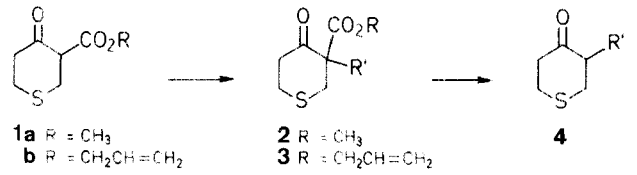
Preparation of 3-Substituted 4-Thianones and Their 1,1-Dioxides via Palladium Mediated Deallyloxycarbonylation

Guy Casy,[a] Alan G. Sutherland,[a] Richard J.K. Taylor,*[a] Peter G. Urben[b]

[a] School of Chemical Sciences, University of East Anglia, Norwich, Norfolk NR4 7TJ, England
[b] Courtaulds Research, PO Box 11, Lockhurst Lane, Coventry CV6 5RS, England

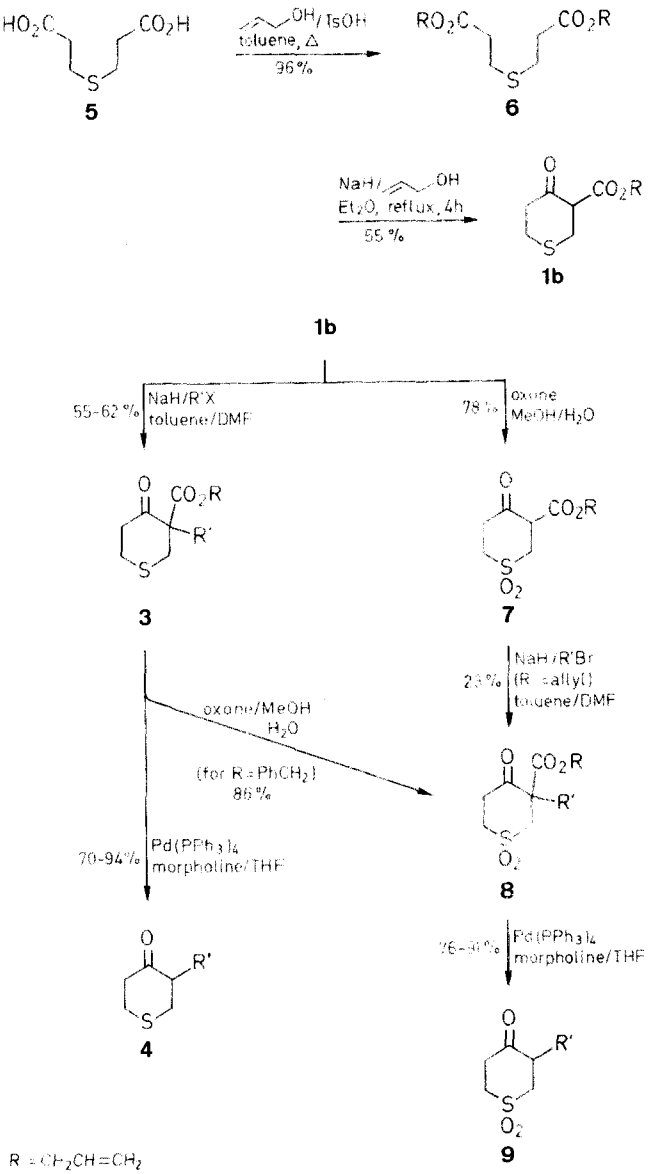
3-Alkyl-4-thianones **4** (3-alkyl-thiacyclohexan-4-ones) can be conveniently prepared by the alkylation of 3-allyloxycarbonyl-4-thianone (**1b**) followed by deallyloxycarbonylation mediated by tetrakis (triphenylphosphine)palladium in the presence of morpholine. The corresponding sulphones **9**, as well as 2,3-dialkyl 4-thianone derivatives **12** and **13** can be prepared by analogous procedures.

