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FACILE ALKYLATION OF 2-METHYL-2-OXAZOLINE: SYNTHESIS OF NOVEL 2-SUBSTITUTED-2-OXAZOLINES

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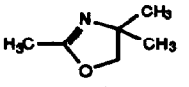
Summary: The synthesis, mechanism of formation and purification of new oxazolines containing binaphthyl and biphenyl moieties based on alkylation of 2-methyl-2-oxazoline with alkyl halides are described. Yields up to 87 % have been realized, and the method is applicable to the syntheses of other 2-substituted-2-oxazolines.

Introduction:

2-Substituted-2-oxazolines, which are important monomers in polymer chemistry and represent one of the most versatile protecting groups for carboxylic acids, most commonly are made from the corresponding carboxylic acids or nitriles in modest to good yields.[1-3] In our effort to develop a more general method for preparation of novel, polymerizable 2-substituted-2-oxazolines, we sought to employ alkylation of the commercially available 2-methyl-2-oxazoline (**2**). Whereas alkylation of the nonpolymerizable oxazoline **1** with alkyl halides, aldehydes and other electrophiles has been used to prepare derivatives of acetic acid,[5] similar alkylation of **2** has received little attention possibly due to its high reactivity and polymerizability in the presence of electrophiles.[4,6] We describe herein a facile and versatile method for alkylating **2** to give novel 2-substituted-2-oxazolines, such as **3** and **4**, in high yield. Compound **3** represents a new class of chiral oxazoline ligands that could be useful for the design of chiral catalysts.[7]



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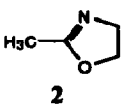

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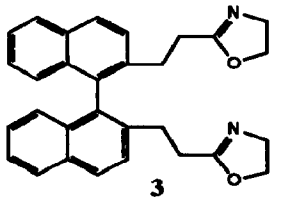

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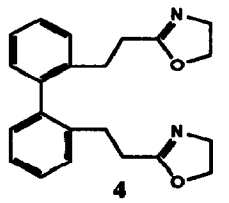

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Results and Discussion:

The best yields of the desired lithiomethyl-2-oxazoline (LiOXZ) derived from **2** were obtained by treatment of **2** with LDA at -78° C for 30 min. Prolonged reaction with LDA or use of either n-BuLi or t-BuLi for a short time gave an unidentified side product not reported in a similar reaction of **1**.[5] Upon quenching the anion with 1 equiv. of alkyl halides, the corresponding oxazolines were obtained and analyzed by GC/MS. Butyl bromide and iodide, and benzyl chloride, bromide and iodide gave mainly the desired products accompanied by less than 10 % dialkylation. However, butyl chloride was too unreactive and gave no alkylation products. When excess electrophile is required a less reactive one is preferred. Thus, while excess benzyl bromide (a very good polymerization initiator) gave many side products probably due to electrophilic ring opening and oligomerization, no such side products were found with excess benzyl chloride. The method was applied successfully to the synthesis of **6**, a potential precursor of **3**, in 98 % purified, isolated yield (Scheme 1).

