Pyridazines LXXVIII [1]. On the Reactivity of 4-Methoxy-[(4-pyridazinyl)methylidene]aniline in Ester Enolate-Imine Condensation Reactions

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Dedicated with best personal wishes to Professor M. Tišler on the occasion of his 70th birthday.

Reactions of the pyridazine derived aldimine **1** with lithium enolates of various α-substituted acetates were investigated. An unprecedented formation of the pyrido[3,4-*d*]pyridazine system due to nucleophilic attack of a carbanion species at the β-position of the pyridazine ring was observed.

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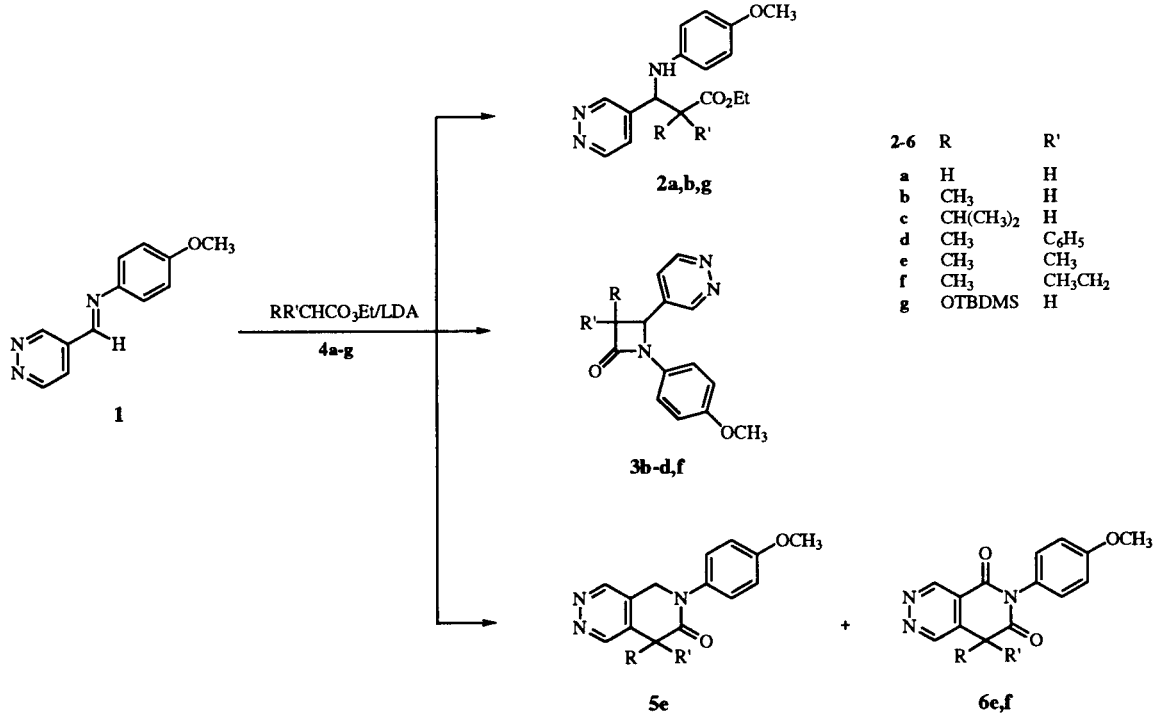
The lithium ester enolate-imine condensation has been used widely for the preparation of β-lactams with suitable substituents at C-3 and C-4 permitting the synthesis of a variety of antibiotics [2]. Though this type of reaction has already been applied to various heteroaromatic carbaldimines [3], the reactivity of pyridazinecarbaldehyde derived imines, however, so far remained largely unexplored. In the course of studies aimed at the preparation of pyridazinylisoserine derivatives, we observed recently that reaction of the imine **1** with the lithium enolate of ethyl *tert*-butyldimethylsilyloxyacetate gave an α-silyloxy-β-aminoester **2g** instead of the expected β-lactam [1]. This finding now prompted us to investigate the reactivity of **1** towards a series of differently sterically hindered lithium enolates as obtained upon treatment of α-substituted acetates **4a-f** with lithium diisopropylamide (LDA). As can be seen in Scheme 1 and Table 1, the course of the condensation reaction differs markedly depending on the substituents at the α-carbon atom of the starting ester.