3-Alkyl-4-thianones (3-alkyl-thiacyclohexan-4-ones) are versatile intermediates in organic synthesis.[1-4] Generally these compounds have been made[1-4] by the alkylation of the enolate derived from 3-methoxycarbonyl-4-thianone (**1a**) followed by demethoxycarbonylation of the adduct **2**[1-4] (Scheme **A**). The dealkoxycarbonylation of quaternary β-keto esters is often difficult[5] and problems have been reported in the conversion of β-keto esters **2** into ketones **4**.[3,4] Aqueous sulphuric acid gives reasonable yields for the preparation of 3-ethyl and 3-methyl-4-thianone (**4**, R′ = methyl and ethyl) by demethoxycarbonylation[1] but for other substituents harsh *O*-alkyl cleavage procedures (e.g. lithium chloride/hexamethylphosphoric amide at 80 °C[2] or lithium iodide/dimethylformamide at 160 °C[3]) are required and the reactions are slow and proceed in variable yields.



Scheme **A**

A recent report[6] by Tsuji et al. of facile palladium-catalyzed deallyloxycarbonylation reactions of carbocyclic allyl β-ketoesters prompted us to investigate the alkylation–deallyloxycarbonylation of 3-allyloxycarbonyl-4-thianone (**1b**) as a possible general route to 3-alkyl-4-thianones **4**. We report here the successful outcome of these investigations, summarized in Scheme **B** and in Tables 1–3.



3, 4, 8, 9	R′
a	H
b	CH_3
c	$CH_2CH{=}CH_2$
d	CH_2Ph

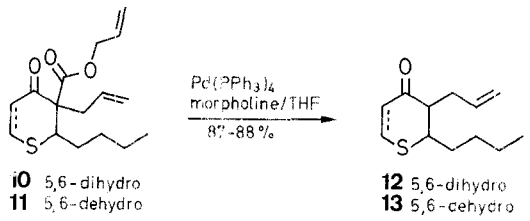
Scheme **B**

β-Ketoester **1b** is easily prepared by Dieckmann cyclization of diallyl 3,3′-thiodipropanoate (**6**), itself obtained by toluenesulphonic acid catalyzed esterification of commercially available 3,3′-thiodipropanoic acid (**5**). Sodium hydride mediated alkylation of β-ketoester **1b** was found to proceed smoothly in good to moderate yields typical of this reaction.[3] 3-Allyloxycarbonyl-4-thianone-1,1,-dioxide (**7**) was prepared by OXONE® (potassium peroxymonosulfate, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) oxidation[8] of **1b** but the alkylation of this compound proceeded in poor yield; the preferred route to 3-alkyl-3-allyloxycarbonyl-4-thianone-1,1-dioxides **8** would therefore appear to be by OXONE® oxidation[8] of the requisite sulphides **3**.

Initial investigations of the deallyloxycarbonylation process revealed that no reaction occured using palladium(II) acetate/triphenylphosphine/triethylammonium formate in either tetrahydrofuran or 1,4-dioxane, the conditions employed by Tsuji et al. for carbocyclic allyl β-ketoesters.[6] We have found, however, that the reaction proceeds smoothly using tetrakis(triphenylphosphine)palladium (0.05 equiv) as catalyst in tetrahydrofuran in the presence of morpholine (20 equiv) as acceptor nucleophile to give 3-alkyl-4-thianones **4** and the corresponding 1,1-dioxides **9** in good to excellent yields (Table 1). This decarboxylation procedure is an adaptation of the one used in the literature[9] for the cleavage of allyl esters of glycopeptides. It is interesting to note that Tsuji et al.[6] found morpholine unsuccessful in the role of acceptor nucleophile in the deallyloxycarbonylation of related carbocyclic allyl β-ketoesters.

We have further applied this methodology to the synthesis of 2,3-dialkyl-4-thianones (Scheme **C**). Thus, 3-allyl-3-allyloxycarbonyl-2-butyl-4-thianone (**10**), readily prepared by modification of a published[3] procedure, was deallyloxycarbonylated to give

thianone **12** in good yield (Scheme C). The methodology is also applicable to related 5,6-dihydro-4-thiinones (e.g. **11** → **13**) and the utility of this transformation has recently been exploited in the synthesis of the natural product tetrahydrodicranenone B.[10]



