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Reductive allylation of 1*H*-pyridine-2-(thio)ones by means of the novel lithium allyldibutylmagnesate reagent

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Abstract—A new, highly efficient allylation reagent—lithium allyldibutylmagnesate (allylBu_2MgLi)—was obtained by mixing allylmagnesium chloride (1 equiv) and *n*-BuLi (2 equiv). *N*-Lithiated and *N*-methyl substituted 1*H*-pyridine-2-thiones and -ones were successfully and regioselectively allylated by treatment with allylBu_2MgLi yielding 6-allyl-3,6-dihydro-1*H*-pyridine-2-(thio)ones and 4-allyl-3,4-di-hydro-1*H*-pyridine-2-(thio)ones. The latter were formed by a 3,3-sigmatropic Cope rearrangement of the former.
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Due to a wide range of biological activity[1] related to the piperidine moiety, multifunctionalized piperidines are attractive synthetic targets.[2] Substituted pyridines are valuable substrates in the synthesis of piperidines.[3] Among recent efforts in this area we achieved a stereocontrolled access to *trans*-fused bicyclic 2-piperidinones (octa-hydro[2]pyrindinones) starting from commercially available 2-mercaptopyridine **1**.[4,5] In this synthetic strategy, the addition of *n*-BuLi to **1** was the first key step, yielding 6-butyl-3,6-dihydro-1*H*-pyridine-2-thione. Formation of a new C–C bond was accompanied by formation of a stable unsaturated piperidine ring. Following our concept of the application of **1** as a precursor in the synthesis of functionalized piperidines, we decided to introduce an allyl substituent by allylation of **1** with organomagnesium reagents. The synthetic goal seemed to be interesting in light of the recent widespread application of RCM methodology in constructing carbocyclic rings from alkenic substituents.[6]

In this letter, we report preliminary results on the allylation of *N*-lithiated and *N*-methyl substituted 1*H*-pyridine-2-thiones and 1*H*-pyridin-2-ones with organomagnesium allylating agents.

In the initial attempt, the use of allyl Grignard compounds was considered. Unfortunately, compound **1** turned out to resist the envisaged allylation when treated with allylmagnesium chloride, even with a large excess of the reagent, longer reaction times or the *N*-lithiated derivative (**1Li**), obtained from **1** and an equimolar amount of *n*-BuLi in THF solution. Surprisingly, when a mixture consisting of **1Li** (1 equiv) and allylmagnesium chloride (1.5 equiv) was treated with 1.5 equiv of *n*-BuLi, the 4-allylated product **6a** was obtained at a reaction temperature from 0 °C to rt after a couple of hours (yield 48%, Table 1, entry 1, Scheme 1). Increasing the amount of *n*-BuLi to two equivalents considerably improved the yield of **6a**. Thus, after 0.5 h at 0 °C and 3.5 h at room temperature the reaction went to completion and **6a** was isolated in 84% yield (Table 1, entry 2). A lower amount of allylMgCl (1.3 equiv) and *n*-BuLi (2.6 equiv) only slightly diminished the yield to 80%.[7] Application of allylMgCl and *n*-BuLi in the ratio 1:3, gave a lower yield (62%) together with minute amounts of a 6-butyl-adduct (~3%, Table 1, entry 4). These results led us to the conclusion that a 1:2 ratio of allylMgCl and *n*-BuLi was the most effective and indicated that a magnesium 'ate' complex (allylBu_2MgLi) was responsible for the allylation.

Although magnesium 'ate' complexes have been known since 1951,[8] their application in synthesis has been explored intensively only recently, mainly focusing on halogen–magnesium exchange reactions.[9] In the past, little attention was devoted to magnesates as alkylating reagents.[10] In 2005, the application of a magnesium 'ate' complex as a highly efficient alkylation reagent was reported.[11] However, according to the best of our knowledge, the formation of allylmagnesates and their application as allylating reagents has not been reported

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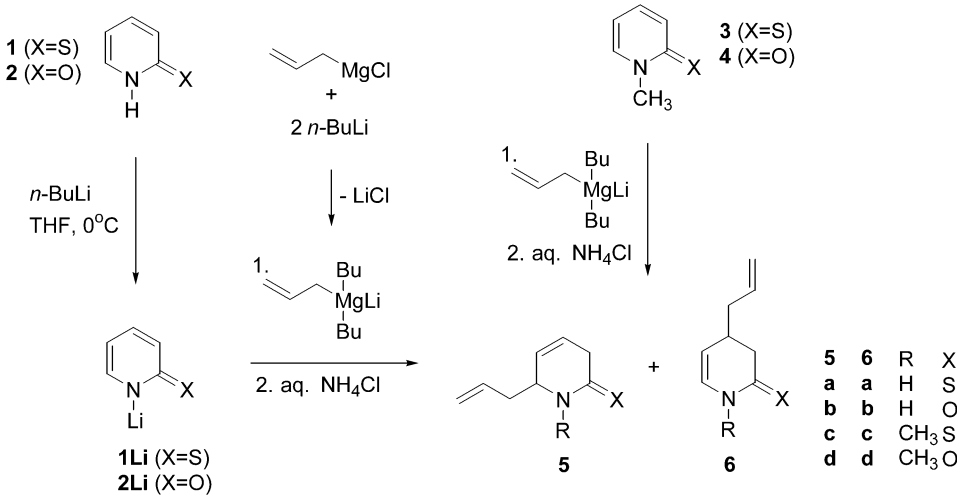
Table 1. Reaction conditions, ratios, and yields of **5**:**6**

