A One-Pot Organometallic Route from a 4-Alkenylpyridine to a 4,4-Spiro-Linked Ethyl 1,4-Dihydropyridine-1-carboxylate

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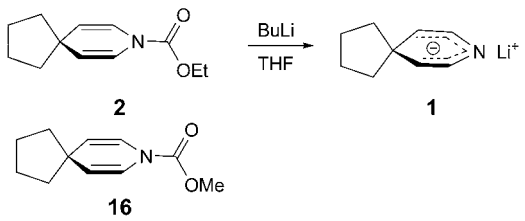
Dedicated to Prof. *Dieter Seebach* on the occasion of his 75th birthday

In a one-pot process without isolation of intermediates, (but-3-en-1-yl)pyridine (**13**) is treated sequentially with dicyclohexylborane, trimethylaluminium, and ethyl carbonochloridate yielding ethyl 1,4-dihydro-4,4-(tetramethylene)pyridine-1-carboxylate (= ethyl 8-azaspiro[4.5]deca-6,9-diene-8-carboxylate; **2**) in 46% yield based on starting alkenylpyridine **13** (*Scheme 5*).

Introduction. – Previous studies of potential spiro conjugation in 4,4-disubstituted dihydropyridine anions such as **1** [1a] required the intermediacy of ethyl 1,4-dihydropyridine-1-carboxylates such as **2** [1b] (*Scheme 1*). Compound **2** was originally prepared *via* a ten step sequence starting with malonic acid esters [1].

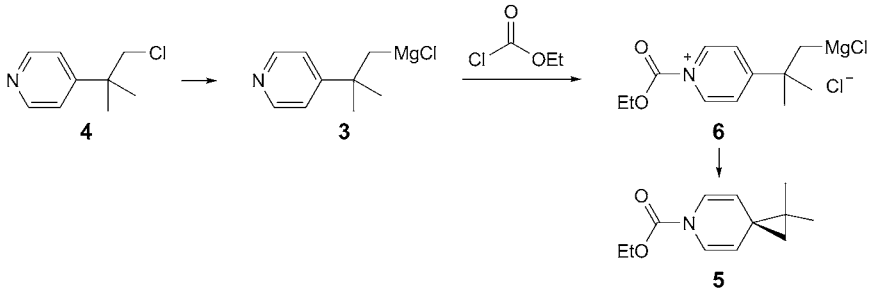
Scheme 1



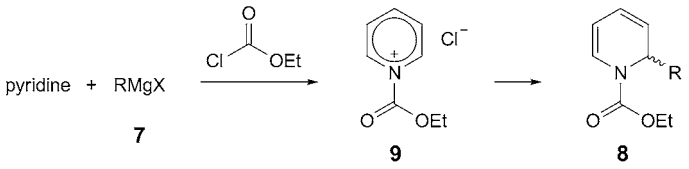
While conversion of alkenes to main group organometallics, *via* the hydroboration/organometallic exchange, has been widely used for over 60 years [2], the procedure has never been applied to the annulation of aromatic heterocycles. The purpose of this article is to report the first example of such a sequence, the highly efficient one-pot conversion of an alkenylpyridine to a spiro-linked dihydropyridine, and to recommend such reactions as an attractive addition to the armamentarium of heterocyclic synthesis, specifically annulation of aromatic N-heterocycles.

For background, we have shown that *Grignard* reagent **3** [3], easily prepared from **4**, reacts exclusively with $ClCO_2Et$ to produce spiro urethane **5** [3], presumably due to the reactive intermediate pyridinium salt **6** (*Scheme 2*). We also showed that whereas mixtures of pyridine with *Grignard* reagents **7** remained unchanged for several days at room temperature, addition of $ClCO_2Et$ to the mixtures immediately produced the ethyl 1,2-dihydropyridine-1-carboxylate **8** [4] (*Scheme 3*). Thus, apparently, formation

Scheme 2



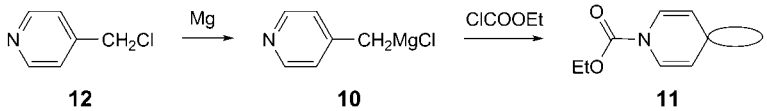
Scheme 3



of the 1-(ethoxycarbonyl)pyridinium salt **9** is competitive with acylation at magnesium bonded C-atom.

