 2.00 mmol), formaldehyde (**9**) solution (8.0 M) in water (0.250 mL, 2.00 mmol), bicyclopropylidene (**2**) (0.09 mL, 1.00 mmol), and NaOAc (0.164 g, 2.00 mmol) in 0.5 mL of ethanol according to GP1 (80 °C, 30 min) gave the product **7d** (0.111 g, 73%) as a colorless oil. IR (film): $\tilde{\nu}$ = 2970 cm^{-1}, 2935, 2885, 2839, 1753, 1379, 1336. ^1H NMR (250 MHz): δ = 0.87–0.91 (m, 2 H, cPr-H), 1.09–1.14 (m, 2 H, cPr-H), 1.35 (s, 9 H), 3.35 (s, 2 H). ^{13}C NMR (62.9 MHz): δ = 7.3 (2 CH_2), 27.9 (3 CH_3), 30.2 (C), 45.5 (CH_2), 64.3 (C), 171.3 (C). MS (EI): *m*/*z* (%) = 153 (10), 138 (100), 84 (5), 70 (100), 57 (40). HRMS (EI) calcd. for $C_9H_{15}NO$ 153.1154 [M^+], found 153.1154.

Ethyl 5-Benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (11a-Et): Column chromatography (R_f = 0.29, 35 g of silica gel, 12 × 2.5 cm column, hexane/Et_2O, 3:1) of the residue obtained from the hydroxylamine **8a** (0.479 g, 3.00 mmol), ethyl glyoxylate (**10**-Et) as a solution in toluene (50% weight) (0.60 mL, 3.00 mmol), bicyclopropylidene (**2**) (0.140 mL, 1.50 mmol), and NaOAc (0.246 g, 3.00 mmol) in 0.70 mL of ethanol according to GP1 (80 °C, 15 min) gave the product **11a**-Et (0.279 g, 72%) as a yellow oil. IR (film): $\tilde{\nu}$ = 2981 cm^{-1}, 1775, 1744, 1496, 1456, 1388, 1199. ^1H NMR (300 MHz): δ = 0.84–0.90 (ddd, *J* = 9.4, 7.8, 4.2 Hz, 1 H), 1.04–1.28 (m, 3 H), 1.20–1.25 (t, *J* = 9.0 Hz, 3 H), 3.98 (s, 1 H), 4.10–4.21 (m, 2 H), 4.21–4.25 (d, *J* = 12.0 Hz, 1 H), 4.86–4.91 (d, *J* = 12.0 Hz, 1 H), 7.22–7.36 (m, 5 H). ^{13}C NMR (75.5 MHz): δ = 6.4 (CH_2), 8.0 (CH_2), 14.2 (CH_3), 37.2 (C), 45.6 (CH_2), 57.5 (CH), 61.3 (CH_2), 127.8 (CH), 128.4 (2 CH), 128.8 (2 CH), 135.3 (C), 169.6 (C), 171.1 (C). MS (EI): *m*/*z* (%) = 259 (4), 231 (18), 186 (5), 158 (39), 91 (100), 65 (15). $C_{15}H_{17}NO_3$ (259.30): C 69.48, H 6.61, N 5.40; found C 68.76, H 6.72, N 5.52.