Scheme 1: Synthesis of 6

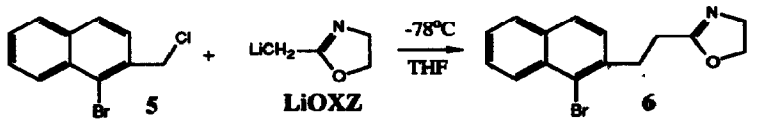


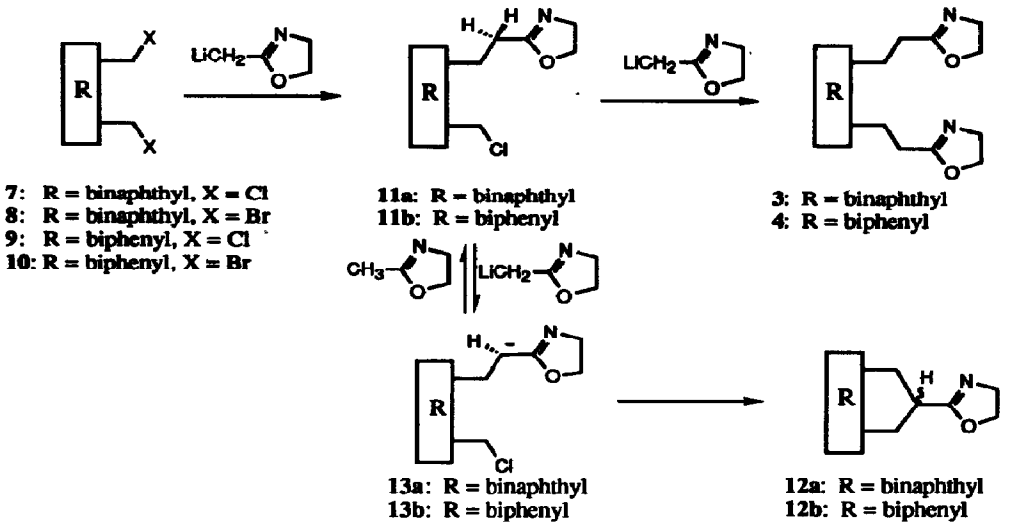
Table 1 summarizes conditions and results of the method applied to the synthesis of **3** and **4**. At -97° C racemic dichloride **7** and 2.6 equiv. LiOXZ (0.6 M) gave mainly the monoalkylation product **11a** (72 %) and the desired product **3** in only 13 % yield plus a trace of cyclic product **12a** (Table 1, entry 1). At -78° C with 10 equiv. LiOXZ (0.6 M) **3** was obtained in 35 % yield and, more importantly, **11a** dropped to 22 % (entry 2). Increasing [LiOXZ] to 0.9 M (10 equiv.) led to slight increases in **11a** and **12a** at the expense of **3** (entry 3). In all cases, traces of a side product identified as **14** (Scheme 3) have been observed and found difficult to completely remove from **3** by column chromatography *(vide infra)*.

Table 1: Alkylation of Methyloxazoline (2, MeOXA) with Dihalides

Entry	Dihalide[a]	Lithio-oxazoline[b]		MeOXA[c]	Temp	Yields (%)[d]			
		equiv.	conc., M	conc., M	°C	11a/b	12a/b	3/4	14[e]
1	7	2.6	0.6		-97	72	<1	13	<1
2	7	10	0.6		-78	22	8	35	<1
3	7	10	0.9		-78	29	18	22	<1
4	7	15	0.2	1M	-78	6	3	45	20
5	7	2.1	0.5	2M	-40	0	0	0	100
6	8	2.5	0.25		-78	0	0	86	0
7	9	15	0.7		-78	0	11.5	40	0.8
8	9	10	0.6		-78	0	9.5	56	2
9	9	15	0.2		-78	0	1.5	54	0
10	9	15	0.2	1M	-78	0	0	87	17
11	10	2.5	0.25		-78	0	0	75	0

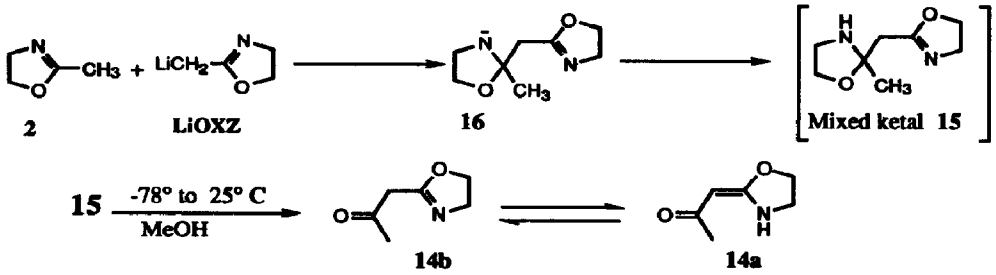
a) Added dropwise to anion solution at -78° C. b) Prepared in THF at -78° C from **2** and 1 equiv. of LDA for 30 min. c) Added excess **2** when generating the anion. d) Yields after purification by column chromatography and based upon dihalide. e) Yield based on LiOXZ and determined from NMR.

