Short Communication

Organocerium(III) Reagent from Pyrimidine in Carbon Bond-Forming Reactions

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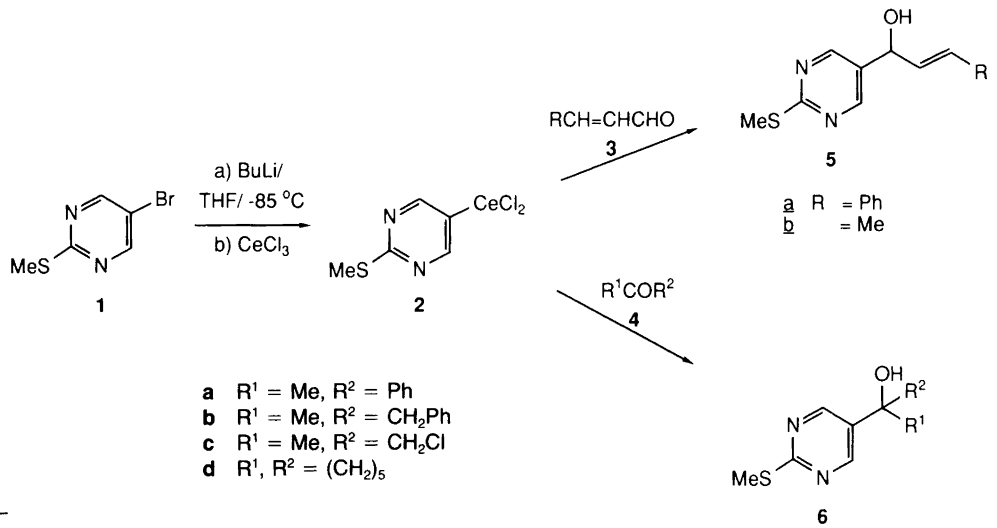
We have recently reported a number of metallation reactions involving pyrimidines.[1-4] The metallopyrimidines are suitable intermediates for the introduction of carbon substituents into the heterocyclic system. For the metallation in the benzenoid 5-position, the bromide and iodide are suitable substrates; in the activated positions a chloride can be used or the metallation can be performed by decarboxylation of a stannyl ester. Stannylation can be achieved with metal stannate(IV) reagents,[3] by Pd(II)-catalyzed coupling reactions with hexaalkyldistannane,[1,3] and by metal–metal exchange with the lithium derivative which itself is generated by a halogen–metal exchange reaction at low temperature.[1-3] Metal–carbon exchange is subsequently effected by Pd(II)-mediated reactions with halides with the halogen attached to an sp^2-hybridized carbon. This last reaction is unsatisfactory for sp^3-hybridized halides and therefore unsuitable for the preparation of hydroxymethyl derivatives which was the purpose of the work described herein. The coupling, however, can be achieved by reversing the polarities of the reactants; under the influence of Pd(II)-catalysis the bromide can be coupled with stannylmethyl silyl ethers; mild conditions are then used for the cleavage of the oxygen–silyl bond.[1] Alternatively, hydroxymethyl derivatives can be prepared from 5-acyl derivatives, available by the above methodology, or by reactions of pyrimidine-5-carboxylic acid chlorides with organomanganese(II) reagents, or from Pd(II)-catalyzed reactions with organotin derivatives.[5]

In the reactions of 5-acylpyrimidine with organometallic reagents or hydrides, however, competition between addition to the carbonyl group and the π-electron deficient heterocycle is expected. We therefore chose to explore reactions between metallated pyrimidine and carbonyl substrates. In particular we were interested in exploring the potential of cerium(III) chlorides because of the recent reports that organocerium(III) chlorides are, in many respects, superior to the corresponding lithium reagents.[6-12] Thus organocerium reagents are reported to show high



a R^1 = Me, R^2 = Ph
b R^1 = Me, R^2 = CH_2Ph
c R^1 = Me, R^2 = CH_2Cl
d R^1, R^2 = $(CH_2)_5$

Scheme 1.

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Table 1. Comparison of yields in the reactions of aldehydes and ketones with (2-methylthiopyrimidin-5-yl)-cerium(III) chloride (Ce) and -lithium (Li).

Aldehyde	Yield (%)		Ketone **4**	Yield (%)	
	Ce	Li		Ce	Li
a	97	59	**a**	83	50
b	70	52	**b**	70	50
			c	87	38
			d	80	50

specificity for 1,2-addition to α,β-unsaturated carbonyl derivatives.[7] Furthermore, the organocerium(III) chlorides are of low basicity, in contrast with the corresponding lithium derivatives, and they are therefore the reagents of choice in reactions with readily enolizable aldehydes and ketones.[8-11] The hydroxymethyl products **5** and **6** in Scheme 1 are themselves intermediates in the preparation of 2-pyrimidinones, which are of biological interest because of their ability to cause the reversible arrest of the cell cycle during metaphase.[13]

