Rearrangements of Activated O-Acyl Hydroxamic Acid Derivatives.

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Abstract: O-acyl hydroxamic acid derivatives (**1a-d, 6a-c, 8a-b**) undergo base catalysed rearrangement to give secondary 2-acyloxyamides (**4a-d, 7a-c, 9a-b**) in moderate to excellent yields (56-98%).
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2-Hydroxy carbonyl compounds are widely distributed in nature and are often used as building blocks in in organic synthesis. In particular since 2-hydroxyamides are useful intermediates for the preparation of ethanolamines[1], oxindoles[2] and oxazolidinediones[3] new methods for their synthesis are of great interest. Few methods for the conversion of amides to 2-hydroxyamides are currently available. Methods include oxidation of tertiary amide enolates with various reagents (MoO5-peroxide[4], sulfonyloxaziridines[5], and dimethyldioxirane[6]), and reaction of α-hydroxyesters with amines[3]. While the former approach is useful for the synthesis of tertiary amides it is less applicable to primary and secondary amides while the latter approach often leads to low reaction yields. There have been very few methods for the synthesis of secondary 2-hydroxyamides directly, the most successful include a Lewis acid catalysed coupling between isocyanides and aldehydes[7] and the base promoted reaction of O-sulfonated hydroxamic acid derivatives in the presence of water[8]. In the previous communication we reported that O-benzoyl hydroxamic acid derivatives (**1a-d**) furnished β-lactam derivatives (**2a-d**) upon reaction with Bu3SnH and AIBN in refluxing toluene[9]. In addition to these products (**2a-d**) and the corresponding reduced amides (**3a-d**) varying amounts of the rearranged amides (**4a** and **4c**) were detected. These latter products represent suitably protected versions of secondary 2-hydroxyamides and as a consequence we decided to study this rearrangement reaction in more detail. We wish to report in this letter our preliminary results in this area.
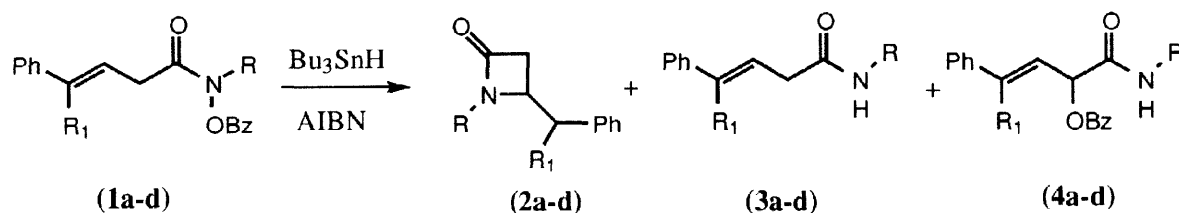

(**1a-d**)
1a) R=Me, R_1=H
1b) R=Bn, R_1=H
1c) R=Bu, R_1=H
1d) R=Bu, R_1=Ph

(**2a-d**)

(**3a-d**)

(**4a-d**)

Scheme 1

Optimisation of the rearrangement reaction.

Postulating that the rearrangement observed during the radical cyclisation reactions may be proceeding via a novel [3,3] sigmatropic rearrangement of the enol form of the hydroxamic acid precursors, similar to that observed in the rearrangement of N,O-divinylhydroxylamines[10], (scheme 2) our initial experiments involved heating the hydroxamic acid derivative (1a)[9] at 110°C in toluene in the absence of radical initiator or Bu3SnH. After 24 hours at this temperature examination of the crude NMR indicated only 10% conversion to the desired product, however upon increasing the temperature to 140°C the reaction proceeded smoothly in good yield (95%), (table 1).

