Pergamon

*Tetrahedron*, Vol. 52, No. 4, pp. 1259-1266, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00956-6

# Electrosynthesis of 2-Benzhydrylidene-4,4-diphenyl-[1,3]oxathiolan-5-one: the Reaction Pathway.

**José I. Lozano and Fructuoso Barba***

Departamento de Química Orgánica. Universidad de Alcalá. 28871-Alcalá de Henares. Madrid. Spain.

***Abstract:*** The pathway for the electrochemical formation of 2-benzhydrylidene-4,4-diphenyl-[1,3]oxathiolan-5-one (**2**), in dichloromethane tetraethylammonium bromide on graphite cathode is proposed. It involves reaction between electrogenerated diphenylketene (**3**), 2-bromo-2,2-diphenylacetyl bromide (**1**) and sulfide anion. The latter is formed from $H_2S$ generated in the anodic compartment and electrogenerated bases.

In our research group, electrochemical techniques have been very successful in the field of heterocyclic organic synthesis. So, we have carried out the synthesis of 3,7-diaryl-2*H*-imidazo[2,1-*b*][1,3,4]oxadiazines by electroreduction of semicarbazones of phenacyl bromide,[1] α- and γ-6-benzyl-3,5-diphenylhydroxypyranones and the corresponding phenylacetate derivative of the latter by cathodic reduction of 2-chloro-2-phenylacetyl chloride[2] and N-substituted 2-imidazolones by reduction of imidazooxadiazines,[3] among others.

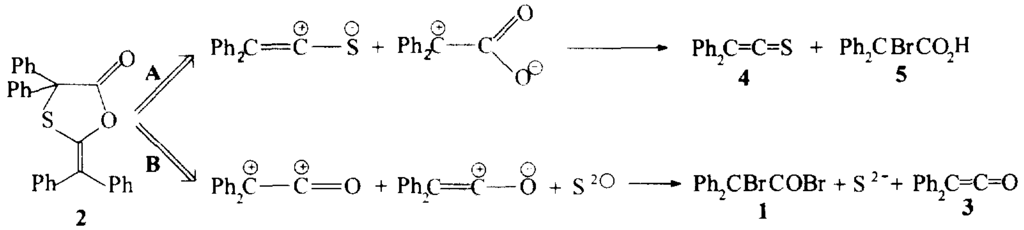
In a previous communication we have described that an [1,3]oxathiolan-5-one can be obtained by electroreduction of a α-haloacyl halide.[4] Several of such compounds have shown pharmaceutical, bactericidal, herbicidal and fungicidal properties. Thus, 2-ylidene-[1,3]oxathiolan-5-ones are used as antiinflammatory agents and bactericides,[5] having chymotrypsin inhibitory activity;[6] 2-trichloromethyl-[1,3]oxathiolan-5-ones inhibit the growth of barley,[7] and many others have been employed as insecticides and fungicides[8] against *Tetranychus telarius* and *Calandra granaria* on scarlet runner beans and seed wheat, *Phytophthora infestants* on tomato plants, etc. Some [1,3]oxathiolan-5-ones are important intermediates in the synthesis of anti-HIV-1 nucleosides for human PBM cells[9] and of compounds to prevent hepatitis B virus infection.[10]

In this work we make a careful study of the mechanism of the electrochemical formation of 2-benzhydrylidene-4,4-diphenyl-[1,3]oxathiolan-5-one (**2**), which opens a new way of synthesis for this interesting compound.

## RESULTS AND DISCUSSION

We have recently reported the cathodic reduction of 2-bromo-2,2-diphenylacetyl bromide (**1**) in dichloromethane tetraethylammonium bromide on graphite cathode, under an argon atmosphere, in a divided cell.[4] To prevent the bromine formed in the anodic process from entering the cathodic compartment, a layer of solid sodium thiosulphate was placed on the diaphragm in the anodic side. Under these conditions, and after the work up of the catholyte, we obtained unexpectedly 2-benzhydrylidene-4,4-diphenyl-[1,3]oxathiolan-5-one (**2**) in 21% yield. We now report a study of the mechanism of the electrochemical formation of **2**.

