$C_{11}H_{11}N$ 157.0892, found 157.0870.

Acknowledgment. We gratefully thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and the National Institutes of Health for providing us with a Biomedical Research Support Grant (BRSG SO7 RR 07066).

Supplementary Material Available: ^1H and ^{13}C NMR spectra for all compounds described in the Experimental Section (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Dehalogenation of Organic Compounds. 3. Dechlorination of Polychlorinated Biphenyls, 4-Chlorobiphenyl, and Chloro-*p*-xylene with Alkoxyborohydrides[†]

Seyed-Mohammad H. Tabaei, Charles U. Pittman, Jr.,* and Keith T. Mead

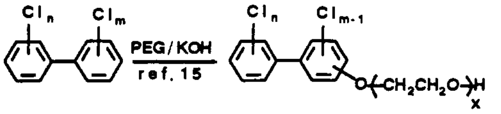
University/Industry Chemical Research Center, Department of Chemistry, Mississippi State University, Mississippi State, Mississippi 39762

Received May 27, 1992

Dechlorinations of organic compounds are widely used chemical transformations for environmental decontamination.[1-7] Polychlorinated biphenyl (PCB) contamination, for example, is a serious concern at several superfund sites.[3,4] The PCB's have been employed for several decades in transformer dielectric fluids and carbonless copy paper[5] due to their thermal stability, flame retardancy, and other chemical inertness. Resistance to degradation and a tendency to accumulate in animal tissue[6] has resulted in control of PCB manufacture, use, and disposal under the Toxic Substances Control Act (TSCA).[7] Inactivation of these noxious chemicals has centered on incineration,[8] plasma incineration,[9] and other chemical methods such as wet oxidation[10] and sodium-based reduction.[11] Each of these methods has limitations. For example, incineration generates HCl while combustion produces small traces of dioxins.[12] Other chemical methods can require inert atmospheres and sensitive reagents. Thus, it is desirable to develop ways to rapidly dehalogenate organic molecules prior to their safe incineration. Hydride reducing agents ($LiAlH_4$, $NaBH_4$) are not very active in aromatic dehalogenations,[13] but reports[14] that hydrides combined with transition metal salts generate M(0) species make hydride/M^{n+} combinations promising candidates for PCB dehalogenation.

Results and Discussion

General Electric Co. pioneered dechlorination of PCB's (eq 1) using polyethylene glycol (PEG)/KOH.[15] However,



(1)

temperatures above 120 °C were routinely required, and only highly chlorinated PCB's were rapidly reduced. PCB mixtures with fewer chlorines, such as Aroclor 1016, resisted dechlorination.[15b] Aroclor 1016 gave no significant dechlorination by PEG/KOH after 14 days versus 99%

Table I. Dechlorination[a] of Commercial Aroclors (PCB's) by PEG/KOH

	Aroclor (wt % Cl)			
	1016	1242	1254	1260
% dechlorination[b] (time in days)	0 (14)	27 (14)	86 (6)	99 (2)
1[c]	2	1		
2[c]	19	13		
3[c]	57	45	1	
4[c]	22	31	15	
5[c]		10	53	12
6[c]			26	42
7[c]			4	38
8[c]				7
9[c]				2

[a] See references 6 and 15b. [b] At ambient temperature using 3000–5000 ppm by wt of Aroclor in a huge molar excess of PEG/KOH (1/1 by wt). The KOH contained 15% water by wt. [c] Number of chlorines per biphenyl unit.

