Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1231–1237

TETRAHEDRON: *ASYMMETRY*

Optically active α-hydroxy-α-(tetrahydroquinoxalin-3-on-2-yl)esters by ring transformation of (*R,R*)-diethyl oxirane-2,3-dicarboxylate

Karsten Woydowski, Burkhardt Ziemer and Jürgen Liebscher *

Institut für Chemie, Humboldt-Universität Berlin, Hessische Str. 1-2, D-10115 Berlin, Germany

Received 4 February 1998; accepted 4 March 1998

Abstract

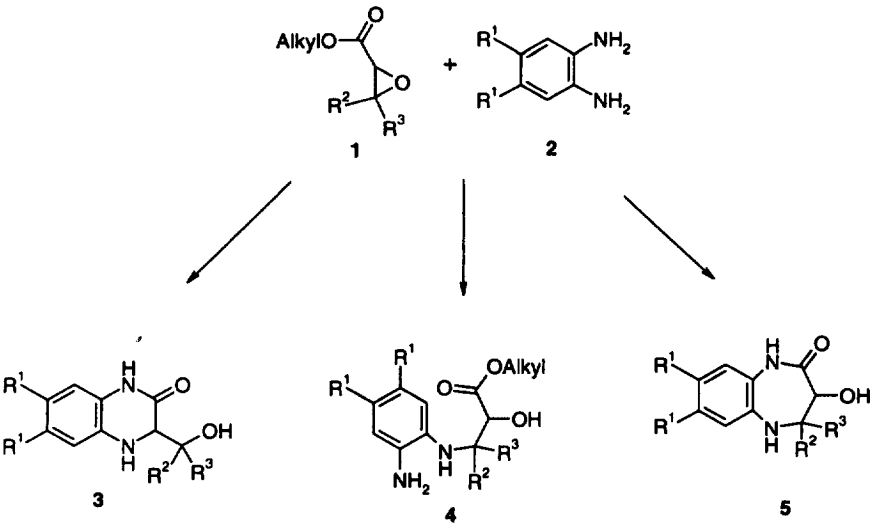
The reaction of (*R,R*)-diethyl oxirane-2,3-dicarboxylate **6** with o-phenylendiamines **7** and 1,8-diaminonaphthalene gave optically active (2*R*,2′*S*)-2-hydroxy-2-(3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-acetates **8** or (2*R*,2′*S*)-2-hydroxy-2-(3-oxo-1,2,3,4-tetrahydronaphtho[1.8-ef][1.4]diazepin-2-yl)-acetate **9**, respectively, in a regio and stereoselective manner. o-Phenylendiamines **7** with an electron-donating substituent gave other regioisomers to the electron-poor **7**. Together with previous investigations in this field the present results demonstrate a dependence of the mode of the reaction of glycidates with o-phenylendiamines on the substituents at the glycidate.

1. Introduction

Reactions of glycidates **1** with o-phenylendiamines **2** have been reported with contradictory results (Scheme 1). Murata et al.[1] described the formation of racemic quinoxalinones **3** (R^2, R^3=H, Me, Et) or 3-arylamino-2-hydroxyesters **4** (R^2=H, Ph; R^3=H) depending on the reaction conditions. No analytical evidence was given for the structure elucidation. Detailed investigations of the reaction of enantiomerically pure alkylglycidic carboxylates **1** (R^3=H, R^2=Alkyl and R^3=Alkyl, R^2=H) with o-phenylendiamines **2** revealed optically active benzo-1,5-diazepinone products **5**[2] after heating both reactants without a solvent while no reactions of o-phenylendiamines **7** ($R^1 \neq R^2$) with glycidates **1** have been reported. Racemic hydroxybenzodiazepinones were obtained from phenyl glycidate.[3]

