reaction mixture was cooled, dissolved in 150 mL of ether, and extracted with four 50-mL portions of 10% HCl. The acid extracts were washed with 50 mL of ether and concentrated under reduced pressure. The residue was treated with 100 mL of saturated K_2CO_3 solution and extracted with ether. The combined organic layer was dried (K_2CO_3/Norite), filtered, and concentrated to give 12.2 g of a light-yellow solid. The solid was recrystallized from 100 mL of hexane to provide 9.6 g (62%) of 4-phenylpyridine as white crystals: mp 73–74 °C (lit.[12] mp 69–70 °C); the NMR spectrum was identical with the published spectrum of authentic 4-phenylpyridine.[13]

4-Butylpyridine. Method B. General Procedure. In a 1-L flask equipped with an overhead stirrer were placed pyridine (12.1 mL, 0.15 mol), CuI (952 mg, 5 mmol), and 250 mL of THF under N_2. The solution was cooled to −20 °C and ethyl chloroformate (9.6 mL, 0.1 mol) was added via syringe with stirring. After 5 min, butylmagnesium bromide (0.1 mol) in 80 mL of ether was added dropwise over 10 min. The mixture was stirred for 15 min at −20 °C and then at room temperature for another 15 min. The isolation of the crude dihydropyridine intermediate was the same as described above for 4-phenylpyridine (method A). The crude dihydropyridine was aromatized with sulfur as described above except that volatiles (EtOH) were distilled from the reaction as it proceeded. The crude product (10.4 g) was vacuum distilled to give 8.4 g (62%) of 4-butylpyridine as a clear oil: bp 88–91 °C (16 mm); picrate mp 112–113 °C [lit.[14] bp 98 °C (20 mm); lit.[15] picrate mp 112.8–113.8 °C].

Acknowledgment. This work was assisted financially by a Utah State University Faculty Research Grant (Biomedical) Project No: USC-1112. A.H.A. expresses appreciation to the Government of Malaysia for a Federal Scholarship. We thank Eric Stroud for lending his expertise in the area of capillary column GC.

Registry No. 3a, 3433-40-7; **3b**, 82902-42-9; **3c**, 82902-43-0; **3d**, 32245-98-0; **3e**, 82902-44-1; **3f**, 82902-45-2; **3g**, 82902-46-3; **3h**, 82902-47-4; **3i**, 82902-48-5; **3j**, 82902-49-6; **4a**, 82902-50-9; **4b**, 82902-51-0; **4c**, 82902-52-1; **4d**, 32245-87-7; **4e**, 82902-53-2; **4f**, 82902-54-3; **4g**, 82902-55-4; **4h**, 82902-56-5; **4i**, 82902-57-6; **4j**, 82902-58-7; **10a** (R^1 = Bu), 5335-75-1; **10a** (R^1 = Bu) picrate, 82902-59-8; **10a** (R^1 = C_6H_{11}), 13669-35-7; **10a** (R^1 = C_6H_{11}) picrate, 13742-76-2; **10a** (R^1 = Ph), 939-23-1; **10b** (R^1 = Et), 536-88-9; **10b** (R^1 = Et) picrate, 5933-90-4; **10b** (R^1 = *i*-Pr), 13854-03-0; **10b** (R^1 = *i*-Pr) picrate, 13896-39-4; **10b** (R^1 = Ph), 15032-21-0; **10b** (R^1 = Ph) picrate, 15032-22-1; **12** (R = Et), 56986-88-0; **12** (R = *i*-Pr), 72693-04-0; **12** (R = Ph), 10273-90-2; **13** (R = Et), 18113-81-0; **13** (R = *i*-Pr), 6343-58-4; **13** (R = Ph), 27012-22-2; **14** (R = Et), 20815-29-6; **14** (R = Et) picrate, 76833-16-4; **14** (R = *i*-Pr), 76160-91-3; **14** (R = *i*-Pr) picrate, 82902-60-1; **14** (R = Ph), 2052-92-8; **14** (R = Ph) picrate, 1689-41-4; CH_3COCl, 75-36-5; EtOCOCl, 541-41-3; *t*-BuCOCl, 3282-30-2; EtMgBr, 925-90-6; PhMgCl, 100-59-4; *i*-PrMgCl, 1068-55-9; EtMgCl, 2386-64-3; BuMgCl, 693-04-9; $C_6H_{11}MgCl$, 931-51-1; 2-picoline, 109-06-8; cuprous iodide, 7681-65-4; pyridine, 110-86-1; 3-picoline, 108-99-6.