Employment of the lithium enolate of ethyl acetate was found to give the β-aminoester **2a** in poor yield instead of the expected β-lactam, whereas a mixture of the β-lactam **3b** and the β-aminoester **2b** was obtained when the enolate of ethyl propionate was used. Upon reaction of **1** with sterically hindered and/or stabilized enolates **4c,d** the 4-(4-pyridazinyl)-3-substituted β-lactams **3c,d** became available in reasonable yields. The nature of the substituent is also of influence on the diastereoselectivity

Scheme 1



2-6	R	R'
a	H	H
b	CH_3	H
c	$CH(CH_3)_2$	H
d	CH_3	C_6H_5
e	CH_3	CH_3
f	CH_3	CH_3CH_2
g	OTBDMS	H

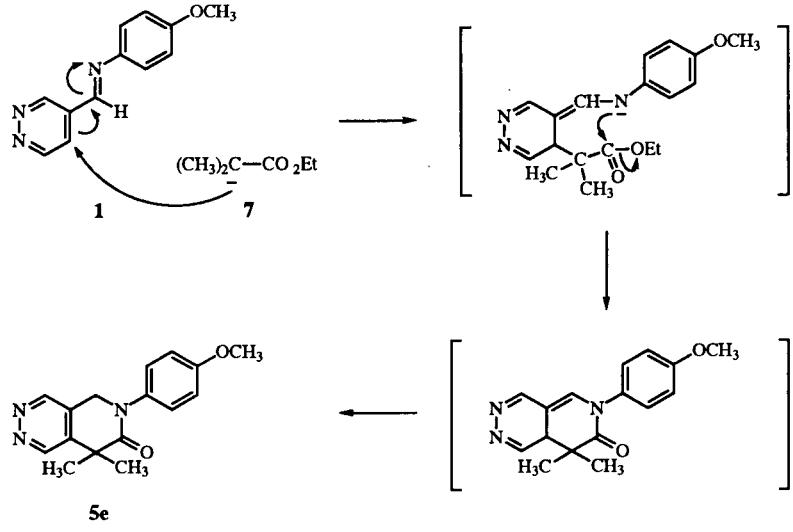
Table 1
Reaction of **1** with Lithium Ester Enolates

No.	R	R'	yield (%)	Ratio [a] *cis/trans* of β-lactams
2a	H	H	8	–
2b	CH_3	H	16	[b]
2g (ref [1])	OTBDMS	H	14	[c]
3b	CH_3	H	22	1/1
3c	$CH(CH_3)_2$	H	65	10/1
3d	CH_3	C_6H_5	62	1/9
3f	CH_3	CH_3CH_2	30	1/1
5e	CH_3	CH_3	35	–

[a] Ratio was determined by ^1H nmr spectroscopy of the crude mixture. [b] Ratio syn/anti:1/1. [c] Only the syn isomer was observed.

for structure **5e**. This assignment is confirmed by the ^{13}C nmr data. The formation of compound **5e** can be explained in terms of nucleophilic attack of the carbanion 7 at C-5 of the pyridazine ring followed by cyclisation (Scheme 2). This interpretation is in agreement with recent findings indicating that the β-position in a pyridazine system bearing electron withdrawing substituents exhibits a high tendency to add nucleophiles [4-6]. The isolation of compound **5e** prompted us to assume that compounds **6e,f** result from oxidation of the initially formed cyclisation product during work-up. Indeed, it could be shown that **5e** is easily converted into **6e** in tetrahydrofuran solution in the presence of atmospheric oxygen.

