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Tetrahedron Letters 48 (2007) 7761–7763
Tetrahedron Letters

Ruthenium-catalysed conversion of oxime ethers into nitriles

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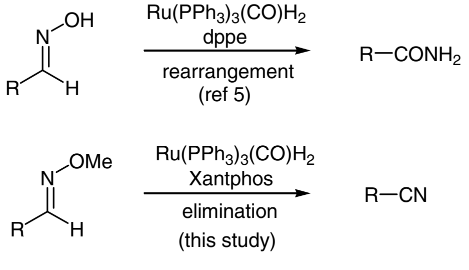
Received 10 August 2007; revised 31 August 2007; accepted 4 September 2007
Available online 8 September 2007

Abstract—The conversion of oxime ethers into nitriles has been achieved under neutral conditions using $Ru(CO)(PPh_3)_3H_2$ and the bidentate ligand Xantphos as the catalyst.

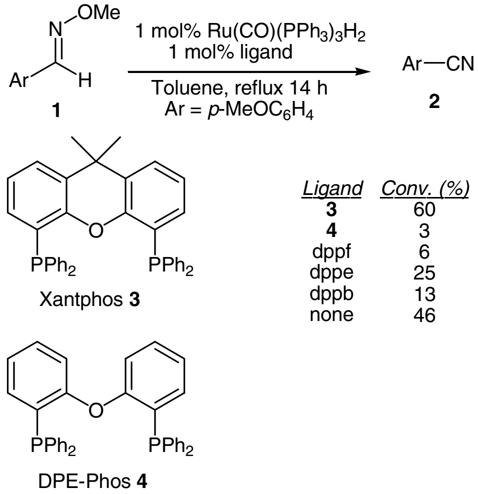
Standard methods for the conversion of oximes into nitriles involve dehydrating agents such as trifluoroacetic anhydride, thionyl chloride,[1] or pivaloyl chloride.[2] Oxime ethers can undergo elimination to give nitriles when treated with strong bases.[2] There are a few reports of transition metal catalysed reactions of oximes leading to either the corresponding nitrile[3] or the amide,[4] depending on the choice of catalyst. Recently, we have shown that the combination of $Ru(CO)(PPh_3)_3H_2$ with dppe leads to the highly selective re-arrangement of oximes into amides.[5] In this Letter, we report that a closely related catalyst is effective for the conversion of oxime ethers to nitriles under neutral conditions (Scheme 1). Iridium catalysts have previously been used for the ring cleavage of cyclobutanone oxime ethers to give nitriles, but we are unaware of any other reports of metal catalysed conversion of oxime ethers into nitriles.[6]



Scheme 1. Reactions of oximes and oxime ethers.

In preliminary experiments, oxime ether **1** was treated with $Ru(CO)(PPh_3)_3H_2$ and several bidentate phosphine ligands and heated to reflux in toluene for 14 h with moderate conversion into nitrile **2** (Scheme 2). With the exception of Xantphos **3**,[7] all the other phosphine ligands examined hindered the progress of the reaction. We have previously noted the reactivity of Ru/Xantphos combinations in other processes,[8] although for oxime to amide re-arrangement, dppe was found to be a better ligand than Xantphos.

We therefore decided to proceed with the reaction using Xantphos as an additive, although the reaction in the



Ligand	Conv. (%)
3	60
4	3
dppf	6
dppe	25
dppb	13
none	46

Scheme 2. Phosphine screen for the elimination of oxime ether to nitrile.

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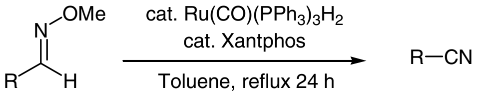
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.09.028



Scheme 3. Conversion of oxime ethers into nitriles.

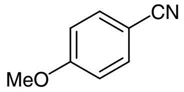
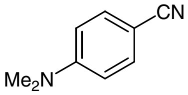
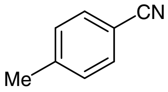
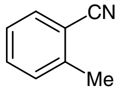
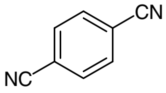
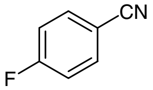
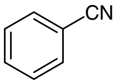
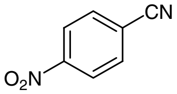
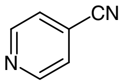
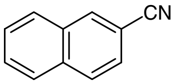
absence of this ligand was almost as effective. Using 2.5 mol % of catalyst demonstrated that toluene was a convenient solvent affording 63% conversion to nitrile **2** after 6 h. The use of DMF as solvent afforded the same conversion, whilst a lower conversion of 37% was obtained in 1,4-dioxane. No reaction was observed in isopropanol or acetonitrile, although these reactions were performed at a lower temperature (80 °C vs 111 °C). The conversion was dependent on the catalyst loading with the reaction (in toluene for 24 h) proceeding to 71% with 1 mol % of catalyst, 89% with 2.5 mol %, 98% with 3.5 mol % and 100% with 5 mol %. The addition of acid ($EtCO_2H$ or $TsOH{\cdot}H_2O$) as a co-catalyst (1 equiv with respect to ruthenium) resulted in no reaction, whilst the use of base (Cs_2CO_3, KOH or ^{t}BuOK) reduced reactivity.