(12) Haworth, B. J.; Heibron, I. M.; Hey, D. H. *J. Chem. Soc.* **1940**, 349.
(13) Pouchert, C. J.; Campbell, J. R. "The Aldrich Library of NMR Spectra"; Aldrich Chemical Co. Inc.: Milwaukee, WI., 1974, Vol. 9, p 7A.
(14) Wibaut, J. R.; Hey, J. W. *Recl. Trav. Chim. Pays-Bas* **1953**, *72*, 513.
(15) Arens, J. F.; Wibaut, J. P. *Recl. Trav. Chim. Pays-Bas* **1942**, *61*, 59.
(16) Lochte, H. L.; Kruse, P. F., Jr.; Wheeler, E. N. *J. Am. Chem. Soc.* **1953**, *75*, 4477.
(17) Siddiqui, R. H. *J. Indian Chem. Soc.* **1939**, *16*, 410.
(18) (a) Gvoindachari, T.; Santhanam, P. S.; Sudarsanam, V. *Indian J. Chem.* **1966**, 4, 398. (b) Katritzky, A. R.; Beltrami, H.; Sammes, M. P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2480.
(19) Bonnier, J.; Court, J.; Fay, T. *Bull. Soc. Chim. Fr.* **1967**, 1204.
(20) Wibaut, J. P.; Vromen, S. *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 545.
(21) Abramovitch, R. A.; Saha, M. *Can. J. Chem.* **1966**, *44*, 1765.

Oxazolines. 3.[1] Regioselective Synthesis of 2-(Monosubstituted phenyl) and/or Unsymmetrically 2-(Disubstituted phenyl) 2-Oxazolines by Cross-Coupling Grignard Reagents to (Haloaryl)-2-oxazolines

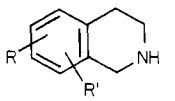
Lendon N. Pridgen

Chemical Technologies, Pre-Clinical Research and Development, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101

Received March 26, 1982

2-(Monosubstituted phenyl) 2-oxazoline **5** (R = H) and unsymmetrically 2-(disubstituted phenyl) 2-oxazolines **5** have been prepared by cross-coupling alkyl and aryl Grignard reagents to 2-(mono- and dihalogenated phenyl) 2-oxazolines **2** and **3** (X = halogen), respectively, under nickel–phosphine complex catalysis. Regioselective cross-coupling was observed with 2-(dihalogenated phenyl) 2-oxazolines **3** (X = halogen) when a halogen was ortho to the 2-oxazolinyl moiety.

We have ongoing in this laboratory an effort to develop a two-step (reduction–cyclization)[1] synthesis of pharmalogically active[2,3] unsymmetrically disubstituted tetrahydroisoquinolines **1** using unsymmetrically 2-(disubstituted phenyl) 2-oxazolines **5** as key intermediates. Con-

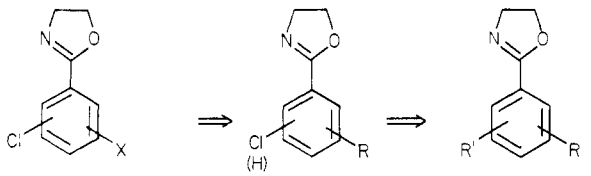


1

(1) For preceding papers in this series, see: (a) Pridgen, L. N.; Killmer, L. *J. Org. Chem.* **1981**, *46*, 5402. (b) Pridgen, L. N.; Killmer, L.; Webb, R. L. *Ibid.* **1982**, *47*, 1985.
(2) Mendelson, W. L.; Spainhour, C. R.; Jones, S. S.; Lam, B. L.; Wert, K. L. *Tetrahedron Lett.* **1980**, 1393.

0022-3263/82/1947-4319$01.25/0

Scheme I[a]



2, X = H
3, X = Br, Cl, or o-CH_3O

4, R ≠ H

5

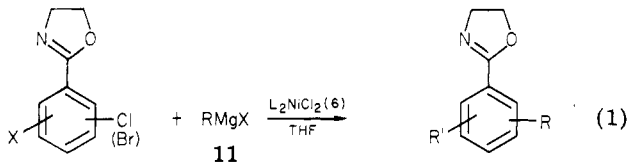
[a] R and R′ may be alkyl, aryl, or hydrogen except in 4 where R ≠ H.

ceivably an approach to these oxazolines 5 from the readily available 2 may be possible by metal–hydrogen exchange on 2 followed by alkylation to yield 4[4] (Scheme I). However, such an approach precludes R or R′ being an aryl substituent and does not allow one to replace the halogen in the subsequently formed 4 by organometallic exchange in the presence of the relatively acidic proton ortho to the 2-oxazolinyl group.[4b-i] Alternatively, an approach using the o-methoxy derivative 3 (X = OCH_3) could be considered. Meyers[4d,5] has demonstrated the ability of the 2-oxazolinyl moiety to activate the o-methoxy group of the 2-(o-methoxyphenyl)-2-oxazoline to nucleophilic displacement by organometallics, e.g., Grignards and organolithium reagents, and in doing so provided the chemist with a valuable synthesis tool for preparing ortho-substituted benzoic acids, esters, aldehydes, and amides.[6] While the o-methoxy displacement reaction is very useful for the preparation of juxtaposed phenyl derivatives, it is limited to displacement of methoxy or fluoro groups ortho to the 2-oxazolinyl moiety by nature of the proposed metal–oxazoline complexation mechanism.[5b,f-h]

Our previously reported Grignard to haloheterocycle cross-coupling reactions,[1,7] catalyzed by nickel–phosphine complexes, should be capable of effecting the transformation of 2 to 5 (R = H), thereby avoiding the limitations imposed by the metal–halogen/hydrogen exchange reactions discussed above. This potentially allows one to alkylate or arylate at any halogenated position. In addition, since the 2-oxazolinyl moiety activates the ortho position toward deprotonation with strong bases (as do, e.g., cyano, carboxylate, dialkyamido, sulfonamido, and dialkylamino functionalities[4a,b,f,i]), we felt we could regioselectively cross-couple at the more reactive 2-halogen in a 2-(dihalogenated phenyl) 2-oxazoline such as 3 (X = 2-halogen) and then elaborate 4 on to the unsymmetrically 2-(disubstituted phenyl) 2-oxazoline 5. We now report our results in preparing 2-(substituted phenyl) 2-oxazolines 5 employing nickel–phosphine complexes as Grignard cross-coupling catalyst.