Table II. Dechlorination of Chloro-*p*-xylene

entry	reagents[a] (mol ratios)	time (h)	dechlorination[b] (mol %)
1	TEG/KOH[b] (46/1)	168	42
2[c]	TEG/KOH/$NaBH_4$[b] (46/1/2)	168	0
3	$NaBH_2(OCH_2CH_2OCH_3)_2$/THF (4/47)	168	28
4[d]	$NaBH_2(OCH_2CH_2OCH_3)_2$/$NiCl_2$/THF (4/3/47)	3	81
5[e]	$NaBH_2(OCH_2CH_2OCH_3)_2$/$NiCl_2$/THF (4/2/47)	2.5	98

[a] All ratios are relative to one mol of chloro-*p*-xylene. [b] Reaction temperature was 130 °C for entries 1 and 2. All other entries were run at 68 °C. [c] Phase separation of $NaBH_4$ occurred. [d] The alkoxyborohydride was added dropwise to substrate in THF/$NiCl_2$. [e] A suspension of $NiCl_2$ in THF was added incrementally to the reaction mixture using 0.20 molar equiv of $NiCl_2$ per portion.

[†] For the first two papers in this series see refs 1 and 2.

(1) Pittman, C. U., Jr.; El. Massry, A. M. *Synth. Commun.* **1990**, *20*(81), 1091.

(2) Tabaei, S. M. H.; Pittman, C. U., Jr.; Mead, K. T. *Tetrahedron Lett.* **1991**, *32*, 2727.

(3) U.S. EPA, Superfund Records of Decision Update. Office of Solid Waste and Emergency Response, Intermittent Bulletin, Vol. 6, No. 1, Publication No. 92005-2161, 1990.

(4) Safe, S. *Mutat. Res.* **1989**, *220*, 31.

(5) Durfee, R. L.; Contos, G.; Whitemore, F. C.; Barden, J. D.; Hackman, E. E., III; Westin, R. A. *PCBs in the United States-Industrial Use and Environmental Distribution*; Prepared for the U.S. Environmental Protection Agency, Office of Toxic Substances, Report No. EPA 560/6-76-005 (NTIS No. PB-252012), 1976; p 488.

(6) (a) Erickson, M. D. *Analytical Chemistry of PCBs*; Butterworth: Ann Arbor, 1986. (b) Hutzinger, O.; Safe, S.; Zitko, V. *The Chemistry of PCBs*; Chemical Rubber Co.: Boca Raton, FL, 1979.

(7) *Toxic Substances Control Act*, Public Law 94-469, 1976.

(8) (a) Weitzman, L. In *Detoxification of Hazardous Waste*; Ann Arbor Science: Ann Arbor, MI, 1982; Chapter 8, p 131. (b) Ahling, B. *Combustion Test with Chlorinated Hydrocarbons in Cement Kilns*; Swedish Water and Air Pollution Research Institute, Stockholm, Sweden, 1978. (c) MacDonald, L. P.; Skinner, D. J.; Hopton, F. L.; Thomas, G. H. *Burning Waste Chlorinated Hydrocarbons in Cement Kilns*; Fisheries and Environment of Canada, Report No. 4-WP-77-2, 1977.

(9) Exner, J. H. In *Detoxification of Hazardous Waste*; Ann Arbor Science: Ann Arbor, MI, 1982; Chapter 10, p 185.

(10) Baillod, R. C.; Lampartes, R. A.; Laddy, D. G. *Wet Oxidation of Toxic Organic Substances*; Purdue Industrial Waste Conference, West Lafayette, IN, May 1978.

(11) (a) Oku, A.; Ysufuku, K.; Dataoka, H. *Chem. Ind. (London)* **1978**, 841. (b) Jordan, O. D. British Patent 2,081,298, 1982. (c) Jordan, O. D. US Patent 4,340,471, 1982. (d) Norman, L. O. US Patent 4,379,752, 1983. (e) Pytlewski, L. L. et al. US Patent 4,417,977, 1983.

(12) Khera, K. S.; Ruddick, J. A. In *Advances in Chemistry Series* **1973**, *120*, Chapter 8.

(13) Paderes, G. D.; Metivier, P.; Jorgensen, W. L. *J. Org. Chem.* **1991**, *56*, 4718.

(14) (a) Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1978**, *43*, 1263. (b) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763. (c) Lin, S. T.; Roth, J. A. *J. Org. Chem.* **1979**, *44*, 309. (d) Satoh, T.; Mitsuo, N.; Nishiki, M.; Nanba, K.; Suzuki, S. *Chem. Lett.* **1981**, 1029.