* Corresponding author. E-mail: liebscher@chemie.hu-berlin.de

PII: S0957-4166(98)00097-4

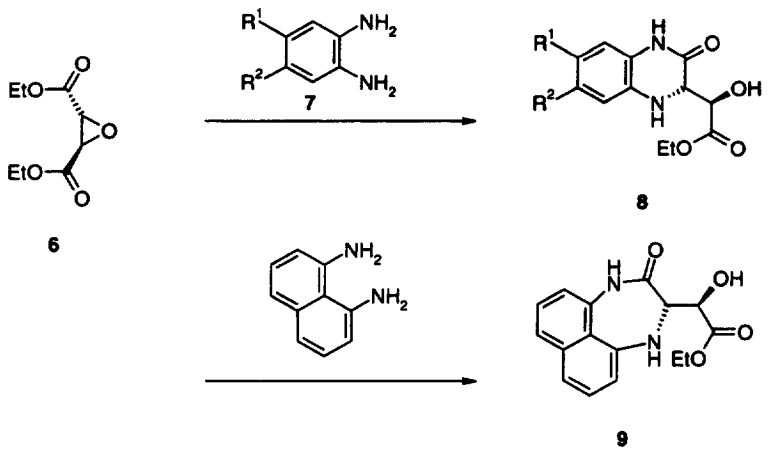


Scheme 1.

2. Results and discussion

We report now the first unambiguous synthesis of optically active 2-(α-hydroxyalkyl)-quinoxalin-3-ones **3** including examples with asymmetrically substituted o-phenylendiamines **7** and, in addition, the reaction of a glycidate with 1,8-diaminonaphthalene. If (*R,R*)-diethyl oxirane-2,3-dicarboxylate **6** obtained from (2*R*,3*R*)-(+)-diethyl tartrate by a known method[4] was reacted with o-phenylendiamines **7** at elevated temperatures optically active tetrahydroquinoxalin-3-ones **8** were obtained mostly in good yields (Scheme 2). While reflux of the reactants in ethanol was appropriate for o-phenylendiamine itself and for **7** substituted by electron-donating substituents (R^1, R^2=H, Me or OMe), 4-nitro-1,2-diaminobenzene **7** (R^1=H, R^2=NO_2) required heating without a solvent to 155°C. In no case could formation of diastereomeric products be observed but mixtures of **8** and their regioisomers where the position of R^1 and R^2 is exchanged were obtained if unsymmetrically substituted o-phenylendiamines **7** ($R^1 \neq R^2$) were used (see Table 1). The extent of regioisomer formation depended on the reaction temperature to some extent (e.g. see Table 1, **8c**). All products **8** appeared free of diastereomers (d.e.>90%) and could be prepared free of isomeric impurities either directly or after recrystallisation (see Table 1).

The structure elucidation of the products obtained was based on spectroscopic data and in particular on X-ray crystal analyses of compounds **8a** and **8f** (see Figs 1 and 2). The regiochemistry of compound **8d** could be proved by the HMBC–NMR technique (coupling between ^{1}HN at position 4 with ^{13}C at position 5. Our structural investigations thus demonstrated a different regiochemistry if asymmetrical o-phenylendiamines **7** were used bearing one electron-donating substituent, i. e. R^1=Me or MeO, R^2=H as compared with electron-poor **7**, i. e. R^1=H, R^2=NO_2 or CF_3. No intermediates were observed in reactions of the oxirane dicarboxylate **6** with o-phenylendiamines **7**. From a mechanistic point of view it is likely that the quinoxalinones **8** were formed by primary attack of one of the amino groups of **7** opening the oxirane ring of **6** by inversion of configuration affording corresponding β-arylamino-α-hydroxy esters similar to **4** (R^2=COOEt, R^3=H). Further attack of the other amino group at the closest ester carbonyl carbon atom (i.e. at R^2 in **4**) forms the ring to afford **8**. In the case of o-phenylendiamines **7** substituted by an electron-donating group (R^2=H, R^1=Me or MeO) the primary attack occurred at the more electron



Scheme 2.

Table 1
Tetrahydroquinoxalin-3-ones **8** and naphthodiazepin-3-one **9**

Product	R^1	R^2	yield(%)[a] / reaction conditions	ratio of **8** : regioisomer [a]
8a	H	H	81/7h reflux EtOH	--
8b	Me	Me	77/6h reflux EtOH	--
8c	Me	H	56/6h reflux EtOH	>95:5
			78/3.5h neat 80°C	88:12
			58[b]	>95:5[b]
8d	MeO	H	81/6h reflux EtOH	95:5
8e	H	NO_2	88/1.25h neat 155°C	87:13
			73[b]	>95:5[b]
8f	H	CF_3	80/25h reflux EtOH	93:7
			71[b]	>95:5[b]
9	--	--	75[a]/3h neat 155°C	82:12 [c]
			60 [b]	> 95:5 [b,c]

[a] of crude product [b] after recrystallisation [c] probably diastereomeric ratio

rich amino group at the p-position to R^1 while electron-deficient **7**, i. e. R^1=H, R^2=NO_2 or CF_3, initially react via the less deactivated amino group in the m-position to R^2.

