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# One-pot synthesis of α-hydroxy ketones from captodative formyl(amino)alkenes

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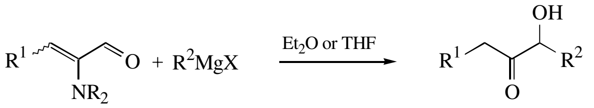
**α-Hydroxy or α-amino ketones were prepared in one step *via* reactions between captodative formyl(amino)alkenes and Grignard reagents.**

α-Hydroxy carbonyl compounds are versatile building blocks in organic synthesis. Among the most efficient general routes to this type of derivatives are classical acyloin condensation, hydrolysis of α-halo ketones and reduction of diketones.[1] The reactions of 2-aminocycloalk-2-enones with Grignard reagents proceed regiospecifically to produce 2-hydroxycycloalkanones in good yields.[2] These methods were succesfully applied to the synthesis of optically pure α-ketols.[3–7] However, the search for new methods of the construction of an α-hydroxy carbonyl moiety is of considerable current interest because this fragment is a common structural unit of many biologically active derivatives.[8–11]

This communication deals with the chemistry of easily available captodative formyl(amino)alkenes **1** for the synthesis of α-hydroxy ketones.[12]

We found that, similarly to S- and P-nucleophiles,[13–16] alkyl- or arylmagnesium halides **2a–d** react as C-nucleophiles with *gem*-substituted formyl(amino)alkenes **1a–c** exceptionally in the 1,2-addition mode. In all cases, no 1,4-adducts could be detected. In both aliphatic **1a**,**b** and aromatic series **1c**, the subsequent hydrolysis of 1,2-adducts affords target α-hydroxy ketones **3a–f** in moderate yields (Scheme 1, Table 1). The structure of **3** is confirmed by NMR ($^1$H, $^{13}$C) and IR spectroscopy, mass spectrometry and C, H analyses or by a comparison of the spectra with published data.†



**1a–c** **2a–d** **3a–f**

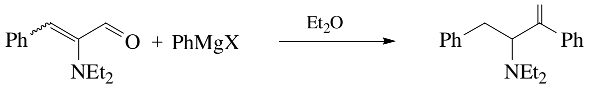
**1a** $R^1 = Me, NR_2 = N(CH_2)_5$
**1b** $R^1 = Me, NR_2 = N(CH_2CH_2)_2O$
**1c** $R^1 = Ph, NR_2 = NEt_2$

**2a** $R^2 = Et, X = Br$
**2b** $R^2 = Am, X = Br$
**2c** $R^2 = Ph, X = Br$
**2d** $R^2 = Bu^s, X = Cl$

**3a** $R^1 = Me, R^2 = Et$
**3b** $R^1 = Me, R^2 = Am$
**3c** $R^1 = Me, R^2 = Ph$
**3d** $R^1 = Me, R^2 = Bu^s$
**3e** $R^1 = Ph, R^2 = Et$
**3f** $R^1 = Ph, R^2 = Am$

**Scheme 1**

As can be seen in Table 1, the method is applicable to the preparation of α-oxyketones **3** including linear and branched alkyl chains and aromatic groups. The $^1$H and $^{13}$C NMR spectra of the reaction mixture indicate that only one carbonyl-bearing compound is formed. For example, in the $^{13}$C NMR spectra, the peaks corresponding to the formyl group of *Z*- and *E*-isomers of formyl(amino)alkenes **1** disappear, while the appearence of a peak characteristic of the carbonyl group of α-hydroxy ketones **3** is observed. Therefore, the reaction occurs with high selectivity. The low yields of ketols **3** is due to the instability of products and decomposition on distillation.[1,11,17]



**1c** **2c** **4** (63%)

**Scheme 2**

**Table 1** Reaction of *gem*-formyl(amino)alkenes **1a–c** with Grignard reagents **2a–d**.

| Entry | Initial reagents | | Product (yield, %) |
|---|---|---|---|
| | 1 | 2 | |
| 1 | **1a** | **2a** | **3a** (35) |
| 2 | **1a** | **2b** | **3b** (49) |
| 3 | **1a** | **2c** | **3c** (37) |
| 4 | **1b** | **2d** | **3d** (24) |
| 5 | **1c** | **2a** | **3e** (53) |
| 6 | **1c** | **2b** | **3f** (56) |
| 7 | **1c** | **2c** | **4** (63) |

To our surprise, on treatment with phenylmagnesium bromide **2c** under the same reaction conditions, aminoalkene **1c** was not converted to the corresponding α-ketol (Scheme 2). Instead, α-aminoketone **4** is formed as a sole isolated product (there is only one peak in the region 180–220 ppm in the $^{13}$C NMR spectrum of the reaction mixture).

