Organic Synthesis Utilizing Beckmann Fragmentation: New Carbon–Carbon Bond Formation by the Reaction of α-Alkoxycycloalkanone Oxime Acetates with Organoaluminium Reagents

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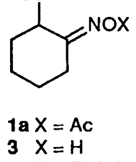
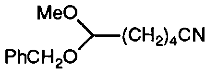
The reaction of α-alkoxycycloalkanone oxime acetates **1** with organoaluminium reagents caused Beckmann fragmentation and subsequent carbon–carbon bond formation to give various types of ω-cyano-α-alkyl (or alkynyl)ethers **2** in high yields.

The Beckmann fragmentation is a useful reaction to convert oximes to ω-nitrile compounds.[1] Recently, we reported Beckmann fragmentation followed by carbon–carbon bond formation of α-alkoxycycloalkanone oximes using silicon-containing carbon nucleophiles.[2] Although this reaction proved to be useful in giving various types of functionalized ω-nitrile compounds, the carbon units introduced are somewhat limited and did not include alkyl or alkynyl carbon units. We show here that the combination of oxime acetates **1** and organoaluminium reagents[3] overcomes this limitation affording the ω-nitrile compounds **2** having alkyl or alkynyl carbon units and that the presence of a Lewis acid dramatically increases the yield.

Initially, we examined the reaction of oxime acetate **1a**,[†] oxime **3**[‡] or oxime benzyl ether **4**[‡] with trimethylaluminium in dichloromethane. As a result, the ω-nitrile compound **2a** was obtained in 54% yield from **1a** (see Table 1, entry 1), whereas unidentified products (no nitrile functionality from IR spectra) from **3** and acetal **5** from **4** were obtained. Therefore,



1a X = Ac
3 X = H
4 X = $PhCH_2$



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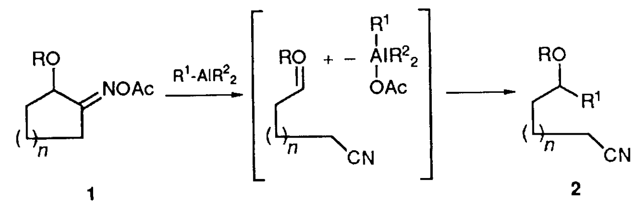
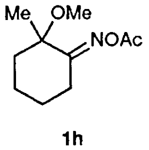
[†] Prepared by acetylation (Ac_2O–pyridine) of oxime **3** in quantitative yield.

[‡] Prepared from the corresponding ketone in the usual way (**3**: $NH_2OH{\cdot}HCl$, NaOH, $MgSO_4$, MeOH; **4**: $NH_2OBn{\cdot}HCl$, NaOH, $MgSO_4$, MeOH) and used without further purification.

Table 1 Reaction of α-alkoxyketoxime acetate **1** with organoaluminium reagents[a]



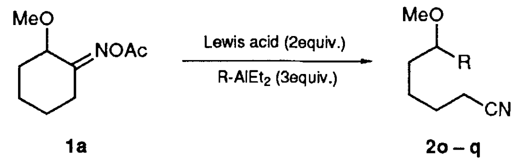


1h

Entry	Oxime acetate **1**	Reagent	Product **2**	Yield (%)[b]
1	**a** $n = 2$, R = Me	Me_3Al	**a** R^1 = Me	54
2	**b** $n = 2$, R = $PhCH_2$		**b** R^1 = Me	79
3	**c** $n = 2$, R = $SiMe_2Bu^t$		**c** R^1 = Me	42
4	**d** $n = 1$, R = Me		**d** R^1 = Me	62
5	**e** $n = 1$, R = $PhCH_2$		**e** R^1 = Me	92
6	**f** $n = 4$, R = Me		**f** R^1 = Me	61
7	**g** $n = 8$, R = Me		**g** R^1 = Me	72
8	**h**	Me_3Al	**h**	61
9	**b**	Et_3Al	**i** R^1 = Et	48
10	**b**	$Bu^i{}_3Al$	**j** R^1 = Bu^i	52
11	**h**	Et_3Al	**k** R^1 = Et	55
12	**h**	$Bu^i{}_3Al$	**l** R^1 = Bu^i	56
13	**b**	$Bu^nC{\equiv}CAlEt_2$[c]	**m** R^1 = Bu^n–C≡C–	66
14	**b**	$PhC{\equiv}CAlEt_2$[c]	**n** R^1 = Ph–C≡C–	72

[a] Oxime acetate **1** (0.1 mmol) and organoaluminium reagent (1.5–2 equiv.) in CH_2Cl_2 (1 ml) were stirred for 4 h at 0 °C and then stirred at room temperature under a nitrogen atmosphere. After completion of the reaction (TLC check), the resulting mixture was quenched by NaF (5 equiv.) at 0 °C. The mixture was dissolved in water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by SiO_2 column chromatography to afford **2**. [b] Yield of the isolated product and not optimized. [c] Prepared by treatment of the corresponding acetylenes with Bu^nLi followed by Et_2AlCl.

Table 2 Reaction of **1a** with organoaluminium reagents in the presence of Lewis acid[a]



Entry	$RAlEt_2$	Lewis acid	Product	Yield (%)[b]
1	Et_3Al	none	**2o**	20
2		$ZnCl_2$	**2o**	35
3		$CF_3SO_3SiMe_3$	**2o**	47
4	Bu^n–C≡C–$AlEt_2$	none	**2p**	trace
5		$ZnCl_2$	**2p**	67
6		$CF_3SO_3SiMe_3$	**2p**	39
7	Ph–C≡C–$AlEt_2$	none	**2q**	trace
8		$ZnCl_2$	**2q**	91
9		$CF_3SO_3SiMe_3$	**2q**	62

[a] **1a** (0.1 mmol) and Lewis acid (2 equiv.) in CH_2Cl_2 (1 ml) were stirred for 10 min at 0 °C and then organoaluminium reagent (3 equiv.) was added to the resulting mixture. The following procedure was performed in the same way as shown below Table 1. [b] Yield of the isolated product and not optimized.

various oxime acetates **1a–h** were treated with organoaluminium reagents and the results are summarized in Table 1. The detailed study was performed by use of Me_3Al (entries 1–8), of which several aspects are noteworthy. First, methyl, benzyl and even silyl ethers are available (entries 1–3). Secondly, the reaction works for medium to large ring systems (entries 6 and 7). Thirdly, even in tertiary alkoxy systems the desired product was obtained (entry 8). Other trialkylaluminium reagents (Et_3Al, $Bu^i{}_3Al$) and alkynyldiethylaluminium reagents similarly reacted with oxime acetates (**1b** and **h**) to give the corresponding ω-nitrile compounds (**2i–n**) (entries 9–14).

Although the reaction of α-methoxy oxime acetate **1a** did not give a satisfactory result (trace–20% yield), the addition of a Lewis acid improved the yield. A dramatic effect was observed in the reactions of alkynyldiethylaluminium reagents. The results are summarized in Table 2.

In conclusion, the methodology presented here opens a new route to various types of functionalized ω-nitriles and suggests the possibility of using other organometallic reagents as carbon nucleophiles.

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References

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3 The success of the Beckmann rearrangement using organoaluminium reagents prompted us to use them as the reagent of choice. K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori and H. Yamamoto, *J. Am. Chem. Soc.*, 1983, **105**, 2831.