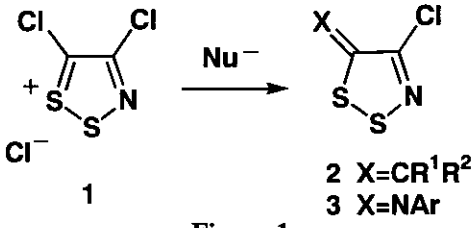
NEW SYNTHESIS OF 5-CYANO-1,2,4-THIADIAZOLES

Tsuneo Iwakawa* and Akira Murabayashi

Aburahi Laboratories, Shionogi & Co., Ltd., Koka, Shiga 520-3423, Japan

Abstract — Treatment of 4-chloro-5-(3-isoxazolylimino)-5*H*-1,2,3-dithiazoles with piperidine in dichloromethane gave 5-cyano-1,2,4-thiadiazoles (51.8 %-92.1 % yield).

Considerable attention has been paid to Appel's salt (4,5-dichloro-1,2,3-dithiazolium chloride) (1) due to its facile preparation and potential synthetic utility.[1] In regard to the field of heterocycles comprising polysulfur-nitrogen bonds, the chemistry of 1 was reviewed, covering useful conversion of compound (2) into benzothiophene derivatives, and 5-arylimino-4-chloro-5*H*-1,2,3-dithiazole (3) into benzothiazole and benzoxazole derivatives or alternatively into cyanoimidoyl chlorides.[2] Furthermore compound (3), prepared by the reaction of Appel's salt with primary arylamine in dichloromethane in the presence of pyridine, was shown to be an interesting class of heterocycle exhibiting a variety of biological activities,[3] and to have potential utility as a synthetic intermediate.[4]



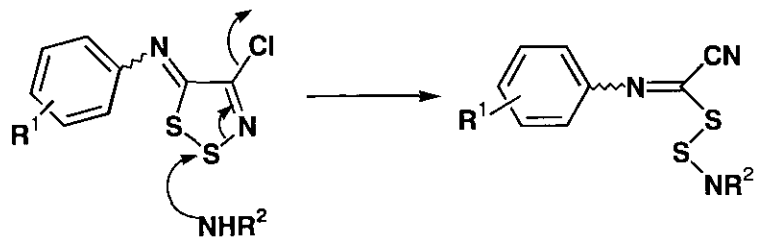
1

2 X=CR¹R²
3 X=NAr

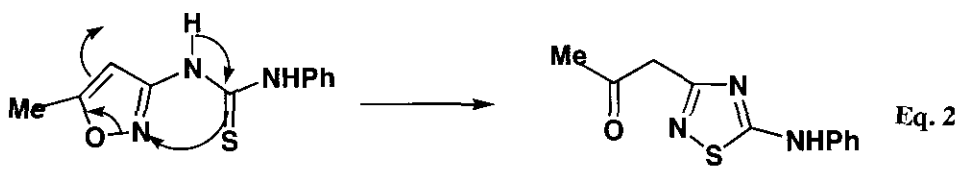
Figure 1

Compound (3) is a heterocycle having nucleophilic centers at the S-1, S-2, C-4 and C-5 positions due to delocalization of 6π electrons over the five membered ring. For instance, nucleophilic participation of the S-2 position was shown by isolation of various

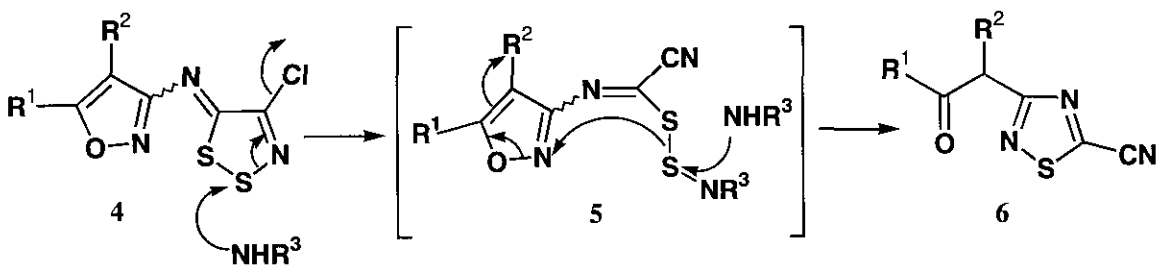
(arylimino)cyanomethyl (alkyl)amino disulfides through the reaction of 3 with either primary or secondary alkylamines.[4b] Treatment of 3 with several bulky secondary alkylamines in dichloromethane at room temperature gave 5-arylimino-4-dialkylamino-5*H*-1,2,3-dithiazoles *via* disulfides.[4c]