Scheme 2



of the formation of the β-lactams: whereas a good diastereoselectivity (Table 1) was observed in the reaction of **1** with enolates prepared from acetates **4c** and **4d**, the use of enolates derived from **4b** gave a 1:1 mixture of the two diastereomers. Upon employment of **4f** as the starting ester we obtained the β-lactam **3f** again as a 1:1 mixture of the *cis* and *trans* stereomers, albeit in only 30% yield. In this case, the formation of an unexpected side product with the elemental composition $C_{17}H_{17}N_3O_3$ (yield 5%) was observed. Surprisingly, the spectroscopic data of this product revealed the structure of a pyrido[3,4-*d*]pyridazine derivative **6f**. An analogous product **6e** was obtained in the reaction of **1** with the enolate prepared from the α,α-dimethyl acetate **4e** in 7% yield. Additionally we isolated instead of the expected β-lactam in this case an isomeric product thereof ($C_{16}H_{17}N_3O_2$) in 35% yield, the structure of which could be established unequivocally based on nmr spectra: lack of a pyridazine H-5 signal and presence of a methylene group resonance in the ^1H nmr spectrum gave indication

EXPERIMENTAL

Infrared spectra were recorded on a Mattson series 3000 FTIR or on a Shimadzu IR-470 spectrophotometer, respectively. Mass spectra were obtained on a Finnigan SSQ 7000 (glc/ms, electron impact, 70 eV). The ^1H- and ^{13}C-nmr spectra were recorded in deuteriochloroform solutions on a Varian Gemini 200 (^1H: 199.98 MHz, ^{13}C: 50.29 MHz) spectrometer. The solvent signal was used as internal standard, which was related to TMS with 7.24 ppm for ^1H and 77.0 ppm for ^{13}C. Melting points were determined on a Reichert Thermovar hot stage microscope and are uncorrected. Elemental analyses were performed at the "Institut für Physikalische Chemie", University of Vienna, Austria. Reactions were monitored by tlc using Polygram SIL G/UV_{254} (Macherey-Nagel) plastic backed plates (0.25 mm layer thickness) and visualized using an UV lamp. Column chromatography was performed employing Merck silica gel 60 Å (70 - 230 mesh).

General Procedure for the Reaction of Imine **1** with Lithium Enolates of Esters **4**.

To a solution of 111 mg (1.1 mmoles) of diisopropylamine in 4 ml of dry tetrahydrofuran under nitrogen atmosphere was

