New Synthesis of 2-Substituted 2-Oxazolines: Transition-Metal-Catalyzed Cross-Coupling of Grignards with 2-(Methylthio)-4,4-dimethyl-2-oxazoline

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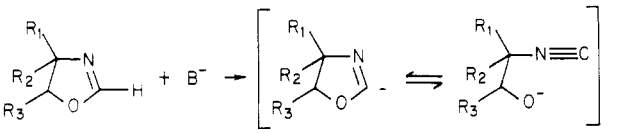
A new synthesis of 2-aryl-4,4-dimethyl-2-oxazolines (**18a–e**) using nickel- and palladium–phosphine complexes to catalyze cross-coupling of Grignard reagents **17** with 2-(methylthio)-4,4-dimethyl-2-oxazoline (**16**) is described. This reaction represents the first reported example of preparing 2-aryl-2-oxazolines by arylation at C-2 of an oxazolinyl moiety.

The chemistry of 2-oxazolines has been extensively explored because of the variety of uses for this reactive class of compounds.[1a] In recent years, the 2-oxazolinyl group has been used to direct ortho metalation of 2-aryl and 2-pyridyl-2-oxazolines[2,3] and influence nucleophilic addition in the latter.[3] Moreover, the synthetic utility of 2-oxazolines has been amply demonstrated by Meyers[4] and Dubois,[5] who used them to prepare ketones,[5] aldehydes,[6] esters, acids, and amides[7] employing mild reaction conditions. However, the synthesis of 2-substituted 2-oxazolines is dependent on the availability of the prerequisite carboxylic acids or nitriles.[1]. An alternative is to alkylate or acylate 2-oxazolines such as **2** (Scheme I). This, in effect, uses 2-lithio-2-oxazolines (**2**) as acyl or formyl anion equivalents. Subsequent hydrolysis of the resulting 2-alkylated (acylated) 2-oxazolines (**4**) would produce homologous carboxylic acid derivatives, obtained without using carboxylic acids or nitriles as starting materials.

Unfortunately, one cannot draw promising conclusions concerning alkylation or acylation of 2-lithio-2-oxazoline (**2**) based on previous investigations into their stability and reactivity. For example, Meyers[6a] deprotonated C-2 of 4,4-dimethyl-2-oxazoline (**1**) with *n*-butyllithium to obtain 2-oxazolinyl anion **2** which yielded 2-deuteriooxazoline (**5**) on treatment with D_2O. But he also demonstrated that oxazolinyl anion **2** is in equilibrium with its open-chain isomer **3** by isolating β-hydroxyethyl isocyanide (**6**) from the reaction mixture. Similarly, Schöllkopf[8] verified that such an equilibrium exists for 1-lithio-4,5-diphenyl-2-oxazoline (**8**) by isolating β-acetoxy-1,2-diphenylethyl isocyanide (**10**) from the reaction mixture of 4,5-diphenyl-2-oxazoline (**7**) and *n*-butyllithium after quenching with acetic anhydride. When benzaldehyde was used as the quenching electrophile, he isolated 2-(phenylhydroxymethyl)-4,5-phenyl-2-oxazoline (**11**). However, in the absence of aromatic groups at the 4- and/or 5-position on the 2-oxazolinyl moiety we were not able to trap a 2-lithio-2-oxazoline with a reactive carbonyl and have not been able to trap **2** or **8** with any alkyl halide.[9]

Scheme I[a]



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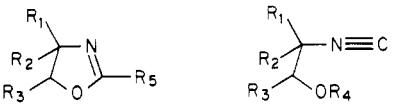
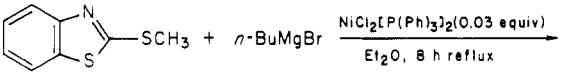


4, R_5 = CH_2Ph; CH_3; etc. 6, R_4 = H
5, R_5 = D 10, R_4 = Ac
11, R_5 = CH(OH)Ph
12, R_1 = R_2 = R_3 = H; R_5 = Cl
13, R_1 = R_2 = H; R_3 = Ph; R_5 = Cl

[a] For **1–6**, R_1 = R_2 = CH_3 and R_3 = H; for **7–11**, R_1 = H and R_2 = R_3 = Ph.

