A new type of plant activator: synthesis of thieno[2,3-*d*][1,2,3]-thiadiazole-6-carboxylic acid derivatives *via* Hurd–Mori cyclization

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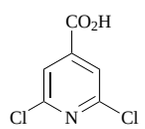
We present a short and efficient synthesis of the title compounds starting with cheap and readily available methylenebutanedioic acid and thioacetic acid. The optimised sequence allows the large-scale preparation of this new type of plant activator in a few steps. *ortho*-Lithiation is used for the introduction of substituents into the 5-position. A modified reaction mechanism for the Hurd–Mori reaction is suggested to explain the unexpected aromatisation.

Introduction

It has long been known that plants, when locally infected with a pathogen, often develop a long lasting, broad spectrum resistance to subsequent infection. In the course of extensive studies of this phenomenon it was discovered that induction of disease resistance in plants, called 'systemic acquired resistance' (SAR), can also be triggered by selected organic compounds which are now called plant activators, *e.g.* 2,6-dichloroisonicotinic acid **1**, or 1,2,3-benzothiadiazole-7-carboxylic acid **2**. At concentrations which control pathogenic activity *in vivo* these plant activators have little or no direct antimicrobial activity *in vitro* but they induce resistance to the same spectrum of pathogens as in the biological model and lead to the expression of the same biochemical markers such as, for example, PR-proteins in the plant.[1]



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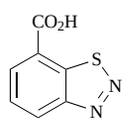
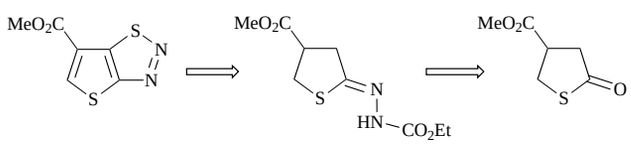


2

As a consequence, chemically mediated SAR was established as a new concept in disease control and just recently the methyl thioester of **2** (Bion®) was introduced as the first commercial product by Novartis.[2]

In the course of our synthetic work towards derivatives of the thieno[2,3-*d*][1,2,3]thiadiazole-6-carboxylic acid,[3] a new class of compounds being bioisosteric with **2**, we were interested in the application of the Hurd–Mori reaction[4] for the construction of the 1,2,3-thiadiazole ring system as an alternative to the diazotization approach which was used previously.[5] The retrosynthetic simplification of the target compound leads *via* the carbazonate **4** to the thiolactone **5**.



3 **4** **5**

Results and discussion

We started the reaction sequence with the 1,4-addition of thioacetic acid to methylenebutanedioic acid **6** to obtain the addition product **7** according to Holmberg.[6] The acetylthio group was hydrolysed to the thiol **8** which formed the thiolactone **9** when simply heated to 140 °C. Since the thiolactone moiety proved to be too sensitive for an acid-catalysed esterification, leading to partial ring opening by transesterification, the methyl ester **5** was obtained in good yield by reaction of **9** with methanol and dicyclohexylcarbodiimide. Selective thionation to the corresponding dithiolactone **10** using Lawesson's reagent was possible by taking advantage of the higher reactivity of thiolactones. The subsequent condensation with ethyl carbazate, achieved in refluxing ethanol, interestingly gave the diastereoisomerically pure *Z*-isomer of the carbazonate **4**. The stereochemistry of this product was established by X-ray analysis (Fig. 1).

In our initial attempt at anellation of the 1,2,3-thiadiazole ring system, **4** was treated at room temperature with thionyl chloride (10 equiv.) in dichloromethane for 22 h. This gave a mixture of the final target compound **3** and a by-product, identified as the chlorinated thienothiadiazole **11** (ratio: *ca.* 8:1), not the expected 5,6-dihydrothienothiadiazole, (Scheme 1). By careful optimisation of the reaction conditions (raising the reaction temperature to 80 °C)[7] we were able to avoid the formation of **11**.