Table 2

Analytical and Spectroscopic Characterization of Compounds Prepared

No.	Molecular Formula (Mol. Mass)	Mp (°C)	Elemental Analysis % (Calcd./Found) C	H	N	IR (KBr) ν(cm^{-1}) (C=O)	MS (m/z %) (M$^+$, base peak)	^{1}H NMR δ (ppm)
2a	$C_{16}H_{19}N_3O_3$ (301.35)	77-78	63.77 63.93	6.38 6.32	13.94 13.86	1728	301 (100)	9.22 (dd, J_{3-5} = 2.40 Hz, J_{3-6} = 1.20 Hz, 1H, pyridazine H-3), 9.07 (dd, J_{3-6} = 1.20 Hz, J_{5-6} = 5.00 Hz, 1H, pyridazine H-6), 7.46 (dd, J_{3-5} = 2.40 Hz, J_{5-6} = 5.00 Hz, 1H, pyridazine H-5), 6.63-6.71 (m, 2H, phenyl), 6.41-6.47 (m, 2H, phenyl), 4.75 (t, J = 7.40 Hz, 1H, CH-N), 4.10 (q, J = 7.20 Hz, 2H, C*H*$_2$CH$_3$), 3.67 (s, 3H, OCH$_3$), 2.81 (d, J = 7.40 Hz, 2H, C*H*$_2$-CO), 1.16 (t, J = 7.20 Hz, 3H, C*H*$_3$CH$_2$)
2b [a]	$C_{17}H_{21}N_3O_3$ (315.57)	oil	[b] M$^+$	Calcd. 315.1582 Found 315.1578		1725 [c]	315 (20) 214(100)	9.16-9.20 (m, 1H, pyridazine H-3), 9.03-9.11 (m, 1H, pyridazine H-6), 7.35-7.45 (m, 1H, pyridazine H-5), 6.65-6.71 (m, 2H, phenyl), 6.37-6.44 (m, 2H, phenyl), 4.01-4.12 (m, 2H, CH$_3$C*H*$_2$) 3.67 (s, 3H, OCH$_3$), 2.82-3.00 (m, 1H, C*H*CO), 1.05-1.31 (m, C*H*$_3$CH$_2$ and C*H*$_3$CH) The C*H*-N proton of the two diastereoisomers exhibits a different chemical shift: 4.65 (m, 1H) and 4.48 (m, 1H)
3b [a]	$C_{15}H_{15}N_3O_2$ (269.30)	172-174	66.29 66.32	5.67 5.27	15.19 [d] 15.46	1739	269 (26) 149 (100)	Protons presenting the same chemical shift for the two diastereomers: 9.10-9.22 (m, 2H, H-3 and H-6 pyridazine), 7.21-7.30 (m, 1H, pyridazine H-5), 7.11-7.24 (m, 2H, phenyl), 6.77-6.84 (m, 2H, phenyl), 3.74 (s, 3H, OCH$_3$) protons characterizing the *cis* isomer: 5.12 (d, J = 6.04 Hz, 1H, CH-N), 3.80 (qd, J = 6.04 Hz, J = 7.60 Hz, 1H, CH-CO), 0.90 (d, J = 7.60 Hz, 3H, CHC*H*$_3$) protons characterizing the *trans* isomer: 4.58 (d, J = 2.12 Hz, 1H, CH-N), 3.13 (qd, J = 2.12 Hz, J = 7.60 Hz, 1H, CH-CO), 1.54 (d, J = 7.60 Hz, 3H, CHC*H*$_3$)
3c [e]	$C_{17}H_{19}N_3O_2$ (297.36)	161-163	68.67 68.29	6.44 6.57	14.13 14.25	1730	297 (88) 213 (100)	9.25 (dd, J_{3-5} = 2.40 Hz, J_{3-6} = 1.10 Hz, 1H, pyridazine H-3), 9.18 (dd, J_{3-6} = 1.10 Hz, J_{5-6} = 5.30 Hz, 1H, pyridazine H-6), 7.42 (dd, J_{3-5} = 2.40 Hz, J_{5-6} = 5.30 Hz, 1H, pyridazine H-5), 7.10-7.16 (m, 2H, phenyl), 6.76-6.81 (m, 2H, phenyl), 5.14 (d, J = 5.80 Hz, 1H, CH-N), 3.74 (s, 3H, OCH$_3$), 3.39 (dd, J = 5.80 Hz, J = 11.10 Hz, 1H, CH-CO), 1.50-1.52 (m, 1H, C*H*(CH$_3$)$_2$), 1.15 (d, J = 6.50Hz, 3H,CH$_3$), 0.55 (d, J = 6.40Hz, 3H, CH$_3$)
3c [f]	$C_{17}H_{19}N_3O_2$ (297.36)							9.25-9.32 (m, 1H, pyridazine H-3), 9.15-9.20 (m, 1H, pyridazine H-6), 7.39-7.41 (m, 1H, pyridazine H-5), 7.10-7.17 (m, 2H, phenyl), 6.76-6.83 (m, 2H, phenyl), 4.71 (d, J = 2.61 Hz, 1H, CH-N), 3.74 (s, 3H, OCH$_3$), 2.92 (dd, J = 2.61 Hz, J = 8.22 Hz, 1H, CH-CO), 1.50-1.52 (m, 1H, C*H*(CH$_3$)$_2$), 1.15 (d, J = 6.50 Hz, 3H, CH$_3$), 0.55 (d, J = 6.40 Hz, 3H, CH$_3$)
3d [f]	$C_{21}H_{19}N_3O_2$ (345.40)	155-156	70.61 70.64	5.73 5.73	11.75 [g] 11.56	1740	345 (8) 149 (100)	9.20-9.24 (m, 2H, pyridazine H-3 and H-6), 7.30-7.51 (m, 6H, pyridazine H-5 and phenyl), 7.17-7.23 (m, 2H, phenyl), 6.80-6.84 (m, 2H, phenyl), 5.17 (s, 1H, CH-N), 3.75 (s, 3H, OCH$_3$), 1.23 (s, 3H, CH$_3$)
3d [e]	$C_{21}H_{19}N_3O_2$ (345.40)	185-186	72.37 72.36	5.60 5.62	12.06 [h] 12.14	1739	345 (100)	8.95 (dd, J_{3-5} = 3.00 Hz, J_{3-6} =1.20 Hz, 1H, pyridazine H-3), 8.78 (dd, J_{3-6} = 1.20 Hz, J_{5-6} = 5.00 Hz, 1H, pyridazine H-6), 6.89 (dd, J_{3-5} = 3.00 Hz, J_{5-6} = 5.00 Hz, 1H, pyridazine H-5), 7.06 (m, 5H, phenyl), 7.09-7.22 (m, 2H, phenyl), 6.78-6.82 (m, 2H, phenyl), 4.99 (s, 1H, CH-N), 3.74 (s, 3H, OCH$_3$), 1.97 (s, 3H, CH$_3$)