Results and Discussion. – In principle, acylation of a (pyridin-4-ylalkyl)magnesium halide such as **10** should easily produce a 4,4-spiro-linked dihydropyridine **11**, by analogy to the above transformation **3** → **6** → **5**. Unfortunately precursor halides to such a required *Grignard* reagent, *e.g.*, **12**, may be unstable, and according to the literature, they convert only inefficiently to *Grignard* reagents [5] (*Scheme 4*). To avoid such problems, we elected to try out a possible one-pot synthesis of **2** starting with hydroboration of 4-alkenylpyridine **13** with dicyclohexylborane. This new process exploits the well-known aluminium-boron exchange [2]. Thus hydroboration of 4-alkenylpyridine **13** [6] followed by treatment of the reaction mixture with trimethylaluminium and then $ClCO_2Et$, in fact, gave the known spiro carbamate **2** [1] after isolation in 48% yield based on starting alkenylpyridine **13** [6] (*Scheme 5*), presumably *via* the proposed intermediates **14** and **15**, neither of which were isolated.

Scheme 4



^{1}H- and ^{13}C-NMR Spectra of **2** are consistent with the given structure. Since all olefinic C- and H-atoms of **2** are magnetically nonequivalent at 25°, rotation around the N–CO bond must be slow relative to the NMR time scale at this temperature. Chemical-shift data are summarized in *Fig. 1*.

Scheme 5

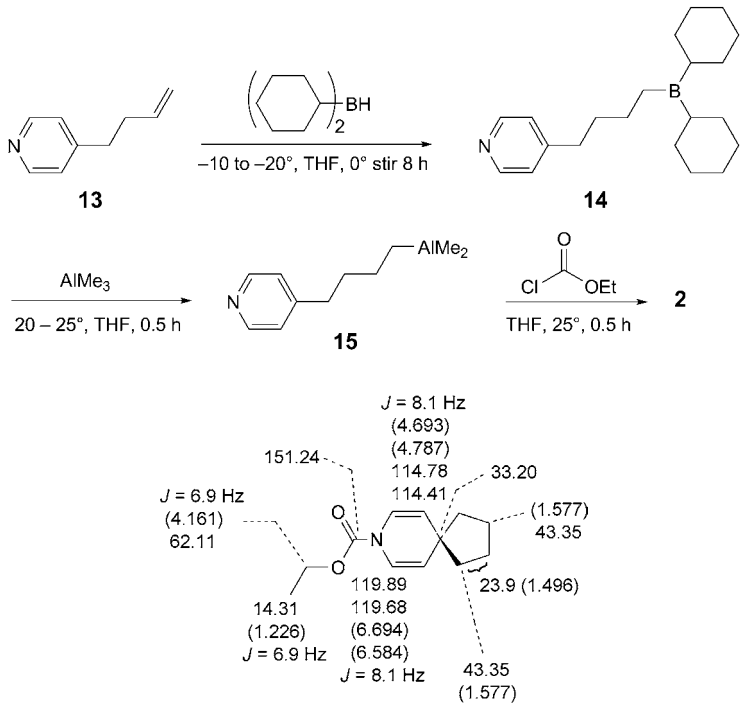


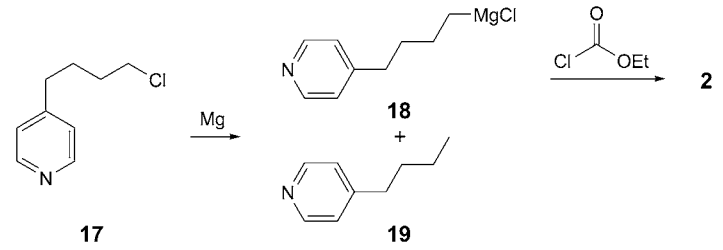
Fig. 1. *^{1}H- and ^{13}C-NMR Data of* **2**. δ in ppm, J in Hz.