Eq. 1



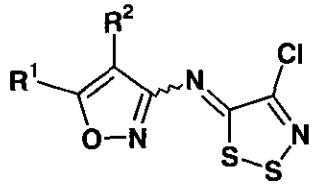
Eq. 2



Scheme

To develop further utilization of Appel's salt in organic synthesis, new routes to heterocyclic compounds were investigated. We assumed that 4-chloro-5-(3-isoxazolylimino)-5*H*-1,2,3-dithiazoles (4) could be converted to 5-cyano-1,2,4-thiadiazole derivatives (6) *via* reaction with a secondary amine, because the secondary amine might attack the sulfur atom at position 2 of the dithiazole ring to give (arylimino)cyanomethyl alkylamino disulfide (Eq. 1),[4b] which might be followed by a conversion reaction, for example, from 3-phenylthioureido-5-methylisoxazole leading to 3-acetonyl-5-phenylamino-1,2,4-thiadiazole in the presence of a base at room temperature (Eq. 2).[5] (Scheme)

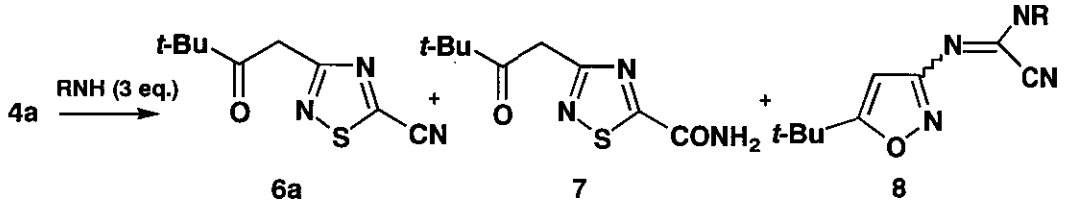
Herein, we describe our effort to develop a new synthetic method for 5-cyano-1,2,4-thiadiazole derivatives by using Appel's salt.



	R^1	R^2		R^1	R^2
4a	*t*-Bu	H	4e	Ph	H
4b	*n*-Bu	H	4f	*t*-Bu	Me
4c	*i*-Pr	H	4g	H	H
4d	Me	H			

Figure 2

The starting compounds, 4-chloro-5-(3-isoxazolylimino)-5*H*-1,2,3-dithiazoles (**4a-4g**), were prepared from the corresponding 3-aminoisoxazoles by a known procedure,[1] and various bases were examined to optimize the reaction conditions, while yields were compared with that in the case of **4a** using 3 equivalents base. The choice of base was found critical for the reaction to proceed favorably as shown in Table 1.



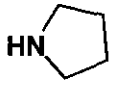
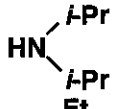
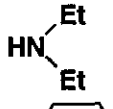
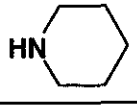
Entry	RNH	Solvent	Reaction conditions		Isolated yield (%)		
			Temperature	Time (h)	6a	7	8
1		CH_2Cl_2	rt	3	60.0	6.1	–
2		CH_2Cl_2	rt	1	37.3	–	43.8
3		$ClCH_2CH_2Cl$	reflux	19	21.1	–	–
4		CH_2Cl_2	rt	1.5	80.3	–	–
5		CH_2Cl_2	rt	1	92.1	–	–