Table 2 (continued)

No.	Molecular Formula (Mol. Mass)	Mp (°C)	Elemental Analysis % (Calcd./Found) C	H	N	IR (KBr) ν(cm⁻¹) (C=O)	MS (m/z %) (M⁺, base peak)	^{1}H NMR δ (ppm)
3f [a]	$C_{17}H_{19}N_3O_2$ (297.36)	87-90	68.67 68.39	6.44 6.48	14.13 14.08	1684 1722	297 (24) 149 (100)	protons presenting the same chemical shift for the two diastereomers: 9.05-9.17 (m, 2H, pyridazine H-3 and H-6), 7.17-7.30 (m, 1H, pyridazine H-5), 7.10-7.16 (m, 2H, phenyl), 6.78-6.84 (m, 2H, phenyl), 3.75 (s, 3H, OCH_3) other protons: 4.80 and 4.74 (s, 1H, CHN), 1.92 (q, J = 7.50 Hz, 2H, CH_2CH_3), 1.26-1.50 (m, 1H, CH_2CH_3), 1.00-1.20 (m, 1H,CH_2CH_3), 1.55 and 0.85 (s, 3H, CH_3), 1.12 and 0.80 (t, J = 7.50 Hz, 3H, CH_3CH_2)
5e	$C_{16}H_{17}N_3O_2$ (283.33)	oil	[b] M^+	Calcd 283.1322 Found 283.1314		1662 [c]	283 (100)	9.25 (s, 1H, pyridazine), 9.00 (s, 1H, pyridazine), 7.17-7.26 (m, 2H, phenyl), 6.93-7.00 (m, 2H, phenyl), 4.85 (s, 2H, CH_2N), 3.83 (s, 3H, OCH_3), 1.66 (s, 6H, $C(CH_3)_2$)
6e	$C_{16}H_{15}N_3O_3$ (297.31)	181-182	64.64 64.59	5.09 5.00	14.13 14.08	1692 1734	297 (100)	9.74 (d, J = 1.07 Hz, 1H, pyridazine), 9.49 (d, J = 1.07 Hz, 1H, pyridazine), 6.95-7.08 (m, 4H, phenyl), 3.83 (s, 3H, OCH_3), 1.78 (s, 6H, $C(CH_3)_2$)
6f	$C_{17}H_{17}N_3O_3$ (311.34)	137-138	65.58 65.49	5.50 5.34	13.37 13.50	1680 1730	311 (100)	9.74 (s, 1H, pyridazine), 9.44 (s, 1H, pyridazine), 6.95-7.08 (m, 4H, phenyl), 3.83 (s, 3H, OCH_3), 2.20-2.50 (m, J_{gem} = 14.53 Hz, 1H, CH_2CH_3), 1.90-2.12 (m, J_{gem} = 14.53 Hz, 1H, CH_2CH_3), 1.77 (s, 3H, CH_3), 0.739 (t, J = 7.20 Hz, 3H, CH_3CH_2)

