Regioselective Addition of Grignard Reagents to Isoxazole-4,5-dicarboxylate Esters†

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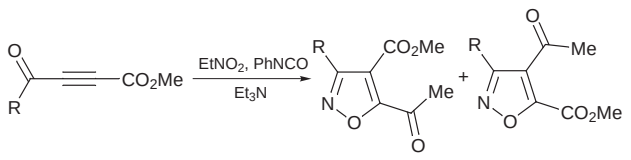
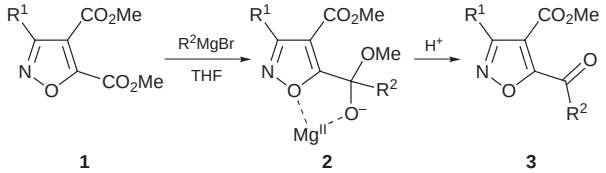
Regioselective mono-addition of a range of Grignard reagents with the 5-esters of 3-methylisoxazole-4,5-diesters affords 5-keto derivatives instead of tertiary alcohols which is explained by the complexing ability of the isoxazole oxygen atom and by the electron withdrawing effect of the isoxazole ring.

Isoxazoles are important medicinal compounds and the synthesis with 4-ester and 5-ketone substituents is challenging and normally involves lengthy procedures.[1,2] In this short paper we report an efficient route which uses the regioselective reactions between a range of Grignard reagents and isoxazole-4,5-diesters. A variety of routes to give a more direct approach to these isoxazoles were initially examined without success. For example, an initial approach using 1,3-dipolar cycloaddition reactions between a nitrile oxide and acetylenic esters substituted with different 3-keto groups afforded a mixture of isoxazole isomers and when R is a large alkyl group, such as a *n*-butyl, the yields from these reactions were low and difficult to reproduce (Scheme 1).



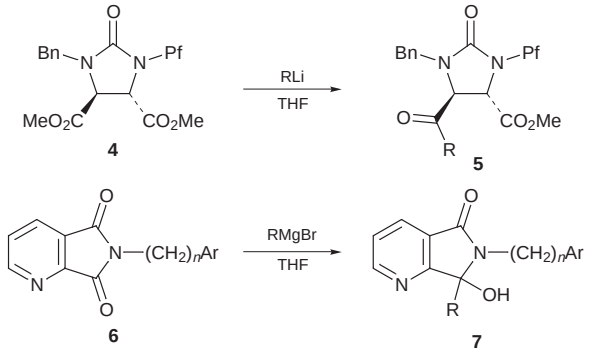
Scheme 1 Dipolar additions between acetylenic esters and nitrile oxides

A more speculative approach to the synthesis of isoxazoles with 4-ester and 5-keto substituents from isoxazole-3,5-diesters **1** was undertaken based on the potential selective reaction of organometallic reagents with the 5-ester due to stabilisation of the tetrahedral intermediate *via* complexation with the oxygen atom of the isoxazole ring, *e.g.* **2** and/or by the electron withdrawing effect of the isoxazole ring. This stabilisation would prevent further reaction to give the usual product from the reaction of organometallic reagents with esters, a tertiary alcohol, and lead to the mono-ketone **3** (Scheme 2).



Scheme 2 Regioselective reaction between isoxazole diesters and Grignard reagents

Similar selectivity has been reported for the addition of organolithium reagents[3] to the diesters **4** to give the mono-ketones **5** (Scheme 3). The electron withdrawing effect of the urea functionality is proposed to stabilise the intermediate. In the addition of Grignard reagents[4] to the imide derivatives **6**, to yield the lactols **7** (Scheme 3), complexation with the pyridine *N*-atom in the intermediate is proposed to explain the regioselectivity. The addition of Grignard reagents to arene-1,2-diesters yield the corresponding phthalides *via* tertiary alcohols, indicating the 'normal' reaction in the absence of a suitably placed hetero-atom for stabilisation of the intermediate or transition state.[5]