Table 1

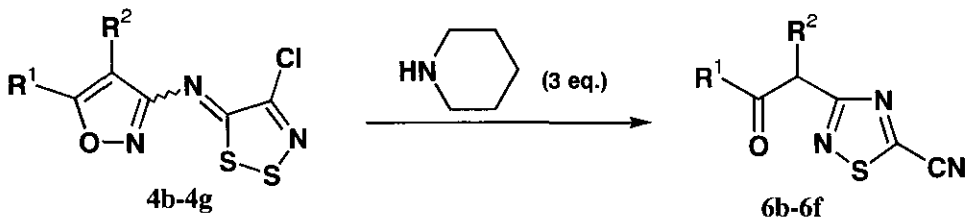
Thus, the reaction of **4a** with morpholine at room temperature for 3 h gave **6a** in 60.0 % yield and **7** in 6.1 % yield while 26.0 % of **4a** was recovered (Entry 1). When **4a** was treated with diisopropylamine, **6a** was obtained in 21.1 % yield with recovery of **4a** (78.0 %) (Entry 3).

The high recovery of **4a** would be due to steric hindrance by the two bulky isopropyl groups. In the case of using pyrrolidine (Entry 2), **6a** and 8 were obtained in 37.3 % and 43.8 % yields, respectively. On the other hand, similar treatment with diethylamine or piperidine (Entry 4 or 5) provided **6a** as the sole product in 80.3 % and 92.1 % yields, respectively.

These results led us to assume that the attack of pyrrolidine at the cyano substituted iminocarbon in the amino iminomethyl disulfide moiety of 5 might be preferred over attack at the sulfur atom α to the nitrogen atom of the amine moiety of 5, whereas either piperidine or diethylamine might selectively attack at the sulfur atom to provide 6 (Scheme).

In order to verify the assumption, attempts were made to isolate 5 (R^1=*t*-Bu,R^2=H), but were without success presumably due to the rapid transformation from 5 (R^1=*t*-Bu,R^2=H) into **6a**.

From these findings, we found that piperidine was the most favorable base among those tested. Having selected piperidine as the base, we next investigated the feasibility of the reaction for several other 4-chloro-5-(3-isoxazolylimino)-5*H*-1,2,3-dithiazoles (**4b-4g**).



4b-4g **6b-6f**

Entry	Substrate	R^1	R^2	Reaction conditions	Solvent	Product	(yield,%)
1	4b	*n*-Bu	H	rt, 1.5 h	CH_2Cl_2	6b	74.2
2	4c	*i*-Pr	H	rt, 1 h	CH_2Cl_2	6c	64.1
3	4d	Me	H	rt, 1 h	CH_2Cl_2	6d	25.7
4	4d	Me	H	-25℃ ⟶ rt	CH_2Cl_2	6d	80.4
5	4e	Ph	H	0℃ 30 min, then rt, 2 h	CH_2Cl_2	6e	70.3
6	4f	*t*-Bu	Me	rt, 2 days	THF	6f	51.8
7	4g	H	H	–	–	6g	0

Table 2

Thus, we carried out reactions of **4b-4g** with piperidine (Entries 1-7) and the results are shown in Table 2. Treatment of **4d** with piperidine at room temperature afforded **6d** in 25.7 % yield (Entry 3), although when the reaction was carried out initially at -25 ℃ and

then gradually warmed up to room temperature, the yield of **6d** was improved up to 80.4 % (Entry 4). In a similar manner, **6e** was obtained in 70.3 % yield (Entry 5).

When compounds (**4b,c**) were treated with piperidine at room temperature, corresponding 5-cyano-1,2,4-thiadiazoles (**6b,c**) were obtained in 74.2 % and 64.1 % yields, respectively (Entries 1,2). These yields could not be improved even when the reactions were conducted in a similar manner as Entry 4.

In the case of **4f**, a longer reaction time (2 days) was required for completion of the reaction. Several attempts to obtain **6g** from **4g** were without success (Entry 7), instead a complex mixture resulted, which may be ascribed to the lability of **6g** under the reaction conditions employed.

With 1,2,4-thiadiazole derivatives, attempts to exchange the highly reactive 5-chloro group with a cyano group were mostly unsuccessful.[6] Only one procedure was shown to synthesize a 5-cyano-1,2,4-thiadiazole derivative, that is, 3,5-dicyano-1,2,4-thiadiazole by the reaction of cyanogen with sulfur, but the yield was quite unsatisfactory (29 %).[7]

In conclusion, we found a new route to synthesize 5-cyano-1,2,4-thiadiazole derivatives from readily available Appel's salt.

