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Acylation of Oxazoles by the Copper-Mediated Reaction of Oxazol-2-ylzinc Chloride Derivatives

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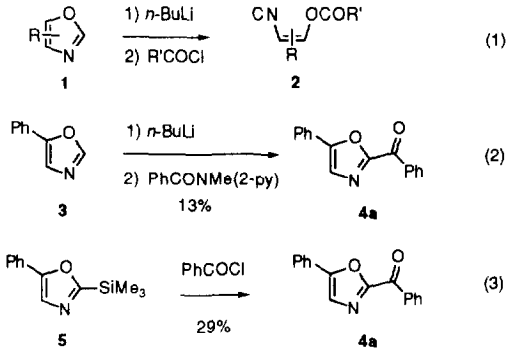
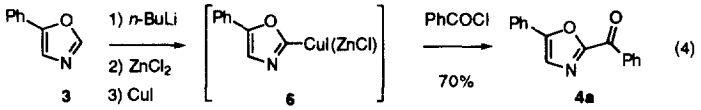
Abstract: C-2 acylation of oxazole derivatives is accomplished by reaction of oxazol-2-ylzinc chloride reagents with acid chlorides in the presence of cuprous iodide. O-acylated vinylisonitriles, which are the sole product from the corresponding reaction employing lithiooxazole, are not observed. The method accommodates substituted and unsubstituted oxazoles with a variety of acid chlorides.

2-Acyloxazoles cannot be prepared from 2-H oxazoles and the corresponding acid chloride by existing methods. Although readily generated, reaction of 2-lithiooxazole derivatives **1** with acid chlorides leads to exclusive production of the corresponding ring-opened O-acylated products **2** (eq 1).[2,3] One solution to this problem includes application of *N*-methyl-*N*-(2-pyridinyl)-carboxamides as the electrophilic coupling partner. This procedure has allowed the synthesis of 2-aroyl and 2-formyl oxazoles in modest yields (eq 2).[4] Aliphatic ketones cannot be prepared by this method. Alternatively, treatment of 2-silyl oxazoles (*e.g.* **5**) or 2-stannyl oxazoles with acid chlorides gives the desired acylated products (eq 3).[5] This method suffers from the inconvenient preparation of the activated oxazole derivative. Moreover, yields appear to be dependent on substrate and are particularly modest for reactions involving **5** (13-29%).



In the course of developing the palladium-catalyzed cross coupling reaction of oxazol-2-ylzinc chloride derivatives, we and others established the propensity for these organometallic reagents to react as the ring-closed tautomer.[6,7] Based on this observation and the chemistry of related bimetallic compounds, we anticipated that these reagents in combination with copper salts might be valuable intermediates for the acylation of oxazoles.[8] We summarize herein our study of this reaction and report conditions which allow the efficient preparation of oxazole-containing ketones from a variety of acid chlorides.

5-Phenyloxazole has proven to be a particularly recalcitrant substrate in the methods previously reported and was therefore chosen as the principal example for development of the new protocol. Treatment of 5-phenyloxazole with *n*-butyllithium leads to rapid deprotonation. If reacted with benzoyl chloride, only the product arising from O-benzoylation is observed.[3b] Addition of a zinc chloride solution to the resulting lithiated oxazole yields the corresponding zinc reagent which is unreactive towards benzoyl chloride even at elevated temperatures. This observation is consistent with the established reactivity of other organozinc reagents.[9] Addition of 1 equivalent of cuprous iodide to the organozinc derivative leads to the generation of a bimetallic species **6** which reacts rapidly at room temperature to furnish the desired ketone **4a** in 70% isolated yield (eq 4). Employing an excess of zinc chloride (2 equiv) led to cleaner reaction mixtures when compared to reactions in which a single equivalent was added. Careful monitoring of the reaction mixture provided no evidence of products arising from the ring-open tautomer. Transmetalation of the lithiooxazole directly with CuI led to the generation of a species which failed to deliver either the ketone or vinyl isonitrile product upon reaction with benzoyl chloride.