One-Pot Protocol Applied to Hydroxylamine 8d and Ethyl Glyoxylate 10-Et: A solution of *tert*-butylhydroxylamine hydrochloride (**8d**) (250 mg, 2.00 mmol), ethyl glyoxylate (**10**-Et) as a toluene solution (50% w/w) (0.408 g, 0.40 mL, 2.0 mmol), bicyclopropylidene (**2**) (80 mg, 0.090 mL, 1.00 mmol) and NaOAc (164 mg, 2.0 mmol) in ethanol (0.50 mL), was sealed in a screw capped vial for the microwave oven and heated at 80 °C for 105 min. After cooling to room temperature, the solution was concentrated under reduced pressure. An equal amount each of water and ethyl acetate (30 mL) was added, and the two phases were separated. The water phase was made basic with $NaHCO_3$ (satd. solution) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were then washed with brine and dried with Na_2SO_4. The crude product was purified by column chromatography (50 g of flash silica gel, 3 × 15 cm column, hexane/Et_2O, 3:1) to give ethyl 8-*tert*-butyl-7-oxa-8-azadispiro[2.0.2.3]nonane-9-carboxylate (**14d**-Et) and ethyl 5-*tert*-butyl-8-oxo-5-azaspiro[2.5]octane-4-carboxylate (**15**) (0.111 g, 44%) in a ratio **14d**-Et/**15** of 1.3:1 and ethyl 5-*tert*-butyl-6-oxo-5-azaspiro-[2.3]hexane-4-carboxylate (**11d**-Et) (0.119 g, 53%) as a yellow solid, m.p. 58–60 °C. (**14d**-Et): IR (film): $\tilde{\nu}$ = 3076 cm^{-1}, 2977, 2936, 1757, 1465, 1363, 1275. ^1H NMR (600 MHz): δ = 0.09–0.13 (ddd, *J* = 10.5, 7.2, 6.3 Hz, 1 H), 0.15–0.18 (m, 1 H), 0.50–0.54 (ddd, *J* = 10.5, 7.1, 5.6 Hz, 1 H), 0.65–0.70 (m, 3 H), 0.82–0.86 (dt, *J* = 11.2, 6.7 Hz, 1 H), 0.90–0.94 (ddd, *J* = 11.2, 7.2, 5.6 Hz, 1 H), 1.13 (s, 9 H), 1.24–1.26 (t, *J* = 7.2 Hz, 3 H), 3.69 (s, 1 H), 4.14–4.19 (dq, *J* = 10.5, 7.1 Hz, 1 H), 4.23–4.28 (dq, *J* = 10.5, 7.1 Hz, 1 H). ^{13}C NMR (62.9 MHz): δ = 4.7 (CH_2), 5.1 (CH_2), 11.4 (CH_2), 12.2 (CH_2), 14.3 (CH_3), 25.4 (3 CH_3), 31.3 (C), 58.8 (C), 60.9 (CH_2), 65.7 (C), 67.9 (CH), 171.7 (C). MS (EI): *m*/*z* (%) = 253 (15), 210 (5), 180 (40), 124 (100), 96 (45), 57 (100), 41 (75). $C_{14}H_{23}NO_3$ (253.34): calcd. C 66.37, H 9.15, N 5.53; found C 66.15, H 9.09, N 5.47. **11d**-Et (R_f = 0.7, hexane/Et_2O, 3:1): IR (film): $\tilde{\nu}$ = 2937 cm^{-1}, 1766, 1749, 1368, 1186. ^1H NMR (250 MHz): δ = 0.68–0.74 (m, 1 H, cPr-H), 1.05–1.24 (m, 3 H, cPr-H), 1.28 (t, *J* = 7.5 Hz, 3 H), 1.37 (s, 9 H), 4.18 (s, 1 H), 4.21 (dq, *J* = 7.5, 2.5 Hz, 2 H). ^{13}C NMR (62.9 MHz): δ = 6.4 (CH_2), 8.0 (CH_2), 14.3 (CH_3), 27.9 (3 CH_3), 35.6 (C), 54.3 (C), 57.8 (CH), 61.3 (CH_2), 170.5 (C), 171.0 (C). MS (EI): *m*/*z* (%) = 225 (15), 210 (80), 182 (100), 152 (35), 136 (20), 96 (40), 41 (35). $C_{12}H_{19}NO_3$ (225.29): C 63.98, H 8.50, N 6.22; found C 64.07, H 8.73, N 6.01.