EXPERIMENTAL

All melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were taken with a JEOLJNM-GSX 270 and a JEOLJNM A-400 spectrometer, respectively. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane, and the coupling constants are in Hz. Silica gel column chromatography was carried out using Kiesel gel 60 (70-230 mesh, Merck). Preparative TLC was performed on Merck Silica gel 60 F_{254} plates (0.5 mm thickness).

5-Cyano-3-(3,3-dimethyl-2-oxobutyl)-1,2,4-thiadiazole (6a)

Piperidine (460 mg, 5.4 mmol) was added in small portions at rt to a solution of 4-chloro-5-(5-*t*-butyl-3-isoxazolylimino)-5*H*-1,2,3-dithiazole (**4a**) (500 mg, 1.8 mmol) in dry CH_2Cl_2 (15 mL), and the mixture was stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2, and the solution was washed with brine. The organic layer was dried over Na_2SO_4, then the solvent was evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt=3:1) to give **6a** (350 mg, 92.1 %), mp 64-66 ℃ (*n*-hexane). IR($CHCl_3$) 2240,

1715, 1475, 1140, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.26 (9H, s), 4.36 (2H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.09 (q, 3C), 40.46 (t), 44.64 (s), 110.15 (s), 157.54 (s), 172.30 (s), 208.98 (s); *Anal.* Calcd for $C_9H_{11}N_3OS$: C, 51.66; H, 5.29; N, 20.08. Found: C, 51.62; H, 5.34; N, 20.03.

5-Cyano-3-(2-oxohexyl)-1,2,4-thiadiazole (6b)

Piperidine (255 mg, 3.0 mmol) was added in small portions at rt to a solution of 4-chloro-5-(5-*n*-butyl-3-isoxazolylimino)-5*H*-1,2,3-dithiazole (**4b**) (275 mg, 1.0 mmol) in dry CH_2Cl_2 (15 mL), and the mixture was stirred for 1.5 h. After addition of cold 1N-HCl (20 mL), the reaction mixture was diluted with CH_2Cl_2, and the whole solution was washed with brine. The organic layer was dried over Na_2SO_4, then the solvent was evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt=4:1) to give **6b** (155 mg, 74.2 %), mp 38-39 ℃ (*n*-hexane). IR(KBr) 2957, 2247, 1710, 1473, 1386, 1146cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, t, J=7.3), 1.34 (2H, m), 1.63 (2H, m), 2.59 (2H, t, J=7.3), 4.25(2H,s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.75 (q), 22.11(t), 25.57 (t), 42.64(t), 45.99(t), 102.21 (s), 157.85 (s), 171.63 (s), 203.89 (s); *Anal.* Calcd for $C_9H_{11}N_3OS$: C, 51.66; H, 5.30; N, 20.08. Found: C, 51.35; H, 5.40; N, 19.76.

5-Cyano-3-(3-methyl-2-oxobutyl)-1,2,4-thiadiazole (6c)

Piperidine (255 mg, 3.0 mmol) was added in small portions at rt to a solution of 4-chloro-5-(5-*i*-propyl-3-isoxazolylimino)-5*H*-1,2,3-dithiazole (**4c**) (262 mg, 1 mmol) in dry CH_2Cl_2 (9 mL), and the mixture was stirred for 1 h. After addition of cold 1N-HCl (20 mL), the reaction mixture was diluted with CH_2Cl_2, and the whole solution was washed with brine. The organic layer was dried over Na_2SO_4, then the solvent was evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt=4:1) to give **6c** (125 mg, 64.1 %), mp 35-36 ℃ (*n*-hexane). IR(KBr) 2975, 2245, 1475, 1718, 1469, 1141, 1047cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.21 (6H, d, J=6.8), 2.79 (1H, sept, J=6.8), 4.32 (2H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 17.95 (q), 41.18(d), 43.75 (t), 100.15 (s), 157.78(s), 171.84 (s), 207.36 (s); *Anal.* Calcd for $C_8H_9N_3OS$: C, 49.43; H, 4.74; N, 21.55. Found: C, 49.22; H, 4.74; N, 21.55.

