A simple method for the α-oxygenation of aldehydes

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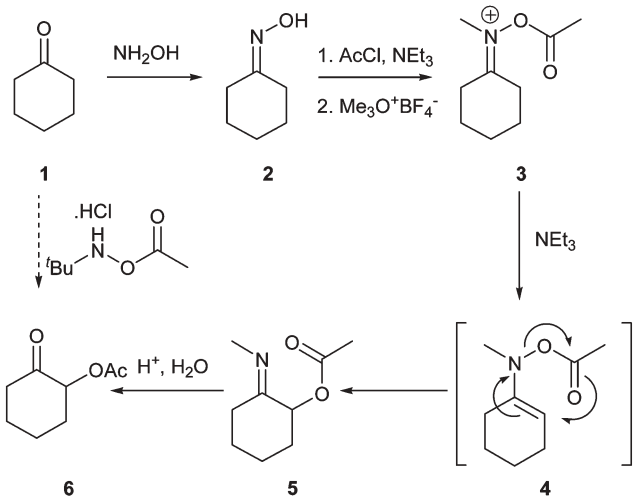
A mild, efficient and general method for the chemospecific α-oxygenation of aldehydes is described. Treatment of a series of aldehydes with *N*-*tert*-butyl-*O*-benzoyl hydroxylamine hydrochloride gives the corresponding α-oxygenated carbonyl *via* a proposed pericyclic rearrangement process.

There has been a recent explosion of interest in the use of metal-free processes to carry out functional group manipulations and transformations due to the accordant potential for academic, industrial, economic and environmental benefit.[1]

α-Hydroxycarbonyl compounds represent important building blocks for organic synthesis and correspond to a key functional group present in a substantial number of important natural products. A number of methods have been reported for the preparation of this crucial functionality including the α-oxygenation of enolates with electrophilic oxidising agents, and the dihydroxylation or epoxidation of preformed enol ethers.[2] More recently, the aminoxylation of aldehydes[3] and ketones[4] has been reported using nitrosobenzene, however the use of at least three equivalents of the carbonyl compound, in conjunction with syringe pump techniques, somewhat limits this innovative and attractive piece of methodology.

Herein, we report a simple method for the α-oxygenation of carbonyl compounds under aerobic, aqueous acidic reaction conditions. The reaction allows for complete control in chemoselectivity for aldehydes over ketones, and is applicable to the transfer of a variety of acyl substituents.



Scheme 1

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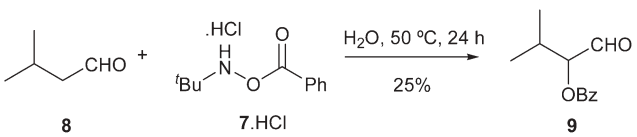
In 1969 House described a five step synthetic protocol for the conversion of cyclohexanone **1**, to α-acetoxycyclohexanone **6** as outlined in Scheme 1.[5] This process involved conversion to the oxime **2**, and then *O*-acylation followed by *N*-alkylation to give the iminium ion **3**. Rearrangement of this salt under basic conditions gave the corresponding α-acetoxyimine **5**, which was then hydrolysed under aqueous acidic conditions to unmask the α-acetoxycarbonyl **6**. It was proposed that the key bond-forming process involved conversion of the salt **3** to the enamine **4** followed by a concerted pericyclic rearrangement.[6] By consideration of the recent elegant work within the literature involving enamine intermediates[7] we were intrigued whether we could develop a one-pot method for the House synthesis.

Preparation of *N*-*tert*-butyl-*O*-benzoyl hydroxylamine **7** proceeded in one step by the reaction of *tert*-butylamine with benzoylperoxide to give the proposed reagent.[8] We initially prepared the hydrochloride salt of **7** and investigated its reactivity with both cyclohexanone **1** and isovaleraldehyde **8**, at both room temperature and 50 °C[9] in water, and were delighted to discover that with isovaleraldehyde the desired product **9** could be isolated in 25% yield, showing that the proposed transformation was viable (Scheme 2). We believe that this process proceeds *via* condensation of the reagents to give an iminium ion, followed by conversion to the enamine and rearrangement to give an α-benzoyloxy imine, which is subsequently hydrolysed under the aqueous acidic reaction conditions to give the observed product **9**. No α-functionalised carbonyl product was detected in the reaction of cyclohexanone with only starting material being isolated from the reaction mixture.

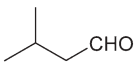
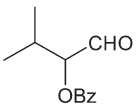
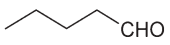
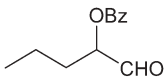
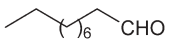
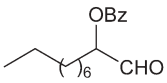
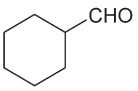
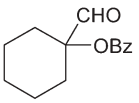
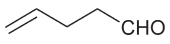
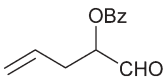
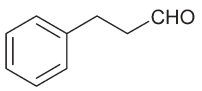
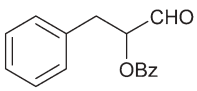
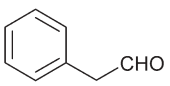
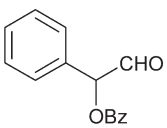


Scheme 2

Encouraged by this initial result we went on to investigate the effect of both the solvent and the nature of the acid involved in the reaction in an attempt to optimise the transformation and eventually adopted a solvent mixture of THF–H_2O (9:1) and HCl as the acid of choice for the reagent.†