Scheme C

3,3′-Thiodipropanoic acid (**5**) was supplied by Courtaulds plc, $Pd(PPh_3)_4$ was prepared by a literature procedure.[11] A commercial sample of methyl iodide was used. Allyl bromide and benzyl bromide were distilled and stored over 4 Å molecular sieves, morpholine was distilled from sodium, THF from sodium/benzophenone, toluene from P_2O_5. DMF was stored over CaH_2. Column chromatography was performed on silica gel (Merck 7734). Melting points are uncorrected. Petroleum ether used refers to bp 40–60°C. Mass spectra (70 eV) were obtained on a Kratos MS25 spectrometer, IR spectra on a Perkin-Elmer 297 spectrophotometer. ^{1}H-NMR spectra were obtained on a Jeol PMX-60SI spectrometer and ^{13}C-NMR spectra on a Jeol FX-100 spectrometer.

Diallyl 3,3′-Thiodipropanoate (6):
3,3′-Thiodipropanoic acid (**5**; 1782 g, 10 mol), allyl alcohol (2040 mL, 30 mol) and TsOH (7.50 g, 0.04 mol) are stirred in toluene (500 mL) and gently heated. The ternary azeotrope of toluene, allyl alcohol, and water

Table 1. Deallyloxycarbonylation Reactions

Substrate	Product	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C) or bp (°C)/mbar	^{1}H-NMR ($CDCl_3$/TMS) δ
1b	**4a**	76	61–63	mp 59.2–61.0[2]	2.55–3.10 (m, 8H)
3b	**4b**	92	oil[d]	bp 68–69/4[1]	1.02–1.18 (m, 3H); 2.46–3.06 (m, 7H)
3c	**4c**	70	oil[d]	oil[3]	2.15–3.15 (m, 9H); 4.80–6.05 (m, 3H)
3d	**4d**	94	oil[d]	bp 149/3[2]	2.48–3.16 (m, 9H); 7.16 (br s, 5H)
7	**9a**	85	163–170	164–167[7]	2.64–3.04 (m, 4H); 3.28–3.62 (m, 4H)[c]
8c	**9c**	76	97–98	$C_8H_{12}O_3S$ (188.2)	2.04–3.56 (m, 9H); 4.85–5.26 (m, 2H); 5.38–6.08 (m, 1H)
8d	**9d**	91	123.5–125	$C_{12}H_{14}O_3S$ (238.2)	2.52–3.56 (m, 7H); 6.98–7.44 (m, 5H)
10	**12**	88	oil[d]	oil[3]	0.68–1.84 (m, 9H); 2.32–3.40 (m, 8H); 4.80–6.08 (m, 3H)

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.17, H ±0.19.
[c] Measured in acetone-d_6/TMS.
[d] ^{1}H-NMR, IR, and mass spectral data consistent with published values.

Table 2. 3-Allyloxycarbonyl-4-thian-ones **3b–d** and Dioxides **7** and **8c, d** Prepared

Product	Yield[a] (%)	mp (°C) or bp. (°C)/mbar	Molecular Formula[b]	IR ($CDCl_3$)[c] ν (cm^{-1})
3b	62	oil	$C_{10}H_{14}O_3S$ (214.3)	1730, 1715
3c	57	oil	$C_{12}H_{16}O_3S$ (240.3)	1735, 1715
3d	55	45–48	$C_{16}H_{18}O_3S$ (290.4)	1735, 1720
7[d]	78	200/0.09	$C_9H_{12}O_5S$ (232.3)	1735, 1660, 1615, 1320, 1120
8c	23	oil	$C_{12}H_{16}O_5S$ (272.3)	1740, 1725, 1320, 1125
8d[e]	86	78–81	$C_{16}H_{18}O_5S$ (322.4)	1740, 1725, 1335, 1140

[a] Yield of isolated product, not optimized.
[b] Satisfactory microanalyses obtained: C ±0.40, H ±0.20.
[c] Except **3c**, neat film.
[d] Obtained by OXONE® oxidation of **1b**.
[e] Obtained by OXONE® oxidation of **3d**.