We also prepared the methyl carboxylate analog of **2**, compound **16** (see *Scheme 1*), in 37% yield after isolation in a similar fashion to *Scheme 5*, substituting diethylborane, diethylzinc [7], and $ClCO_2Me$ for dicyclohexylborane, trimethylaluminium, and $ClCO_2Et$, respectively.

Finally in a third and less efficient process, reaction of 4-(4-chlorobutyl)pyridine (**17**) [8] with Mg in THF gave a mixture of *Grignard* reagent **18** and 4-butylpyridine (**19**) in a ratio of 55 : 45, determined by analysis of the ^{1}H-NMR spectrum of the reation mixture (*Scheme 6*). Treatment of this mixture with $ClCO_2Et$ gave a 25.5% yield of **2** based on the content of *Grignard* reagent **18** in the reaction mixture.

The X-ray crystallographic data of **16** are summarized by the ORTEP diagram in *Fig. 2*. The angles and bond lengths are listed around the structure in *Fig. 3*, and selected torsional angles are collected in *Table 1*. Bond lengths and torsional angles reveal coplanarity of the azadiene and methoxycarbonyl group and thus extended conjugation throughout, see *Fig. 3*. Interestingly, these results are quite similar to published crystallographic data for several *N*-acetyl-1,4-dihydropyridines [9]. Note that while C(3) of **16** lies in the plane of the dihydropyridine moiety, the four CH_2 C-atoms of the spiro ring C(3) to C(7) are out of the plane of the rest of the molecule. This five-membered ring contains a C-atom which is disordered over two sites, C(6a) and C(6b). The ORTEP diagram of **16**, (*Fig. 2*) includes C(6a). Interestingly, the four CH_2 C-atoms are near coplanar with a torsional angle C(4)–C(5)–C(6a)–C(7) = – 5.7(4)°.

Scheme 6



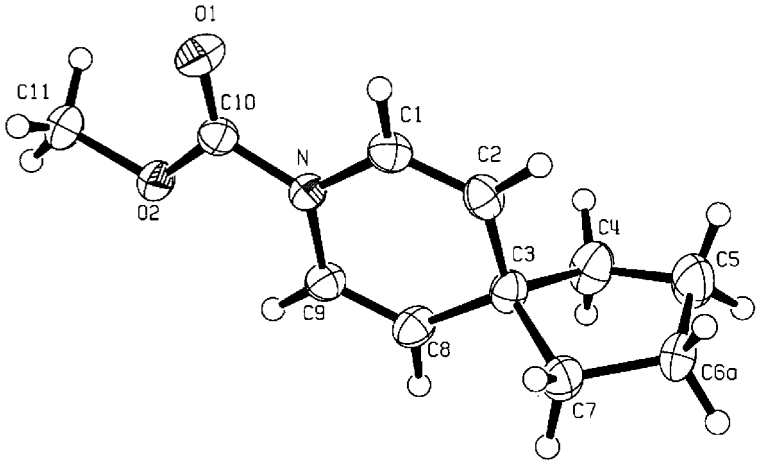


Fig. 2. *ORTEP Diagram of compound* **16**. Drawn with 50% probability displacement ellipsoids for the non-H-atoms; the H-atoms are drawn with an artificial radius. Arbitrary atom numbering. Atom C(6) is disordered over two sites, and only one of these is shown as C(6a).

Table 1. *Selected Torsional Angles* [°] *of Compound* **16**

C(1)–N–C(9)–C(8)	2.3 (2)	C(1)–N–C(10)–O(1)	4.9 (2)
N–C(1)–C(2)–C(3)	0.5 (2)	C(1)–N–C(10)–O(2)	174.91 (10)
C(9)–N–C(10)–O(1)	179.69 (12)	C(4)–C(5)–C(6a)–C(7)	5.7 (4)
C(9)–N–C(10)–O(2)	0.5 (2)	C(3)–C(4)–C(5)–C(6a)	25.4 (3)
N–C(9)–C(8)–C(3)	1.2 (2)		

However the torsional angle for the four CH_2 C-atoms with the other disordered C-atom, C(6b), *i.e.*, C(4)–C(5)–C(6b)–C(7)°, is $-33.6(14)°$.