3-Acetonyl-5-cyano-1,2,4-thiadiazole (6d)

A solution of piperidine (2.19 g, 25.7 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to a

pre-cooled solution of 4-chloro-5-(5-methyl-3-isoxazolylimino)-5*H*-1,2,3-dithiazole (**4d**) (2.0 g, 8.56 mmol) in dry CH_2Cl_2 (60 mL) at -25 ℃. The dry ice bath was removed, and the reaction mixture was stirred at rt for 25 min. After addition of cold 2N-HCl (30 mL), the mixture was extracted with CH_2Cl_2, and the extract was washed with brine, then dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane-AcOEt=2:1) to give **6d** (1.15 g, 80.4 %), mp 50-52 ℃ (*n*-hexane-toluene). IR($CHCl_3$) 2240, 1733, 1475, 1161, 1142 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 2.33 (3H, s), 4.27 (2H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 29.96 (q), 46.84 (t), 110.09 (s), 157.91 (s), 171.34 (s), 201.25 (s); *Anal.* Calcd for $C_6H_5N_3OS$: C, 43.10; H, 3.01; N, 25.13. Found: C, 43.11; H, 3.14; N, 25.21.

5-Cyano-3-phenacyl-1,2,4-thiadiazole (6e)

A solution of piperidine (860 mg, 10.1 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to an ice-cooled solution of 4-chloro-5-(5-phenyl-3-isoxazolylimino)-5*H*-1,2,3-dithiazole (**4e**) (1.0 g, 3.4 mmol) in dry CH_2Cl_2 (40 mL) and the resulting mixture was stirred for 30 min. The ice bath was removed, and the reaction mixture was stirred at rt for 2 h. After addition of cold 2N-HCl (20 mL), the mixture was extracted with CH_2Cl_2, and the extract was washed with brine, then dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane-AcOEt=2:1) to give 11 (545 mg, 70.3 %), mp 72-73 ℃ (*n*-hexane). IR ($CDCl_3$) 2245, 1698, 1478, 1335, 1142 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 4.84 (2H, s), 7.52 (2H, t, J=7.9), 7.63 (1H, dd, J=7.9, 1.8), 8.02(2H, dd, J=7.9, 1.8); ^{13}C-NMR.($CDCl_3$, 100 MHz) δ 42.53 (t), 110.17 (s), 128.46 (d, 2C), 128.90 (d, 2C), 133.90 (d), 135.69 (s), 157.92 (s), 171.92 (s), 193.31 (s); *Anal.* Calcd for $C_{11}H_7N_3OS$: C, 57.63; H, 3.08; N, 18.33. Found: C, 57.58; H, 3.26; N, 18.40.

5-Cyano-3-(3,3-dimethyl-1-methyl-2-oxobutyl)-1,2,4-thiadiazole (6f)

Piperidine (128 mg, 1.5 mmol) was added in small portions at rt to a solution of 4-chloro-5-(5-*t*-butyl-4-methyl-3-isoxazolylimino)-5*H*-1,2,3-dithiazole (**4f**) (145 mg, 0.5 mmol) in dry THF (10 mL), and the mixture was stirred for 2 days. After removal of the solvent, the residue was purified by preparative silica gel TLC with 25 % AcOEt in hexane to give **6f** (58 mg, 51.8 %), oil. IR(KBr) 2972, 2237,1712, 1465, 1141, 986 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.24 (9H, s), 1.63(3H, d, J=6.7), 4.85 (1H, q, J=6.7); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 17.19 (q), 26.10 (q, 3C), 43.95 (d), 45.39 (s), 110.22 (s), 157.55 (s), 176.96 (s), 212.18 (s); *Anal.* Calcd for $C_{10}H_{13}N_3OS$: C, 53.79; H, 5.87; N, 18.82. Found: C, 53.91; H, 5.94; N, 18.62.