Results and Discussion

Oxazolines 7–10[8] were synthesized and effectively cross-coupled with Grignards in the presence of a catalytic quantity of a nickel–phosphine complex.[9] Our results in eq 1 are listed in Table I. Products 16 and 17 are derived



11

(1)

7–10, X = H
7, 2-Cl
8, 3-Cl
9, 4-Cl
10, 2-Br
23, 2,4-Cl_2
24, 2,5-Cl_2
25, 3,4-Cl_2
26, 3,5-Cl_2
27, 2-SCH_3-4-Cl

12–19, R′ = H
12, 3-Ph
13, 3-(4-CH_3O-Ph)
14, 3-CH_2CH_3
15, 3-$CH_2CH_2CH_3$
16, 2-$CH_2CH_2CH_3$
17, 2-CH_3
18, 2-CH_2Ph
19, 4-$CH_2CH_2CH_3$
28, 2-CH_3-3-Cl
29, 2-CH_3-4-Cl
30, 2-CH_3-5-Cl
33, 2-CH_3-4-$CH_2CH_2CH_3$

from 7, while 18 is derived from 10. The yields in most cases are excellent and only with allylmagnesium bromide did the reaction fail to give cross-coupling product. In this case, multiple allyl addition products were produced. When phenylmagnesium bromide was reacted with 7 or 10, multiple products were obtained and the major components identified by GC/MS. The best result in this case was obtained with 10, using $NiCl_2$(dppp) 20 as catalyst in THF at ambient temperature over 16 h. The desired product 2-(o-phenylphenyl)-2-oxazoline was obtained in only 23% yield along with the reduction product 2-phenyl-2-oxazoline (15%) and recovered starting material (17%).[10] We interpret our results to mean that unfa-

(3) (a) Hudlicky, T. *J. Org. Chem.* **1981**, *46*, 1738 and references therein. (b) Ellefson, C. R.; Prodan, K. A.; Brougham, L. R.; Miller, A. *J. Med. Chem.* **1980**, *23*, 977 and references therein. (c) Kohli, J. D.; Goldberg, L. I. *J. Pharm. Pharmacol.* **1980**, *32*, 225. (d) Niebch, G.; Klinger, K. H.; Eikelmann, G.; Kucharczyk, K. *Ibid.* **1978**, *28*, 765. (e) Shamma, M. "The Isoquinoline Alkaloids, Chemistry and Pharmacology"; Academic Press: New York, 1973. (f) Shamma, M.; Moniot, J. L. "Isoquinoline Alkaloid Research: 1972–1977"; Plenum Press: New York, 1978.

(4) However, it is possible for the halogen in 4 to be substituted by alkyls via oxidative metalation: (a) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: New York, 1974. (b) Gschwend, H. W.; Rodriguez, H. R. "Heteroatom-Facilitated Lithiations"; Dauben, W. G., Ed.; Wiley-Interscience: New York, 1979; Vol. 26, Chapter 1. (c) Ellefson, C. R. *J. Org. Chem.* **1979**, 44, 1533. (d) Meyers, A. I.; Avila, W. B. *Ibid.* **1981**, *46*, 3881 and references therein. (e) Meyers, A. I.; Mihelich, E. D. *Ibid.* **1975**, *40*, 3158. (f) Beak, P.; Brown, R. A. *Ibid.* **1979**, *44*, 4463. (g) Gschwend, H. W.; Hamdan, A. *Ibid.* **1975**, *40*, 2008. (h) Meyers, A. I.; Avila, W. B. *Tetrahedron Lett.* **1980**, 3335. (i) Meyers, A. I., Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4464.

(5) (a) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. (b) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383. (c) Meyers, A. I.; Gabel, R. A. *Tetrahedron Lett.* **1978**, 227. (d) Meyers, A. I.; Gabel, R. A. *Heterocycles* **1978**, *11*, 133. (e) Meyers, A. I.; Campbell, A. L. *Tetrahedron Lett.* **1979**, 4155, 4159. (f) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372. (g) Meyers, A. I.; Gabel, R. *Ibid.* **1977**, *42*, 2653. (h) Meyers, A. I.; Reuman, M.; Gabel, R. A. *Ibid.* **1981**, *46*, 783. (i) Meyers, A. I.; Williams, B. E. *Tetrahedron Lett.* **1978**, 223. (j) We have found that 2-(o-methoxyphenyl)-2-oxazolines polymerize on standing at room temperature. On the contrary, the corresponding halooxazolines were found to be quite stable.