Thus it appears that in the solid state, **16** assumes two very similar structures, **16a** and **16b**, which differ in the arrangement around the five-membered rings as illustrated

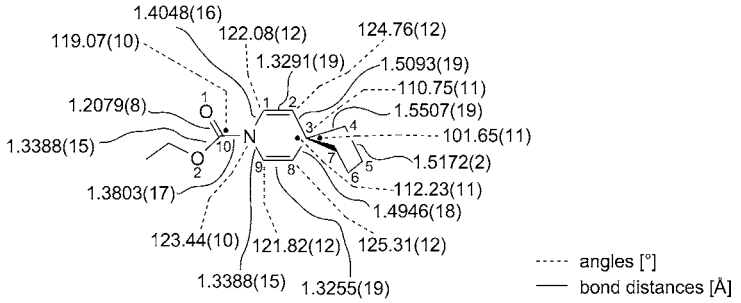


Fig. 3. *Selected X-ray crystallographic bond distances* [Å] *and angles* [°] *of compound* **16**. Arbitrary atom numbering.

by the ORTEP diagrams in *Fig. 4*. *Fig. 5* shows the five-membered rings of **16a** and **16b**, respectively, viewed from the direction C(3) to N. Further, it is also interesting that in the solid state, the five-membered ring is bent in the direction of the C=O O-atom.

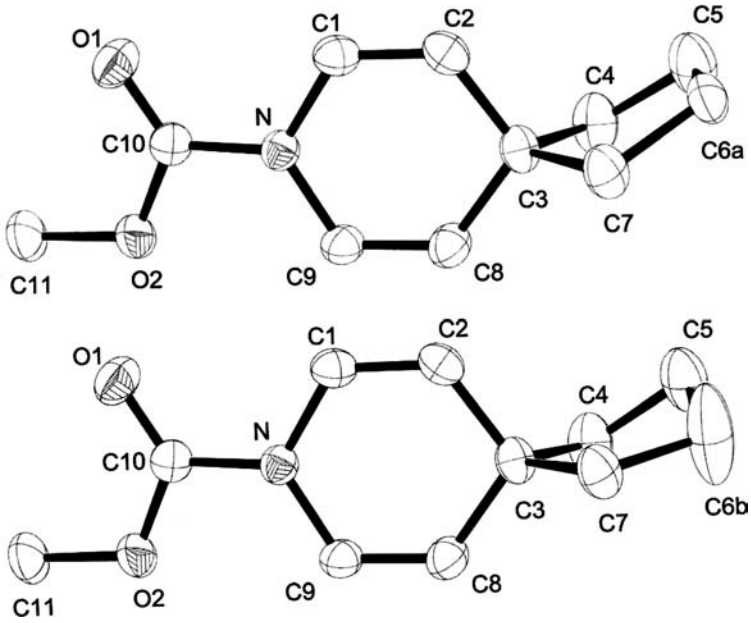


Fig. 4. *ORTEP Diagrams of* **16a** (top) *and* **16b** (bottom). Arbitrary atom numbering.

The NMR data of **16** are very similar to that of **2**. In both, all olefinic C- and H-atoms are magnetically nonequivalent, most likely due to slow rotation around the N–C(carbonyl) bond, as noted above. The NMR spectra provide no information on the orientation or orientations of the five-membered ring. However, should different conformers be present in solution, interconversion between them would be fast enough to average out shifts among them, even at low temperature.

