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Research Article

Directed Metalation of Heterocycles, 5-Methoxy-2-phenyloxazol-4-yllithium: An Approach to α,β-Dehydroamino Acids

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5-Methoxy-2-phenyloxazole was deprotonated at C_4 (by *n*-BuLi or LDA, in THF at −78°C). The resulting anion was generally unreactive to alkylation (except methylation with MeI-TMEDA) but added to PhCHO and Me_2CHCHO. The alcohols thus produced dehydrated and ring opened in acid, to the corresponding α,β-dehydroamino acids in moderate overall yields.

1. Introduction

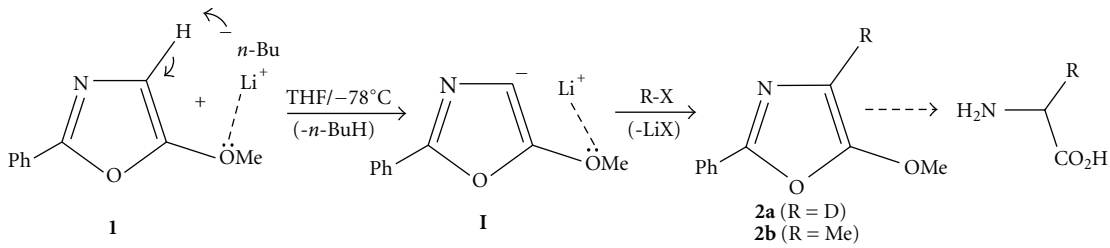
Directed metalation (sometimes also "*ortho*-metalation") is now firmly established as an important synthetic strategy in aromatic chemistry [1]. This involves deprotonation at a site *ortho* to a directing group such as OMe or NMe_2; this is assisted either by coordination of the counterion of the attacking base with the heteroatom lone pairs, or by electron withdrawal by the heteroatoms (or both). Thus, the formation of the anionic product is facilitated both kinetically and thermodynamically, with its subsequent electrophilic reactions leading to products not easily accessed otherwise.

Interestingly, however, heteroaromatic examples of directed metalation have been relatively scarce [2]. In particular, we have been interested in the possibility that the analogous reaction in the case of 5-methoxy-2-phenyloxazole (**1** → **I**, Scheme 1) would define a novel approach to α-amino acids, via hydrolysis of the resulting C_4 substituted derivatives (Scheme 1). The 5-methoxy group would then not only function as a directing group but also maintain C_5 as a masked carboxyl centre. We report in what follows preliminary results from our study.

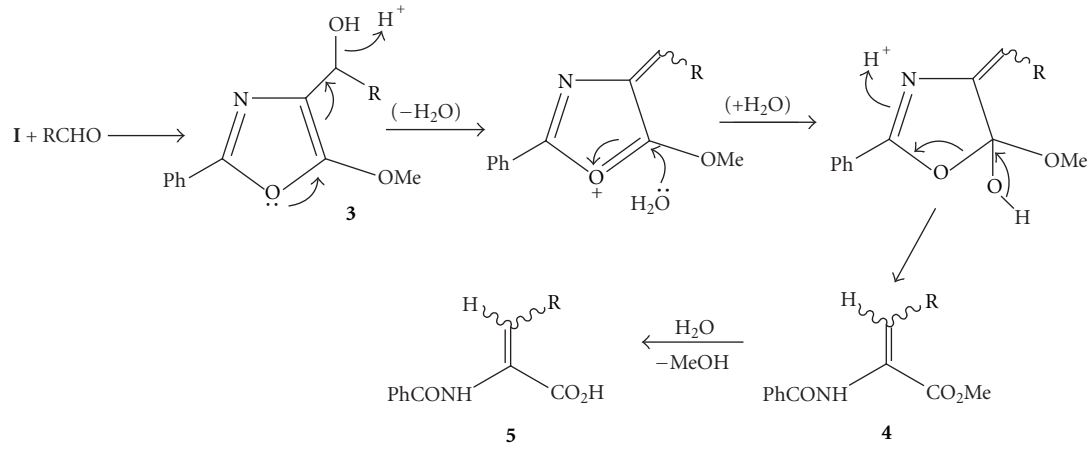
2. Results and Discussion

5-Methoxy-2-phenyloxazole (**1**) [3, 4] was treated with an equivalent of *n*-butyllithium (*n*-BuLi) in THF at −78°C for 3 hours, and the reaction mixture quenched with D_2O. ^1H NMR showed evidence of deuterium incorporation (88%), as seen by the disappearance of the C_4–H resonance at δ 5.80 (cf. **2a**). When the deprotonation was followed by treatment with methyl iodide, no reaction was observed; however, when the methylation was conducted in the presence of one equivalent of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, −70 to −40°C/3 h), 5-methoxy-4-methyloxazole (**2b**) was formed in 63% yield. These reactions also occurred in lower yields with lithium diisopropylamide (LDA, vide infra) as base [5].

