The Direct Formation of α-Carbamates from Carbonyl Compounds

Adrian Hall,[b] Edouard P. Huguet,[a] Kerri L. Jones,[a] Teyrnon C. Jones,[a] Niall M. Killeen,[a] Sze Chak Yau,[a] Nicholas C. O. Tomkinson*[a]

[a] School of Chemistry, Main Building, Cardiff University, Park Place, Cardiff, CF10 3AT, UK
Fax +44(29)20874030; E-mail: tomkinsonnc@cardiff.ac.uk

[b] Neurology & GI Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, UK

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Abstract: A simple one-pot method for the direct introduction of carbamates α to carbonyl groups that proceeds at room temperature in the presence of both moisture and air has been developed. Treatment of aldehydes and both cyclic and acyclic ketones with *N*-methyl-*O*-carbamoyl hydroxylamine hydrochlorides provides the α-functionalised products in 50–88% isolated yield. The transformation is tolerant of a range of functional groups within the substrate and is also effective for the introduction of a variety of oxycarbamoyl groups.

Key words: metal-free synthesis, hydroxylamine, carbamate, array methods

The rapid introduction of molecular diversity during the preparation of molecules of pharmaceutical interest is pivotal to lead optimisation in drug discovery.[1] In conjunction with combinatorial methods this allows for the synthesis of molecular arrays for biological testing.[2] Therefore, novel, simple methods for the introduction of scaffolds present in molecules of biological interest that can be applied in a combinatorial manner are much sought after. Within this letter we present a series of reagents that provide the first method for the direct introduction of the carbamate function α to carbonyl groups, providing a new chemical tool for diversity-oriented synthesis.

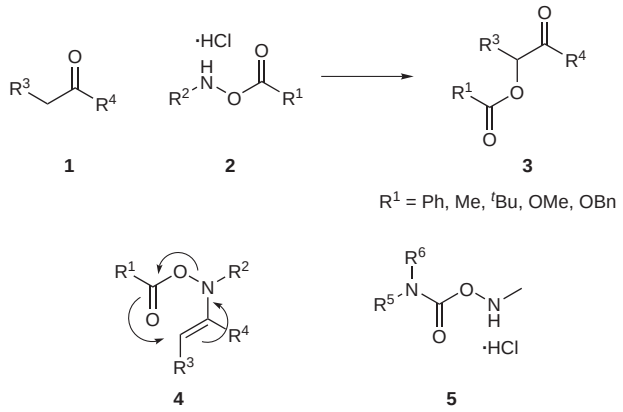
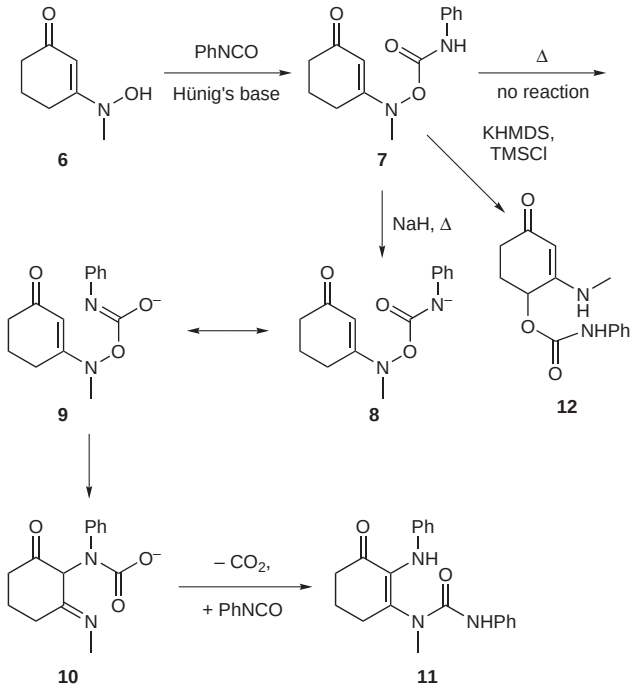


Figure 1 α-Functionalisation of carbonyl compounds

We have recently reported a series of novel reagents for the α-oxybenzoylation of both aldehydes[3] and ketones.[4] Within these processes the hydroxylamine-based reagents **2** were reacted, generally at room temperature in the presence of both moisture and air, with a variety of carbonyl compounds **1**, providing the α-functionalised products **3** in good to excellent yield (Figure 1). We believe these processes proceed via the enamine intermediate **4**, which undergo a concerted [3,3]-sigmatropic rearrangement, followed by hydrolysis of the resulting imine to give the product. We were interested to discover whether an analogous process could also be developed for the preparation of carbamates, and reasoned that functionalised hydroxylamines **5** might react in a direct fashion with carbonyl compounds.