Scheme 3 Selective reactions using Grignard and organolithium reagents

Results and discussion

The results of our studies are summarised in Table 1. When diesters **1** were treated with Grignard reagents (R^2MgBr, R^2 = Bu, Pr^i, Ph, allyl, butenyl, vinyl) (1.1 equiv.) at 0 °C the C-5 mono-ketones **3** were obtained as the sole products. At lower temperatures no reaction occurred. None of the reactions gave a product resulting from attack at the 4-ester group. The addition of titanium tetrachloride ($TiCl_4$) gave the best yield possibly due to the formation of a more stable intermediate complex. sp^2-Centred Grignard reagents gave poor yields. Smaller Grignard reagents (R^2MgBr, R^2 = Me, Et) mainly gave the bis-isoxazole **8**. The most probable mechanism for the unusual formation of the dimer **8** is an aldol reaction either in the reaction or during work-up as shown in Scheme 4.

Both the selective mono-addition Grignard reagent and the exclusive regioselectivity of addition to the C-5 ester over the C-4 ester are noteworthy. The most obvious explanation is that initial complexation of the Grignard reagent with the isoxazole oxygen atom guides the attack selectively to the 5-ester and that the sp^3 intermediate is stabilised by complexation of the Mg^{II} with the isoxazole ring oxygen as well as the newly formed alkoxy anion as shown in **2**

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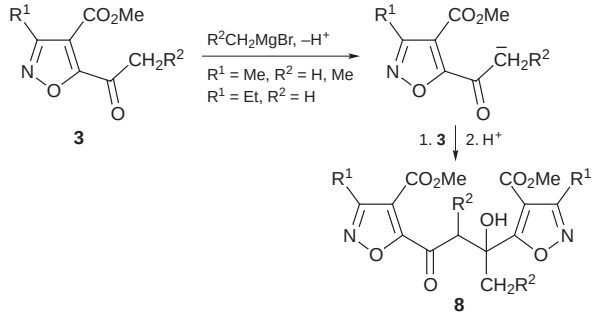
† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Reactions between isoxazole-4,5-diesters **1** and Grignard reagents[a]

R^1	R^2 in Grignard reagent R^2MgBr	Product (yield%)
Me	Bu	**3**(37)
Et	Bu	**3** (35)
Me	Bu (2.0 equiv.)	Mixture of **3** and **8**[b]
Me	Bu	**3**(37)
	$+TiCl_4$ (1.1 equiv.)	**3**(51)
Me	$BuCeCl_2$ (1.1 equiv.)	**3**(23)
Me	Pr^i	**3**(46)
Me	Ph	**3**(10)
Me	Allyl	**3**(38)
Me	Butenyl	**3**(39)
Me	Et	Mixture of **3** and **8**[b]
Et	Vinyl	**3**(5)
Me	Me	**8**(56)
Et	Me	**8**(86)

[a]The diester **1** was treated with the Grignard reagent (1.1 equiv.) in dry THF at 0 °C unless otherwise stated. [b]Mixture of **3** and bis-isoxazole **8**.

in Scheme 2. In summary we have shown that suitably positioned hetero-atoms can be used to guide regioselectivity in organometallic reactions, *i.e.* isoxazole-4,5-diesters react regioselectively with relatively bulky alkyl, alkenyl and aryl Grignard reagents to yield C-5 mono-keto derivatives. This regioselectivity should prove useful synthetically in other related systems which contain a suitable heteroatom for complexing the organometallic reagent.



Scheme 4 Aldol condensation during work-up

Experimental

Melting points were determined on a Gallenkamp mp apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba 1106/1 elemental analyser. IR spectra were recorded on a Unicam FTIR 3020 spectrometer. ^1H and ^{13}C NMR spectra were recorded at 250 MHz on Bruker AC250 and AM 360 spectrometers using TMS as the internal standard with deuteriochloroform. Mass spectra were recorded on a Finnegan MAT 8200 spectrometer. Flash chromatography was carried out using Sorbsil silica gel (40–60 μm). Light petroleum refers to the fraction with bp 40–60 °C.