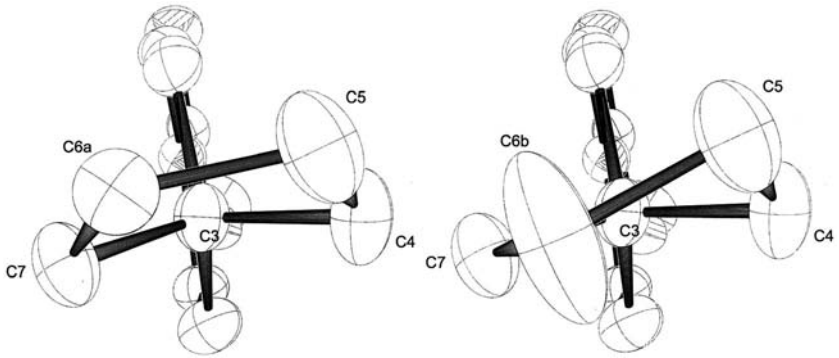


Fig. 5. *ORTEP Diagram of the five-membered rings of* **16a** (left) *and* **16b** (right). Viewed from the direction C(3) to N. Arbitrary atom numbering.

On warming a (D_6)benzene solution of **16** above 280 K, there is progressive averaging of the δ(H) and δ(C) of H–C(1) with H–C(9) and of H–C(2) with H–C(8) (see *Fig. 2* for atom numbering). Careful NMR line shape analysis of these changes yields $\Delta H^{\ddagger} = 19$ kcal/mol and $\Delta S^{\ddagger} = +12$ eu for rotation around the N–C(carbonyl) bond. Note that while entropies of activation for conformational changes are largely expected to be near neutral, positive deviations have been reported, *e.g.*, for amide rotation in aromatic solvents [10]. In those cases, it has been proposed that there is a substantial decrease in polarity in the transition state for rotation compared to the ground state. The difference in interaction of the two states with aromatic solvent has been ascribed responsible for the large positive change in $\Delta S^{\ddagger}$ for rotation. Interestingly, most barriers to rotation in urethanes have been reported as $\Delta G^{\ddagger}_{300}$ values of 15 kcal/mol to 18 kcal/mol, determined from coalescence measurements [11]. The $\Delta G^{\ddagger}_{300}$ coalescence measurement for **16** is 15 kcal/mol, obtained also from the line-shape calculation.

In sum, we showed how organometallic spirocyclization of the pyridinium system is an unusually rapid and efficient route to potentially important spiro-connected dihydropyridines especially when use is made of the organoboron/organoaluminium or organozinc exchange[1]).

This research was generously supported by the *National Science Foundation*. We also thank the late Dr. *Charles Cottrell* (deceased), *Central Campus Instrumentation Center* for untiring technical assistance.

Experimental Part

General. Commercially available materials were used without purification. ^{1}H- and ^{13}C-NMR Spectra: *Bruker Avance 300*; at 300 (^{1}H) and 75.47 MHz (^{13}C); δ in ppm rel. to Me_4Si as internal standard, *J* in Hz.

Ethyl 1,4-Dihydro-4,4-(tetramethylene)pyridine-1-carboxylate (= *Ethyl 8-Azaspiro[4.5]deca-6,9-diene-8-carboxylate*; **2**). Cyclohexene (20.5 g, 0.25 mol) was added to 1M diborane in THF (125 ml) at 0°.

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[1]) The ^{1}H- and ^{13}C-NMR spectra of new compounds are available as *Supplementary Material* from the corresponding authors.

The mixture was stirred at 0° for 1 h. Dicyclohexylborane precipitated from this soln. A soln. of 4-(but-3-en-1-yl)pyridine (**13**; 18.32 g, 0.025 mol) was slowly added to the dicyclohexylborane soln. at −10 to −20°. The mixture was then brought to 0° and stirred at 0° for 8 h. At the conclusion of stirring, the alkenylpyridine could not be detected by ^{1}H-NMR. Then, a soln. of trimethylaluminium (9.0 g, 0.125 mol) in THF (12 ml) was slowly added to the mixture at 20–25°. After stirring for 0.5 h, $ClCO_2Et$ (41 g, 0.375 mol) was added dropwise to the mixture, which was then stirred for 0.5 h at r.t. Then, the mixture was dropped into sat. aq. NaCl soln. (200 ml) cooled with an ice-water bath. The aq. layer was extracted with Et_2O, the combined Et_2O phase washed with H_2O, dried, and concentrated, and the residue distilled at 102–113°/0.25 Torr: **2** (6.1 g, 47.2% rel. to **13**). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.226 (*t*, *J* = 7.2, 3.04 H); 1.44 (*m*, 4.09 H); 1.557 (*m*, 4.11 H); 4.170 (*q*, *J* = 7.2, 2.04 H); 4.703 (*d*, *J* = 8, 1.01 H); 4.792 (*d*, *J* = 8, 1.01 H); 6.593 (*d*, *J* = 8, 1 H); 6.707 (*d*, *J* = 8, 1 H). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 14.33 (Me); 24.40 (CH_2); 43.87 (CH_2); 114.48 (CH); 114.91 (CH); 119.7 (CH); 119.90 (CH); 151.25 (C). MS: 207.12621 ($C_{12}H_{17}NO_2$; calc 207.12590).