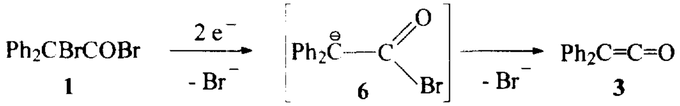
Retrosynthetic analysis suggests two diferent pathways by which **2** might be formed (Scheme 1):



**Scheme 1**

Route A involves 2-bromo-2,2-diphenylacetic acid (**5**), which can only be formed if water is present in the reaction medium, and diphenylthioketene (**4**). We can reject this route due to the fact that **4** is very unstable, polymerizing immediately,[11] and the reaction is carried out in an anhydrous medium. Route B seems to be more likely because intermediates corresponding to the synthons shown can be formed from the starting material in a logical process.

The electrochemical reduction of **1** in the absence of sodium thiosulfate, using the general electrolysis procedure, led to the formation of diphenylketene (**3**) in an almost quantitative yield. In this manner, the presence of **3** in the reaction medium was confirmed (Scheme 2).



**Scheme 2**

To determine how a sulfur atom has been put in **2** when the only sulfur compound in the cell was sodium thiosulfate (placed as a solid layer in the anodic side of the diaphragm), some chemical and electrochemical reactions were carried out. A porous frit glass was employed in the electrochemical reaction, and it is possible that a part of this layer could pass through the diaphragm to the cathodic compartment either mechanically or by the ammonium salt employed as electrolyte in a phase-transfer process.[12] To reject this theory, a chemical reaction between **1** and sodium thiosulfate in dichloromethane, using tetraethylammonium bromide as a phase-transfer catalyst, and argon atmosphere, was carried out. After 24 h with vigorous stirring, reagents were recovered without change. When this mixture was electrolyzed, using the general procedure, **3** was obtained.

On the other hand, in the literature decomposition of thiosulfuric acid in anhydrous media was described:[13]

$$Na_2S_2O_3 + 2\,H^+ \xrightarrow[\text{medium}]{\text{anhydrous}} \left[H_2S_2O_3\right] \xrightarrow[\text{room temp.}]{\text{fast}} H_2S + SO_3$$

**Scheme 3**

Therefore, due to the anodic compartment always has acidic character, it is logical to consider the formation of thiosulfuric acid, which could supply hydrogen sulfide to the reaction medium by decomposition ( its smell was detected ). To confirm this process, a new electroreduction of **1** was carried out in which a layer of anhydrous potassium carbonate was placed between the anodic side of the diaphragm and the thiosulfate layer. Under these conditions, **2** was not formed due to the neutralization of the acid produced.

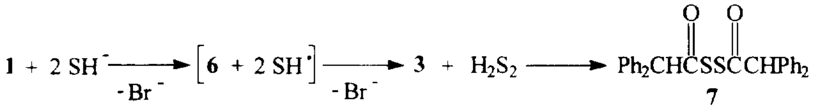
Hydrogen sulfide formed in the anodic compartment could pass to the catholyte either as itself or as an oxidized specie ($S^0$ or even $S^{+2}$) on the anode. The last hypothesis was discarded on the basis of several electrochemical reductions of **1** without sodium thiosulfate in the anode. In a first one, a layer of $S_8$ was placed on the anodic side of the diaphragm and the process did not lead to **2**. In a second one, stoichiometric amounts of **1** and $S_8$ were reduced together, under the general electrolysis procedure, giving a mixture of diphenylacetyl disulfide (**7**) and **3**. The possible influence of $S^{+2}$ in the formation of **2** was determined by electroreduction of **1** using a carbon-sulphur electrode as anode, instead of platinum, as a source of $S_x^{+2}$ in solution.[14] Under these conditions **2** was not formed. Therefore, hydrogen sulfide has to be responsible for forming **2**.

The reduction of **1** in the presence of a saturated solution of $H_2S$, the latter bubbled directly into the catholyte, led to a mixture of **3** and products formed by reaction of intermediates with the solvent. However, when the reaction was performed in the presence of a small amount of $H_2S$, **2** was now obtained.

To form **2**, $H_2S$ which passed through the diaphragm to the cathodic compartment, could react as itself, be reduced to sulfide or hydrogensulfide anion on the cathode, or be deprotonated toward these products by electrogenerated bases. When dry hydrogen sulfide was bubbled at 0°C in a mixture of **1** and **3**, **2** was not formed. Cyclic voltametry and preparative electrolysis of a saturated solution of $H_2S$ in dichloromethane at 20°C showed that the latter is not reduced at the reaction potential of **1**. Thus, hydrogen sulfide has to be deprotonated by electrogenerated bases towards $HS^-$ or $S^{2-}$.