Methyl 5-(4-Methoxybenzyl)-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (11b-Me): Column chromatography (R_f = 0.12, 70 g of flash silica gel, 20 × 3 cm column, hexane/Et_2O, 3:2) of the residue obtained from the hydroxylamine **8b** (0.486 g, 2.00 mmol), methyl glyoxylate **10**-Me (0.176 g, 2.00 mmol), bicyclopropylidene (**2**) (0.090 mL, 1.00 mmol), and NaOAc (0.164 g, 2.00 mmol) in 1.10 mL of ethanol according to GP1 (80 °C, 120 min) gave the product **11b**-Me (0.215 g, 78%) as a light-yellow oil. IR (film): $\tilde{\nu}$ = 2954 cm^{-1}, 2837, 1775, 1735, 1612, 1514, 1392, 1248. ^1H NMR (250 MHz): δ = 0.84–0.91 (m, 1 H, cPr-H), 1.04–1.30 (m, 3 H, cPr-H), 3.71 (s, 3 H), 3.80 (s, 3 H), 3.99 (s, 1 H), 4.14–4.20 (d, *J* = 15 Hz, 1 H), 4.82–4.88 (d, *J* = 15 Hz, 1 H), 6.84–6.90 (m, 2 H, Ar-H), 7.15–7.21 (m, 2 H, Ar-H). ^{13}C NMR (62.9 MHz): δ = 6.6 (CH_2), 8.0 (CH_2), 37.1 (C), 45.1 (CH_2), 52.2 (CH), 55.3 (CH_3), 57.3 (CH_3), 114.1 (2 CH), 127.2 (C), 129.8 (2 CH), 159.2 (C), 170.2 (C), 170.9 (C). MS (EI): *m*/*z* (%) = 275 (4), 243 (5), 215 (5), 188 (25), 148 (10), 121 (100), 78 (15). $C_{15}H_{17}NO_4$ (275.30): C 65.44, H 6.22, N 5.09; found C 65.17, H 6.20, N 4.91.

Deprotection of β-Lactam 11b-Me: To a stirred solution of β-lactam **11b**-Me (0.114 g, 0.41 mmol), in acetonitrile (3.0 mL) was added a solution of ceric ammonium nitrate (CAN) (0.50 g, 0.90 mmol) in water/acetonitrile (2.0:3.0 mL). After 1 h of stirring at room temperature additional CAN (0.110 g, 0.20 mmol) was added. After 30 min, $Na_2S_2O_3 \cdot 5\ H_2O$ (0.273 g, 1.1 mmol) was added, and the color of the suspension turned to a lighter yellow. $NaHCO_3$ was also added until the pH turned from 1 to 7. The suspension was evaporated to dryness, methanol (15 mL) was added, and the suspension obtained was filtered through a pad of silica gel (soaked with diethyl ether) to eliminate salts. The column was washed with methanol (≈ 200 mL), and the 68 mg of crude product, obtained after evaporation of the solvent, was purified by column chromatography. The β-lactam **17**-Me [R_f = 0.47, 70 g of flash silica gel, 20 × 3 cm column, CH_2Cl_2/MeOH (1 vol.-% NH_4OH concd.) 50:1] was obtained as a light-yellow oil (58 mg, 90%). IR (film): $\tilde{\nu}$ = 3006 cm^{-1}, 2955, 1792, 1733, 1438, 1289. ^1H NMR (250 MHz): δ = 0.87–0.97 (m, 1 H, cPr-H), 1.08–1.31 (m, 3 H, cPr-H), 3.73 (s, 3 H), 4.24 (s, 1 H). ^{13}C NMR (62.9 MHz): δ = 7.2 (CH_2), 8.5 (CH_2), 38.3 (C), 52.3 (CH), 54.9 (CH_3), 170.7 (C), 172.8 (C). MS (EI): *m*/*z* (%) = 155 (1), 135 (15), 112 (22), 96 (30), 85 (62), 83 (100), 82 (8), 69 (8), 48 (50), 46 (22). $C_7H_9NO_3$ (155.15): C 54.19, H 5.85, N 9.03; found C 53.94, H 5.74, N 8.78.

Protection of β-Lactam 17-Me: Di-*tert*-butyl pyrocarbonate (Boc_2O, 0.113 g, 0.52 mmol) and DMAP (3 mg, 0.03 mmol) were added in one portion to β-lactam **17**-Me (40.0 mg, 0.26 mmol) in anhydrous acetonitrile (3.90 mL) at 0 °C. After 1 h, the starting material was no longer detectable by TLC. The reaction mixture was stirred at ambient temperature for an additional 13 h, diluted with dichloromethane (20 mL), washed successively with 5% aq. $NaHSO_3$ solution (3 × 20 mL), aq. satd. $NaHCO_3$ solution (1 × 20 mL), dried and concentrated under reduced pressure. Col-