Analogously to o-phenylendiamines **7** 1,8-diaminonaphthalene reacted with the oxirane dicarboxylate **6** affording the naphthodiazepinone **9**. The formation of the 7-membered ring rather than a 8-membered ring could be confirmed by HMBC–NMR technique showing coupling between ^{1}HN at position 1 and ^{13}CO at position 3. The crude product **9** contained an isomeric impurity which due to the similarity of the ^{1}H and ^{13}C NMR spectra could be a diastereomer rather than a regioisomer.

The aforementioned results demonstrate the first synthesis of optically active 3-(α-hydroxyalkyl)-tetrahydroquinoxalin-2-ones and of a α-hydroxyalkylnaphthodiazepinone. As compared with our pre-

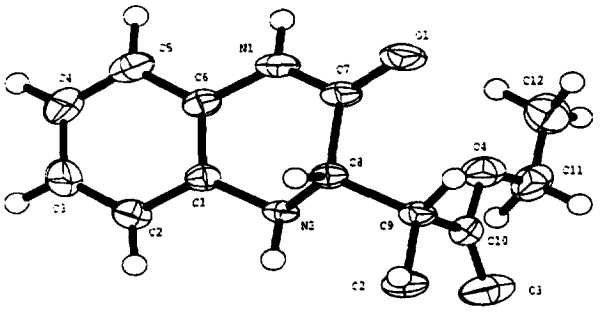


Fig. 1. X-Ray crystal analysis of tetrahydroquinoxalin-3-one **8a**

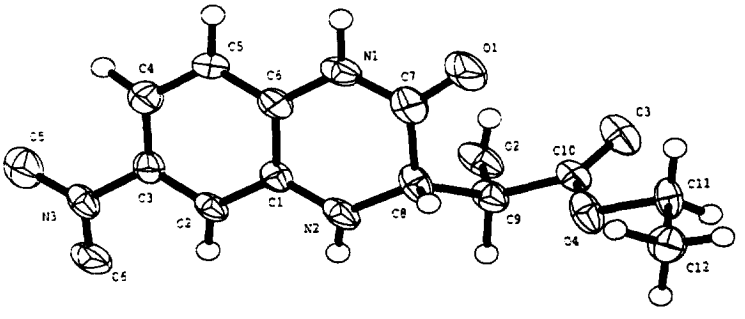


Fig. 2. X-Ray crystal analysis of tetrahydroquinoxalin-3-one **8e**

vious investigations[2] of reactions of o-phenylendiamines with alkyl substituted optically active glycidate affording benzodiazepinone the results reported here revealed that the outcome of such reactions (formation of quinoxalines rather than benzodiazepines) can depend on the substituents R^2 or R^3 (ester moiety rather than an alkyl group) attached to the β-position of the starting glycidate **1**.

3. Experimental

3.1. General

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively on a BRUKER AC-300 with TMS as the internal standard. Mass spectra (HP 5995 A) were measured at 70 eV. Optical rotation was determined with a Perkin–Elmer polarimeter 241. For preparative column chromatography silica gel (0.04–0.063 mm, Merck) was used. (*R,R*)-(+)-Diethyl oxirane-2,3-dicarboxylate **6** was prepared starting from (+)-diethyl tartrate according to a known procedure.[4]

3.2. General procedure for α-hydroxy-α-tetrahydroquinoxalinyl-esters 8 and the naphthodiazepinone 9

3.2.1. Method A

A mixture of (*R,R*)-diethyl oxirane-2,3-dicarboxylate **6** (200 mg, 1.06 mmol), the o-phenylendiamine **7** (1.17 mmol but for **8d** and **8f** only 1.06 mmol) and dry EtOH (2 ml) was refluxed under argon for between 4 and 7 h (see Table 1). If crystallisation occurred after cooling to room temperature ether (2 ml) was added and the product was isolated by filtration. Otherwise the solvent was evaporated and the remainder purified by column chromatography ($CHCl_3$/MeOH=8/2). Complete removal of the minor diastereomer was possible by recrystallisation.