To explain the facile aromatisation in the course of the Hurd–Mori cyclisation as well as the formation of the chlorinated by-product **11**, we offer a modified mechanistic model of the Hurd–Mori reaction (see Scheme 2). The first step is the cyclisation of **4** with thionyl chloride to the *N*-ethoxycarbonyl-

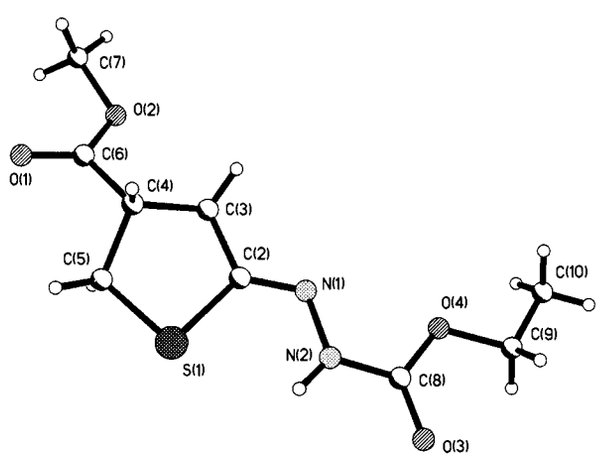
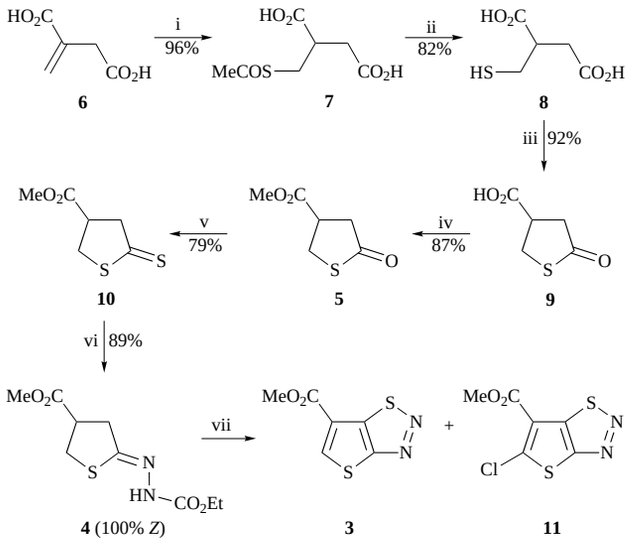
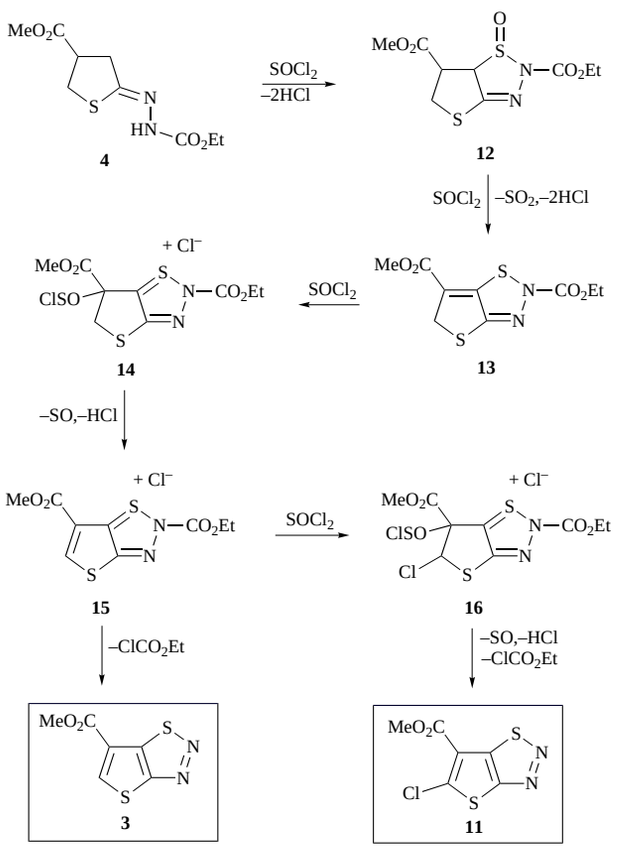


Fig. 1



Solvent	Temp. (°C)	Ratio **3**:**11**	Yield of **3** (%)
CH_2Cl_2	25	8:1	60
$C_2H_4Cl_2$	80	1:0	66