To establish which of these last species is responsible for forming **2**, a chemical reaction between **1** and **3** with tetraethylammonium hydrogensulfide[15] was carried out, leading to the formation of **7** in 40% yield and a large amount of **3**, without evidence of the corresponding products of nucleophilic substitution on **1** (Scheme 4). The fact that a non-brominated acyldisulfide and a ketene were formed in this reaction shows the existence of a redox process between **1** and $HS^-$. In this process hydrogensulfide anion transfers an electron on **1**, forming $HS^\cdot$ and $Ph_2\dot{C}COBr$ radicals. A further electron transfer by other hydrogensulfide anion on the last radical produces **6**, which decomposes to **3**, and other $HS^\cdot$ radical. The latter is very reactive and dimerizes immediately to hydrogen disulfide.

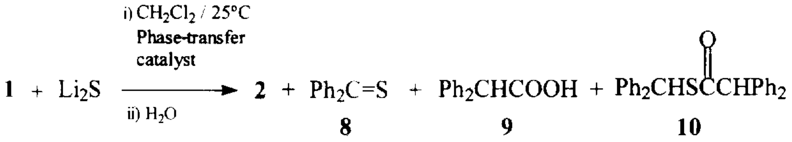
To favor cross coupling between $HS^\cdot$ and $Ph_2\dot{C}COBr$ radicals and to avoid a second electron transfer on the last radical, a new chemical reaction was carried out in which a stoichiometric amount of tetraethylammonium hydrogensulfide was added dropwise over **1**. Under these conditions **1** was in a high excess with respect to $HS^-$ and the same compounds were formed again. All of these reactions lead us to reject to $HS^-$ as a reagent in the process.



$$1 + 2\,SH^- \xrightarrow[-Br^-]{} \left[6 + 2\,SH^\bullet\right] \xrightarrow[-Br^-]{} 3 + H_2S_2 \longrightarrow \underset{7}{Ph_2CH\overset{O}{\overset{\|}{C}}SS\overset{O}{\overset{\|}{C}}CHPh_2}$$

**Scheme 4**

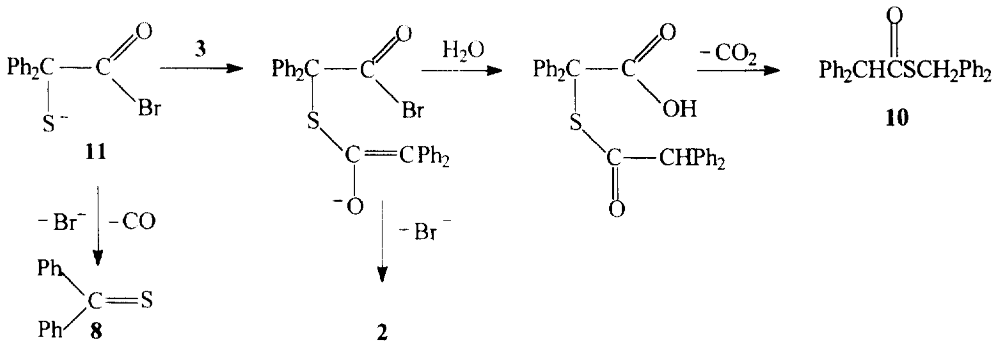
On the other hand, reaction between equimolecular amounts of **1** and lithium sulfide, in the presence of a phase-transfer catalyst, gave **2** (3%), thiobenzophenone (**8**) (6%), diphenylacetic acid (**9**) (82%) and diphenylthioacetic acid S-diphenylmethyl ester (**10**) (6%). The formation of **2** confirms the sulfide route to be the correct one.



$$1 + Li_2S \xrightarrow[\text{ii) } H_2O]{\text{i) } CH_2Cl_2\,/\,25°C\ \text{Phase-transfer catalyst}} 2 + \underset{8}{Ph_2C{=}S} + \underset{9}{Ph_2CHCOOH} + \underset{10}{Ph_2CHS\overset{O}{\overset{\|}{C}}CHPh_2}$$