Entry	Substrate (1 equiv)	AllylMgCl/*n*-BuLi	Temperature (°C)	Reaction time (h)	Ratio[a] **5**:**6**	Ratio **5**:**6** after chromatography	Total yield[a] (%)
1	**1Li**	1:1	0	0.5		0:100	48
			rt	3.5			
2	**1Li**	1:2	0	0.5		0:100	84
			rt	3.5			
3	**1Li**	1:2	0	0.2	(73:27)		
			0	0.5	(49:51)	41:59	31
			rt	0.5	(22:78)		
				1.0	(5:95)		
				3.5	(0:100)	0:100	80 (81)
4	**1Li**	1:3	0	1			
			rt	4		0:100	(62)[b]
5	**2Li**	1:2	0	6		0:100	50 (52)
6	**3**	1:2	0	0.5	(85:15)	84:16	80 (83)
7	**4**	1:2	0	0.3	(95:5)	96:4	61 (69)

[a] Values estimated by NMR are given in the parenthesis.
[b] Formation of 6-butyl-3,6-dihydro-1*H*-pyridine-2-thione was observed by NMR; the yield was estimated to ~3%.



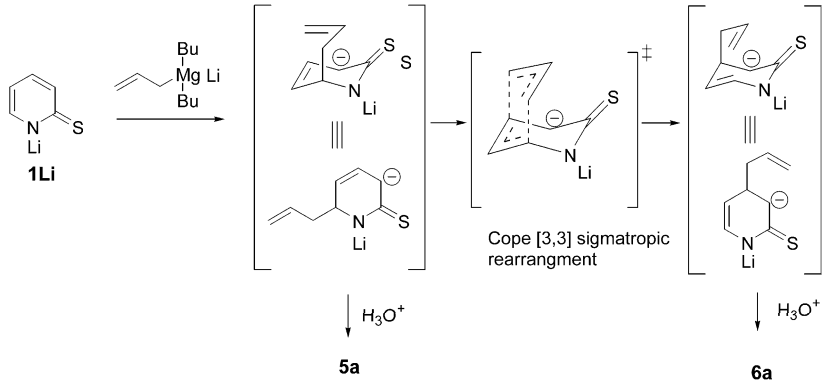
Scheme 1.

until now. As far as the preparation of magnesates is concerned, a couple of examples have been published in the literature indicating that lithium magnesates can be prepared using Grignard and organolithium reagents as precursors.[9,11]

Encouraged by the above-mentioned results, we next examined *N*-lithiated 1*H*-pyridin-2-one (**2Li**) as well as *N*-methyl substituted 1*H*-pyridine-2-thione (**3**) and 1*H*-pyridin-2-one (**4**) as analogues of pyridinethione **1** (Scheme 1). Thus, lithium allyldibutylmagnesate, prepared simply by mixing 1.3 equiv of allylMgCl (in THF) and 2.6 equiv of *n*-BuLi (in pentane or hexane), was used. Under these conditions, the reactions proceeded smoothly for *N*-lithiated pyridin-2-ones **2Li** as well as for *N*-methyl substituted pyridine-2-thiones **3** and -ones **4** and products **5** and **6** were obtained in good yields, especially when using sulfur analogs (X = S) (Scheme 1, Table 1). Albeit similar to **1Li**, lithiated pyridin-2-one **2Li** gave 4-allylated derivative **6b** rather than the 6-isomer **5b**. Opposite regioselectivity was observed for *N*-methylpyridine-2-thione **3** and -one **4**. These compounds gave the 6-allylation products **5c** and **5d** as major isomers, respectively (Table 1, Scheme 1).