We had hoped to use our experience with nickel–phosphine complexes in the coupling of Grignard reagents with halopyridines[10] and haloisoquinolines[11] to apply this same coupling reaction to 2-halo-2-oxazolines (**12** or **13**). Unfortunately, we were unable to develop a satisfactory synthesis of either **12** or **13**.

In the course of our study, Takei and co-workers[12] reported the stereospecific coupling of phenyl Grignard to alkenyl and aryl sulfides in the presence of $NiCl_2[P(Ph_3)]_2$ to give stilbenes and arylphenyl coupling products, respectively. They also extended this reaction to cover allylic sulfides[13] and 2-methylthio heterocycles, e.g., pyrimidines, benzothiazoles, pyridines, and furans (eq 1).[14] Because



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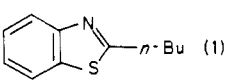

15 (93%)

of their precedent, we decided to explore the possibility

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(2) Meyers, A. I.; Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4464.
(3) (a) Hauck, A. E.; Giam, C. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2070. (b) Meyers, A. I.; Gabel, R. A. *Heterocycles* **1978**, *11*, 133.
(4) For a review on the synthetic utility of 2-oxazolines see: Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270.
(5) (a) Dubois, J. E.; Lion, C. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1972**, *274*, 303. (b) Dubois, J. E.; Lion, C. *Tetrahedron* **1973**, *29*, 3417. (c) Dubois, J. E.; Lion, C. *Bull. Soc. Chim. Fr.* **1973**, 2673. (d) Dubois, J. E.; Lion, C. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1973**, *277*, 1383.
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(9) Pridgen, L. N., unpublished results.
(10) Pridgen, L. N. *J. Heterocycl. Chem.* **1975**, *12*, 443.
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(13) Okamura, H.; Takei, H. *Tetrahedron Lett.* **1979**, 3425.
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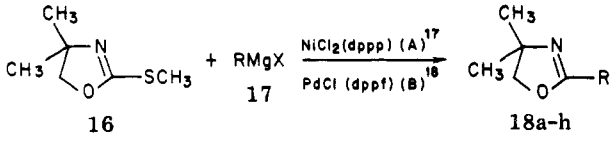
0022-3263/81/1946-5402$01.25/0

Table I. Cross-Coupling of 2-(Methylthio)-4,4-dimethyl-2-oxazoline (16) with Grignard Reagents (17) Catalyzed by Transition Metal-Phosphine Complexes[16]



16 18a-h

run[f]	Grignard	product R	% yield[a] catalyst A[b]	% yield[a] catalyst B[c]
1	phenylmagnesium bromide	C_6H_5 (18a)	77	84
2	*p*-tolylmagnesium bromide	4-$CH_3C_6H_4$ (18b)	65	94
3	*p*-anisylmagnesium bromide	4-$CH_3OC_6H_4$ (18c)	46	73
4	3,4-dimethylphenylmagnesium bromide	3,4-$(CH_3)C_6H_4$ (18d)	71	93
5	*p*-ethylphenylmagnesium bromide	4-CH_3CH_2-C_6H_4 (18e)	72	90
6	benzylmagnesium chloride	$PhCH_2$ (18f)	20[d]	0
7	*n*-propylmagnesium chloride	$CH_3CH_2CH_2$ (18g)	5[e]	
8	*n*-butylmagnesium chloride	$CH_3CH_2CH_2$-CH_2 (18h)		0[e]

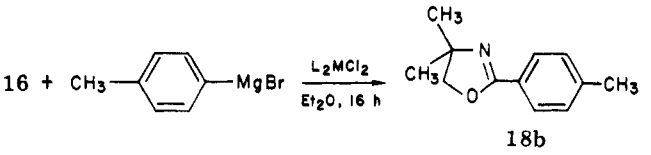
[a] Yields are based on isolated and distilled products except where indicated. Molar ratio of L_2MCl_2/16/RMgX (17) is 0.013-0.03/1.0/1.2-1.5. [b] Conducted in THF/Et_2O at 50-60 °C for 4 h. [c] Conducted in ether at ambient temperature. For consistency, all reactions presented in this column were done by using a reaction time of 16 h. However, the reactions using catalyst B were essentially complete after 1-3 h. [d] Determined by NMR integration. [e] Determined by GC. [f] The starting material was 16 in every case.

of using a 2-(methylthio)-2-oxazoline as our 2-oxazolinyl substrate. Herein we present the details of our efforts employing nickel- and palladium-phosphine complexes as catalysts to prepared 2-substituted 4,4-dimethyl-2-oxazolines **18a–h** by cross-coupling 2-(methylthio)-4,4-dimethyl-2-oxazolines (**16**)[15] and Grignard reagents **17**. We also describe how this new synthesis may be used to prepare aromatic esters, acids, aldehydes, ketones, and (β-hydroxyethyl)benzamides.