Table 3. NMR Data of Compounds **3b–d**, **7**, and **8c, d**

Compound	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ
3b	1.42 (s, 3H); 2.77–3.23 (m, 6H); 4.66 (br d, 2H, J = 5.4); 5.08–6.26 (m, 3H)	20.8 (q); 30.6, 39.9, 42.7 (t); 59.0 (s); 66.0 (t); 118.8 (t); 131.4 (d); 171.5 (s); 205.1 (s)
3c	2.48–2.75 (m, 2H); 2.89 (br s, 5H); 3.20 (br s, 1H); 4.64 (br d, 2H, J = 5.4); 4.83–6.09 (n, 6H)	30.6, 38.0, 38.8, 43.2 (t); 62.8 (s); 66.1 (t); 119.0, 119.1 (t); 131.4, 132.5 (d); 170.1 (s); 204.7 (s)
3d	2.58–3.54 (m, 8H); 4.54 (br d, 2H, J = 5.4); 5.06–5.90 (m, 3H); 7.21 (br s, 5H)	30.6, 38.0, 39.7, 43.4 (t); 64.2 (s); 66.1 (t); 119.1 (t); 126.9, 128.1, 130.5, 131.2 (d); 135.6 (s); 169.7 (s); 204.6 (s)
7	2.76–3.64 (m, 4.2H); 3.83 (br s, 2H); 4.66 (br d, 2H, J = 5.4); 5.08–5.52 (m, 2H); 5.61–6.28 (m, 1H); 12.64 (s, 0.8H)	29.3, 46.3, 47.3, 66.0 (t); 99.2 (s); 119.2 (t); 131.1 (d); 169.6 (s); 170.0 (s)
8c	2.48–4.08 (m, 8H); 4.68 (br d, 2H, J = 5.5); 4.90–6.32 (m, 6H)	37.4, 39.1, 50.6, 56.1 (t); 59.4 (s); 67.2 (t); 119.7, 121.1 (t); 131.2, 131.3 (d); 168.8 (s); 199.3 (s)
8d	2.71–3.97 (m, 8H); 4.54 (br d, 2H, J = 5.4); 4.93–6.23 (m, 3H); 7.17 (s, 5H)	37.2, 39.7, 50.0, 55.5 (t); 60.4 (s); 67.0 (t); 119.5 (t); 127.4, 128.3, 130.8 (d); 134.1 (s); 168.5 (s); 199.1 (s)

is distilled through an efficient column and the upper layer of the distillate returned to the reaction vessel until a homogeneous distillate is obtained. The residue is then stirred with sat. aq. $NaHCO_3$ solution (1600 mL), separated, and dried ($MgSO_4$). Removal of the solvent under reduced pressure affords the crude product as a pale yellow oil (2470 g, 96%) suitable for Dieckmann cyclization. Kugelrohr distillation of 10.26 g of this oil gives diallyl 3,3'-thiodipropanoate **(6)** as a colourless oil; yield: 10 g (93%); bp 115°C/0.133 mbar.

$C_{12}H_{18}O_4S$	calc.	C 55.79	H 7.02	S 12.41
(258.3)	found	55.77	7.22	12.58

IR (neat): $\nu = 1740\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.40-3.02$ (m, 8H); 4.56 (br d, 4H, $J = 5.4$ Hz); 5.04–5.48 (m, 4H); 5.60–6.22 (m, 2H).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 26.8$, 34.8 (t); 65.1 (t); 117.9 (t); 132.4 (d); 171.0 (s).

MS: m/z (%) = 258 (12); 201 (8); 199 (11); 159 (11); 143 (27); 55 (74); 41 (100).

3-Allyloxycarbonyl-4-thianone (1b):

Allyl alcohol (10.6 mL, 0.155 mol) is added dropwise to a stirred suspension of NaH (dry powder; 3.72 g, 0.155 mol) in anhydrous Et_2O (50 mL) at r.t. under N_2. After stirring for 15 min, a solution of diallyl 3,3'-thiodipropanoate (**6**; 20.0 g, 0.0774 mol) in anhydrous Et_2O (50 mL) is added dropwise over 15 min, and the mixture is heated and reflux for 4 h, then cooled to 0°C. A solution of glacial AcOH (10 mL) in water (50 mL) is added with stirring and the layers separated. The aqueous layer is extracted with Et_2O (2 × 50 mL) and the combined organic layers are washed with aq. sat. $NaHCO_3$ (3 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Column chromatography on silica gel using 5–10% Et_2O/petroleum ether as eluent gives 3-allyloxycarbonyl-4-thinone (**1b**) as a colourless oil (approximately 85% in its enol form); yield 8.64 g (55%); b.p. 128–130°C/3 mbar.