For the metallation reactions, 5-bromo-2-methylthiopyrimidine was lithiated at −90 to −88 °C and treated with anhydrous cerium(III) chloride. After the metal–metal exchange reaction had taken place, the pyrimidinylcerium derivative was treated with an aldehyde or a ketone whereupon the hydroxymethyl derivatives were formed. For comparison of reactivities, the pyrimidinyllithium precursor was also treated with the same carbonyl compounds. The yields obtained in the two series of reactions are given in Table 1. The organocerium derivative was invariably superior to the lithium analogue in terms of yields. In the case of the α,β-unsaturated carbonyl reactants, the desired allylic alcohols **5**, generated by 1,2-adduct formation, were obtained in 70–97 % yields from 5-pyrimidinylcerium(III) chloride **2** as compared with 52–59 % yields from the corresponding lithium derivative. For the readily enolizable benzyl ketone **4b**, the yields using the cerium or the lithium reactants were 70 and 50 %, respectively. In the case of the chemically sensitive chloromethyl ketone **4c**, the alcohol **6c** was isolated in 87 % yield from the cerium derivative and in only 38 % from its lithium analogue.

Experimental

^{1}H NMR spectra were recorded at 60 MHz in deuteriochloroform.

Preparation of (2-methylthiopyrimidin-5-yl)cerium(III) chloride (**2**) *and its reactions with carbonyl derivatives.* Butyllithium (1.6 M; 1.90 ml, 3.0 mmol) was added dropwise from a syringe to a stirred solution of 5-bromo-2-methylthiopyrimidine (0.62 g, 3.0 mmol) in dry THF (50 ml) at −90 °C under N_2, and the mixture was stirred at −85 °C for 1 h. A solution of anhydrous cerium trichloride (0.74 g, 3.0 mmol) in dry THF (5 ml) was then added at such a rate that the temperature did not rise above −85 °C. The mixture was stirred at this temperature for 1 h before the carbonyl reactant (3.0 mmol) was added, after which it was stirred for 3 h at −85 °C and then allowed to reach −5 °C overnight. Saturated aqueous ammonium chloride was then added, and the mixture was extracted with ethyl acetate. The dried ($MgSO_4$) extracts were evaporated and the residual product was purified by chromatography on silica gel using light petroleum–EtOAc (1:1). The product (oily material) was isolated by evaporation of the appropriate eluted fractions.

(2-Methylthiopyrimidin-5-yl)lithium and its reactions with carbonyl derivatives. The lithium derivative was prepared as above, and the reactions were run under the same conditions as above except for the addition of the cerium trichloride which was omitted.

(E)-*5-(1-Hydroxy-3-phenyl-2-propen-1-yl)-2-methylthiopyrimidine* (**5a**). Anal. $C_{14}H_{14}N_2OS$: C, H. ^{1}H NMR: δ 2.52 (MeS), 4.1 (OH, br), 5.32 (H-1′, d, *J* 6.8 Hz), 6.26 (H-2′, dd, *J* 15.9, 6.8 Hz), 6.64 (H-3′, d, *J* 15.9 Hz), 7.2 – 7.3 (Ph), 8.53 (H-4,6, s.).

(E)-*4-(1-Hydroxy-2-buten-1-yl)-2-methylthiopyrimidine* (**5b**). Anal. $C_9H_{12}N_2OS$: C, H. ^{1}H NMR: δ 1.72 (Me, d), 2.57 (MeS), 3.65 (OH, br), 5.1–5.2 (H-1′), 5.55–5.7 (H-3′), 5.7–5.8 (H-2′), 8.47 (H-4,6, s).

5-(1-Hydroxy-1-phenylethyl)-2-methylthiopyrimidine (**6a**). Anal. $C_{13}H_{14}N_2OS$: C, H. ^{1}H NMR: δ 1.92 (Me), 2.52 (MeS), 7.3–7.4 (Ph, OH), 8.47 (H-4,6, s).

5-(2-Hydroxy-1-phenyl-2-propyl)-2-methylthiopyrimidine (**6b**). Anal. $C_{14}H_{16}N_2OS$: C, H. ^{1}H NMR: δ 1.54 (Me), 2.54 (MeS), 2.6 (OH, br), 3.0 (CH_2), 7.0–7.3 (Ph), 8.47 (H-4,6, s).

5-(1-Chloro-2-hydroxy-2-propyl)-2-methylthiopyrimidine (**6c**). Anal. $C_8H_{11}ClN_2OS$: C, H. ^{1}H NMR: δ 1.83 (Me), 2.60 (MeS), 3.78 (CH_2Cl), 4.0 (OH, br), 8.70 (H-4,6, s).

5-(1-Hydroxycyclohexyl)-2-methylthiopyrimidine (**6d**). Anal. $C_{11}H_{16}N_2OS$: δ 1.3–1.8 (10 H), 2.35 (OH, br), 2.56 (MeS), 8.62 (H-4,6, s).

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