These results clearly indicate the formation and intermediacy of 5-methoxy-2-phenyloxazol-4-yllithium (**I**). Intriguingly, however, this did not react with longer chain alkylating agents, for example, *n*-BuI, n-$C_7H_{15}Br$, $PhCH_2Br$, and allyl bromide. (**I** could also be generated with LDA and methylated with MeI and added hexamethylphosphoramide (HMPA).) It seems likely that TMEDA and HMPA act by chelating the lithium counterion of **I,** thus breaking down aggregates into more reactive monomeric and dimeric forms.



Scheme 1: The directed metalation strategy as applied to 5-methoxy-2-phenyloxazole (**1**), shown reacting with *n*-BuLi to form the oxazolyllithium **I;** this reacted with D_2O to form **2a** (R = D, 88%) and with MeI-TMEDA to form **2b** (R = Me, 63%).



	R	Yield (%) 3	5
a	Ph	54	52
b	Me_2CH	65	78

Scheme 2: Addition of the oxazolyllithium **I** to benzaldehyde and iso-butyraldehyde to form the alcohols **3,** and their acid catalyzed rearrangement, ring cleavage, and hydrolysis to furnish the corresponding *N*-benzoyl dehydroamino acids **5**.

However, the oxazolyllithium **I** was found to add to benzaldehyde and iso-butyraldehyde to furnish the expected alcohols **3,** in moderate yields (Scheme 2). Interestingly, **3** underwent rearrangement with ring cleavage and hydrolysis in dilute acid, to form the corresponding *N*-benzoyl *α,β*-dehydroamino acids **5** in fair yields [5].

A probable mechanism is shown, with the double bond geometry in **5** being known to be variable [6, 7]. (The corresponding esters **4** were isolated and characterized spectrally. 4-Alkylideneoxazol-5-ones reportedly fragment similarly [8].) Dehydroamino acids have gained importance in recent times, particularly as immediate precursors for homochiral amino acids [9, 10].

2.1. Experimental: General Remarks. ν_{max} are in cm^{-1} and *J* are in Hz; δ_H were recorded at 300 MHz and δ_C at 75 MHz. *Metalation and methylation of oxazole 1.* A stirred mixture of *n*-BuLi (1.6 mmol in 1.0 mL hexane) and TMEDA (1.6 mmol) at −78°C was treated dropwise with a solution of the oxazole [3, 4] (1 mmol in 3.0 mL THF). After 3 hours the mixture was warmed to −40°C, treated with MeI (1.6 mmol), and allowed to reach room temperature. Work-up with EtOAc and satd. NH_4Cl, followed by chromatography (SiO_2 eluting with 20% EtOAc-hexane), led to the 4-Me derivative **1b** (63%); ν_{max} 1663; δ_H 2.12 (s, 3H), 3.99 (s, 3H), 7.37–7.44 (m, 3H), 7.89–7.93 (m, 2H); δ_C 10.1, 61.1, 113.1, 125.3, 127.7, 128.6, 129.4, 152.0, 155.0; HRMS 190.0856 (Calcd. for $C_{11}H_{11}NO_2$ + H 190.0868). *iso*-Butyraldehyde adduct **3b**: ν_{max} 3410, 2957, 1654; δ_H 0.88 (d, 3H, *J* 6.6), 1.07 (d, 3H, *J* 6.6), 2.09–2.16 (m, 1H), 2.53–2.55 (m, 1H), 4.00 (s, 3H), 4.26–4.31 (m, 1H), 7.38–7.41 (m, 3H), 7.89–7.91 (m, 2H); δ_C 18.3, 18.8, 33.6, 60.8, 71.4, 118.3, 125.5, 128.6, 129.6, 152.2, 154.7; HRMS 270.1110 (Calcd. for $C_{14}H_{17}NO_3$ + Na 270.1106). *N*-Benzoyl 2-amino-4-methylpent-2-enoic acid (**5b**): ν_{max} 3267, 1697, 1640; δ_H 1.09 (d, 6H, *J* 6.6), 2.60–2.80 (m, 1H), 6.73 (d, 1H, *J* 10.5), 7.44–7.54 (m, 3H), 7.79–7.87 (m, 2H); δ_C 21.5, 28.4, 122.8, 127.4, 128.6, 132.0, 132.2, 133.8, 147.2, 166.4, 168.9, 170.8; HRMS 256.0960 (Calcd. for $C_{13}H_{15}NO_3$ + Na 256.0950).

3. Conclusions

We have demonstrated the feasibility of the directed metalation strategy in the case of a heterocycle that is a potential amino acid synthon. The resulting carbanion is generally unreactive towards several alkylating agents (except MeI). However, addition to aldehydes, followed by rearrangement and hydrolysis in acid, led to α,β-dehydroamino acids in fair yields in two cases.

Acknowledgment

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