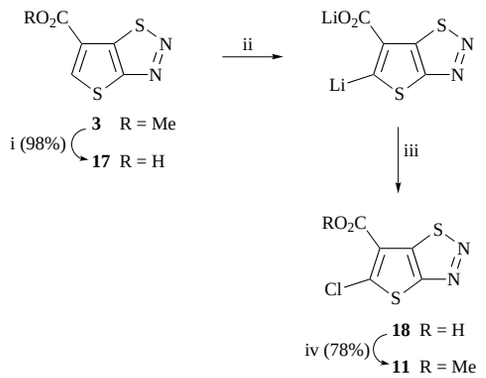
Scheme 1 *Reagents and conditions*: i, MeC(O)SH, 80 °C, 150 min; ii, NaOH; iii, 140 °C, 3 h; iv, MeOH, DCC, Et_2O, 25 °C; v, Lawesson's reagent, toluene, 18 h, reflux; vi, EtO_2CNHNH_2, EtOH, 5 h, reflux; vii, $SOCl_2$ (10 equiv.), 22 h



Scheme 2

dihydrothiadiazole *S*-oxide[8] **12**. A Pummerer-like rearrangement initiated by the attack of thionyl chloride on the O atom of the SO group followed by subsequent elimination of hydrochloric acid leads to the intermediate **13**. Addition of thionyl chloride to the push-pull substituted double bond furnishes the sulfinyl chloride **14** which forms **15** by *syn*-elimination.[9] The *N*-ethoxycarbonylthiadiazolium chloride **15** can now lose ethyl chloroformate to give **3** as the main product or its push-pull substituted double bond again can add thionyl chloride to yield the corresponding sulfinyl chloride **16** which furnishes the by-product **11** by *syn*-elimination and aromatisation. At higher reaction temperatures the aromatisation of **15** is obviously preferred to the addition of thionyl chloride leading now exclusively to **3** (see also Scheme 1).

Because of the promising biological profile of the by-product **11** we were interested in an efficient conversion of **3** into **11**. Attempted electrophilic chlorination failed. The transformation was achieved by *ortho* metallation[10] of the carboxylic acid **17** with lithium diisopropyl chloride and subsequent quenching of the organolithium intermediate with hexachloroethane.[11] In the last step the chlorinated carboxylic acid **18** was again esterified with dicyclohexylcarbodiimide and methanol (Scheme 3).



Scheme 3 *Reagents and conditions*: i, NaOH, EtOH, H_2O; ii, LDA (2.5 equiv.), THF, −50 °C, 90 min, iii, C_2Cl_6 (2.2 equiv.), 90 °C to RT, 120 min; iv, MeOH, DCC, CH_2Cl_2

Experimental

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. Diethyl ether and tetrahydrofuran were distilled from sodium–benzophenone immediately prior to use. Toluene and dichloromethane were distilled from phosphorus pentoxide. Ethanol and methanol were distilled from magnesium turnings. Flash chromatography was carried out using silica gel 60 (Merck) and the indicated solvent system. Boiling and melting points are not corrected. The NMR spectra were recorded on a Bruker AC 200 FT-NMR spectrometer. Chemical shifts are expressed in δ values (ppm) downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in the order: δ, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), number of protons, coupling constant(s) in Hz. Elemental analyses were obtained from the Institute of Physical Chemistry, University of Vienna.

Acetylthiomethylbutanedioic acid 7

A mixture of methylenebutanedioic acid **6** (400 g, 3.07 mol) and thioacetic *s*-acid (280 g, 3.68 mol) was stirred for 2 h at 90–100 °C. After cooling to room temperature the highly viscous mixture was treated with diisopropyl ether (300 ml) to promote crystallisation. The crystals were collected and washed with cold diisopropyl ether to obtain colourless crystals (602 g, 96%) mp 89–91 °C (lit.,[6] 90.5–91.5 °C); $\delta_H([^2H_6]DMSO)$ 2.3 (s, 3H), 2.40–60 (m, 2H), 2.75–3.20 (m, 3H) and ~12 (br s, 2H); $\delta_C([^2H_6]DMSO)$ 29.6, 30.6, 34.7, 40.9, 172.7, 174.1 and 194.9.