**Scheme 5**

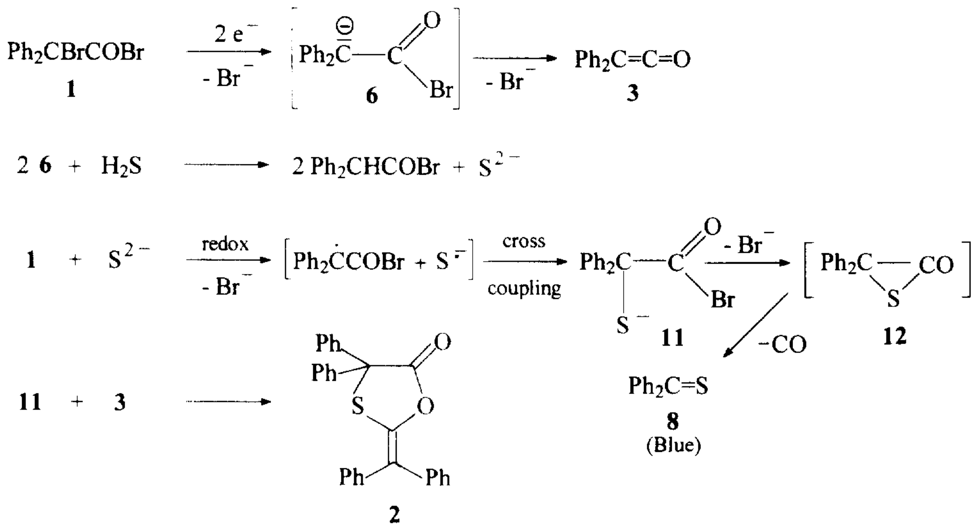
The formation of a large amount of **9** involves a two-electron redox process occurring on **1** in the same way as in the reaction with hydrogensulfide anion. In this case, the process can be rationalized by the formation of a $Ph_2\dot{C}COBr$ radical which can undergo either a second electron-transfer process, yielding **3**, or cross coupling with the $S^{-\bullet}$, formed by oxidation of $Li_2S$, to form the thiolate anion **11**. The higher stability of $S^{-\bullet}$ radical anion with respect to $HS^\bullet$ radical is the reason which justifies the existence of cross-coupling products in the reaction of **1** with sulfide anion. The presence of **8** and **10** confirms the existence of **11** in the reaction medium (scheme 6). **8** can be formed by a decarbonylation reaction of diphenyl-α-thiolactone (**12**), which has been produced by intramolecular cyclization of **11**, because these compounds lose CO by heating, yielding the corresponding thioketones.[16]



**Scheme 6**

The presence of **10** can be explained by the reaction of the intermediate formed between **3** and **11** with traces of water and further decarbonylation (tetraethyammonium chloride or bromide are very hygroscopic and when these salts were extremely dried only traces of **10** were observed). Intermolecular reaction of that intermediate yield **2**. The low yield of the latter compound and the large amounts of **3** found in this reaction suggest that the main route is the electron transfer, although we cannot reject that a small amount of **2** be formed through a direct nucleophilic substitution of $S^{2-}$ on the 2-position of **1**.

The route we propose for the electrochemical formation of **2** is summarized in scheme 7. Thus, in the anode, sodium thiosulfate forms thiosulfuric acid, which decomposes to $H_2S$. Hydrogen sulfide passes through the diaphragm to the catholyte and from there to the cathode surface (electrical interface), where **1** is reduced to **6**. The latter is a strong base and takes protons from hydrogen sulfide to form a sulfide anion. This anion reacts with starting material, in a redox process with further cross coupling, yielding the thiolate anion **11**, which can undergo either intramolecular cyclization and decarbonylation, giving thiobenzophenone (**8**), or rapid reaction with diphenylketene (**3**), followed by cyclization, leading to **2**.



**Scheme 7**

The whole process can be summed up as follows:

$$\underset{\mathbf{1}}{4\,Ph_2CBrCOBr} + H_2S \xrightarrow{6\,e^-} \mathbf{2} + 2\,Ph_2CHCOBr + 6\,Br^-$$

**Scheme 8**

Taking into account the proposed mechanism, **2** could be obtained by pure chemical methods. Thus, many chemical reactions have been performed with **1**, **3** and lithium sulfide to improve the yield of **2**, in which different solvents, phase-transfer catalysts and temperatures were employed. In no case could the electrochemical yield (42% based on the new mechanim) be surpassed, because in the electrochemical method a heterogeneous catalysis reaction occurs. On the electrode surface exists a much higher concentration of **1** than in the bulky solution, due to the polarization effect of the electrode on the latter. So, the $H_2S$ which has diffused towards the electrical interface finds a high concentration of strong bases, forming a sulfide anion. The latter, in the presence of a very high concentration of **1**, yields **11**. Therefore, the process has high dependence on the concentration of $H_2S$ in the electrical interface.

We can conclude that the electrochemical method is currently the best for the formation of **2**.