3.2.2. Method B

A neat mixture of (*R,R*)-diethyl oxirane-2,3-dicarboxylate **6** (200 mg, 1.06 mmol) and the o-phenylendiamine **7** (1.06 mmol) or 1,8-diaminonaphthalene (185 mg, 1.17 mmol) was heated under argon (for temperature and time see Table 1). After cooling to room temperature the solid mixture was purified by recrystallisation.

3.3. Ethyl (2R,2′S)-2-hydroxy-2-(3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-acetate ***8a***

Colourless crystals; mp. 140°C (EtOAc); $[\alpha]_D^{20}$=+62.7 (c 1, MeOH); ^{1}H NMR (CD_3OD) δ/ppm, J/Hz: 1.09 (t, J=1.15, 3H, CH_3); 3.79–4.02 (m, CH_2); 4.40 (m, CH–N); 4.53 (d, J=2.78, CH–O); 6.54–6.80 (m, 4×CH_{Ph}). ^{13}C NMR (CD_3OD) δ/ppm: 14.2 (CH_3); 61.9 (CH–N); 62.5 (CH_2); 73.7 (CH–O); 114.4, 116.0, 119.0, 124.8 (CH_{Ph}); 127.3, 134.1 (C_{Ph}); 167.3, 173.0 (C=O). $C_{12}H_{14}N_2O_4$ (250.28): anal. calcd C 57.58, H 5.65, N 11.20; found C 57.69, H 5.48, N 11.09.

3.4. Ethyl (2R,2′S)-2-hydroxy-2-(6,7-dimethyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-acetate ***8b***

Colourless crystals; mp. 190–95°C (decomp.; EtOAc); $[\alpha]_D^{20}$=+58.5 (c 1, MeOH); ^{1}H NMR (DMSO-d_6) δ/ppm, J/Hz: 1.06 (t, J=7.15, CH_3); 2.01 (s, CH_3); 2.03 (s, CH_3); 3.80–3.95 (m, CH_2); 4.18 (m, CH–N); 4.35 (m, CH–O); 5.62 (d, J=5.93, OH); 5.85 (d, J=1.21, NH); 6.39 (s, CH_{Ph}); 6.42 (s, CH_{Ph}); 10.14 (s, CONH). ^{13}C NMR (DMSO-d_6) δ/ppm: 16.1 (CH_3); 20.8 (CH_3); 21.2 (CH_3); 62.5 (CH_2); 62.5 (CH–N); 74.9 (CH–O); 116.4, 117.7 (CH_{Ph}); 124.8, 126.1, 131.9, 133.0 (C_{Ph}); 166.7, 173.4 (C=O). $C_{14}H_{18}N_2O_4$ (278.34): anal. calcd C 60.41, H 6.53, N 10.07; found C 60.17, H 6.45, N 9.99.

3.5. Ethyl (2R,2′S)-2-hydroxy-2-(6-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-acetate ***8c***

Colourless crystals; mp. 175–77°C (EtOAc); $[\alpha]_D^{20}$=+35.7 (c 1, MeOH); ^{1}H NMR (DMSO-d_6) δ/ppm, J/Hz: 1.05 (t, J=7.07, CH_3); 2.10 (s, CH_3); 3.80–3.95 (m, CH_2); 4.21 (s, CH–N); 4.73 (m, CH–O); 5.64 (d, J=5.75, OH); 5.95 (s, NH); 6.41–6.54 (m, 3×CH_{Ph}); 10.23 (s, CONH). ^{13}C NMR (DMSO-d_6) δ/ppm: 14.1 (CH_3); 20.6 (CH_3); 60.5 (CH_2); 60.5 (CH–N); 73.0 (CH–O); 112.9, 115.2, 122.7 (CH_{Ph}); 125.1, 125.7, 131.0 (C_{Ph}); 165.0, 171.5 (C=O). $C_{13}H_{16}N_2O_4$ (264.31): anal. calcd C 59.07, H 6.11, N 10.60; found C 59.19, H 6.07, N 10.54.