Having established the best reaction conditions we then went on to examine the applicability of the transformation (Table 1). The transformation was effective for a range of simple aliphatic aldehydes, with both valeraldehyde (entry 2) and decanal (entry 3) giving the desired product in good yield. The reaction also worked

Table 1 [a]

Entry	Substrate	Product	Yield (%)
1			79
2			72
3			74
4			82
5			76
6			69
7			67
8	*endo*/*exo* 9:1	9	1	62
9	*endo*/*exo* 1:1	9	1	61

[a] All reactions were performed with 1 equivalent of reagent, 0.5 M concentration, at 50 °C in a 9:1 mixture of THF and water except entry 7 which was carried out at room temperature.

for rearrangement into tertiary centres with cyclohexane carboxaldehyde giving the desired product in 82% isolated yield (entry 4). The reaction was also tolerant of a variety of functional groups, for example, 4-pentenal (entry 5) and 3-phenylpropanal (entry 6) both smoothly gave the desired product in good yield. Interestingly, when phenylacetaldehyde was used as the substrate for the procedure, the reaction was complete in just 45 minutes at room temperature (entry 7), possibly due to the increased acidity of the α-proton, accelerating enamine formation in the proposed reaction sequence. We also discovered that treatment of a Diels–Alder adduct as a 9:1 mixture of *endo*- and *exo*-isomers (entry 8) gave the α-functionalised product in 62% isolated yield in an identical ratio to the starting material. However, when the ratio of the *endo*- and *exo*-isomers of the starting material was 1:1 (entry 9), the *endo*–*exo* ratio of the products was once again 9:1, suggesting that these two reactions proceed *via* the same intermediate.

We were not able to detect any reaction product with acetone, cyclohexanone, propiophenone or ethylacetoacetate under our standard reaction conditions, and use of both acetone and cyclohexanone as the reaction solvent (40 equivalents, 50 °C, 72 h) also led to no detectable products when treated with one equivalent of the reagent, which indicated that **7**·HCl is chemospecific for aldehydes over ketones. This was further supported by a competition experiment, where reaction of one equivalent of both isovaleraldehyde **8** and cyclohexanone **1** in the same flask, under our standard conditions for 16 hours, gave the α-functionalised aldehyde product **9** in 73% isolated yield.

Finally, in an effort to determine if alternative groups could be transferred within this reaction, we prepared *N*-*tert*-butyl-*O*-acetyl hydroxylamine hydrochloride **10** and *N*-*tert*-butyl-*O*-pivaloyl hydroxylamine hydrochloride **12**. Reaction of these with isovaleraldehyde and cyclohexane carboxaldehyde, respectively, gave the expected products **11** (72%) and **13** (64%) (Fig. 1), suggesting this should be an effective method for the introduction of a variety of acyl systems.

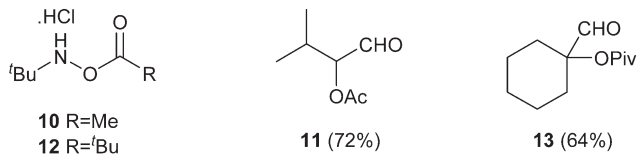


Fig. 1

In summary, we have developed an operationally simple and effective method for the α-functionalisation of aldehydes that can be carried out in the presence of both moisture and air, without the need for purification of solvents or any specialist reaction techniques. The *N*-*tert*-butyl-*O*-benzoyl hydroxylamine hydrochloride can be prepared in one step, is air stable and can be stored at room temperature for prolonged periods of time without loss of reactivity. The rearrangement is also effective for the introduction of both aliphatic and aromatic acyl groups, greatly adding to the utility of this procedure. We are currently investigating whether this transformation is also applicable to the formation of C–N and C–S bonds and will report on our findings in due course.

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Notes and references

† Typical experimental procedure: to a solution of *N*-*tert*-butyl-*O*-benzoyl hydroxylamine hydrochloride **7**·HCl (0.25 g, 1.09 mmol) in a mixture of THF and water (9:1 v/v, 2.2 mL) was added isovaleraldehyde **8** (92 mg, 1.09 mmol) and the resulting mixture was warmed to 50 °C for 14 h. The reaction mixture was diluted with brine (15 mL) and extracted with ethyl

acetate (4 × 15 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to give the crude product which was purified on silica eluting with diethyl ether–light petroleum (15:85) to give 1-formyl-2-methylpropyl benzoate **9** as a colourless oil (174 mg, 79%); IR (thin film) 2968, 1720, 1602, 1452, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, 1H, *J* 0.7 Hz, C*H*O), 8.03 (d, 2H, *J* 8.2 Hz, Ar*H*), 7.53 (dd, 1H, *J* 8.2 & 8.2 Hz, Ar*H*), 7.4 (dd, 2H, *J* 8.2 & 8.2 Hz, Ar*H*), 5.0 (dd, 1H, *J* 4.5 & 0.7 Hz, C*H*OBz), 2.30–2.45 (m, 1H, C*H*$(CH_3)_2$), 1.06 (d, 3H, *J* 6.9 Hz, CH_3), 1.03 (d, 3H, *J* 6.9, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 199.2, 133.5, 129.8, 129.2, 128.4, 82.7, 29.3, 18.9, 17.3; *m*/*z* (APCI) 207 (M + H); HRMS (found 207.1016; $C_{12}H_{14}O_3$ requires 207.1016).

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9 Heating the reaction mixture above this temperature for extended periods of time resulted in decomposition of the reagent.