These results can be rationalized by the sequence of reactions shown in Scheme 2. The α-hydrogens of **11a** are relatively acidic and can be readily abstracted by the oxazoline anion to give **13a** plus **2**. The deprotonation becomes competitive with the addition of a second oxazoline anion especially in the case of the relatively less reactive chlorides. The anion **13a** can either cyclize intramolecularly to give **12a** or, in the presence of excess **2**, revert to **11a**. Indeed, addition of **2** almost completely suppressed the formation of **12a** (by disfavoring the formation of **13a**) and gave a higher yield of **3**, but it also significantly increased the amount of **14** (entry 4). At a higher temperature (-40° C), use of 2.1 equiv. LiOXZ in the presence of excess **2** gave exclusively **14** (entry 5). Switching to the more reactive dibromide makes bis alkylation the major pathway. Thus, **3** was prepared in 86 % yield from **8** and 2.5 equiv. LiOXZ (entry 6).[8, 9] In the case of the biphenyl derivative **4** satisfactory results were obtained with both the dichloride **9** and the dibromide **10**. Under various conditions **9** gave **4** in 40-56 % yield with none of **11b** (entries 7-9). Together with **2** and a large excess of LiOXZ, **9** gave **4** in 87 % and **14** (based on LiOXZ) in 17 % yields (entry 10). The dibromide **10** gave **4** in 75 % yield with no by-products (entry 11). The difference between biphenyl and binaphthyl derivatives may be attributed to steric reasons since biphenyls have less hindered rotation around the 1,1'-bond.



Scheme 2: Proposed mechanism for the formation of products

Efforts to purify 3 and 4 by column chromatography on either active silica or water-deactivated silica led to significant decomposition and loss. Basic and neutral alumina also gave unsatisfactory results. Successful chromatographic purification was effected with either silica gel and eluents containing 0.5 % Et_3N (by volume) or basic silica (prepared by treating silica with 5 % $NaHCO_3$ aqueous solution for 5 minutes and heating at 140° C in a vacuum oven) and eluents containing no Et_3N. Mono(oxazolines), however, did not show extensive decomposition when chromatographed over untreated silica. Highly pure 3 and 4 were obtained by recrystallization from acetonitrile and 3 vol % ethyl acetate in hexanes, respectively.



Scheme 3: Proposed mechanism for the formation of 14a and 14b

As indicated earlier keto-oxazoline **14b** and its tautomer **14a** (Scheme 3) were observed after work-up when an excess of 2-methyl-2-oxazoline was used. At -40° C this side reaction became the predominant pathway, and **14a** and **14b** (10:1 mol ratio) were the only products observed (entry 5). Meyers and coworkers found that the corresponding mixed ketal derived from **1** was stable, could be isolated and then hydrolyzed at elevated temperature to give structures analogous to **14a** and **14b**.[5] We postulate that **14** forms via **15** according to the mechanism outlined in Scheme 3 which is similar to that proposed by Meyers and coworkers

for the formation of their stable mixed ketal.[5,10] In our case, the postulated intermediate ketal could not be isolated. Presumably, the absence of 3,3-substituents makes **15** so unstable that transformation into **14a** and **14b** becomes rapid even at or below ambient temperatures used and with little methanol or water present.

In conclusion we have shown that 2-substituted-2-oxazolines can be made in high yield by alkylating the anion of the commercially available and inexpensive 2-methyl-2-oxazoline using the relatively less reactive benzyl chlorides. In the case of convergent bis(oxazoline) monomers **3** and **4**, where monoalkylation and formation of cyclic compounds are a concern, it is preferable to use the corresponding more reactive bromides and excess oxazoline anion, taking care to avoid excess alkylating agent. Purification of the bis(oxazolines) can be accomplished using basic chromatographic systems. Application of the method to the syntheses of other bis(oxazoline) monomers are in progress.