$C_9H_{12}O_3S$	calc.	C 53.98	H 6.04	S 16.01
(200.3)	found	54.27	6.18	16.13

IR (neat): $\nu = 1225$, 1615, 1660, 1715, 1745 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.40-3.39$ (m, 6.15H); 4.66 (br d, 2H, $J = 5.4$ Hz); 5.08–5.54 (m, 2H); 5.64–6.32 (m, 1H); 12.52 (s, 0.85H).

^{13}C-NMR ($CDCl_3$/TMS), *keto tautomer*: $\delta = 30.4$, 32.5, 43.6 (t); 58.7 (d); 65.9 (t); 118.5 (t); 131.6 (d); 171.0 (s); 203.1 (s).

enol tautomer: $\delta = 23.5$, 24.6, 30.9 (d); 65.2 (t); 97.2 (s); 118.2 (t); 131.9 (d); 168.2 (s); 172.7 (s).

MS: $m/z = 200$ (21); 159 (21); 141 (44); 115 (28); 55 (100); 41 (89).

3-Allyloxycarbonyl-4-thianone-1,1-dioxide (7) and 3-Allyloxycarbonyl-3-benzyl-4-thianone-1,1-dioxide (8d); General Procedure:

A solution of OXONE® (4.61 g, 0.0075 mol, 0.015 mol of $KHSO_5$) in water (20 mL) is added dropwise to a stirred solution of the sulphide **1b** or **3d** (0.005 mol) in MeOH (20 mL) at 0°C and stirring continued at r.t. until the reaction is complete (TLC analysis, **7**, CH_2Cl_2/EtOAc, 1:1, **8d**, Et_2O/petroleum ether, 7:3). The mixture is diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers are washed with water (20 mL), brine (20 mL), and dried ($MgSO_4$). The solvent is evaporated, and the residue is purified by Kugelrohr distillation (**7**) or column chromatography on silica gel [**8d**, ether/petroleum ether (1:1)].

3-Alkyl-3-allyloxycarbonyl-4-thianones 3b–d and dioxide 8c; General Procedure:

NaH (dry powder, 0.060 g, 0.00252 mol) is added in one portion to a solution of 3-allyloxycarbonyl-4-thianone (**1b** or its dioxide **7**; 0.0025 mol) and alkyl halide (0.0025 mol) in dry toluene (2.5 mL) and dry DMF (2.5 mL) at room temperature under N_2. Stirring is continued until no starting material remains (TLC analysis, development with 1% $FeCl_3$ in MeOH). The mixture is poured into water (12 mL) and extracted with Et_2O (3 × 8 mL). The combined organic layers are washed with brine (8 mL) and dried ($MgSO_4$). The solvent is evaporated and the residue is purified by column chromatography on silica gel [**3b** and **3c**, Et_2O/petroleum ether (3:7); **3d** and **8c**, Et_2O/petroleum ether (2:3)].

3-Allyl-3-allyloxycarbonyl-2-butyl-4-thianone (10):

3-Allyloxycarbonyl-5,6-dihydro-4-thiinone:[3] A mixture of 3-allyloxycarbonyl-4-thianone (**1b**; 2.30 g, 11.5 mmol) and activated MnO_2 (10.0 g, 0.115 mol) in $CHCl_3$ (100 mL) is heated under azeotropic reflux in a Soxhlet apparatus containing 4 A molecular sieves for 2 h. The mixture is cooled, filtered through Celite and the filtrate is concentrated under reduced pressure. Column chromatography on silica gel eluting with petroleum ether → EtOAc, 7:3 gives 3-allyloxycarbonyl-5,6-dihydro-4-thiinone as a colourless oil; yield: 1.25 g (55%).