[a] Mixture of the two diastereomers. [b] Characterized by high resolution mass spectrometry. [c] Recorded from chloroform. [d] Calculated for $C_{15}H_{15}N_3O_2$•0.14H_2O. [e] *cis* isomer. [f] *trans* isomer. ^{1}H nmr data were obtained from the spectra of the mixture of the two diastereomers. [g] Calculated for $C_{21}H_{19}N_3O_2$•2/3H_2O. [h] Calculated for $C_{21}H_{19}N_3O_2$•0.17H_2O.

added at -78° 0.7 ml (1.1 mmoles) of a 1.6 *M* solution of *n*-butyllithium in *n*-hexane. The solution was stirred for 10 minutes followed by addition within 5 minutes of 1.0 mmole of the appropriate ester in 2.0 ml of tetrahydrofuran. The solution was stirred for 50 minutes at -78° followed by addition of 213 mg (1.0 mmole) of **1** in 5 ml of tetrahydrofuran within 10 minutes. The solution was stirred at -78° for 2 hours and then allowed to warm up slowly (2 hours) to room temperature and was further stirred for 3 hours. The resulting solution was diluted with 25 ml of diethyl ether and washed sequentially with 12 ml of 1 *M* aqueous hydrochloric acid and 12 ml of water. The combined aqueous phases were extracted with dichloromethane. The combined organic layers were dried and concentrated *in vacuo*.

Further processing for the purification of the crude product is indicated in the subsequent paragraphs. Physical, analytical, and spectroscopic data of the newly prepared compounds are collected in Table 2.

Ethyl 3-(4-Methoxyphenylamino)-3-(4-pyridazinyl)propanoate (**2a**).

Purification of the residue by column chromatography using ethyl acetate as eluent gave **2a** which was crystallized from dichloromethane-ether to afford 24 mg (8%) of orange crystals.

Ethyl 3-(4-Methoxyphenylamino)-2-methyl-3-(4-pyridazinyl)-propanoate (**2b**) and 1-(4-Methoxyphenyl)-3-methyl-4-(4-pyridazinyl)-2-azetidinone (**3b**).

The crude mixture was purified by column chromatography (ethyl acetate) to give 59 mg of **3b** (22%) and 50 mg of **2b** (16%) as oils. In each case, attempts to separate the diastereoisomers remained unsuccessful. Compounds **3b** gave colorless crystals upon crystallization from diethyl ether.

3-Isopropyl-1-(4-methoxyphenyl)-4-(4-pyridazinyl)-2-azetidinone (**3c**).

Column chromatography (ethyl acetate) of the crude product afforded 195 mg (66%) of a mixture of the *cis* and *trans* β-lactams **3c** (ratio 10/1) as colorless crystals. The pure *cis* isomer was obtained by recrystallization from diisopropyl ether.

1-(4-Methoxyphenyl)-3-methyl-3-phenyl-4-(4-pyridazinyl)-2-azetidinone (**3d**).