(6) Reference **5a** gives a review to 1976 of the synthetic utility of 2-oxazolines. For an excellent summary of references since then, see ref **4d** and references therein.

(7) (a) Pridgen, L. N. *J. Heterocycl. Chem.* **1975**, *12*, 443. (b) Pridgen, L. N. *Ibid.* **1980**, *17*, 1289.

(8) Unlike its more commonly used 4,4-dimethyloxazolinyl analogue, this oxazolinyl moiety can not be formed by treatment of the (β-hydroxyethyl)benzamide with $SOCl_2$ since this leads only to the (β-chloroethyl)benzamide derivative. The 2-oxazoline is then formed in consistently high yields on treatment of this β-chloro derivative with NaH in THF (see Experimental Section). Indeed, even ortho-substituted benzamides readily form 2-oxazolines with this method, in contrast to the difficulty encountered by Meyers in the synthesis of 2-(ortho-substituted phenyl) 2-4,4-dimethyl-2-oxazolines: Meyers, A. I.; Hanagan, M. A.; Mazzu, A. L. *Heterocycles* **1981**, *15*, 361. However, we have encountered low yields in the synthesis of 2-(2,3- and 2,6-dichlorophenyl)-2-oxazolines using our procedure, presumably due to steric complications.

(9) The nickel catalysts, or their prerequisite ligands, used in this report may be obtained from Matthey Bishop, Inc., and Strem Chemicals, Inc. Abbreviations for ligands are as follows: $Ph_2(CH_2)_nPPh_2$; dppe, n = 2 and dppp, n = 3.

Table I. Nickel(II)-Phosphine Complex Catalyzed Cross-Coupling of Grignards to 2-Oxazolines 5

entry	oxazoline	catalyst[a]	% yield[b,h]	mp or bp, °C (mm)	MS, m/e	IR, cm^{-1}	NMR, δ[g]
1	12	20	95	105-107	223	1640, 1470, 1350, 1235, 1060, 940, 760, 700	8.2-7.2 (m, 9 H), 4.65-3.85 (m, 4 H)
2	13	20	69	118-120	253	1650, 1250, 840, 800, 700	8.12 (s, 1 H), 7.9-6.8 (m, 7 H), 4.58-3.9 (m, 4 H), 3.8 (s, 3 H)
3	14[c]	21	94	120 (0.4)	175	2960, 1640, 1355, 1060, 940, 700	8.0-7.0 (m, 4 H), 4.2 (octet, 4 H), 2.6 (q, 2 H), 1.25 (t, 3 H)
4	15	21	90	126 (0.4)	189	2940, 1650, 1350, 1060, 700	7.75-7.25 (m, 4 H), 4.2 (octet, 4 H), 2.7 (t, 2 H), 1.65 (quintet, 2 H), 0.9 (t, 3 H)
5	16[i]	21	94	95 (0.3)	189	2940, 1640, 1050	8.0-7.0 (m, 4 H), 4.2 (octet, 4 H), 2.9 (t, 2 H), 1.6 (quintet, 2 H), 0.9 (t, 3 H)
6	17[d]	20	85	120 (0.4)	161	2940, 1640, 1350, 1245, 1040, 940, 725	7.8-7.0 (m, 4 H), 4.2 (octet, 4 H), 2.55 (s, 3 H)
7	18[e]	21	56	140 (0.7)	237	1645, 1040, 740, 700	7.9-7.0 (m, 9 H), 4.4 (s, 2 H), 4.4-3.7 (m, 4 H)
8	19[f]	21	77	95 (0.3)	189	2940, 1650, 1070, 940, 675	8.5 (q, 4 H), 4.25 (octet, 4 H), 2.65 (t, 2 H), 1.65 (m, 2 H), 0.93 (t, 3 H)

[a] Catalysts: (1,3-diphenylphosphinopropane)nickel(II) chloride **20** [$NiCl_2$(dppp)]; (1,2-diphenylphosphinoethane)-nickel(II) chloride **21** [$NiCl_2$(dppe)]. See general cross-coupling procedure in the Experimental Section for reaction conditions. [b] Isolated and distilled yields. [c] Calcd for $C_{11}H_{13}NO \cdot 0.75H_2O$. [d] Calcd for $C_{10}H_{11}NO \cdot 0.25H_2O$. [e] High-resolution mass spectrum, m/e 237.115 (M^+; $C_{16}H_{15}NO$ requires 237.115). [f] High-resolution mass spectrum, m/e 189.115 (M^+; $C_{12}H_{15}NO$ requires 189.115). [g] Measured in $CDCl_3$ with internal Me_4Si. [h] Satisfactory analytical data (±0.4 for C, H, N) were reported for all oxazolines except as noted in footnotes. [i] Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.65; H, 7.68; N, 7.33.

vorable steric interactions between the phenyl Grignard and the oxazolinyl group prevent formation of the intermediate σ-diorganonickel complex,[12] and/or prevent it from reductively eliminating to yield the cross-coupled product. As a consequence, reduction to 2-phenyl-2-oxazoline becomes a major side reaction.