All reactions were conducted in THF which led to a competing process involving the zinc-mediated ring opening of the solvent with the acid chloride to generate the corresponding 4-chlorobutyl ester.[10,11] As a consequence, all oxazole products required purification by either silica gel chromatography or crystallization. The ratio of desired product to the impurity was optimized by employing excess acid chloride and a stoichiometric amount of copper iodide. Catalytic quantities of either CuI or $Pd(PPh_3)_4$ effected the desired reaction, but reaction rates were compromised and a three-fold increase in the undesired 4-chlorobutyl ester was observed. The amount of THF ring opening was reduced by only 5% when the amount of zinc chloride was changed from 2 to 1 equivalent. Attempts to replace THF with MTBE, ether, ether/TMEDA, or toluene were unsuccessful due to poor solubility of the organometallic reagents. Ketone formation could be accomplished in dimethoxymethane; however, the metal-mediated reaction of the acid chloride with the acyclic solvent was not suppressed.[11]

The acylation protocol proved general for aroyl, alkenoyl and alkoyl chlorides (Table).[12] For aromatic substrates, the efficiency of the reaction paralleled the electrophilicity of the substrate (entries 1, 4, 5). Acylation with cinnamoyl chloride was accomplished in good yield without interference from 1,4 addition processes (entry 6). Straight chain and branched alkyl substituents were readily accommodated (entries 9-11). Successful acylation with the alkoyl chlorides further distinguishes this method from the reactions involving lithiooxazoles and *N*-methyl-*N*-(2-pyridinyl)-carboxamides in which only negligible acylation was observed when the ethyl carboxamide was employed.[4] Further complications were also reported for the reaction of the *tert*-butyl carboxamide derivative in which only the product arising from bis-addition of the lithiooxazole was isolated.[4] The standard reaction conditions employed for 5-phenyloxazole were also suitable for the acylation of the unsubstituted oxazole (entry 12) and benzoxazole (entry 13). C-acylation was uniformly accomplished in each example without competitive O-acylation.

Table. Acylation Reactions of Oxazol-2-ylzinc Chloride Derivatives

entry	substrate	R'COCl	conditions[a]	ketone	%, yield
1		Ph	CuI, 1 equiv	**4a**	70
2		Ph	CuI, 5 mol%[b]	**4a**	54
3		Ph	$Pd(PPh_3)_4$, 5 mol%[b]	**4a**	54
4		*p*-MeOPh	CuI, 1 equiv	**4b**	65
5		*p*-NO_2Ph	CuI, 1 equiv	**4c**	80
6		PhCH=CH	CuI, 1 equiv	**4d**	58
7		CH_3O	CuI, 1 equiv	**4e**	0
8		CH_3	CuI, 1 equiv	**4f**	0
9		$CH_3(CH_2)_2$	CuI, 1 equiv	**4g**	67
10		$(CH_3)_2CH$	CuI, 1 equiv	**4h**	67
11		$(CH_3)_3C$	CuI, 1 equiv	**4i**	64
12		Ph	CuI, 1 equiv	**7**	74
13		Ph	CuI, 1 equiv	**8**	63

[a] Reaction complete within 1 h unless otherwise indicated. [b] Reaction time 5 h.

Limitations of the method were encountered upon attempted reaction of acetyl chloride or methyl chloroformate with the bimetallic phenyloxazole derivative (entries 7-8). The desired product was not observed in either case employing the standard conditions. In both instances, 5-phenyloxazole remained unchanged after prolonged exposure to the acid chloride.

Preparation of **4a** is representative of the general procedure. To a solution of 1.3 mmol of 5-phenyloxazole in 10 mL of THF at -70° C under a nitrogen atmosphere was added 1.1 equiv of *n*-BuLi as a solution in hexanes. The resulting solution was stirred 20 min and 2 equiv of a 1M $ZnCl_2$ solution in ether was added. The mixture was warmed to 0 °C and stirred for 45 min and 1 equiv of CuI was added. After 10 min, 2 equiv of benzoyl chloride was added. The reaction was complete within 1h. The organic solution was diluted with ethyl acetate and washed sequentially with 1:1 NH_4OH/water, water and brine. The product was purified by silica gel chromatography (4:1 $CHCl_3$:hexanes) to give analytically pure **4a**.

In conclusion, we have developed an efficient and expeditious method for the preparation of oxazole-containing ketones. The method provides for a one-pot conversion of 2H-oxazoles to their acylated counterparts. Unlike previously reported strategies, this protocol allows the direct functionalization of substituted and unsubstituted oxazoles to the corresponding aryl, alkenyl and alkyl ketones in synthetically

useful yields without requiring the isolation of activated precursors. The reactivity of the bimetallic oxazole species generated in this study is distinguished from that of the corresponding lithiooxazole derivatives and provides additional insight into the organometallic chemistry of the oxazole heterocycle.[2] The bimetallic oxazole reagents described should also be valuable intermediates for effecting further C-2 functionalizations of oxazoles.

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12. All structures were confirmed by ^{1}H NMR, ^{13}C NMR, infrared and mass spectroscopy. Acceptable combustion analyses were obtained for all samples (±0.4%).

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