Crystallization of the crude product from ethyl acetate afforded 142 mg of *trans*-**3d** isomer as colorless needles. The filtrate was evaporated *in vacuo* and purified by column chromatography. Elution of the column with ethyl acetate gave additional 51 mg of the *trans* product (total yield: 56%) and 22 mg of the *cis* isomer (6%). Compound *cis*-**3d** was recrystallized from dichloromethane:ether to afford colorless crystals.

3-Ethyl-1-(4-methoxyphenyl)-3-methyl-4-(4-pyridazinyl)-2-azetidinone (**3f**) and 8-Ethyl-6-(4-methoxyphenyl)-8-methylpyrido[3,4-*d*]pyridazine-5,7(6*H*, 8*H*)-dione (**6f**).

Purification of the crude mixture by column chromatography (dichloromethane:methanol; 20:1) afforded 89 mg (30%) of **3f** as a mixture of the *cis* and *trans* isomers and 12 mg (5%) of **6f** as colorless oils. Compounds **3f** and **6f** were recrystallized from diethyl ether-dichloromethane and diethyl ether, respectively, to give colorless crystals.

5,8-Dihydro-6-(4-methoxyphenyl)-8,8-dimethylpyrido[3,4-*d*]-pyridazin-7(6*H*)-one (**5e**) and 6-(4-Methoxyphenyl)-8,8-dimethylpyrido[3,4-*d*]pyridazin-5,7(6*H*,8*H*)-dione (**6e**).

The crude mixture was purified by column chromatography (chloroform:methanol 19:1) to afford 99 mg (35%) of **5e** as pale yellow oil and 21 mg (7%) of **6e** as colorless crystals. Compound **6e** was recrystallized from tetrahydrofuran-*n*-hexane.

Compound **5e** had ^{13}C nmr, 172.1 (C=O), 158.7 (*C*ar-OCH_3), 148.7 and 147.7 (C-3 and C-6 pyridazine), 140.7 (Car-N) 129.6 and 134.7 (C-4 and C-5 pyridazine), 127.2 and 114.7 (4 Car), 55.5 (OCH_3), 50.37 (CH_2), 40.7 ($C(CH_3)_2$), 25.5 ($C(CH_3)_2$).

Conversion of Compound **5e** to **6e**.

A solution of 50 mg (1.76 mmoles) of **5e** in tetrahydrofuran was stirred at room temperature for 48 hours. The solvent was evaporated *in vacuo* and the crude mixture was purified by column chromatography (chloroform:methanol, 19:1) to afford 25 mg (47%) of **6e** and 20 mg (39%) of starting material.

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REFERENCES AND NOTES

[1] Part **77** of this series: G. Heinisch, T. Langer, J. Tonnel, K. Mereiter and K. Wurst, *Heterocycles*, **43**, 1057 (1996).

[2a] D. J. Hart and C. Lee, *J. Am. Chem. Soc*, **108**, 6054 (1986); [b] T. Chiba, M. Nagatsuma and T. Nakai, *Chem. Letters*, 1927 (1984); [c] G. Cainnelli, M. Panunzio, T. Basile, A. Bongini, D. Giacomoni and G. Martelli, *J. Chem. Soc., Perkin Trans. 1*, 2637 (1987).

[3a] C. Gluchowski, L. Cooper, D. E. Bergbreiter and C. Newcomb, *J. Org. Chem.*, **45**, 3413 (1980); [b] G. I. Georg, G. Harriman, M. Hepperle, R. Himes, *Bioorg. Med. Chem. Letters*, **4**, 1381 (1994).

[4] G. Heinisch, B. Matuszczak and K. Mereiter, *Heterocyles*, **38**, 2081 (1994).

[5] N. Haider, G. Heinisch and J. Moshuber, *Tetrahedron*, **47**, 8573 (1991).

[6] K. Czech, N. Haider and G. Heinisch, *Monatsh Chem.*, **122**, 413 (1991).