Mercaptomethylbutanedioic acid 8

To a stirred, ice-cooled solution of sodium hydroxide (126.1 g, 3.15 mol) in water (750 ml) **7** (130.0 g, 0.63 mol) was added in small portions. The reaction mixture was stirred at room temperature under nitrogen for 17 h after which it was acidified to pH 1 with concentrated hydrochloric acid and extracted with

diethyl ether. The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The crude product was washed with cold dichloromethane and dried *in vacuo*, to give colourless crystals (85.5 g, 83%) mp 107–108.5 °C (lit.,[6] 107.5–108.5 °C); $\delta_H([^2H_6]$-DMSO) 2.3–2.6 (m, 2H), 2.7–3.0 (m, 4H) and ~12.3 (br s, 2H); $\delta_C([^2H_6]$DMSO) 25.3, 34.0, 43.6, 172.9 and 174.0.

5-Oxotetrahydrothiophene-3-carboxylic acid 9

This compound was prepared by heating **8** (85.5 g, 0.52 mol) at 140–150 °C for 3 h. After cooling to room temperature the solid was crushed and pulverized to afford colourless crystals (71.6 g, 95%) mp 106–108 °C (lit.,[6] 109–110 °C); $\delta_H([^2H_6]$DMSO) 2.65–2.85 (m, 2H), 3.35–3.70 (m, 3H) and ~12.8 (br s, 1H); $\delta_C([^2H_6]$DMSO) 34.3, 42.1, 43.1, 173.0 and 206.4.

Methyl 5-oxothiophene-3-carboxylate 5

A mechanically stirred solution of **9** (20.00 g, 136.8 mmol), DMAP (0.50 g, 4.1 mmol) and dry MeOH (8.77 g, 273.6 mmol) in dry diethyl ether (500 ml) was treated with small portions of dicyclohexylcarbodiimide (28.23 g, 136.8 mmol) at 5 °C. After 3.5 h, the white precipitate was filtered off and the ethereal solution was washed twice with 2M hydrochloric acid and satd. aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to dryness to give colourless crystals (18.63 g, 85%), mp 33–35 °C; $\delta_H(CDCl_3)$, 2.70–3.00 (m, 2H), 3.35–3.70 (m, 3H) and 3.77 (s, 3H); $\delta_C(CDCl_3)$ 34.2, 42.5, 43.3, 52.5, 171.5 and 204.9 (Found: C, 44.99; H, 5.03. $C_6H_8O_3S$ requires C, 45.15, H, 4.87%).

Methyl 5-thioxothiophene-3-carboxylate 10

A solution of **5** (18.1 g, 113.0 mmol) and Lawesson's reagent (25.14 g, 62.2 mmol) in dry toluene (150 ml) was heated under reflux for 18 h after which the solvent was removed *in vacuo* and the oily residue distilled bulb-to-bulb to yield a yellow liquid (17.3 g, 87%); bp 130–140 °C/0.03 mbar; $\delta_H(CDCl_3)$, 3.25–3.42 (m, 2H), 3.52–3.80 (m, 5H) and 3.85–3.95 (m, 1H); $\delta_C(CDCl_3)$, 40.8, 47.1, 52.4, 56.7, 171.0 and 241.1 (Found: C, 40.89; H, 4.58. $C_6H_8O_2S_2$ requires C, 41.19; H, 4.79%).

Methyl 5-(ethoxycarbonylhydrazono)tetrahydrothiophene-3-carboxylate 4

A solution of **10** (14.00 g, 79.43 mmol) and ethyl carbazate (8.27 g, 79.43 mmol) in dry ethanol was heated under reflux for 5 h after which the solvent was removed *in vacuo* and the crude product was recrystallised from isopropyl alcohol to give colourless crystals (17.60 g, 90%), mp 88–91 °C; $\delta_H(CDCl_3)$ 1.30 (t, 3H, *J* 7), 3.05–3.15 (m, 2H), 3.17–3.35 (m, 1H), 3.40–3.65 (m, 2H), 3.73 (s, 3H), 4.25 (q, 2H, *J* 7) and ~6.9 (br s, 1H); $\delta_C(CDCl_3)$ 14.4, 35.5, 38.6, 44.2, 52.9, 61.9, 153.7, 154.6 and 171.5 (Found: C, 43.89; H, 5.73; N, 11.37. $C_9H_{14}N_2O_4S$ requires C, 44.09; H, 5.71; N, 11.33%).