Methyl 1,4-Dihydro-4,4-(tetramethylene)pyridine-1-carboxylate (= *Methyl 8-Azaspiro[4.5]deca-6,9-diene-8-carboxylate*; **16**). Diethyl borane (31.5 mmol), was freshly prepared [7b] by mixing triethylborane (2.6 g, 21 mmol) and borane–dimethyl sulfide (1.05 ml, 10.5 mmol) under Ar at 0° for 10–30 min. Over 10 min under Ar, **13** (2.1 g, 15.8 mmol) was added slowly to the diethylborane. Stirring was continued for 0.5 h at 0° and another 0.5 h at r.t. Then dimethyl sulfide and excess diethylborane were removed under vacuum (1 Torr, 0.5–1 h). The remaining mixture was dissolved in dry THF (20 ml) and cooled to 0°. Then 1.5M diethyl zinc in toluene (11 ml) (17 ml, 16.5 mmol, 1.04 equiv.) was added dropwise over 10 min. Stirring was continued for 0.5 h at 0° and another 0.5 h at r.t. $ClCO_2Me$ (2.53 ml, 3.1 g, 32.7 mmol, 2.07 equiv.) then was added to the mixture, and stirring was continued overnight. Finally, the reaction soln. was slowly added to degassed cooled sat. NaCl soln. The aq. phase containing a white precipitate was extracted with Et_2O (3 × 30 ml). The combined org. phase was dried ($MgSO_4$) and concentrated and the residue purified by CC (SiO_2, AcOEt/hexane 1:19): **16** (1.15 g, 37%). During removal of the solvents, just described, crystals suitable for X-ray diffraction studies were obtained. ^{1}H-NMR (300 MHz $CDCl_3$): 1.484 (*m*, 4.2 H); 1.590 (*m*, 4.2 H); 3.668 (*s*, 3.02 H); 4.654 (*d*, *J* = 8.1, 1.0 H); 4.742 (*d*, *J* = 8.1, 1.0 H); 6.511 (*d*, *J* = 8.1, 1.0 H); 6.652 (*d*, *J* = 8.1, 1.0 H). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 22.92; 43.95; 52.67; 114.43; 114.86; 119.48; 119.82; 151.51.

Spiro Compound **2** *from 4-(Pyridin-4-yl)butylmagnesium Chloride* (**18**). Mg (0.19 g, 0.079 mol) was treated with 4-(4-chlorobutyl)pyridine (**17**; 1.35 g, 8 mmol) in dry THF (20 ml) under Ar and stirred overnight at r.t. (→ orange mixture). The NMR spectra of a sample of this mixture, with the solvent replaced by (D_8)THF, included a *t* δ(H) at −0.55 and a signal at δ(H) 7.82 ascribed to the CH_2MgCl of *Grignard* reagent **18**, and a *t* at δ(H) 0.86 and a signal at δ(C) 14.25 most likely due to Me of 4-butylpyridine (**19**). These results establish the formation of **18** and its hydrolysis product **19** in a ratio of 65:35.