Results and Discussions

Our results in Table I show that 2-aryl-4,4-dimethyl-2-oxazolines **18a–e** are prepared in good yields by using $NiCl_2$(dppe) (A)[17] and in excellent yields by using $PdCl_2$(dppf) (B)[18], as catalysts. In the former case the product tended to be somewhat impure and contained colored impurities. Entries 6–8 show that in this 2-oxazoline series alkyl Grignards are reluctant to couple. This is contrary to results obtained by Takei who obtained excellent yields with *n*-butyl- and (2-phenylethyl)magnesium bromide in his 1,3-heterocyclic series.[14]

Table II. Cross-Coupling of 2-(Methylthio)-4,4-dimethyl-2-oxazoline (16) with *p*-Tolylmagnesium Bromide



18b

run	catalyst (25 mg)	temp, °C	product distribution,[a] % 18b	16
1	$NiCl_2[P(Ph)_3]_2$	35	2	25[b]
2	$NiCl_2$(dppe)	35	64	10
3	$PdCl_2$(dppe)	35	9	74
4	$PdCl_2[P(Ph)_3]_2$	35	24	26
5	$NiCl_2$(dppp)	35	21	49
6	$PdCl_2$(dppb)	35	79	
7	$NiCl_2$(dppf)	35	21	59
8	$PdCl_2$(dppf)	35	61	12
9	$PdCl_2$(dppf)	20	99	
10	$PdCl_2$(dppb)	20	87	
11	$NiCl_2$(dppe)	20	69	17
12		35	5	62

[a] Determined by GC on a concentrated reaction mixture by using reference standards and benzophenone as an internal standard. Molar ratio of 16/ArMgX (17) is 1.7/2.15. The remaining material is composed of 4,4'-dimethylbiphenyl, the diadduct **19**, and other unidentified components. [b] The diadduct **19** is 59% of the reaction mixture.

The excellent catalyzing ability of $PdCl_2$(dppf) (B) was unexpected since Takei had concluded that palladium complexes were less reactive than nickel complexes in his allylic sulfide series.[13] To determine if our observation was an abnormality, we studied the catalyzing ability of other readily available nickel- and palladium-phosphine complexes (Table II).[16] Entries 2, 6, and 8 of Table II show the palladium complexes to be just as effective, if not more so, as the nickel complexes in refluxing ether and are demonstrably better at ambient temperature. However, temperatures higher than ambient should be avoided where possible when running this coupling reaction to decrease self-coupling of the Grignard reagent. Also, at higher temperatures we obtained significant amounts of a double addition product (**19**, eq 2).[19] The palladium complex reactions run at ambient temperature (entries 9 and 10) were cleaner than the $NiCl_2$(dppe) reaction run at ambient temperature (entry 11), where some starting material was detected. Entry 12 verifies that these transition-metal complexes are necessary for this reaction to proceed satisfactorily.

The mechanism for the coupling reaction with alkenyl, allylic, aryl, and heterocyclic sulfides,[12-14] as well as with alkenyl and phenyl selenides,[20] is thought to be similar to that proposed for Grignard coupling with organohalides.[21] The Grignard coupling with **16** occurs after cleavage of the azomethine (C_{sp^2}–S) bond with expulsion of methyl mercaptan. Coupling products resulting from cleavage of the

(15) Clapp, R. C.; Long, J., Jr.; Hasselstrom, T. *J. Org. Chem.* **1963**, *28*, 1308. The precursor, 4,4-dimethyloxazolidine-2-thione (**26**) is available from Tridom Chemical, Inc.