Scheme 2
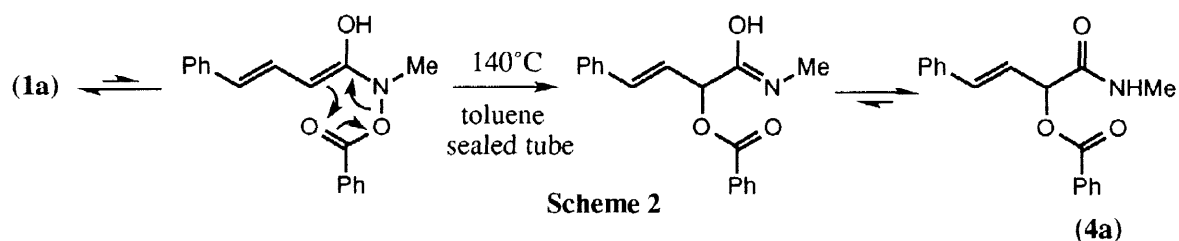
A more convenient procedure however was to heat the precursors in toluene (110°C) or dichloromethane (40°C) with either 1 equivalent or a catalytic amount (20mol%) of triethylamine. Although other bases were briefly examined (including LiHMDS, KHMDS, NaH, Et_2iPrN, NaOMe, and quinine) Et_3N proved to be the most convenient. In addition to the precursor (1a) described above the other substrates (1b-d) also underwent exclusive rearrangment under these conditions[11].

Scheme 3
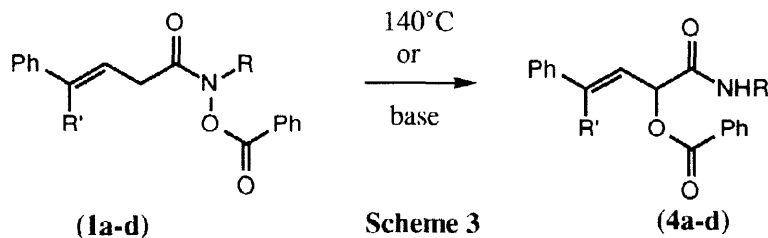
| Compound	solvent	temperature	base	time	yield
1a	toluene	110°C	-	24hrs	<10%[a]
1a	toluene	140°C	-	24hrs	95%
1a	toluene	110°C	Et_3N	45mins	85%
1a	CH_2Cl_2	40°C	Et_3N	4 hrs	56%
1a	toluene	110°C	Et_3N (cat)	10 mins	58%
1b	CH_2Cl_2	40°C	Et_3N	12hrs	62%
1c	CH_2Cl_2	40°C	Et_3N	4hrs	63%
1d	CH_2Cl_2	40C	Et_3N (cat)	12hrs	98%

a = Determined by NMR   **Table 1**

A typical procedure is as follows: O-acyl-N-alkyl hydroxamic acid (1) (1mmol) was dissolved in toluene (1ml) and triethylamine (1eq or 0.2 eq) was added. The reaction was refluxed for 45 minutes and the solvent removed in vacuo. The residue was either recrystallised or chromatographed to give the desired products.

Scope and limitation of the rearrangment:-Effect of O-acyl group.

In order to evaluate the scope and limitation of this procedure we first examined the effect of the O-acyl group. The O-acyl precursors (6a-c) were prepared by acylation (acid chloride, pyridine, 0°C) of the known N-methyl hydroxamic acid (5) and their corresponding rearrangement reactions examined, (table 2).
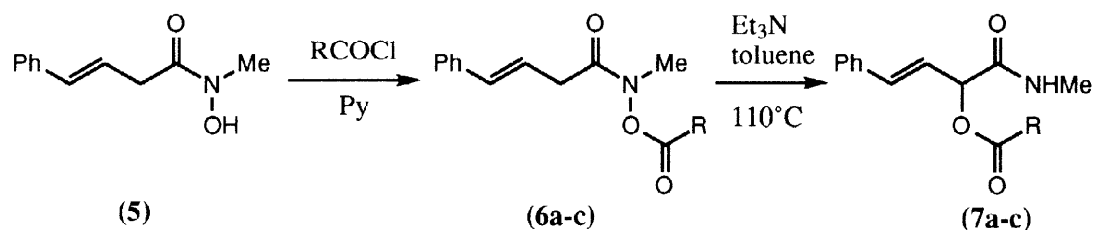
Scheme 4

Interestingly, the p-nitrobenzoyl derivative (6a) required only 5 minutes at 110°C for complete reaction indicating that either the acidity of the α-carbonyl protons or the nature of the nitrogen leaving group is important in the rate determining step. Rearrangement of the O-acetyl (6b) and O-pivaloyl (6c) derivatives was also facile.