The variety of Grignard reagents that cross-couple with oxazolines **7–10** is surprising since we were unable to cross-couple alkyl Grignards containing β hydrogens (reducing Grignards) in other oxazolinyl systems.[1] As entries 3–5 (Table I) show, excellent yields were obtained with $NiCl_2$(dppe) **21** as catalyst in cross-coupling alkyl Grignards. Generally, catalyst **21** was more effective than catalyst **20** or $NiCl_2[P(Ph_3)]_2$ **22**. Preparation of 2-(*o*-phenylmethylphenyl)-2-oxazoline (**18**) by this cross-coupling procedure, albeit in moderate yield, complements the metal–halogen/hydrogen exchange procedure. Benzyllithium or Grignards do not satisfactorily displace the *o*-methoxy in 2-(*o*-methoxyphenyl)-2-oxazolines.[5f]

When X is halogen, as in oxazolines **23–26**, sequential replacement of each halogen with different alkyl or aryl groups presented an intriguing problem of regiocontrol. The activating effect of the oxazolinyl group in this system should direct cross-coupling toward the 2-position. Although Kumada has shown that organometallics catalyzed by palladium–phosphine complexes sequentially replace halogens on dihalogenated phenyls,[14] it is not known if a third substituent could influence the site of initial cross-coupling. When exactly 1 equiv of methylmagnesium bromide was added to 2-(2,4-dichlorophenyl)-2-oxazoline (**23**) in the presence of $NiCl_2[P(Ph_3)]_2$ **22**, 88% yield of 2-(2-methyl-4-chlorophenyl)-2-oxazoline (**29**) was obtained (eq 1). Similarly, 2-(2,5-dichlorophenyl)-2-oxazoline (**24**) produced 2-(2-methyl-5-chlorophenyl)-2-oxazoline (**30**) in 83% yield with **22** as catalyst. Catalyst $NiCl_2$(dppe) **21** was not as effective on the dihalogenated phenyloxazoline **23–26**, apparently because of the reduced nucleophilicity of those oxazolines and their subsequent reduced reactivity when compared to monohalogenated phenyloxazolines **7–10**. With catalysts **20** and **21**, both starting material and

(10) Nickel acetylacetonate, which was reported to be very effective in catalyzing the cross-coupling of sterically hindered 1,8-diarylnaphthalenes,[11] was used similarly with **10** to yield a mixture consisting of 44% 2-(*o*-phenylphenyl)-2-oxazoline, 32% 2-phenyl-2-oxazoline, and 5% starting material **10**. We obtained similar product distributions from the reactions of methyl, *n*-propyl, and phenyl Grignards with 2-(3-chloro-2-methylphenyl)-2-oxazolines (**28**).

(11) Clough, R. L.; Mison, P.; Roberts, J. D. *J. Org. Chem.* **1976**, *41*, 2252.

(12) Kochi, J. K. "Organometallic Mechanism and Catalysis"; Academic Press: New York, 1978.

dimethylated phenyloxazoline were major impurities. Clearly **22** is the superior catalyst in this dihalogenated phenyl system. *Without catalyst, starting material was recovered (average 98%) from attempted reactions of 23 and 27 with methyl and phenyl Grignards, respectively.* This result for **23** was not unexpected in view of Beak's reported stability of the *o*-chloro function of *o*-chloro-*N,N*-diethylbenzamide to *sec*-BuLi/TMEDA.[4f] However, the stability of **27** toward uncatalyzed Grignard displacement of the 2-methylthio group is surprising. *In fact,* **27** *did not undergo cross-coupling with bis(1,1'-diphenylphosphino)ferrocene–palladium (II) chloride (31) as catalyst in refluxing THF,* even though this catalyst is effective in catalyzing cross-coupling of aryl Grignards to 2-(methylthio)-4,4-dimethyl-2-oxazoline (**32**).[1a,b] Catalyst **22**, however, successfully catalyzes the formation of **29** from **27**. These results indicate that the oxazolinyl moiety may be electronically activating the 2-C–X bond toward nickel insertion, thereby leading to cross-coupled product. Activation of the arene ring by metal–oxazolinyl complexation does not appear to be a factor in the above cases, since reaction does not occur in the absence of catalyst. Oxazolines **25** and **26** reacted with methyl Grignard as expected with no regioselectivity, yielding a mixture of starting materials as well as mono- and dimethylated phenyloxazolines. In the dihalogenated phenyloxazolines **23–24** to date, only methyl Grignard gives satisfactory yields of 2-(2-alkylated monohalogenated phenyl) 2-oxazoline **4**.