(16) The nickel and palladium 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: dppp = $Ph_2P(CH_2)PPh_2$; dppe = $Ph_2P(CH_2)_2PPh_2$; dppb = $Ph_2P(CH_2)_4PPh_2$; dppf = 1,1'-bis(diphenylphosphino)ferrocene.

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(19) We have isolated and fully characterized a similar diadduct obtained in another study to be submitted for publication.

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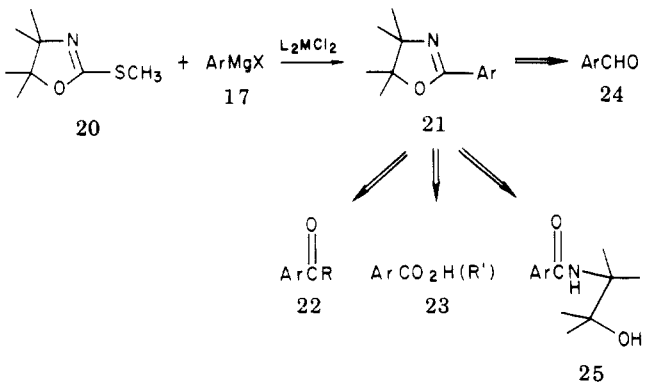
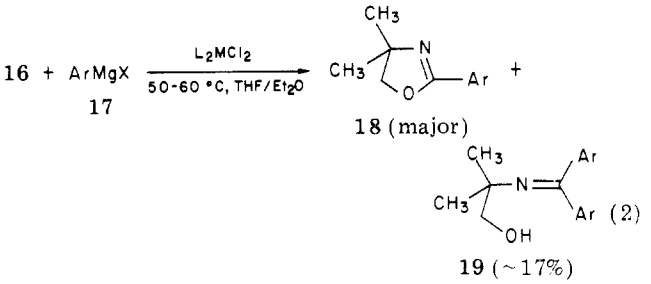
(21) For a pertinent review of the nickel- and palladium-phosphine complex catalyst cross-coupling reaction of Grignards and organohalides, including discussions on possible mechanisms, see: (a) Kumada, M.; *Pure Appl. Chem.* **1980**, *52*, 669. (b) Kochi, J. K. "Organometallic Mechanism and Catalysis"; Academic Press: New York, 1978.

Scheme II



methyl sulfide (C_{sp^3}–S) bond was not observed by us. The Grignard of 4-bromo-*m*-xylene did not appreciably undergo coupling with **16** (<10% yield by GC), presumably because of steric hindrance from the *o*-methyl.

Although Meyers has used a 2-oxazolinyl moiety as a carboxyl protecting group[7] under Grignard reaction conditions, caution should be exercised in its continued use as such since we have found that Grignards **17** do in fact add to 2-oxazolines to yield the imine **19**. However, in our case coordination of the transition metal to nitrogen probably facilitates nucleophilic addition of the aryl Grignard to the azomethine bond of **18**, yielding **19**.[22] Treatment of **18** in refluxing ether with 1 equiv of Grignard reagent **17** and $NiCl_2$(dppp) in a catalytic amount yielded 17% of the diadduct **19** by GC/MS (eq 2). Under similar conditions without catalyst **19** *was not detected.*



Summary

The transition-metal-catalyzed cross-coupling of aryl Grignards to 2-(methylthio)-2-oxazolines (**20**, Scheme II) presented in this work demonstrates a new method of preparing 2-aryl-2-oxazolines such as **21**. Oxazolines **21** may be converted to ketone **22**,[5] carboxylic acid **23**,[7] aldehyde **24**,[6] or (β-hydroxyethyl)benzamide **25**[7] (Ar = phenyl). Our synthesis of 2-aryl-2-oxazolines (**18**) complements existing methods and provides the chemist with an alternative synthesis when the prerequisite benzoic acid or benzonitrile derivative is not readily available. Additionally, the inexpensiveness and ready availability of starting materials add to the attractiveness of our synthesis.[15] Undoubtedly, this method can be used to prepare more complex aryl or alkyl heterocycles. We are currently expanding the utility of this cross-coupling reaction employing other 2-(methylthio)-2-oxazolines.

Experimental Section

^{1}H NMR spectra were obtained on a Perkin-Elmer R-600 or R-24 with Me_4Si as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 283 spectrometer. GC/MS data were obtained on a Finnigan-3600 using a 4 ft × 0.078 in. column filled with 3% OV-17 on Chromasorb WHP.

