Synthesis of 2-Substituted Oxazoles by Cross-Coupling of Grignard Reagents with 2-(Methylthio)-oxazoles Employing Transition Metal-Phosphine Catalysis

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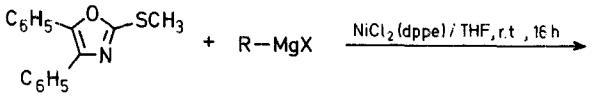
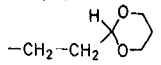
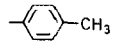
The emergence of 2-substituted oxazoles as a major class of heterocycles being exploited for transformation into more complex heterocycles or for use as latent functional-group equivalents is evidenced by the increasing number of oxazole-related reports[1–6]. The principal method of synthesizing such 2-substituted oxazoles, which does not involve forming the oxazole ring, is by alkylation of a 2-lithiomethyloxazole[1,2]. However, problems arise in such syntheses when acidic protons are present in the alkylating agent or if other protons on the oxazole moiety are more acidic than those of the 2-methyl group[3]. It is our aim to circumvent this problem, at least to the limitations imposed by the use of a Grignard reagent.

We have previously reported our success in cross-coupling arylmagnesium halides with 2-methylthio-4,4-dimethyl-2-oxazolines using transition metal-bidentate phosphine complexes as catalysts[6]. In that report, we were unable to demonstrate satisfactory results employing alkylmagnesium halides, even though positive results had been reported for benzothiazoles[7]. We now report that we have been able to



1 2

2,3	R	X
a		Br
b	C_2H_5	Br
c	n-C_4H_9	Cl
d		Br
e		Br

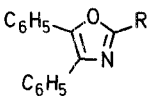


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Table. 2-Substituted Oxazoles (3) prepared

3	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr		M.S. (M^+) *m/e*		^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
		found	reported	calc.	found	
a	90	m.p. 114–115°	m.p. 115°[11]	297.35	297	7.3–8.4 (m, 15H)
b	95.5, 89[b]	b.p. 118–120°/0.2	b.p. 119–120°/0.4[12]	249.115	249.115[e]	1.45 (t, 3H); 3.0 (q, 2H); 7.9 (m, 10H)
c	96	b.p. 128–130°/0.1	$C_{19}H_{19}NO$[f]	277.147	277.146[e]	0.8 (m, 7H); 2.85 (t, 3H); 7.6 (m, 10H)
d	76[c]	oil[d]	$C_{21}H_{21}NO_3$[f]	335.152	335.153[e]	1.2–1.65 (m, 2H); 2.15 (m, 2H); 2.9 (t, 2H); 3.5–4.3 (m, 4H); 4.7 (t, 1H); 7.45 (m, 10H)
e	82	m.p. 126–127°	m.p. 130.5°[13]	311.4	311	2.35 (s, 3H); 7.0–7.75 (m, 12H); 8.0 (d, 2H)

[a] Yields are of isolated chromatographically pure products using the typical conditions.
[b] Yield obtained using refluxing tetrahydrofuran for 8 h.
[c] Purified by radial chromatography over silica gel using petroleum ether/ether (9/1).
[d] b.p. not determined.
[e] Recorded on a Varian MAT-CH$_5$ double-focusing spectrometer.
[f] Satisfactory microanalysis could not be obtained.

prepare cleanly and in high yields 2-alkyl- and 2-aryl-4,5-diphenyloxazoles (**3**) from 2-methylthio-4,5-diphenyloxazole[8] (**1**) using similar conditions as we previously reported[6] employing 1,2-bis[diphenylphosphino]-ethanenickel(II) chloride [$NiCl_2$(dppe)][9] as catalyst. 1,1'-Bis[diphenylphosphino]ferrocenepalladium(II) chloride [$PdCl_2$(dppf)][10] was also found to be effective in boiling tetrahydrofuran.

A possible explanation for the success of the cross-coupling reaction of alkyl magnesium halides (**2b, c, d**) with oxazoles and not with oxazolines may be due to a decrease in the electron density on nickel as a result of its interaction with the π-electron system of the 4,5-phenyls and the oxazole ring. Such an interaction should minimize the potential for β-hydrogen elimination of the alkylmagnesium halide. This type of elimination is commonly encountered when reducing Grignards reagents are used in transition-metal cross-coupling reactions[14].

Attempts to synthesize compound **3d** by the usually employed literature method[1,2], i.e., by alkylating 2-lithiomethyl-4,5-diphenyloxazole with 2-iodomethyl-1,3-dioxan, were unsuccessful. The problems encountered in this case were the slow reactivity of the iodo-substituted acetal at −90 °C and the propensity of the 2-lithiomethyloxazole to self-condense at higher temperatures. Synthesis of **3d** was satisfactorily accomplished in 76% yield utilizing the cross-coupling procedure with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxan[15]. Thus, for general synthesis of 2-substituted oxazoles our results indicate that this cross-coupling procedure may prove to be the method of choice for introduction of a 2-alkyl of 2-aryl group in the absence of other functionality that is intolerant of Grignard reagents.

2-Butyl-4,5-diphenyloxazole (3c); Typical Procedure:
To a stirred solution of 2-methylthio-4,5-diphenyloxazole[8] (**1**; 1.0 g, 3.745 mmol) in tetrahydrofuran (40 ml) are added a solution of butylmagnesium chloride (5 mmol) in ether and 1,2-bis[diphenylphosphino]ethanenickel(II) chloride[9] (50 mg, 0.0947 mmol, 2.5 mol %). Stirring is continued at ambient temperature for 18 h, and the reaction then quenched by pouring the mixture onto saturated aqueous ammonium chloride solution (50 ml). The aqueous layer is extracted with ether (3 × 50 ml), the combined organic layers are dried with magnesium sulfate, and the solvent is evaporated to give crude **3c**; yield: 1.28 g. The product is purified by flash chromatography over silica gel using petroleum ether/ether (9/1) as eluent; yield: 1.0 g (3.6 mmol, 96%); b.p. 128–130 °C/0.1 torr.

Received: February 17, 1984

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