3.6. Ethyl (2R,2′S)-2-hydroxy-2-(6-methoxy-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-acetate ***8d***

Light brown crystals; mp. 148–49°C (EtOAc/hexane=7/1); $[\alpha]_D^{20}$=+29.3 (c 1, MeOH); ^{1}H NMR (DMSO-d_6) δ/ppm, J/Hz: 1.26 (t, J=7.07, CH_3); 3.80 (s, CH_3–O); 3.98–4.14 (m, CH_2); 4.36 (d, J=1.69, CH–N); 4.56 (m, CH–O); 5.83 (d, J=5.48, OH); 5.97 (s, NH); 6.51–6.75 (m, 3×CH_{Ph}); 10.42 (s, CONH). ^{13}C NMR (DMSO-d_6) δ/ppm: 14.1 (CH_3); 55.2 (CH_3–O); 60.6 (CH_2); 60.7 (CH–N); 72.7 (CH–O); 101.5, 107.7, 113.6 (CH_{Ph}); 126.2, 127.3, 151.8 (C_{Ph}); 165.4, 171.5 (C=O). $C_{13}H_{16}N_2O_5$ (280.31): anal. calcd C 55.70, H 5.77, N 10.00; found C 55.61, H 5.69, N 9.76.

3.7. Ethyl (2R,2′S)-2-hydroxy-2-(7-nitro-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-acetate ***8e***

Red crystals; mp. 218–20°C (EtOAc); $[\alpha]_D^{20}$=+164.5 (c 1, MeOH); $[\alpha]_{546}^{20}$=+219.6 (c 1, MeOH); ^{1}H NMR (DMSO-d_6) δ/ppm, J/Hz: 1.09 (t, J=7.09, CH_3); 3.90–4.02 (m, CH_2); 4.41 (d, J=3.56, CH–N); 4.41 (d, J=3.56, CH–O); 5.90 (d, J=5.24, OH); 6.82 (d, J=8.41, CH_{Ph}); 6.97 (s, NH); 7.44–7.50 (m,

2×CH_{Ph}); 10.94 (s, CONH). ^{13}C NMR (DMSO-d_6) δ/ppm: 14.1 (CH_3); 59.7 (CH–N); 60.7 (CH_2); 73.6 (CH–O); 106.6, 113.2, 114.2 (CH_{Ph}); 131.2, 134.1, 142.9 (C_{Ph}); 164.8, 171.6 (C=O). IR (KBr) (cm^{-1}): 1686 (C=O), 1744 (C=O), 3341 (OH). MS (70 eV) m/z (%): 295 (M^+, 2), 192 (100), 146 (74), 104 (48). $C_{12}H_{13}N_3O_6$ (295.28): anal. calcd C 48.81, H 4.45, N 14.23; found C 48.71, H 4.38, N 14.03.

3.8. Ethyl (2R,2′S)-2-hydroxy-2-(7-trifluoromethyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-acetate 8f

Colourless crystals; mp. 169–70°C (EtOAc/hexane=3/7); $[\alpha]_D^{20}$=+72.3 (c 1, MeOH); ^1H NMR (DMSO-d_6) δ/ppm, J/Hz: 0.81 (t, J=7.11, CH_3); 3.64–3.69 (m, CH_2); 4.11 (d, J=6.60, CH–N); 4.13 (d, J=2.71, CH–O); 5.56 (d, J=4.97, OH); 6.42 (s, NH); 6.55–6.65 (m, 3×CH_{Ph}); 10.38 (s, CONH). ^{13}C NMR (DMSO-d_6) δ/ppm, J/Hz: 14.1 (CH_3); 60.0 (CH–N); 60.6 (CH_2); 73.4 (CH–O); 108.4 (J=15), 112.0 (J=15), 114.5 (CH_{Ph}); 117.0 (J=123) (C_{Ph}); 125.9 (J=1074) (CF_3); 128.3, 134.0 (C_{Ph}); 164.7, 171.1 (C=O). $C_{13}H_{13}N_2O_4F_3$ (318.28): anal. calcd C 49.05, H 4.13, N 8.80; found C 49.18, H 4.28, N 8.88.