Compound	R	Yield	
		(6)	(7)
6a	p-NO$_2$C$_6$H$_4$	88%	58%
6b	Me	75%	98%[a]
6c	tBu	92%	80%[a]

a = 0.2 eq Et$_3$N   Table 2

Effect of N-acyl group

The nature of the N-acyl side chain was next examined in order to determine if the rearrangement was limited to activated hydroxamic acid derivatives. The phenyl (8a) and 2-naphthyl (8b) precursors were prepared by initial N-acylation of N-methylhydroxylamine hydrochloride with either phenylacetyl chloride or 2-naphthylacetyl chloride followed by O-acylation of the corresponding hydroxamic acids. Upon treatment with Et$_3$N in refluxing toluene the rearrangements took place smoothly as before, (scheme 5). The derivative (10), on the other hand, failed to undergo the rearrangement, either with Et$_3$N or thermally under forcing conditions (160°C for 3 days), thus highlighting the need for an easily enolisable substrate when Et$_3$N is used as base.
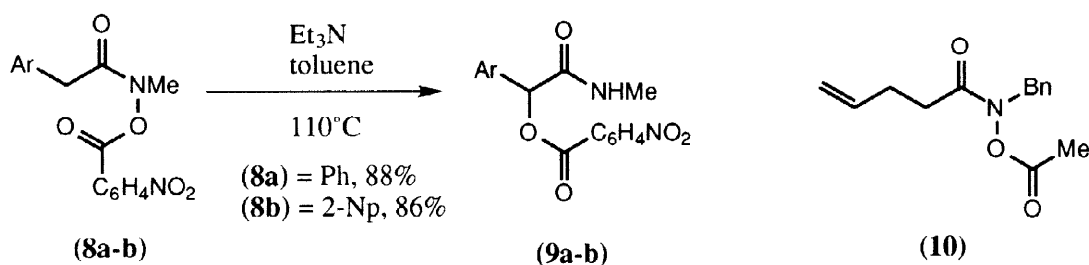
Scheme 5

Work is currently ongoing to facilitate the rearrangement of unactivated hydroxamic acid derivatives by utilising strong bases such as LDA or LDA/TMSCl. The results of this work will be published in due course.

In conclusion we have demonstrated that suitably activated O-acyl-N-alkylhydroxamic acid derivatives can undergo a thermal or base catalysed rearrangement reaction to give secondary 2-acyloxyamides in moderate to excellent yields. The reaction most likely proceeds via an anionic hetero[3,3] sigmatropic rearrangment of the corresponding enol or enolate. However, at this stage the alternative possibility of an initial intramolecular displacement of the O-acyl leaving group by the enolate to furnish an α-lactam which ring opens to an ion pair and is subsequently trapped by the carboxylate ion cannot be ruled out. This latter mechanism is conceptually similar to that hypothesised for the reaction of N-mesyloxyamides with base in the presence of water as the trapping nucleophile[12].

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11. All new compounds gave satisfactory spectroscopic data. Selected data for (**4c**) is given.
   ^{1}H NMR (400MHz, CDCl$_3$); 8.10 (2H, d, J = 8.8Hz, Ar), 7.60 (1H, t, J = 7.4Hz, Ar), 7.50-7.25 (7H, m, Ar), 7.04 (1H, dd, J = 15.3, 5.2Hz, olefin), 6.61 (1H, d, J = 5.2Hz, CH), 6.02 (1H, d, J = 15.3Hz, olefin), 5.60 (1H, brs, NH), 3.28 (2H, q, J = 6.9Hz, NCH$_2$), 1.42 (2H, quin, J = 7.4Hz, CH$_2$), 1.32 (2H, quin, J = 7.4Hz, CH$_2$), 0.89 (3H, t, J = 7.4Hz, Me); ^{13}C NMR (100MHz, CDCl$_3$); 165.32, 164.83, 140.59, 137.69, 133.34, 129.79, 128.83, 128.70, 128.50, 127.58, 124.58, 104.95, 74.97, 39.46, 31.62, 20.09, 13.75.

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