0022-3263/92/1957-6669$03.00/0

Table III. Dechlorination of 4-Chlorobiphenyl

entry	reagents[a] (mol ratios)	time (h)	dechlorination[a,b] (mol %)
1	TEG/KOH[b] (46/1)	168	0
2	$NaBH_4$/THF (9/81)	168	0
3	$NaBH_2(OCH_2CH_2OCH_3)_2$/THF (6/70)	24	46
4[c]	$NaBH_2(OCH_2CH_2OCH_3)_2/NiCl_2$/THF (6/3/70)	3	90
5[d]	$NaBH_2(OCH_2CH_2OCH_3)_2/NiCl_2$/THF (6/2.5/70)	1.25	100

[a] All ratios are relative to 1 mol of 4-chlorobiphenyl. Biphenyl was the only dechlorination product detected. [b] A reaction temperature of 130 °C was employed in entry 1. All other entries were run at 68 °C. [c] Alkoxyborohydride was added dropwise to substrate in THF/$NiCl_2$. [d] A suspension of $NiCl_2$ in THF was incrementally added to the reaction mixture using 0.50 molar equiv of $NiCl_2$ per portion.

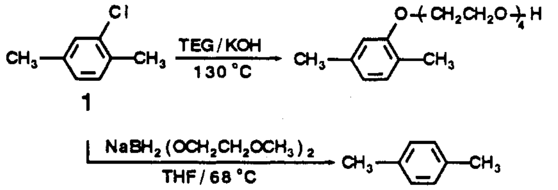
Table IV. Dechlorination of Aroclor 1016

entry	reagents[a] (mol ratios)	time (h)	dechlorination[a,b] (mol %)
1	TEG/KOH[b] (10/0.70)	336	30
2	$NaBH_4$/THF (3/20)	336	0
3	$NaBH(OCH_3)_3$/THF (12/20)	168	7
4	$NaBH_2(OCH_2CH_2OCH_3)_2$/THF (6/20)	168	53
5	$NaBH_4/NiCl_2$/THF/CH_3OH	168	55
6[c]	$NaBH_2(OCH_2CH_2OCH_3)_2/NiCl_2$/THF (6/1/20)	168	76
7[d]	$NaBH_2(OCH_2CH_2OCH_3)_2/NiCl_2$/THF (6/0.75/20)	36	90[e]

[a] All ratios are relative to the mol of chlorine in Aroclor 1016. Dechlorination mol % refers to the total mol of chlorine atoms removed as a percentage of the total chlorine present in Aroclor 1016 used. [b] A reaction temperature of 150 °C was employed for entry 1. All other entries were run at 68 °C. [c] The alkoxyborohydride was added dropwise to substrate in THF/$NiCl_2$. [d] A suspension of $NiCl_2$ in THF was added portionwise to the reaction mixture using 0.10 molar equiv of $NiCl_2$ per portion. [e] A total of 93.3 mol % of the original PCB molecules were converted to biphenyl, and 3.2 mol % of a monochlorobiphenyl isomer and 3.1 mol % of a dichlorobiphenyl isomer were obtained.

dehalogenation of Aroclor 1260 in 2 days under the same conditions (Table I).[15b] Therefore, Aroclor 1016 and the model compounds chloro-*p*-xylene, **1**, and 4-chlorobiphenyl, **2**, were selected as test substrates in this study to challenge dechlorination systems based on $NaBH_4$, alcohols, and KOH studied previously in our labs.[2,16] Many combinations of sodium borohydride, alcohols, and KOH (with added metal salts in some cases) resulted in powerful dechlorination media.[2,16] Such systems dechlorinated model compounds that were inert to sodium borohydride alone. Alkoxyborohydrides formed in situ were very powerful dechlorinating agents. For example, Mirex, one of the most stable aliphatic chlorinated pesticides, previously was dechlorinated within 1 h at 58 °C by $NaBH_2(OCH_2CH_2OCH_3)_2$ in TEG/KOH/THF along with a Bu_3SnH/AIBN catalyst.[2]