umn chromatography (R_f = 0.17, 12 g of silica gel, 2 × 8 cm column, hexane/Et_2O, 2:1) furnished **18**-Me (54 mg, 82%) as a colorless solid, m.p. 69–70 °C. IR (film): $\tilde{\nu}$ = 2978 cm^{-1}, 2950, 1814, 1743, 1723, 1382, 1319, 1151. ^1H NMR (250 MHz): δ = 0.95–1.01 (m, 1 H), 1.24–1.44 (m, 3 H), 1.51 (s, 9 H), 3.78 (s, 3 H), 4.48 (s, 1 H). ^{13}C NMR (50.3 MHz): δ = 8.7 (CH_2), 10.5 (CH_2), 27.9 (3 CH_3), 36.1 (C), 51.5 (CH_3), 57.2 (CH), 83.6 (C), 168.4 (C), 168.7 (2 C). MS (EI): *m/z* (%) = 200 (1), 140 (19), 96 (10), 57 (100). MS (DCI): *m/z* (%) = 273 (100) [M + NH_4^+]. $C_{12}H_{17}NO_5$ (255.3): C 56.46, H 6.71, N 5.49; found C 56.50, H 6.89, N 5.54.

One-Pot Protocol Applied to the Hydroxylamine 8a and Formaldehyde (9) with Methylenecyclopropane (1) as Dipolarophile: A solution of benzylhydroxylamine hydrochloride (**8a**) (0.479 g, 3.00 mmol), formaldehyde (**9**) solution (8 M) in water (0.375 mL, 3.00 mmol), methylenecyclopropane (**1**) (81 mg, 0.1 mL, 1.5 mmol) and NaOAc (0.246 g, 3.0 mmol) in ethanol (1.0 mL), was sealed in a screw-capped vial for the microwave oven, and heated at 80 °C for 70 min. After cooling to room temperature, the solution was concentrated under reduced pressure. An equal amount each of water and ethyl acetate (30 mL) was added, and the two phases were separated. The water phase was made basic with $NaHCO_3$ (satd. solution) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were then washed with brine (2 × 30 mL) and dried with Na_2SO_4. After filtration and evaporation of the solvent a crude mixture was obtained, containing 1-benzylazetidin-2-one (**6a**, R^1 = Bn; R^2 = H) and 6-benzyl-5-oxa-6-azaspiro[2.4]heptane (**16**). Column chromatography (35 g of silica gel, 15 × 2.5 cm column, hexane/Et_2O, 3:1) of the residue gave **16** (0.234 g, 82%): R_f = 0.28. IR (film): $\tilde{\nu}$ = 3087 cm^{-1}, 3068, 2997, 2867, 1496, 1454, 1030, 1018. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 0.73–0.81 (m, 4 H, cPr-H), 2.97 (s, 2 H), 3.88 (s, 2 H), 4.09 (s, 2 H), 7.28–7.43 (m, 5 H, Ar-H). ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 10.2 (2 CH_2), 24.8 (C), 61.8 (CH_2), 62.2 (CH_2), 72.9 (CH_2), 126.9 (C), 128.0 (2 CH), 128.8 (2 CH), 137.4 (C). MS (EI): *m/z* (%) = 190 (2) [M + H^+], 189 (12), 161 (2), 106 (4), 91 (100), 77 (5). $C_{12}H_{15}NO$ (189.25): C 76.16, H 7.99, N 7.40; found C 76.18, H 7.72, N 7.22. A second column chromatography (12 g of silica gel, 8 × 2 cm, column, hexane/Et_2O, 2:1) was necessary to separate **6a** (R^1 = Bn; R^2 = H) (21 mg, 9%, R_f = 0.12) from benzylhydroxylamine.

Acknowledgments

This work was supported by the State of Niedersachsen, the Fonds der Chemischen Industrie as well as the companies BASF AG and Bayer CropScience AG. The authors are grateful to Dr. Burkhard Knieriem, Göttingen, for his careful proofreading of the final manuscript.

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Received: October 26, 2005
Published Online: December 27, 2005