## EXPERIMENTAL SECTION

Nuclear magnetic resonance $^1H$ and $^{13}C$ were recorded in deuterochloroform on Varian Unity 300 apparatus. The chemical shifts were referred to internal TMS ($^1H$) or ($^{13}C$), and they are given in ppm. Perkin Elmer Model 583 infrared spectrophotometer was used to determine IR spectra (as dispersion in KBr). Mass spectra (70 eV) were determined using a Hewlett-Packard Model 5988A, with mass-selective detector equipped with a HP MS Chem-Station. Cyclic voltametric potentials were determined on a Metrohm apparatus Model 663 VA Stand. Melting points were determined on a Reichter Thermovar microhot stage apparatus and were uncorrected.

*General electrolysis procedure*.- Electroreductions were performed in a concentric cell with two compartments separated by a glass frit diaphragm of medium porosity, and under constant cathodic potential of -0.6 V vs SCE in dry $CH_2Cl_2$-anhydrous $Et_4N^+Br^-$ (or chloride) (0.2 M); 50 ml and 10 ml of this solution were placed in the cathodic and anodic compartments respectively and an argon atmosphere was used (a flow of dry argon being previously bubbled through the catholyte solution until the total removal of oxygen). A graphite disk was employed as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred and the temperature was maintained at 20°C by cooling.

### *Electroreduction of 1 in the presence of* $Na_2S_2O_3$.

0.88 g (2.5 mmole) of **1** and 4 g (25 mmole) of anhydrous sodium thiosulfate were placed in dry $CH_2Cl_2$ (25 ml) / 0.2 M anhydrous $Et_4N^+Cl^-$ under argon atmosphere. After 24 h of vigorous stirring, reagents were recovered without change. This mixture was electrolyzed at -0.6 V vs ECS and, after consuming 2 F mol$^{-1}$, the crude reaction product was obtained after stripping the solvent to dryness. Then, the product was extracted with ether (25 ml x 2) and water, giving diphenylacetic acid (**9**) in an almost quantitative yield.

### *Electroreduction of 1 and* $S_8$.

A mixture of 1.77 g (5 mmole) of **1** and 0.64 g (2.5 mmole) of crystallized $S_8$ was dissolved in dichloromethane and reduced cathodically at -0.6 V vs ECS. After consuming 4 F mol$^{-1}$ the solvent was evaporated and the crude reaction mixture was extracted with ether and water. The ethereal phase was washed with aqueous 5% NaOH, dried over anhydrous sodium sulfate, stripped to dryness, and chromatographed over silica-gel (hexane/dichloromethane 7:3). 0.420 g (37%) of diphenylacetyl disulfide (**7**) was obtained. This showed the following properties: m.p.: 112-3°C (from hexane). IR $\nu$[cm$^{-1}$] : 3058, 3038, 2906, 1708 (CO), 1595, 1491, 1450, 1337, 1302, 1233, 1183, 1077, 1031, 987, 842, 798, 739, 696, 620. $^1H$-NMR $\delta$[ppm]: 5.39

(s, 1H, CH), 7.30-7.36 (m, 10H, arom). $^{13}$C-NMR δ[ppm]: 64.29, 127.88, 128.82, 129.12, 137.12, 193.25. MS (CI-methane) m/z (relative intensity %): 455 ($M^{+}$+1, 2), 423 (5), 395 (4), 257 (3), 229 (9), 195 (47), 167 (100). Anal. Calcd. for $C_{28}H_{22}O_2S_2$: C, 73.98; H, 4.88; S, 14.10. Found: C, 73.80; H, 4.99; S, 13.98.
Neutralization of the above basic solution led to diphenylacetic acid (**9**), 0.636g (60%).

*Electroreduction of 1 in the presence of a small amount of $H_2S$.*

1.77 g (5 mmole) of **1** were cathodically reduced in the presence of a small amount of $H_2S$ (g), previously bubbled on the catholyte at 15°C. It is important that the gas flow be controled because otherwise sulphur compouns formed by reaction of intermediates and the solvent were obtained in a high yield. After consuming nearly 2.5 F mol$^{-1}$ and working up the catholyte, 42 mg (4%) of **2** (m.p.: 137-8 °C) was found, by column chromatography over silica-gel using hexane/$CH_2Cl_2$ (7:3) as eluent. The mayor product formed was diphenylacetic acid (**9**), 0.912 g (86%).