5-Carbamoyl-3-(3,3-dimethyl-2-oxobutyl)-1,2,4-thiadiazole (7)

Morpholine (940 mg, 10.8 mmol) was added in small portions at rt to a solution of 4-chloro-5-(5-*t*-butyl-3-isoxazolylimino)-5*H*-1,2,3-dithiazole (**4a**) (1.0 g, 3.6 mmol) in dry CH_2Cl_2 (30 mL), and the mixture was stirred for 3 h. The reaction mixture was diluted with CH_2Cl_2, and the whole solution was washed with brine. The organic layer was dried over Na_2SO_4, then the solvent was evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt=3:1) to give **6a** (450 mg, 60.0 %) and 7 (50 mg, 6.1 %), mp 154-156 ℃ (*n*-hexane-AcOEt). IR($CHCl_3$) 3520, 3400, 1695, 1580, 1495 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.26 (9H, s), 4.27 (2H, s), 5.74 (1H, br s), 7.00 (1H, br s); *Anal.* Calcd for $C_9H_{13}N_3O_2S$: C, 47.56; H, 5.77; N, 18.49. Found: C, 47.46; H, 5.84; N, 18.23.

***N'*-(5-*t*-Butyl-3-isoxazolyl)-*N,N*-(butane-1,4-diyl)cyanoformamidine (8)**

A solution of pyrrolidine (770 mg, 10.8 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to an ice-cooled solution of 4-chloro-5-(5-*t*-butyl-3-isoxazolylimino)-5*H*-1,2,3-dithiazole (**4a**) (1.0 g, 3.6 mmol) in dry CH_2Cl_2 (30 mL) and the whole mixture was stirred for 10 min. After removing the ice bath, the reaction mixture was stirred at rt for 1 h and diluted with CH_2Cl_2, then the whole mixture was washed with brine. The organic layer was dried over Na_2SO_4 and evaporated, and the product was purified by silica gel column chromatography (*n*-hexane-AcOEt=2:1) to give **6a** (280 mg, 37.3 %) and 8 (890 mg, 43.8 %), mp 69-70 ℃ (*n*-hexane-AcOEt). IR($CHCl_3$) 2992, 1620, 1597, 1390, 1372 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.34 (9H, s), 2.04 (4H, brs), 3.59 (2H, brs), 3.78(2H, brs), 5.86(1H, s); *Anal.* Calcd for $C_{13}H_{18}N_4O$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.09; H, 7.29; N, 22.61.

REFERENCES AND NOTES

1.(a) R. Appel, H. Janssen, M. Siray, and F. Knoch, *Chem. Ber.*, 1985, **118**, 1632. (b) J. J. Folmer and S. M. Weinreb, *Tetrahedron Lett.*, 1993, **34**, 2737. (c) A. M. Cuadro and J. Alvarez-Builla, *Tetrahedron*, 1994, **50**, 10037.

2. C. W. Rees, *J. Heterocycl. Chem.*, 1992, **29**, 639.

3. (a) J. E. Moore, U.S. Patent, 1977, 4059590 [*Chem. Abstr.*, 1978, **88**, 50874a]. (b) R. Mayer, E. Foerster, and B. Matauschek, Ger. (East) DD, 1984, 212387 [*Chem. Abstr.*, 1985, **102**, 113064s]. (c) G. Cottenceau, T. Besson, V. Gautier, C. W. Rees, and A.-M.

Pons, *Bio. Med. Chem. Lett.*, 1996, 6, 529. (d) V. Thiéry, C. W. Rees, T. Besson, G. Cottenceau, and A.-M. Pons, *Eur. J. Med. Chem.*,1998, 33, 149.

4. (a) K. C. Oh, H. Lee, and K. Kim, *Tetrahedron Lett.*, 1992, 33, 4963. (b) H. Lee and K. Kim, *J. Org. Chem.*, 1993, 58, 7001. (c) H. Lee, K. Kim, D. Whang, and K. Kim, *J. Org. Chem.*, 1994, 59, 6179. (d) H.-S. Lee and K. Kim, *Tetrahedron Lett.*, 1996, 37, 869.
5. N. Vivona, G. Cusmano, and G. Macaluso, *J. Chem. Soc., Perkin Trans.1*, 1977, 1616.
6. (a) J. Goerdeler, H. Groschopp, and U. Sommerlad, *Chem. Ber.*, 1957, 90, 182. (b) J. Goerdeler and K.-H. Heller, *Chem. Ber.*, 1964, 97, 225.
7. H.W. Roesky, K. Keller, and J.W. Bats, *Angew. Chem., Int. Ed. Engl.*, 1983, 22, 881.

Received, 17th December, 1998