Methyl thieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylate 3

A solution of **4** (0.50 g, 2.03 mmol) in dry 1,2-dichloroethane (10 ml) was treated with thionyl chloride (1.50 ml, 20.3 mmol) and the mixture stirred at 80 °C for 22 h after which the solvent and the excess of thionyl chloride were evaporated off. The residue was diluted with dichloromethane and washed with satd. aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and evaporated to dryness. The crude product was recrystallised from ethyl acetate to yield beige crystals (0.27 g, 66%), mp 140–142 °C; $\delta_H(CDCl_3)$ 4.00 (s, 3H) and 8.60 (s, 1H); $\delta_C(CDCl_3)$ 52.7, 122.3, 141.3, 145.8, 161.0 and 163.1 (Found: C, 35.99; H, 2.01; N, 13.99. $C_6H_4N_2O_4S_2$ requires C, 36.25; H, 1.80; N, 14.05%).

Thieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylic acid 17

A suspension of **3** (40.00 g, 199.3 mmol) in ethanol (300 ml) was treated with a solution of sodium hydroxide (15.90 g, 398.5 mmol) in water (100 ml) and stirred for 1.5 h at room temperature. The homogeneous solution was then diluted with water (500 ml) and acidified with concentrated hydrochloric acid to give a white precipitate which was filtered off, washed with water and dried *in vacuo* (36.50 g, 98%), mp 270–273 °C; $\delta_H([^2H_6]$DMSO) 8.90 (s, 1H); $\delta_C([^2H_6]$DMSO) 123.0, 143.3, 145.8, 161.6 and 162.5 (Found: C, 32.25; H, 1.08; N, 15.04. $C_5H_2N_2O_4S_2$ requires C, 32.51; H, 1.04; N, 15.29%).

5-Chlorothieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylic acid 18

A mechanically stirred suspension of **17** (15.00 g, 80.6 mmol) in dry tetrahydrofuran (150 ml) was treated slowly at −90 °C with LDA [201.6 mmol, freshly prepared at −30 °C from 20.40 g diisopropylamine (20.40 g) and butyllithium (201.6 mmol) in dry tetrahydrofuran (200 ml)] after which the mixture was allowed to warm to −50 °C. After being stirred at this temperature for 1.5 h, the solution was cooled to −90 °C and treated with a solution of hexachloroethane (42.00 g, 177.2 mmol) in dry tetrahydrofuran (70 ml). After the reaction mixture had been allowed to warm to room temperature within 2 h, it was poured into water and acidified with concentrated hydrochloric acid. The white precipitate was filtered off, washed with water and dried *in vacuo* at 100 °C (17.55 g, 99%), mp 255–265 °C. An analytical sample was prepared by recrystallisation from ethanol, mp 263–265 °C; $\delta_C([^2H_6]$DMSO) 120.7, 145.5, 145.6, 154.7 and 160.8 (Found: C, 27.26; H, 0.46; N, 12.70. $C_5HN_2ClO_2S_2$ requires C, 27.23; H, 0.60; N, 12.46%).

Methyl 5-chlorothieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylate 11

To a mechanically stirred solution of **17** (15.00 g, 68.0 mmol), DMAP (0.42 g, 3.4 mmol) and dry methanol (10.90 g, 340 mmol) in dry dichloromethane (300 ml) dicyclohexylcarbodiimide (14.00 g, 68.0 mmol) was added in small portions at 5 °C. After 16 h the white precipitate was filtered off, and the filtrate was washed twice with 2 M hydrochloric acid and satd. aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography using silica gel (150 g) (eluent: light petroleum–dichloromethane, 1:1) to afford colourless crystals (12.45 g, 78%); mp 124–126 °C; $\delta_H(CDCl_3)$ 4.00 (s, 3H); $\delta_C(CDCl_3)$ 52.8, 119.1, 145.0, 146.9, 155.2 and 159.9 (Found: C, 30.71; H, 1.29; N, 11.94. $C_6H_3N_2ClO_2S_2$ requires C, 31.00; H, 1.45; N, 11.98%).