General Procedure for the Grignard Reactions.–Methyl 3-*Methyl*-5-*pentanoylisoxazole*-4-*carboxylate* **3** (R^1 = Me, R^2 = Bu). Dimethyl 3-methylisoxazole-4,5-dicarboxylate **1** (R^1 = Me) (3.0 g, 15 mmol) was dissolved in dry tetrahydrofuran (THF) and stirred at 0 °C under anhydrous conditions and an atmosphere of nitrogen. *n*-Butylmagnesium bromide (2 M solution, 8.9 cm^3, 16.5 mmol) was added slowly. The resultant mixture stirred at 0 °C for 2 h by which time TLC analysis showed that no starting material was left. The reaction mixture was poured onto a saturated solution of ammonium chloride (100 cm^3) and extracted with diethyl ether. The ethereal solution was dried and evaporated to dryness. The residue was purified using flash chromatography using ethyl acetate and light petroleum as eluant to yield *methyl* 3-*methyl*-5-*pentanoylisoxazole*-4-*carboxylate* as a clear oil (1.1 g, 37%); ν_{max}/cm^{-1} (film) 1735 and 1710; δ_H 0.92 (3 H, t), 1.41 (2 H, m), 1.72 (2 H, m), 2.48 (3 H, s, 3-Me), 2.97 (2 H, t, OCH_2) and 4.15 (3 H, s, CO_2Me) (Found: C, 58.5; H, 6.5; N, 6.0. $C_{11}H_{15}NO_4$ requires C, 58.7; H, 6.6; N, 6.2%).

Methyl 3-*Methyl*-5-(2-*methylpropanoyl*)*isoxazole*-4-*carboxylate* **3** (R^1 = Me, R^2 = Pr^i). Dimethyl 3-methylisoxazole-4,5-dicarboxylate **1** (R^1 = Me) (2.4 g, 12 mmol) and isopropylmagnesium bromide (2 M solution, 6.63 cm^3, 13 mmol) were reacted using the general procedure for 1 h to yield *methyl* 3-*methyl*-5-(2-*methylpropanoyl*)-*isoxazole*-4-*carboxylate* (1.17 g, 46%) as a clear oil (Found: C, 56.5; H, 6.5; N, 6.4. $C_{10}H_{13}NO_4$ requires C, 56.9; H, 6.2; N, 6.6%); ν_{max}/cm^{-1} (film) 1730 and 1705; δ_H 1.21 (3 H, d), 1.38 (3 H, d), 2.48 (3 H, s, 3-Me), 3.32 (1 H, septet, C*H*Me_2) and 3.88 (3 H, s, CO_2Me).

Methyl 5-(3-*Hydroxy*-3-{3-*methyl*-4-[(*methyloxy*)*carbonyl*]*isoazol*-5-*yl*}*butanoyl*)-3-*methylisoxazole*-4-*carboxylate* [*bis-isoxazole* **8** (R^1 = Me, R^2 = H)]. Dimethyl 3-methylisoxazole-4,5-dicarboxylate **1** (R^1 = Me) (2.0 g, 9.4 mmol) and methylmagnesium bromide (3 M solution, 3.13 cm^3, 9.4 mmol) were reacted using the general procedure except that 2 M aqueous hydrochloric acid was used instead of a solution of ammonium chloride to yield the bis-isoxazole **8** (0.96 g, 56%) as a colourless oil (Found: C, 52.5; H, 5.1; N, 7.4. $C_{16}H_{18}N_2O_8$ requires C, 52.5; H, 4.95; N, 7.65%); ν_{max}/cm^{-1} (film) 3600–3200, 1735 and 1710; δ_H 1.71 (3 H, s), 2.41 (3 H, s, 3-Me), 2.45 (3 H, s, 3′-Me), 3.58 (1 H, d) 3.78 (1 H, d), 3.87 (3 H, s, CO_2Me), 3.95 (3 H, s, CO_2Me) and 6.26 (1H, br s, OH); δ_C 11.14 (CH_3),12.31 (CH_3), 27.2 (CH_3), 50.99 (CH_2), 52.54 (CH_3), 52.84 (CH_3), 70.84 (s), 108.21 (s), 112.78 (s), 159.84 (s), 160.31 (s), 161.22 (s), 165.0 (s), 166.68 (s), 181.47 (s), 186.67 (s); *m/z* 366 (M^+).

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