Dechlorination of PCB's, chloro-*p*-xylene, and 4-chlorobiphenyl was readily accomplished using alkoxyborohydrides, both with and without addition of stoichiometric quantities of nickel chloride. These dechlorinations were superior to those using tetraethylene glycol (TEG)/KOH. Several dechlorinations of chloro-*p*-xylene, **1**, are summarized in Table II. Treatment of **1** with TEG/KOH at 130 °C gave 42% dechlorination to *p*-xylene in 1 week (entry 1, Table II, and eq 2). The use of NaBH₄/TEG/KOH led to phase separation problems and after 168 h at 130 °C starting material was recovered (entry 2). In contrast, the use of the alkoxyborohydride, $NaBH_2(OCH_2CH_2OCH_3)_2$ in THF, gave 28% reduction to *p*-xylene in 1 week at only 68 °C (see entry 3 and eq 3). This soluble alkoxyborohydride does not give phase separation and it is a stronger hydride donor.

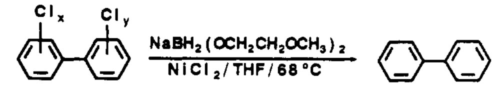


(2)

(3)

The rate of chlorine displacement was greatly increased when $NiCl_2$ was added to the sodium alkoxyborohydride (81% dechlorination in 3 h at 68 °C in the presence of 3 equiv of Ni^{2+}; see entry 4 in Table II). However, a black nickel-containing precipitate formed which did not promote further dechlorination, even after the addition of fresh alkoxyborohydride. Portionwise addition of $NiCl_2$ to alkoxyborohydride/substrate solutions gave better results (Entry 5) with less $NiCl_2$ (2 equiv) added.

Several dechlorination systems were examined for converting 4-chlorobiphenyl, **2**, to biphenyl (eq 4). Representative results are shown in Table III. Neither TEG/KOH at 130 °C nor $NaBH_4$/THF at 68 °C dechlorinated 4-chlorobiphenyl (entries 1 and 2). However, the use of $NaBH_2(OCH_2CH_2OCH_3)_2$ in THF did give steady dechlorination at 68 °C (entry 3). Addition of $NiCl_2$ to this system significantly enhanced dechlorination activity (entry 4). Portionwise addition of $NiCl_2$ to the alkoxyborohydride/THF solution gave complete dechlorination in less than 75 min at 68 °C (entry 5).



2, x=0, y=1

3, Aroclor 1016

(4)

Studies of 4-chlorobiphenyl reduction as a function of time before and after $NiCl_2$ portions were added demonstrated that approximately 1 equiv of substrate could be dechlorinated per equiv of $NiCl_2$. For example, after 0.15 equiv of $NiCl_2$ was added 0.13 equiv of biphenyl had formed. All the 4-chlorobiphenyl was converted to biphenyl when 1.20–1.35 equiv of $NiCl_2$ had been added. The reduction rate was fast following incremental $NiCl_2$ addition, but the process was not catalytic. The stoichiometry appeared to approach 1:1 as the amount of $NiCl_2$ per portion was decreased or where solutions of $NiCl_2$ were pumped continuously into the reaction.

Each of the dechlorination systems was applied to the least reactive PCB mixture, Aroclor 1016, **3**, (see Table IV and eq 4). Rapid dechlorination of Aroclor 1016 did not occur with TEG/KOH (entry 1) or $NaBH_4$/THF (entry 2). Even $NaBH(OCH_3)_3$/THF led to very slow dechlorination to biphenyl at 68 °C (entry 3). However, $NaBH_2(OCH_2CH_2OCH_3)_2$ (6 mol excess) in THF was more reactive (entry 4) at 68 °C. Initial reaction with added $NiCl_2$ gave only modest improvements versus results with $NaBH_2(OCH_2CH_2OCH_3)_2$ alone (compare entry 6 with entry 4). Once again, much better results were obtained by *portionwise* addition of $NiCl_2$ to $NaBH_2(OCH_2CH_2OCH_3)_2$ (6 mol excess) in THF solutions in the presence of substrate (entry 7). Thus, 93.7 mol % biphenyl was produced together with 3.2 and 3.1 mol % of a mono- and a dichlorinated biphenyl, respectively, from the complex