X-ray structure determination of compound 4

Crystal data. Plate-shaped colourless crystals with dimensions 0.4 × 0.4 × 0.1 mm, $C_9H_{14}N_2O_4S$ $M = 246.28$, triclinic, space group *P*-1 (No. 2), $a = 7.142(1)$, $b = 9.721(2)$, $c = 10.066(2)$ Å, $\alpha = 90.96(3)$, $\beta = 110.51(3)$, $\gamma = 111.43(3)°$, $V = 600.8(2)$ Å^3, $Z = 2$. $D_X = 1.361$ g cm^{-3}. Data were measured on a Philips PW 1100 diffractometer with graphite monochromated Mo-K_α radiation. A total of 2244 reflexions [1315 with $I > 2\sigma(I)$] were collected using the ω-2θ scan technique to a maximum ω value of 25°. The structure was solved by direct methods and refined by full-matrix least squares on F^2 with all non-hydrogen atoms anisotropic.[12] The resulting molecule turned out to be nearly planar with some extreme thermal displacements in the perpendicular direction. Therefore the subsequent refinement was carried out with split atoms S(1), O(2), C(4), C(5), C(7) with an occupation factor 0.5, called *S*(1), *S*(1′) *etc.* This model refined well and allows an interpretation with a chemically meaningful molecule, which actually cannot be co-planar. This disordering can be interpreted as a symmetry transformation of a pseudo monoclinic cell with $a = 11.935$, $b = 7.142$, $c = 14.110$ Å, $\alpha = 89.90$, $\beta = 92.38$ and $\gamma = 90.30°$, with the transformation matrix: (−1, −1, −1; 1, 0, 0; 0, −1, 1). Final R_1 for $F > 4\sigma(F) = 0.060$, wR_2 for all data = 0.186 with weighting scheme $w^{-1} = [\sigma^2(F_o^2) + (0.11P)^2]$. The final ΔF synthesis showed no peaks outside the range +0.18 to −0.29 e Å^{-3}.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic

Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web pages (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/181.

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References

1 For reviews see: H. Kessmann, T. Staub, J. Ligon, M. Oostendorp and J. Ryals, *European J. Plant Pathology*, 1994, **100**, 359; H. Kessmann, T. Staub, C. Hofmann, T. Maetzke and J. Herzog, *Annu. Rev. Phytopathol*, 1994, **32**, 439; H. D. Sisler and N. N. Ragsdale, in *Modern Selective Fungicides*, H. Lyr (ed), Gustav Fischer Verlag, Jena, 1995, 543.
2 R. Schurter, W. Kunz and R. Nyfelter, R. Eur. Pat. Appl. EP 0.313.512A2, 17.8.1988, *Chem. Abstr.*, 1990, **112**, 17750y; W. Kunz; R. Schurter and T. Maetzke, *Pest. Sci.*, 1997, in press.
3 P. Stanetty and W. Kunz, Eur. Pat. App. EP 780394A1, 1997.
4 C. D. Hurd and R. J. Mori, *J. Am. Chem. Soc.*, 1955, **77**, 5359.
5 P. Stanetty, M. Mihovilovic and E. Görner, submitted.
6 B. Holmberg and E. Schjanberg, *Chem. Zentralbl.*, 1941, 2553.
7 F. M. Sieberth, Diploma Thesis, Vienna University of Technology, 1996.
8 M. Fujita, K. Nimura, Y. Kobori, T. Hiyama and K. Kondo, *Heterocycles*, 1995, **41**, 2413.
9 K. Oka, *Synthesis*, 1981, 661 and literature cited therein.
10 D. W. Knight and A. P. Nott, *J. Chem. Soc.*, *Perkin Trans. 1*, 1981, 1125.
11 S. Gronowitz, A. B. Hörnfeldt and K. Peterson, *Synth. Commun.*, 1973, **3**, 213.
12 G. M. Sheldrick, SHELXTL/PC Version 5.03, Siemens Analytical Instrumentation Inc., Madison, WI, 1994.

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