Alternative oxime ethers were readily prepared in good yields from the corresponding aldehyde and *O*-methylhydroxylamine hydrochloride using the literature procedures.[9] We then examined the conversion of these oxime ethers into nitriles using either 3.5 or 5 mol % of $Ru(CO)(PPh_3)_3H_2$/Xantphos in toluene at reflux for 24 h. All reactions were run at 0.5 M in substrate.[10] We were pleased to find that the majority of oxime ethers were cleanly converted into nitriles with good conversions and with good isolated yields (Scheme 3 and Table 1). The reaction was successful when there were electron-donating substituents (entries 1 and 2), as well as for other *p*-substituted aryl groups. The presence of an *o*-substituent did not appear to compromise reactivity (entry 4). The process did not require an aryl group, as evidenced by the success of the reaction of the oxime ether derived from octanal (entry 11). The considerably lower conversion obtained with the *p*-nitro substituted oxime (entry 8) may be due to electronic effects, although since the aliphatic substrate was reactive, it is possible that the catalyst is being deactivated by the nitro group.[11] It is also likely that the lower reactivity of the pyridyl-containing substrate (entry 9) is due to inhibition of the catalyst by co-ordination.

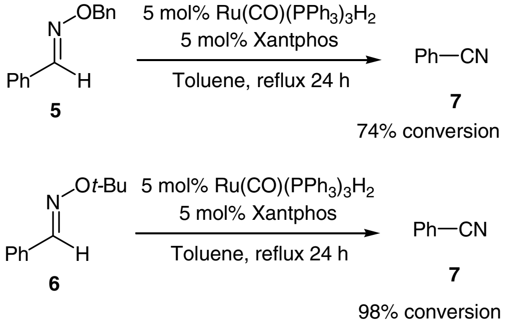
Whilst the use of the *O*-methylhydroxylamine-derived oxime ethers is convenient, we also wished to determine whether alternative oxime ethers would undergo conversion into nitriles, and therefore examined the reactions of oxime ethers **5** and **6**, derived from *O*-benzylhydroxylamine and *O*-*t*-butylhydroxylamine, respectively (Scheme 4). In both cases, these reactions provided the corresponding nitriles, although a slightly lower conversion was observed for the reaction with oxime ether **5**, perhaps because of the easier oxidation of the liberated benzyl alcohol, which may result in carbonylation and de-activation of the catalyst.[12]

We are currently investigating the nature of the catalyst, and the reasons for the benefits that the bidentate ligand provides in these reactions. We assume that the elimination of alcohol is facilitated by N-co-ordination of the oxime ether to the ruthenium catalyst to give a nitrile complex which then dissociates.[6]

Table 1. Yields of nitriles from the corresponding oxime ether

Entry	Product	Catalyst[a] (%)	Yield[b] (%)
1		3.5	98 (81)
2		3.5	89 (80)
3		3.5	94
4		3.5	98 (83)
5		5.0	99 (80)[c]
6		3.5	96
7		5.0	95
8		5.0	28
9		5.0	73
10		5.0	99 (85)
11	C_7H_{15}—CN	3.5	100 (83)

[a] $Ru(CO)(PPh_3)_3H_2$/Xantphos.
[b] Conversion, with isolated yield in parentheses.
[c] The starting material was the *p*-NC-substituted oxime ether.



Scheme 4. Reactions with *O*-benzyl and *O*-*t*-butyl oximes.

In summary, oxime ethers can be converted into nitriles using a similar catalyst combination to one that is effective for the conversion of the parent oximes into amides.

Acknowledgements

We wish to thank the Royal Society for a Visiting Fellowship (to N.A.), the Higher Education Dept., Govt. of Jammu and Kashmir, India, as well as AstraZeneca and the EPSRC for further funding.

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10. *Typical experimental conditions*: $Ru(CO)(PPh_3)_3H_2$ (32 mg, 3.5 mol %) and Xantphos (21 mg, 3.5 mol %) were heated at reflux in dry toluene (1.5 mL) under an atmosphere of nitrogen for 10–15 min. Oxime ether (1 mmol) in dry toluene (0.5 mL) was added and the reaction was heated at reflux for 24 h. After cooling and evaporation of solvent in vacuo, the product was isolated by column chromatography (silica, hexane/ethyl acetate).
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