---

(15) (a) Brunelle, D. J.; Singleton, D. A. *Chemosphere* **1983**, *12*, 183. (b) Brunelle, D. J.; Singleton, D. A. *Ibid.* **1985**, *14*, 173. (c) Brunelle, D. J. *Ibid.* **1983**, *12*, 167. (d) Brunelle, D. J.; Mendiratta, A. K.; Singleton, D. A. *Environ. Sci. Technol.* **1985**, *19*, 740.

(16) Pittman, C. U., Jr.; Mead, K. T.; Tabaei, S. M. H. *ACS 42nd S.E./46th S.W. Combined Regional Meeting*; New Orleans, Dec 5–7 1990, Abstract No. 397, p 163.

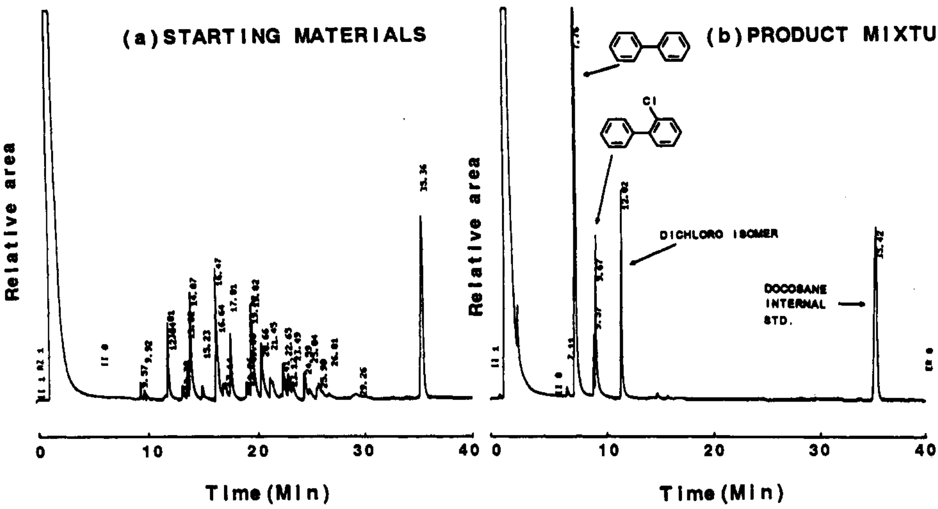


Figure 1. Gas chromatograms of Aroclor 1016 (a) before and (b) after treatment with $NiCl_2/NaBH_2(OCH_2CH_2OCH_3)_2$ in THF at 68 °C for 36 h.

Aroclor 1016 mixture after addition of 0.75 equiv of $NiCl_2$. Figure 1 shows the gas chromatograms of Aroclor 1016 (a) before and (b) after this treatment. When 1 equiv of $NiCl_2$ was slowly pumped into this Aroclor 1016 dehalogenation (other stoichiometry identical to entry 7) a 98.5 mol % yield of biphenyl was achieved. Complete dechlorination to biphenyl occurred when larger excesses of $NaBH_2(OCH_2CH_2OCH_3)_2$ or more than 1 equiv of $NiCl_2$ were used. $NaBH_4/NiCl_2$ in THF/CH_3OH (entry 5) provided significantly more effective dechlorination than $NaBH_4$ in the absence of $NiCl_2$ (entry 2).