Scheme 1 Rearrangement of functionalised ene-hydroxylamines

It was not apparent from literature precedent that the desired rearrangement would be observed with **5**. Lobo has shown that the ene-hydroxylamine **6**, prepared in one step from cyclohexanedione, can be reacted with phenylisocyanate to give the adduct **7** (Scheme 1).[5] Surprisingly, in contrast to findings with alternative substrates, this

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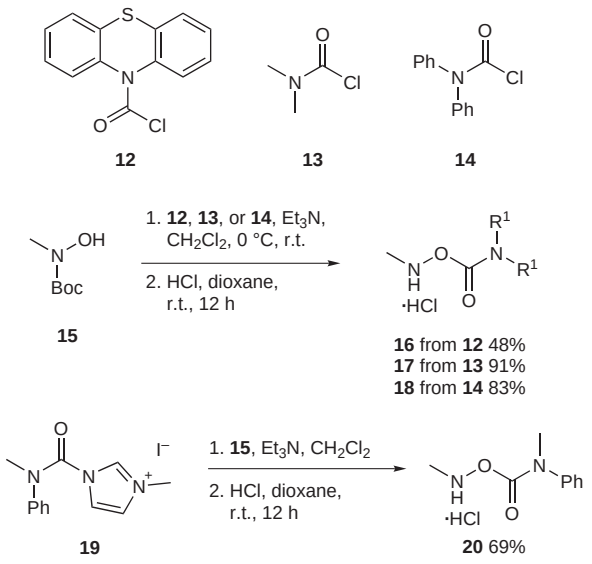
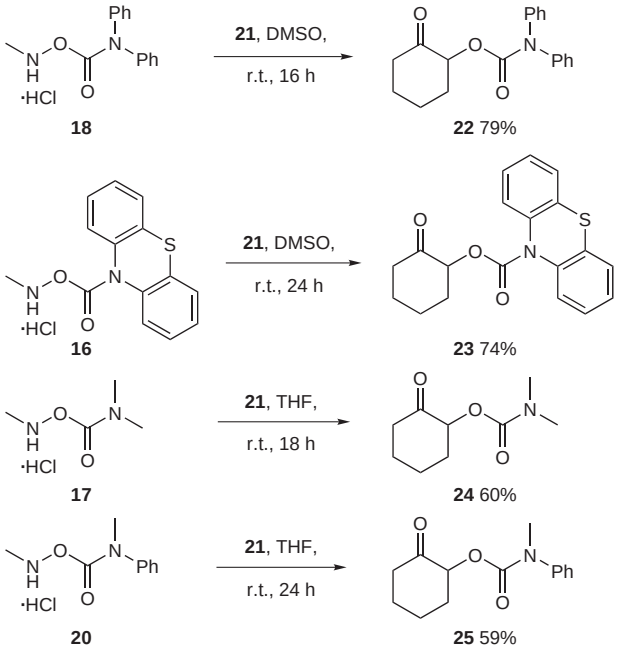
hydroxylamine derivative was thermally stable and did not rearrange to give an α-functionalised carbamate. Instead, treatment of **7** with sodium hydride followed by thermolysis in refluxing THF gave the amine **11** in 49% isolated yield. Compound **11** was believed to have arisen by a concerted [3,3]-sigmatropic rearrangement of the derived anion **9**, addition of a second equivalent of phenylisocyanate and loss of a molecule of CO_2. It was also reported that a C–O bond forming process could be brought about by treatment of the adduct **7** with an excess of KHMDS and TMSCl followed by thermolysis and acidic aqueous work-up to give the carbamate **12** in 54% isolated yield. Although these examples suggested that we may not be able to introduce the expected carbamate functionality through the regents **5** we sought to develop methods for their preparation and to determine their associated reactivity.

The investigation began with the preparation of the carbamoylation reagents, which were made by one of two methods, both of which were amenable to scale-up and allowed access to good quantities of material. Commercial availability of a range of carbamoyl chlorides allowed for carbamoylation of the *tert*-butoxycarbonyl-protected *N*-methyl hydroxylamine **15**[6] under basic conditions. Removal of the protecting group with freshly prepared HCl in dioxane led to the desired reagents **16**–**18** in good yield, which crystallised directly from the reaction mixture (Scheme 2). An equally effective route started from the appropriate amine and treatment with carbonyldiimidazole followed by N-methylation to give the activated imidazolium salt **19** as reported by Batey.[7] Treatment of the salt **19** with *N*-Boc-*N*-methyl hydroxylamine (**15**) under basic reaction conditions, followed by deprotection in an analogous manner to that described above led to the alternative carbamoylation reagent **20**. These two complimentary routes provided rapid access to oxycarbamoylation reagents with varying amine functionality.