The remainder of the mixture was transferred to a flask and divided into two equal parts. One part was hydrolyzed with degassed H_2O and extracted into Et_2O (3 × 10 ml). The combined org. phase was dried ($MgSO_4$) and concentrated. CC (SiO_2, AcOEt) of this material yielded **19** (0.47 g, 44% rel. to **17**), contaminated with a small amount of **17**. ^{1}H-NMR ($CDCl_3$): 0.800 (*t*, *J* = 7.3, 3.08 H); 1.23 (*m*, 2.1 H); 1.434 (*m*, 2.0 H); 2.425 (*t*, *J* = 7.7, 2.0 H); 6.805 (*d*, *J* = 5.7, 2.16 H); 8.288 (*d*, *J* = 5.7, 2.10 H). ^{13}C-NMR ($CDCl_3$): 13.44; 21.85; 32.02; 34.50; 121.26; 123.48; 149.21; 151.23.

The second portion of the mixture obtained from Mg and **17** was cooled to 0°. Then $ClCO_2Et$ (0.19 g, 0.08 ml, 8.4 mmol) was added dropwise, and stirring was continued for 3 h while the mixture was allowed to warm to r.t. Degassed H_2O was added to the mixture which was extracted with Et_2O (3 × 10 ml). The combined org. phase was dried ($MgSO_4$) and concentrated and the residue subjected to CC (SiO_2, AcOEt/hexanes 1:19): **2** (0.23 g, 14% rel. to **17**). NMR Data: identical to those described above for **2**.

Crystallography[2]). The data-collection crystal of **16** was a clear, colorless rectangular rod. Data was collected with a *Nonius-Kappa-CCD* diffractometer at 150 K and an *Oxford-Cryosystems-Cryostream* cooler (*Table 2*). The data-collection strategy was set up to measure a quadrant of reciprocal space with a

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[2]) CCDC-890670 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.dc.ac.uk/data_request/cif.

Table 2. *Crystallographic Data of* **16** *and Structure-Refinement Details*

Chemical formula	$C_{11}H_{15}N_1O_2$	Absorption coefficient, μ [mm^{-1}]	0.085
M_r	193.24	θ range for data collection [°]	2.28 to 27.48
Crystal system	monoclinic	No. of reflections measured	19896
a [Å]	5.8949(1)	No. of independent reflections	2367
b [Å]	10.6130(2)	R_{int}	0.034
c [Å]	16.5751(4)	Completeness to $\theta = 27.48°$	100.0%
β [°]	95.893(1)	Data, restraints, parameters	2367, 2, 138
Unit cell volume [$Å^3$]	1031.50(4)	Final R_1 values ($I > 2\sigma(I)$)	0.0445
Temperature [K]	150(2)	Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1129
Space group	$P2_1/n$	Final R_1 values (all data)	0.0607
No. of formula units per unit cell, Z	4	Final $wR(F^2)$ values (all data)	0.1214
Radiation type	MoK_α (0.71073 Å)	Largest diff. peak and hole [e $Å^{-3}$]	0.171; −0.223
Crystal size	0.16 × 0.16 × 0.40 mm	Goodness of fit on F^2	1.057
Density (calc.) [Mg/m^3]	1.244	CCDC number	890670

redundancy factor of 3.9, which means that 90% of these reflections were measured at least 3.9 times; ϕ and ω scans with a frame width of 2.0° were used. Data integration was done with Denzo [12], and scaling and merging of the data was done with Scalepack [12].

The structure was solved by the direct methods program in SHELXS-97 [13]. Full-matrix WinGX package [14]. The five-membered ring contains a C-atom which is disordered over two sites; least-squares refinements based on F^2 were performed in SHELXL-97 [13], as incorporated in the two sites: C(6a) and C(6b). Restraints were used in the least-squares refinement of the bond lengths involving these two atoms.

For the Me group, the H-atoms were added at calculated positions by using a riding model with $U(H) = 1.5 \cdot U_{eq}$ (bonded C-atom). The torsion angle which defines the orientation of the Me group about the O–C bond was refined. The rest of the H-atoms were included in the model at calculated positions by using a riding model with $U(H) = 1.2 \cdot U_{eq}$ (bonded atom). Neutral atom scattering factors were used and include terms for anomalous dispersion [15].

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