Stoichiometry in $NiCl_2$ approached 1:1 in dechlorinations when methanol solutions of $NiCl_2$ were added dropwise or continuously pumped into the borohydride agent and substrate in THF. Phenylcyclohexane was observed in addition to biphenyl in some cases where $NiCl_2$ had been added. The rate of dechlorination caused by the borohydride reagent in the absence of added $NiCl_2$ was quite slow. Presumably active Ni(0) species must react with RCl prior to Ni(0) deactivation caused by particulate residue formation. Whether deactivation is due to diffusion limitations or chemical modifications which poison reduced Ni species is unknown.

Experimental Section

General Procedure without $NiCl_2$. Into a dry, 50-mL three-neck flask equipped with a thermometer, magnetic stirring bar, and reflux condenser were added 235 mmol (19.1 mL) of THF and 200 mg of tetradecane which was used as the internal standard for gas chromatography. Docosane was used as the internal standard in the dehalogenations of PCB mixtures since it did not overlap with any peaks in the system. Chloro-*p*-xylene (5 mmol, 0.67 mL) then was added. As the temperature was increased to 68 °C, $NaBH_4$ (20 mmol, 0.96 g) and $CH_3OCH_2CH_2OH$ (40 mmol, 3.16 mL) were added forming $NaBH_2(OCH_2CH_2OCH_3)_2$ in situ. Samples, taken at intervals using a syringe technique, were treated with dilute aqueous sulfuric acid solution and extracted with CH_2Cl_2. After being dried over anhydrous Na_2SO_4, organic samples in CH_2Cl_2 were analyzed by both GC (30 m, DB-5 capillary column, FID detector; 80 °C, 2 min, with subsequent heating at 10 °C/min to 220 °C where it was held for 9 min) and GC/MS.

Incremental $NiCl_2$ Addition. All equipment and conditions were as described in the general procedure with the exception that a suspension of $NiCl_2$ in THF was incrementally added to the reaction mixture by syringe after addition of sodium borohydride and 2-methoxyethanol was completed and the temperature had reached 68 °C. The amount of $NiCl_2$ and time between increments were varied in different reactions. Alternately, a $NiCl_2/CH_3OH$ solution was either continuously added dropwise or slowly pumped, at a constant rate, into the reaction mixture. Aliquots were removed for analysis at regular intervals before and after $NiCl_2$ incremental portions were added. The analyses were performed as described above. For reactions of Aroclor 1016 the GC temperature program employed was (130 °C held for 2 min, heated 10 °C/min to 190 °C where it was held for 1 min and then heated to 220 °C at 1 °C/min and held at 220 °C for 1 min).

Acknowledgment. This work was supported by contracts 100MSU3144 and 108MSU0144 from the Gulf Coast Hazardous Substance Research Center. Partial support was provided by the National Science Foundation (Grant Nos. ST1-8902064 and R11-8902064), the State of Mississippi, and Mississippi State University.

Bistratamides C and D. Two New Oxazole-Containing Cyclic Hexapeptides Isolated from a Philippine *Lissoclinum bistratum* Ascidian[1]

Mark P. Foster,[†] Gisela P. Concepción,[‡] Gina B. Caraan,[‡] and Chris M. Ireland*[,†,2]

Department of Medicinal Chemistry, University of Utah, Salt Lake City, Utah 84112, and Marine Science Institute, University of the Philippines, Diliman, Quezón City, Philippines

Received July 9, 1992

Introduction

Lissoclinum spp. ascidians have become well-known as prolific producers of cytotoxic cyclic peptides with highly modified amino acid residues (e.g., ascidiacyclamide, ulithiacyclamide)[3] and macrolides with mixed polyketide/peptide biosynthesis (e.g., patellazoles,[4] bistramide A[5]). As part of our continuing effort to isolate biologically active compounds from this genus of ascidians, we collected a sample of *Lissoclinum bistratum* in the Philippines. The organism lacked any of the metabolites previously described from this organism, but contained a novel family of cyclic hexapeptides (1, 2) containing oxazole (Ozl) residues—a modified amino acid not previously seen in the vast array of modified cyclic peptides previously reported from this genus. Oxazoles from marine invertebrates were

---

[†] University of Utah.

[‡] University of the Philippines.