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8. Typical procedure: To 15 mL THF and 1.2 mL diisopropylamine (2.5 equiv.) at 0° C under nitrogen was added 3.4 mL 2.5M n-butyllithium (2.5 equiv.). The mixture was stirred at 0° C for 15 min and cooled to -78°C. The LDA solution was added dropwise to a solution of 0.73 mL 2-methyl-2-oxazoline (2.5 equiv.) in 15 mL THF at -78°C and stirred for 30 min. To this was added dropwise a precooled (-78° C) solution of 1.5g (1 equiv.) of **8** in 15 mL THF. The reaction was quenched with methanol after 30 min. stirring and evaporated. The residue was redissolved in $CHCl_3$ and washed with water (neutral pH) and brine. The organic layer was dried over $NaSO_4$ and evaporated. The crude product was purified by column chromatography on basic silica with $CHCl_3$ as eluent.
9. **3**: M.p. >250° C (decomp.). ^1H NMR (400 MHz, $CDCl_3$, δ): 2.35 (m), 2.70 (m), 3.68 (m), 4.04 (m), 7 (d), 7.18 (t), 7.38 (t), 7.55 (d), 7.9 (2 d). ^{13}C NMR ($CDCl_3$, δ): 28.66, 29.86, 54.14, 67.02, 125.33, 126.16, 126.20, 127.01, 129.84, 128.18, 132.30, 132.31, 133.11. 133.12, 134.33, 136.91, 167.63. IR (KBr): 1663 cm^{-1}. HRMS(EI): Calc. for M^+: 448.215078. Found: 448.215078. **4**: M.p. 104.4-105.5° C. ^1H NMR (200 MHz, $CDCl_3$, δ): 2.35 (m, 2H), 2.70 (m, 2H), 3.74 (m, 2H), 4.14 (m, 2H), 7.08-7.35 (m, 8H). ^{13}C NMR ($CDCl_3$, δ): 29.01, 20.41, 54.29, 67.11, 126.08, 127.65, 128.81, 129.92, 138.36, 140.53, 167.62. IR (KBr): 1663 cm^{-1}. GC/MS: 348 (M^+). HRMS(EI): Calc. for M^+: 348.183778. Found: 348.183319. **11a**: ^1H NMR (200 MHz, $CDCl_3$ δ): 2.35 (m, 2H), 2.70 (m, 2H), 3.65 (m, 2H), 4.0 (m, 2H), 4.3 (AB, 2H, J = 11 Hz), 6.95-8.0 (2 d, 2 t, 2 t, 2 d, m, total 12H). ^{13}C NMR ($CDCl_3$, δ): 28.71, 29.91, 33.85, 44.53, 54.21,125.3-137.7 (39 peaks), 167.47, 171,07. EI: 399 (M^+). **12a**: ^1H NMR (400 MHz, $CDCl_3$, δ): 2.67 (d, 1H, J = 12.85 Hz), 2.70 (dd, 1H, J = 13.4 and J = 3.7 Hz), 2.94 (dd, 1H, J = 13.1 and 5.5 Hz), 3.07 (d, 1H, J = 13.4 Hz), 3.27 (m, 1H), 3.81 (t, 2H, J = 9.2Hz), 4.24 (t, 2H, J = 8.8 Hz), 7.25 (2H, 2 dd, J = 7.1 Hz), 7.33 (2 d, 2H, J = 8.4 and 8.2 Hz), 7.41 (2 dd, 2H, J = 7 Hz), 7.52 (2 d, 2H, J = 8.2 Hz), 7.9 (2 d, 2H, 8.2 Hz), 7.89 (2 d, 2H, J = 8.5 Hz). EI: 363 (M^+). **12b**: ^1H NMR (200 MHz, $CDCl_3$, δ): 2.75 (m, 4H), 3.28 (m, 1H), 3.8 (t, 2H, J = 9.3 Hz), 4.25 (t, 2H, J = 9.3 Hz), 7.3 (m, 8H). HRMS(EI): 263.130951.
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