Conversion of 3-Allyloxycarbonyl-5,6-dihydro-4-thiinone to 3-Allyloxycarbonyl-2-butyl-4-thianone: A solution of CuI (2.09 g, 11 mmol) in anhydrous Me_2S (8 mL) is added dropwise to a stirred solution of BuLi (1.48 M solution in hexanes, 7.43 mL, 11.0 mmol) in anhydrous Et_2O at −78°C under N_2. After 15 min a solution of 3-allyloxycarbonyl-5,6-dihydro-4-thiinone (1.982 g, 10.0 mmol) in anhydrous Me_2S (10 mL) is added dropwise and stirring is continued for 25 min. The reaction is quenched with 2% H_2SO_4 (70 mL), and extracted with Et_2O (3 × 50 mL). The combined organic extracts are washed with 5% ammonia solution (30 mL), filtered and washed sequentially with 5% aq. ammonia solution (30 mL), aq. sat. NH_4Cl solution (30 mL) and brine (30 mL). The solution is dried ($MgSO_4$), the solvent evaporated and the residue purified by column chromatography on silica gel eluting with petroleum ether/Et_2O (9:1), to give 3-allyloxycarbonyl-2-butyl-4-thianone as a pale yellow oil; yield: 2.182 g (85%). The spectroscopic data are consistent with literature[3] values (keto/enol ratio, ~ 30:70).

Alkylation of 3-Allyloxycarbonyl-2-butyl-4-thianone with Allyl Bromide to **10**: 3-Allyloxycarbonyl-2-butyl-4-thianone is alkylated immediately using NaH and allyl bromide following the general procedure described earlier to give 3-allyl-3-allyloxycarbonyl-2-butyl-4-thianone (**10**) as a colourless oil; yield: 2.00 g (88%). The following spectroscopic data are in agreement with reported[3] values.

IR (neat): $\nu = 1640$, 1730 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 0.68-3.28$ (m, 16H); 4.52–4.80 (m, 2H); 4.87–6.28 (m, 6H).

Deallyloxycarbonylation Products 4a–d, 9a, c, d and 12; General Procedure:

Morpholine (0.872 mL, 10 mmol), then $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol) are added to a stirred solution of allyl β-ketoester **3** or **8** (1.0 mmol) in dry THF (10 mL) under N_2 at room temperature. Stirring is continued until TLC analysis indicates that all starting material has disappeared. The mixture is filtered, concentrated under reduced pressure, then purified by column chromatography on silica gel [**4a, b** and **d**, Et_2O/petroleum ether (1:9); **4c**, Et_2O/petroleum ether (1:4); **9a**, CH_2Cl_2/ EtOAc (2:1); **9c**, Et_2O; **9d**, Et_2O/ petroleum ether (1:1 → Et_2O); **12**, Et_2O/petroleum ether (1:5)].

We would like to thank the S.E.R.C. for studentships (G.C. and A.G.S.), the Royal Society of Chemistry for the award of a Hickinbottom Fellowship (R.J.K.T.) and Courtaulds Research plc for further financial assistance.

Received: 26 January 1989; revised: 28 March 1989

(1) Takemura, T., Jones, J.B. *J. Org. Chem.* **1983**, *48*, 791.
(2) Matsuyama, H., Miyazawa, Y., Takei, Y., Kobayashi, M. *J. Org. Chem.* **1987**, *52*, 1703.
(3) Lane, S., Quick, S.J., Taylor, R.J.K. *J. Chem. Soc. Perkin Trans. 1* **1985**, 893.
(4) Casy, G., Lane, S., Taylor, R.J.K. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1397.
(5) Hashimoto, S., Shinoda, T., Ikegami, S. *J. Chem. Soc. Chem. Commun.* **1988**, 1137, and references therein.
(6) Tsuji, J., Nisar, M., Shimizu, I. *J. Org. Chem.* **1985**, *50*, 3416.
(7) Fehnel, E.A., Carmack, M. *J. Am. Chem. Soc.* **1948**, *70*, 1813.
(8) Trost, B.M., Curran, D.P. *Tetrahedron Lett.* **1981**, *22*, 1287.
(9) Friedrich-Bochnitschek, S., Kunz, H., Waldmann, H. *J. Org. Chem.* **1989**, *54*, 751, and references therein.
(10) Casy, G., Taylor, R.J.K. *J. Chem. Soc. Chem. Commun.* **1988**, 454. Casy, G., Taylor, R.J.K. *Tetrahedron* **1989**, *45*, 455.
(11) Coulson, D.R. *Inorg. Synth.* **1972**, *13*, 121.