These results may be interpreted by a mechanism shown in Scheme 3. Undoubtedly, the first step involves the addition of the Grignard reagent to the formyl group of aminoalkene **1** leading to 1,2-adduct **5**. The general way is the hydrolysis of its enamine moiety to give finally target α-ketols **3**. Contrary to the above discussion, intermediate **5** ($R^1 = R^2 = Ph$) undergoes isomerization to more stable alkene **6**. Enol **7**, formed under the usual treatment of the reaction mixture with saturated $NH_4Cl$ solution, is quickly transformed to α-amino ketone **4**. An analogous sequence of transformations has been proposed previously to explain the formation of esters and thiol esters of tertiary α-amino acids from substrates **1**.[13,14]

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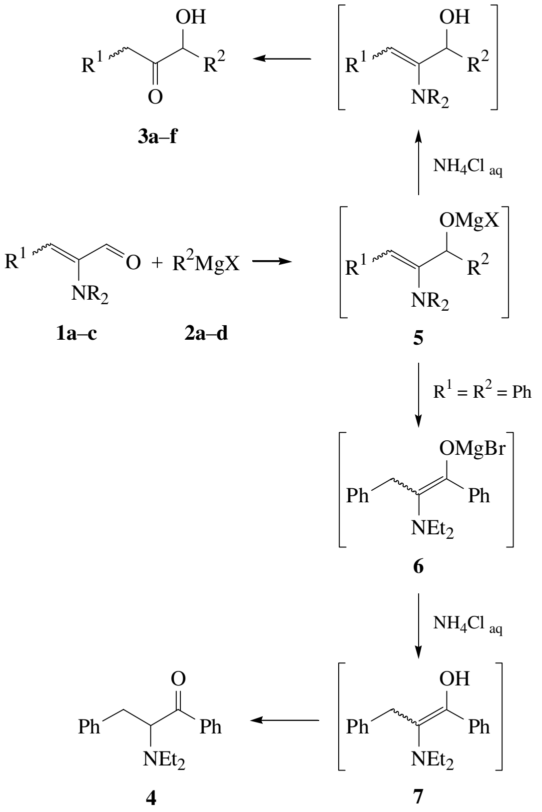
† Typical experimental procedure for the preparation of 1-phenyl-3-hydroxy-2-pentanone **3e**: a solution of 2-diethylaminocinnamaldehyde **1c** (1.5 g, 7.4 mmol) in $Et_2O$ was added dropwise to a stirred solution of ethylmagnesium bromide **2a** obtained from Mg (0.2 g, 8.3 mmol) and bromoethane (0.9 g, 8.3 mmol) in $Et_2O$ under Ar. After refluxing for 2 h, the mixture was treated with a saturated solution of $NH_4Cl$ and extracted with diethyl ether (4×50 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. Pure product **3e** (0.7 g, 53%) was obtained by vacuum distillation.

$^1$H NMR ($CDCl_3$) $\delta$: 0.86 (t, 3H, *J* 7.6 Hz), 1.50–1.70 (m, 1H), 1.80–2.00 (m, 1H), 3.71 (AB system, 2H, *J* 15.8 and 2.3 Hz), 4.20 (dd, 1H, *J* 6.8 and 4.1 Hz), 7.10–7.35 (m, 5H). $^{13}$C NMR ($CDCl_3$) $\delta$: 8.88 (Me), 26.61 ($CH_2$), 44.81 ($PhCH_2$), 76.85 (CH), 127.22, 128.73, 129.42, 133.08 (Ph), 209.85 (C=O). IR ($\nu$/cm$^{-1}$): 1700 (C=O), 3440 (OH). MS, *m/z* (%): 178 (1, M$^+$), 160 (21), 121 (35), 91 (100). Found (%): C, 74.14; H, 7.53. Calc. for $C_{11}H_{14}O_2$ (%): C, 74.13; H, 7.92.

Amino ketone **4** was prepared by the same procedure starting from 2-diethylaminocinnamaldehyde **1c** (2.0 g, 10 mmol) and Grignard reagent **2c** obtained from Mg (0.2 g, 8.3 mmol) and PhBr (1.6 g, 10 mmol) in $Et_2O$. The crude product was purified by column chromatography on silica gel ($CH_2Cl_2$:MeOH = 10:1) to give pure ketone **4**. $^1$H NMR ($CDCl_3$) $\delta$: 1.11 (t, 6H, *J* 7.2 Hz), 2.65–2.85 (m, 4H), 2.99 (dd, 1H, *J* 9.5 and 3.6 Hz), 3.40 (dd, 1H, *J* 9.5 and 3.6 Hz), 4.58 (dd, 1H, *J* 9.5 and 3.6 Hz), 7.25–8.05 (m, 10H). $^{13}$C NMR ($CDCl_3$) $\delta$: 14.29 (Me), 31.05 ($PhCH_2$), 44.73 ($NCH_2$), 66.70 (CH), 125.95, 128.25, 128.39, 128.65, 129.53, 132.48, 137.94, 140.06 (Ph), 199.70 (C=O). IR ($\nu$/cm$^{-1}$): 1678 (C=O). MS, *m/z* (%): 281 (< 1, M$^+$), 176 (100), 105 (17), 77 (40). Found (%): C, 81.55; H, 8.38; N, 4.82. Calc. for $C_{19}H_{23}NO$ (%): C, 81.10; H, 8.24; N, 4.98.



**Scheme 3**

What is the cause of the difference in the reaction ways? It was found that the treatment of captodative formyl(amino)alkenes **1** with soft nucleophiles leads to unexpected derivatives of tertiary α-amino acids.[13–16] In contrast, the reactions of substrates **1** with primary amines give only the corresponding azomethines in good yield.[18] The Grignard reagents, as C-nucleophiles, have an intermediate position between very soft S- and P-nucleophiles, on the one hand, and hard N-nucleophiles, on the other. Therefore, in this case, relatively trivial changes in substituents present in formyl(amino)alkene **1**, as well as in the nature of reagent, may lead to the completely different types of products (see a review[19] on the chemistry of enamines). The simplicity of this reaction and mild experimental conditions make this approach to α-functionally substituted ketones to be convenient.

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