Finally, to complete the original objective of synthesizing unsymmetrically 2-(disubstituted phenyl) 2-oxazolines **5**,[21] 2-oxazoline **29** was reacted with *n*-propyl Grignard in the presence of catalyst **21** to yield 2-(2-methyl-4-*n*-propylphenyl)-2-oxazoline (**33**) in 94% yield. Thus we have shown that 2-(substituted phenyl) 2-oxazolines **5** (R' and R = alkyl, aryl, or hydrogen) may be prepared from readily accessible 2-(halogenated phenyl) 2-oxazolines **2** and **3**. The resulting oxazolines may, of course, be readily converted to aryl acids (esters and amides),[5a,16] alkehydes,[5a,16] ketones,[17] (β-hydroxyethyl)aminomethyl derivatives[1b] and 1,2,3,4-tetrahydroisoquinolines **1**.[1b]

Experimental Section[18]

^{1}H NMR spectra were taken on Varian CFT-20(80 MHz) with Me_4Si as internal standard. Infrared spectra were obtained on either a Perkin-Elmer 580 or 283 spectrometer. Low-resolution mass spectra by electron impact (EI) were obtained at 70 eV on a Hitachi Perkin-Elmer RMU-6E by direct insertion. High-resolution and field desorption (FD) mass spectra were obtained on a Varian MAT-CH5 double-focusing spectrometer. GC/MS data were obtained on a Finnigan-3600 instrument using a 4 ft × 0.078 in. column filled with 3% OV-17 on Chromasorb WHP. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Tetrahydrofuran was distilled from benzophenone ketyl under a nitrogen atmosphere. Grignard reagents were titrated by either the method of Bergbreiter and Pendergrass[19] or that of Watson.[20]

General Procedure for Cross-Coupling Grignard Reagents to (Halophenyl)-2-oxazolines (Table I, Oxazolines 12–19). A 100-mL three-necked flask containing a stirring bar was fitted with gas inlet and outlet tubes (the outlet connected to a gas bubbler containing silicon oil) and then was heated and swept with nitrogen. After the apparatus cooled, ~2 mol % of nickel–phosphine catalyst **20**, **21**, or **22** (~50 mg of catalyst to 1 g of halophenyl substrate) was added to a THF solution of the appropriate (halophenyl)-2-oxazoline. The flask was then fitted with a neoprene septum and the Grignard reagent (1.2 equiv) was added under positive nitrogen pressure via syringe. The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 3–16 h and then poured onto 50 mL of aqueous ammonium chloride. The organic layer was removed and the aqueous layer extracted several times with ether. The combined and dried ($MgSO_4$) ether layers were concentrated to an oil that was distilled to yield the desired product.

2-(2-Methyl-4-chlorophenyl)-2-oxazoline (**29**) was prepared as described above, using exactly 1 equiv of methylmagnesium bromide and 2-(2,4-dichlorophenyl)-2-oxazoline (**23**) or 2-[2-(methylthio)-4-chlorophenyl)]-2-oxazoline (**27**) with $NiCl_2[P(Ph_3)]_2$ **22** as catalyst: bp 77 °C (0.2 mm); mass spectrum, *m/e* 195 (M^+, 1 Cl); IR (film) 1650, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 3 H), 4.25 (octet, 4 H), 2.55 (s, 3 H).

Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.59; H, 5.27; N, 6.89.

2-(2-Methyl-5-chlorophenyl)-2-oxazoline (**30**) was prepared as described above, using exactly 1 equiv of methylmagnesium bromide and 2-(2,5-dichlorophenyl)-2-oxazoline (**24**) with $NiCl_2[P(Ph_3)]_2$ **22** as catalyst: bp 93 °C (0.25 mm); mass spectrum, *m/e* 195 (M^+, 1 Cl); IR (film) 1650, 1490, 1050, 950, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 1 H), 7.25 (m, 2 H), 4.25 (octet, 4 H), 2.55 (s, 3 H).

Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.52; H, 5.08; N, 7.11.

2-[2-(Methylthio)-4-chlorophenyl]-2-oxazoline (**27**). Following the conditions of Beak,[4f] 2-(*p*-chlorophenyl)-2-oxazoline (**9**; 5.0 g, 27.6 mmol) was treated with *sec*-BuLi/TMEDA (29 mmol) in THF at −60 °C. The reaction solution was allowed to stand 1 h at that temperature and then was treated with dimethyl sulfide (2.7 g, 29 mmol). The reaction mixture was allowed to warm to ambient temperature, quenched with aqueous ammonium chloride, and extracted several times with ether. The combined and dried organic solution was concentrated to yield an oily solid. Recrystallization from petroleum ether/acetone yielded 3.2 g (14 mmol, 51%) of the desired product **27**: mp 105–107 °C; mass spectrum, *m/e* 227 (M^+, 1 Cl); IR (film) 1635, 1240, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (q, 2 H), 7.25 (s, 1 H), 4.15 (m, 4 H), 2.4 (s, 3 H).

Anal. Calcd for $C_{10}H_{10}ClNOS$: C, 52.74; H, 4.43; N, 6.15. Found: C, 52.94; H, 4.47; N, 6.17.

2-(2-Methyl-3-chlorophenyl)-2-oxazoline (**28**). With use of similar conditions as above for **27**, 2-(*m*-chlorophenyl)-2-oxazoline (**8**; 3.0 g, 16.6 mmol) was treated with 1.2 equiv of *sec*-BuLi/TMEDA and methyl iodide in THF to yield the desired product **28**: 3.0 g (15.3 mmol, 93%); bp 90 °C (0.05 mm); mass spectrum, *m/e* 195 (M^+, 1 Cl); IR (film) 2940, 1650, 1070, 1010, 945 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 3 H), 4.25 (m, 4 H), 2.65 (s, 3 H).

Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.12, H, 5.10; N, 6.91.

2-(2-Methyl-4-*n*-propylphenyl)-2-oxazoline (**33**). Following the above general cross-coupling procedure 2-(2-methyl-4-chlorophenyl)-2-oxazoline (**29**; 0.65 g, 3.3 mmol) was treated with *n*-propylmagnesium bromide (1.2 equiv) in THF at room temperature with catalyst $NiCl_2$(dppe) **21** to yield the desired product **33**: 0.55 g (31 mmol, 94%); bp 90 °C (0.3 mm); IR (film) 2940, 1640, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 3 H), 4.25 (octet, 4 H), 2.6 (m, 5 H), 1.75 (sextet, 2 H), 0.95 (t, 3 H); high-resolution mass spectrum, *m/e* 203.131 (M^+; $C_{13}H_{17}NO$ requires 203.131).

(13) For a review of nickel–phosphine complex catalyzed cross-coupling of Grignards and organohalides, see: Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669.

(14) Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.* **1980**, 845.

(15) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.

(16) (a) Meyers, A. I.; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676. (b) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531.

(17) (a) Dubois, J. E.; Lion, C. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1973**, *277*, 1383. (b) Dubois, J. E.; Lion, C. *Tetrahedron* **1973**, *29*, 3417. (c) Dubois, J. E.; Lion, C. *Bull. Soc. Chim. Fr.* **1973**, 2673.

(18) Spectral data and physical constants of (β-hydroxyethyl)- and (β-chloroethyl)benzamides **34–49**, intermediates in the preparation of oxazolines **7–10** and **23–26**, are available as supplementary material.

(19) Bergbreiter, D. E.; Pendergrass, E. *J. Org. Chem.* **1981**, *46*, 219.

(20) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(21) **Note Added in Proof**: After this work was submitted for publication Professor A. I. Meyers [*Tetrahedron Lett.* **1982**, 2091] reported the syntheses of 2-(2,3-disubstituted phenyl) 2-oxazolines via a benzyne intermediate derived from the 4,4-dimethyloxazolinyl analogue of **8**.

General Procedure for Preparation of 2-Oxazolines 7-10 and 23-26. 2-(o-Bromophenyl)-2-oxazoline (10).[18] To a stirred (250 mL) methylene chloride solution of ethanolamine (42.06 g, 0.69) was added dropwise 0.5 equiv (0.34 mol) of o-bromobenzoyl chloride in methylene chloride while the temperature was maintained at 5 °C. The resulting suspension was then allowed to stir at ambient temperature 0.5 h. At the end of this time 200 mL of water was added and the organic layer was separated and the aqueous layer extracted with methylene chloride several times. The combined and dried organic layer was concentrated to yield 92.0 g of crude N-(β-hydroxyethyl)-o-bromobenzamide (**34**): mp 93-95 °C (petroleum ether-ether).

The amide **34** (88.0 g, 0.36 mol) was treated with 53 mL of thionyl chloride in chloroform under reflux 0.5 h. At the end of this time the solvent and excess thionyl chloride were removed under vacuum. The residue was treated with K_2CO_3(aq) and extracted with chloroform several times. The combined and dried organic layer was concentrated to yield 67.34 g (0.25 mol, 71%) of N-(β-chloroethyl)-o-bromobenzamide (**35**): mp 73-75 °C (petroleum ether-ether).

Amide **35** (63.34 g, 0.24 mol) was treated with NaH (8.17 g, 0.34 mol) in THF at reflux 0.5 h. At the end of this time the suspension was filtered and the filtrate dried ($MgSO_4$) and concentrated to yield 43.1 g (0.19 mol, 79%) of the desired product **10**: bp 94 °C (0.05 mm); IR (film) 2940, 1650, 1090, 940, 760, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9-7.2 (m, 4 H), 4.3 (octet, 2 H); high-resolution mass spectrum, m/e 224.979 (M^+, 1 Br; C_9H_8BrNO requires 224.979).

2-(o-Chlorophenyl)-2-oxazoline (7) was prepared as described above: bp 90 °C (0.015 mm); IR (film) 1650, 1090, 1040, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9-7.1 (m, 4 H), 4.25 (octet, 2 H); mass spectrum, m/e 181 (M^+, 1 Cl).

Anal. Calcd for $C_9H_8ClNO \cdot 0.33H_2O$: C, 57.61; H, 4.48; N, 7.46. Found: C, 57.70; H, 4.27; N, 7.20.

2-(m-Chlorophenyl)-2-oxazoline (8) was prepared as described above: mp 46 °C; IR (film) 1650, 1350, 1250, 940, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (m, 2 H), 7.35 (m, 2 H), 4.2 (m, 4 H); mass spectrum, m/e 181 (M^+, 1 Cl).

Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.38; H, 4.56; N, 7.69.

2-(p-Chlorophenyl)-2-oxazoline (9) was prepared as described above: mp 77-78 °C; IR (film) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (q, 4 H), 4.15 (m, 4 H); mass spectrum, m/e 181 (M^+, 1 Cl).

Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.70; H, 4.54; N, 7.54.

2-(2,4-Dichlorophenyl)-2-oxazoline (23) was prepared as described above: bp 95 °C (0.2 mm); IR (film) 1650, 1590, 1480, 1100, 1040, 950, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.8-7.1 (m, 3 H), 4.25 (octet, 4 H); mass spectrum, m/e 215 (M^+, 2 Cl).

Anal. Calcd for $C_9H_7Cl_2NO$: C, 50.03; H, 3.27; N, 6.48. Found: C, 49.85; H, 3.26; N, 6.49.

2-(2,5-Dichlorophenyl)-2-oxazoline (24) was prepared as desired above: bp 107 °C (0.5 mm); IR (film) 1650, 1470, 1405, 1100, 1040, 950, 420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.8 (m, 1 H), 7.32 (m, 2 H), 4.25 (octet, 4 H); mass spectrum, m/e 215 (M^+, 2 Cl).

Anal. Calcd for $C_9H_7Cl_2NO$: C, 50.03; H, 3.27; N, 6.48. Found: C, 50.02; H, 3.18; N, 6.21.

2-(3,4-Dichlorophenyl)-2-oxazoline (25) was prepared as described above: mp 90-91 °C; IR (film) 1650, 1070, 710, cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0 (d, 1 H), 7.6 (q, 2 H), 4.6-3.8 (m, 2 H); mass spectrum, m/e (M^+, 2 Cl).

Anal. Calcd for $C_9H_7NOCl_2$: C, 50.03; H, 3.27, N, 6.48. Found: C, 50.19; H, 3.20;, N, 6.24.

2-(3,5-Dichlorophenyl)-2-oxazoline (26) was prepared as described above: mp 61-63 °C; IR (film) 1650, 1560, 800 $cm^{1;}$ ^1H NMR ($CDCl_3$) δ 7.70 (s, 3 H), 4.6-3.75 (m, 4 H); mass spectrum, m/e 215 (M^+, 2 Cl).

Anal. Calcd for $C_9H_7Cl_2NO$: C, 50.03; H, 3.27; N, 6.48. Found: C, 50.20; H, 3.30; N, 6.59.

Acknowledgment. I am indebted to the Analytical and Physical Chemistry Department for the analytical data: Ms. E. Reich for combustion analyses, Mr. David B. Staiger and Mr. Gary E. Zuber for NMR/IR spectra, Mr. Walter P. Johnson and Mr. Gerald D. Roberts for mass spectra, and Mr. Lewis B. Killmer and Ms. Mary Mentzer for GC/MS data.

Registry No. **7**, 82891-76-7; **8**, 82891-77-8; **9**, 7399-68-0; **10**, 51816-27-4; **12**, 82891-78-9; **13**, 82891-79-0; **14**, 82891-80-3; **15**, 82891-81-4; **16**, 82891-82-5; **17**, 43221-62-1; **18**, 82891-83-6; **19**, 82891-84-7; **20**, 15629-92-2; **21**, 38754-20-0; **22**, 14264-16-5; **23**, 82891-85-8; **24**, 82891-86-9; **25**, 82891-87-0; **26**, 82891-88-1; **27**, 82891-89-2; **28**, 82891-90-5; **29**, 82891-91-6; **30**, 82891-92-7; **33**, 82891-93-8; **34**, 82891-94-9; **35**, 51816-16-1; ethanolamine, 141-43-5; o-bromobenzoyl chloride, 7154-66-7.

Supplementary Material Available: Spectral data and physical constants of (β-hydroxyethyl)- and (β-chloroethyl)-benzamides **34-49**, intermediates in the synthesis of oxazolines **7-10** and **23-26** (5 pages). Ordering information is given on any current masthead page.

2-Hydroxyindazoles

Kotaro Takada, Thoe Kan-Woon, and A. J. Boulton*

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, England

Received April 2, 1982

Thermolysis of 2-azidophenyl ketoximes provides 2-hydroxyindazoles, which in aqueous solution usually exist in the alternative 1*H*-indazole 2-oxide tautomeric forms. Both N- and O-substituted derivatives are produced on alkylation.

In the course of a study of a general rearrangement reaction of heterocycles, it was found that the oximes of 4-formylbenzofurazan oxides (**1**) were transformed on heating into 2-hydroxy-7-nitroindazoles (**2**).[1] At that time a search of the literature revealed only two prior examples of 3-unsubstituted 2-hydroxyindazoles: the simplest, **3**, reported by Bamberger and Demuth in 1902,[2] and the 7-methoxy-4-nitro compound **4**.[3] Both had been made by thermal decomposition of the corresponding azides (**5**), and

(1) Boulton, A. J.; Thoe K.-W.; Balasubrahmanyam, S.N.; Mallick, I. M.; Radhakrishna, A. S. *J. Org. Chem.* **1980**, *45*, 1653.

(2) Bamberger, E.; Demuth, E. *Chem. Ber.* **1902**, *35*, 1885.

(3) Boulton, A. J.; Ghosh, P. B.; Katritzky, A. R. *J. Chem. Soc. B* **1966**, 1011.

0022-3263/82/1947-4323$01.25/0