Apart from the reactivity of lithium allyldibutylmagnesate obviously being greater relative to that of allylmagnesium chloride, some other features of allylBu_2MgLi should be emphasized. According to Hatano et al.,[11] in the reactions with 'mixed' magnesates of type R^1Bu_2MgLi (R^1 = Me, Ph), the butyl group was transferred to the substrate rather than a methyl or phenyl group. In the case of allylBu_2MgLi, the allyl moiety was transferred while the butyl group remained at Mg. Moreover, the reaction of *n*-BuLi with *N*-methylpyridin-2-one **4** resulted in the formation of a self-adduct by initial anion generation at the *N*-Me group,[12] while allyl magnesate (allylBu_2MgLi) did not affect the *N*-Me group, thus indicating magnesates as more nucleophilic and less basic than organolithium reagents. A lower basicity of the magnesates was also observed for the alkylation of ketones.[11]

As far as the mechanism and the regioselectivity of the reaction of pyridine-2-thiones **1** with allylBu_2MgLi is concerned, the progress of the reaction of **1Li** with lithium allyldibutylmagnesate was monitored by determination of the ratio of isomers **5a**:**6a** at several time intervals. (Table 1, entry 3). The results revealed the



Scheme 2.

formation of the 6-allyl isomer **5a** in the first reaction step. Subsequently, **5a** being less thermodynamically stable rearranged to a more stable 4-allyl substituted isomer **6a** in a Cope process (Scheme 2). Quenching the reaction after 0.5 h allowed the isolation of **5a** in 13% yield (Table 1, entry 3). This operation permitted a full spectroscopic analysis of **5a**.[13] The existence of **5a** in the form of a lithium salt seemed to be crucial for the rearrangement process to the 4-allyl isomer **6a** as only *N*-lithiated **5a** underwent transformation to **6a** while the *N*-methylpyridine-2-thione derivative **5c** was stable.[14]

In summary, we have demonstrated that lithium allyldibutylmagnesate can be formed directly by mixing allylMgCl and *n*-BuLi. The 'ate' complex being highly nucleophilic is a powerful allylating reagent and allylates pyridine-2-thiones and -ones regioselectively. 6-Allyl- or 4-allyl products are formed depending whether or not a Cope rearrangement can occur at the primarily formed 6-isomer, that is, if the nitrogen atom is unsubstituted or not. Investigation of the scope and the limitation of the application of allylmagnesates to other pyridine-2-thiones and -ones is currently underway.

Acknowledgements

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7. The procedure for allylation of **1** was as follows: To a cooled and stirred solution of pyridine-2-thione (2-mercaptopyridine, 3.33 g, 30 mmol) in dry THF (70 ml) at 0 °C 15.0 ml (30 mmol) of *n*-BuLi solution (2.0 M in pentane) was added via syringe over 5 min under argon. Simultaneously in a second Schlenk flask, 39 mmol (19.5 ml) of allylMgCl (2.0 M in THF) was kept under argon. *n*-BuLi (2.0 M in pentane, 78 mmol, 39 ml) was added via syringe at 0 °C over 5 min and the white suspension formed was stirred for 5 min. Subsequently, the suspension containing the lithium allyldibutylmagnesate was transferred to the solution of lithiated pyridine-2-thione via syringe. The resulting brown-orange solution was stirred for 0.5 h at 0 °C and then for 3.5 h at rt. After quenching with aqueous saturated NH_4Cl (10 ml), the water layer was extracted with ethyl acetate (2 × 100 ml) and the combined organic layers were dried over $MgSO_4$. Filtration,

concentration in vacuo, and purification by flash column chromatography (silica gel, *n*-hexane/ethyl acetate = 8:2) yielded **6a** in 80% (3.66 g, 24 mmol) as a yellow solid, which was recrystallized from *n*-hexane. 4-Allyl-3,4-dihydro-1*H*-pyridine-2-thione (**6a**). Pale yellow solid, mp 53-55 °C from *n*-hexane; ν_{max} (KBr pellet): 3188 br, 3144 br, 2996, 1640, 1522, 1436, 1404, 1364, 1324, 1300, 1140, 1106, 1056, 992, 976, 936, 914, 812, 742, 708 cm^{-1}; MS (EI, 70 eV): *m*/*z* = 153 (M^+, 33); 112 (100), 78 (46); ^1H NMR (400.1 MHz, $CDCl_3$): δ = 2.15 (2H, t *J* 7.1 Hz, 4-CH_2), 2.44–2.56 (1H, m, CH-4), 2.77 (1H, dd *J* 17.0, 9.7 Hz, C*H*H-3), 3.02 (1H, dd *J* 17.0, 6.9 Hz, CH*H*-3), 5.06–5.13 (2H, m, =CH_2), 5.41 (1H, dd *J* 7.5, 3.8 Hz, =CH-5), 5.66–5.79 (1H, m, =CH), 6.09 (1H, ddd, *J* 7.5, 4.3, 1.8 Hz, CH-6), 9.72 (1H, br s, NH); ^{13}C NMR (100.6 MHz $CDCl_3$): δ = 30.24 (CH-4), 38.10 (4-CH_2), 43.87 (CH_2-3), 114.88 (=CH-5), 117.78 (=CH_2), 123.85 (=CH-6), 134.64 (=CH), 199.88 (C-2). Anal. Calcd for $C_8H_{11}NS$: 62.70; H, 7.24; N, 9.14; S, 20.92. Found: C, 62.64; H, 7.40; N, 9.05; S, 21.35.

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