3.9. Ethyl (2R,2′S)-2-hydroxy-2-(3-oxo-1,2,3,4-tetrahydronaphtho[1.8-ef][1.4]diazepin-2-yl)-acetate 9

Light brown crystals; mp. 183–85°C (EtOAc/hexane=1/1); $[\alpha]_D^{20}$=−53.3 (c 1, MeOH); ^1H NMR (DMSO-d_6) δ/ppm, J/Hz: 1.13 (t, J=7.10, CH_3); 3.95–4.06 (m, CH_2, CH–N); 4.34 (m, CH–O); 5.73 (d, J=7.20, OH); 6.32 (d, J=4.70, NH); 6.77–7.44 (m, 6×CH_{Ph}); 10.10 (s, CONH). ^{13}C NMR (DMSO-d_6) δ/ppm: 14.2 (CH_3); 60.7 (CH_2); 62.8 (CH–N); 69.3 (CH–O); 111.8, 115.0, 119.4, 119.9 (CH_{Ph}); 118.5, 135.2, 136.8, 144.8 (C_{Ph}); 170.0, 171.7 (C=O). IR (KBr) (cm^{-1}): 1673 (C=O), 1731 (C=O), 3368 (OH). MS (70 eV) m/z (%): 300 (M^+, 6), 197 (42), 169 (92), 29 (100). $C_{16}H_{16}N_2O_4$ (300.34): anal. calcd C 63.98, H 5.38, N 9.33; found C 63.83, H 5.42, N 9.15.

3.10. Crystal structure determination for the compound 8a

Crystals were obtained by crystallisation from hot ethyl acetate. A colourless crystal of **8a** with the dimensions 1.06×0.65×0.23 mm^3 was measured on a STOE Stadi4 diffractometer using MoK_α radiation (λ=0.71071 Å). Crystal data: $C_{12}H_{14}N_2O_4$, M=250.28, orthorhombic space group $P2_12_12_1$, a=5.0511(7) Å, b=12.266(2) Å, c=19.619(3) Å, V=1215.5(4) $Å^3$, Z=4, D_c=1.368 g/cm^3, F(000)=528 μ, (MoK_α)=0.064 mm^{-1}. At 293(2) K in the range of 1.96°<Θ<27.48° 5746 reflections were measured ($R_{(sig)}$=0.0254) of which 2805 were unique ($R_{(int)}$=0.0286) and 2559, flagged as observed, had intensities larger than 2σ(I). The structure was solved by direct methods and refined by least squares procedure within the SHELX program system. The final residuals were $wR_{2\,(all)}$=0.1082, $R_{1\,(all)}$=0.0456 and $R_{1\,(obs)}$=0.0406. The maximum and minimum peaks in the final difmap were 0.190 and −0.162 e/$Å^3$, respectively.[5]

3.11. Crystal structure determination for the compound 8e

Crystals were obtained by crystallisation from hot ethyl acetate. A colourless crystal of **8e** with the dimensions 0.78×0.28×0.24 mm^3 was measured on a STOE Stadi4 diffractometer using MoK_α radiation (λ=0.71073 Å). Crystal data: $C_{12}H_{13}N_3O_6$, M=295.28, triclinic space group P1, a=5.0741(15) Å, b=5.673(2) Å, c=11.686(4) Å, α=99.71(3)°, β=94.62(3)°, γ=102.75(3)°, V=321.0(2) $Å^3$, Z=1, D_c=1.528 g/cm^3, F(000)=154 μ, (MoK_α)=0.080 mm^{-1}. At 200(2) K in the range of 23.56°<Θ<24.15° 1815 reflections were measured ($R_{(sig)}$=0.0416) of which 1815 were unique ($R_{(int)}$=0.1767) and 1533, flagged as observed, had intensities larger than 2σ(I). The structure was solved by direct methods and refined by

least squares procedure within the SHELX program system. The final residuals were $wR_{2\,(all)}$=0.2142, $R_{1\,(all)}$=0.0879 and $R_{1\,(obs)}$=0.0798. The maximum and minimum peaks in the final difmap were 0.357 and −0.375 e/Å^3, respectively.[6]

Acknowledgements

We gratefully acknowledge financial support by Deutsche Forschungsgemeinschaft and by Fonds der Chemischen Industrie.

References

1. Murata, S.; Sugimoto, T.; Matsuura, S. *Heterocycles* **1987**, *26*, 883.
2. Woydowski, K.; Liebscher, J. *Synthesis*, in press.
3. El Meslouhi, H.; Essassi, E. M.; Zerzouf, A.; Salem, M.; Petrus, C.; Viallefont, P. *Bull. Soc. Chim. Belg.* **1996**, *105*, 785.
4. Mori. K.; Iwasawa, H. *Tetrahedron* **1980**, *36*, 87.
5. Full details have been deposited at the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshaven, Germany; this material can be obtained on quoting a full literature citation and deposition number CSD-408180.
6. Full details have been deposited at the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshaven, Germany; this material can be obtained on quoting a full literature citation and deposition number CSD-408181.