Tetrahydrofuran was distilled from benzophenone ketyl under a nitrogen atmosphere. Grignard reagents were titrated by either the method of Bergbreiter and Pendergrass[23] or that of Watson.[24]

General Procedure: 2-(4-Methylphenyl)-4,4-dimethyl-2-oxazoline (18b). A 100-mL three-necked flask containing a stirring bar was fitted with nitrogen inlet and outlet tubes and then was heated and swept with nitrogen. After the apparatus cooled, 130 mg (0.178 mmol) of $PdCl_2$(dppf)[16,18] and 2.0 g (13.8 mmol) of 2-(methylthio)-4,4-dimethyl-2-oxazoline (**16**)[15] were added along with 75 mL of dry ether. The flask was fitted with a neoprene septum, and *p*-tolylmagnesium bromide (1.2 equiv) was added under a nitrogen atmosphere via syringe. The reaction mixture was stirred at ambient temperature under positive nitrogen pressure for 3 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 of **18b**: 2.45 g (12.9 mmol, 94%); bp 56 °C (0.01 mm); IR (film) 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.5 (q, 4 H), 4.1 (s, 2 H), 2.4 (s, 3 H), 1.35 (s, 6 H); high-resolution mass spectrum, *m/e* 189.1145 (M^+) ($C_{12}H_{15}NO$ requires 189.1154).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.37; H, 7.83; N, 7.68.

2-Phenyl-4,4-dimethyl-2-oxazoline (18a)[25] was prepared as described above: bp 62 °C (0.2 mm); IR (film) 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 5 H), 4.1 (s, 2 H), 1.4 (s, 6 H); high-resolution mass spectrum, *m/e* 175.0990 (M^+) ($C_{11}H_{13}NO$ requires 175.0997).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.39; H, 7.48. Found: C, 75.75; H, 7.07.

2-(4-Methoxyphenyl)-4,4-dimethyl-2-oxazoline (18c)[26] was prepared as described above: bp 89 °C (0.1 mm); IR (film) 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.4 (q, 4 H), 4.1 (s, 2 H), 3.85 (s, 3 H), 1.35 (s, 6 H); high-resolution mass spectrum, *m/e* 205.1093 (M^+) ($C_{12}H_{15}NO_2$ requires 205.1103).

Anal. Calcd for $C_{12}H_{15}NO_2 \cdot 0.25H_2O$: C, 68.71; H, 7.33; N, 6.68. Found: C, 68.74; H, 7.20; N, 6.27.

2-(3,4-Dimethylphenyl)-4,4-dimethyl-2-oxazoline (18d). Prepared as described above: bp 86 °C (0.1 mm); IR (film) 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.5 (m, 3 H), 4.1 (s, 2 H), 2.3 (s, 6 H), 1.4 (s, 6 H); high-resolution mass spectrum, *m/e* 203.1312 (M^+) ($C_{13}H_{17}NO$ requires 203.1310).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 77.20; H, 8.40.

2-(4-Ethylphenyl)-4,4-dimethyl-2-oxazoline (18e) was prepared as described above: bp 102 °C (0.5 mm); IR (film) 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.5 (q, 4 H), 4.1 (s, 2 H), 2.65 (q, 2 H), 1.35 (s, 6 H); high-resolution mass spectrum, *m/e* 203.1306 (M^+) ($C_{13}H_{17}NO$ requires 203.1310).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.57; H, 7.96.

Registry No. 16, 53244-68-1; **17a**, 108-86-1; **17b**, 106-38-7; **17c**, 104-92-7; **17d**, 583-71-1; **17e**, 1585-07-5; **17f**, 100-44-7; **17g**, 540-54-5; **17h**, 109-69-3; **18a**, 19312-06-2; **18b**, 79568-30-2; **18c**, 53416-46-9; **18d**, 79568-31-3; **18e**, 79568-32-4; **18f**, 1569-08-0.

(22) Coordination of transition metals to oxazolines has been reported: (a) Bartel, K.; Fehlhammer, W. P. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 599. (b) Witte, H.; Seeliger, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 287.

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(26) Gschwend, H. W.; Handan, A. *J. Org. Chem.* **1975**, *40*, 2008.