*Chemical reaction of 1, 3 and tetraethylammonium hydrogensulfide.*

0.354 g (1 mmol) of **1** and 0.194 g (1 mmol) of diphenylketene (**3**), formed by the usual method from **1** and Zn (dust) in dry THF at 0°C, were dissolved in 20 ml of dry $CH_2Cl_2$. 0.326 g (2 mmole) of tetraethylammonium hydrogensulfide[15] were added to this solution, under an argon atmosphere, and the reaction mixture was stirred at 25°C during 16 h. Then, the solvent was evaporated and the crude was extracted with ether and water. By column chromatography, 0.182 g (40%) of **7** and 0.212 g (50%) of **9** were obtained. This reaction was attempted in acetonitrile (tetraethylammonium hydrogensulfide reacts with $CH_2Cl_2$[17] in the absence of **1**), using equimolecular amounts of these three reagents, and adding dropwise a solution of the hydrogensulfide over **1** and **3**. The final products were the same as in the former case.

*Reaction between 1 and Lithium sulfide.*

0.708 g (2 mmol) of **1** were dissolved in 10 ml of dry dichloromethane. Then, 46 mg (1 mmol) of lithium sulfide and 0.330 g (2 mmole) of anhydrous $Et_4N^{+}Cl^{-}$ were added with vigorous stirring at 25°C during 2 h under argon atmosphere. After stripping the solvent to dryness, extraction with ether and water, and column chromatography, 13 mg (3%) of 2-benzhydrylidene-4,4-diphenyl-[1,3]oxathiolan-5-one (**2**), 24 mg (6%) of thiobenzophenone (**8**), 0.348 g (82%) of diphenylacetic acid (**9**) and 24 mg (6%) of diphenylthioacetic acid S-diphenylmethyl ester (**10**) were formed. **10** has shown the following properties: m.p.:139-40 °C. IR ν[cm$^{-1}$]: 1689 (CO). $^{1}$H-NMR δ[ppm]: 5.20 (s, 1H, $C\underline{H}COS$), 5.96 (s, 1H, $C\underline{H}SCO$), 7.21-7.29 (m, 20H, arom). $^{13}$C-NMR δ[ppm]: 52.50, 64.83, 127.22, 127.41, 128.31, 128.48, 128.58, 128.84, 138.02, 140.52, 196.95. MS (CI-methane) m/z (relative intensity %): 395 ($M^{+}$+1, 6), 229 (1), 195 (7), 167 (100). Anal. Calcd. for $C_{27}H_{22}OS$: C, 82.20; H, 5.62; S, 8.13. Found: C, 81.97; H, 5.50; S, 8.21.

## ACKNOWLEDGEMENT:

This study was financed by the DGICYT PB94-0341.

## REFERENCES

1. Barba, F.; Batanero, B. *J. Org. Chem.* **1993**, *58*, 6889.
2. Lozano, J. I.; Barba, F. *Heterocycles* **1994,** *38,* 1339.
3. Barba, F.; Batanero, B. *Electrochim. Acta.* in press.
4. Lozano, J. I.; Barba, F. *Tetrahedron Lett.* **1994**, *37*, 9623.
5. Ogawa, K; Terada, T. *Jpn. KoKai Tokkyo Koho* Jp 60.146.887, **1985**.
6. Taiho Pharmacceutical Co. *Jpn. KoKai Koho* Jp 57.193.474, **1982**.
7. Krumkalns, E. V. US 4.282.030, **1981**.
8. Kay, I. T. Ger. Offen. 2.131.745, **1971**.
9. Choi, W. B. US 5.210.085, **1993**.
10. Cheng, Y. C.; Chung, K.; Kim, H. O.; Shanmuganathan, K. *PCT Int. Appl.* WO 92 18.517, **1992.**
11. Staudinger, H.; Rathsam, G.; Kjelsberg, F. *Helvetica Chim. Acta* **1920**, *3*, 853.
12. Dehmlow, E. V. *Angew. Chem. Int. Ed. Eng.* **1977**, *16*, 493.
13. Trotman-Dickerson, A. F. *Comprenhensive Inorganic Chemistry.* Pergamon Press:1973; Vol.2 p 884.
14. Le Guillanton, G.; Do, Q. T.; Simonet, J. *J Chem. Soc., Chem. Comm.* **1990**, 393.
15. Schaumann, E.; Wriede, U.; Ehlers, J. *Synthesis* **1980**, 907.
16. Schaumann, E.; Behrens, U. *Angew. Chem. Int. Ed. Engl.* **1977**, *16,* 722.
17. Herriott, A. W. *Synthesis* **1975**, 447.

(*Received in UK* 12 *July* 1995; *revised* 30 *October* 1995; *accepted* 2 *November* 1995)