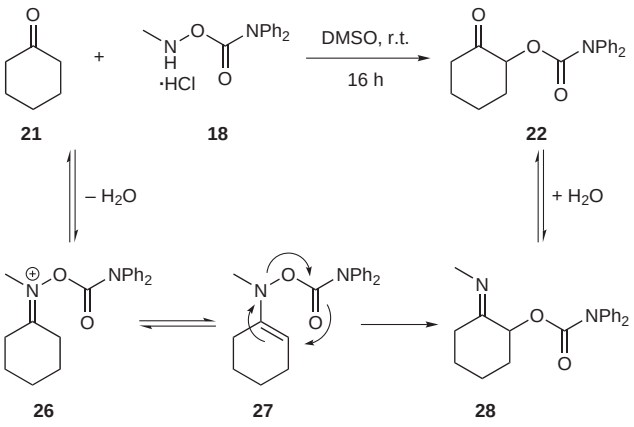
Scheme 2 Preparation of reagents

Having prepared the desired hydroxylamines, we then went on to investigate their reactivity with carbonyl compounds. Each reagent was treated with cyclohexanone (**21**) as a test substrate and we were delighted to discover in each case that the reaction proceeded to give the expected α-oxycarbamoylation products **22**–**25** in good to excellent yield (Scheme 3).[8] With aromatic substituted reagents **18** and **16** we found DMSO to be the most effective solvent, whereas when the reagents contained aliphatic substituents on the carbamoyl nitrogen, higher conversions and better product recovery was observed using THF as the reaction medium.



Scheme 3 Reaction with cyclohexanone

In line with previous observations[3,4] we believe these reactions proceed via condensation of reagent **18** with cyclohexanone (**21**), to give iminium ion **26** followed by conversion to enamine **27**. Concerted [3,3]-sigmatropic rearrangement then provides imine **28** which is hydrolysed under the aqueous acidic reaction conditions to give the observed α-functionalised product **22** (Scheme 4).



Scheme 4 Proposed mechanism of α-oxycarbamoylation

Table 1 Scope of Transformation

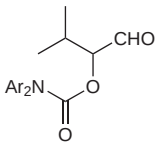
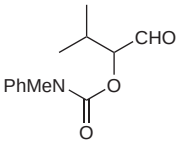
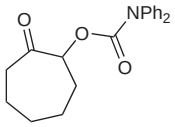
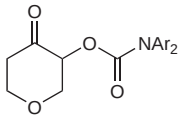
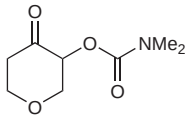
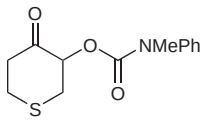
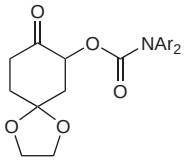
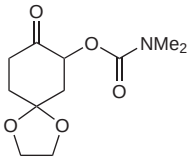
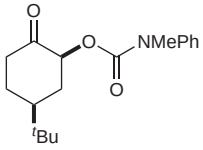
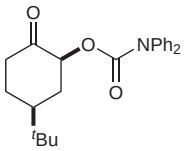
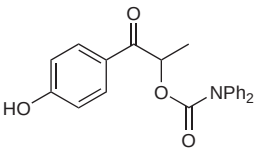
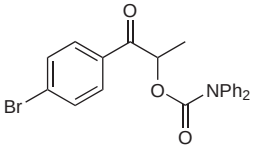
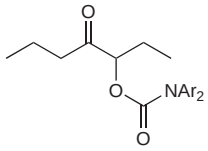
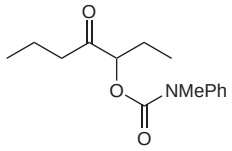
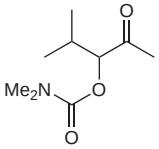
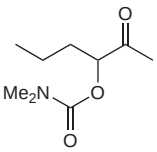
Entry	Reaction	Product	Yield (%)
1[a]	**16** + **29**	 **40**	88
2[b]	**20** + **29**	 **41**	59
3[a]	**18** + **30**	 **42**	72
4[a]	**16** + **31**	 **43**	80
5[b]	**17** + **31**	 **44**	55
6[b]	**20** + **32**	 **45**	82
7[a]	**16** + **33**	 **45**	57
8[b]	**17** + **33**	 **47**	59
9[b]	**20** + **34**	 **48**	76

Table 1 Scope of Transformation (continued)

Entry	Reaction	Product	Yield (%)
10[a]	**18** + **34**	 **49**	84
11[a]	**18** + **35**	 **50**	79
12[a]	**18** + **36**	 **51**	78
13[a]	**16** + **37**	 **52**	73
14[b]	**20** + **37**	 **53**	60
15[b]	**17** + **38**	 **54**	64
16[b]	**17** + **39**	 **55**	50

[a] Reactions performed in DMSO as solvent.
[b] Reactions performed in THF as solvent

After completing these preliminary experiments we went on to investigate the generality of the procedure for a series of carbonyl compounds (Table 1). Pleasingly, the reaction worked well for a wide variety of substrates providing direct access to the α-carbamoyl products of aldehydes (entries 1 and 2), cyclic ketones (entries 3–10) and acyclic ketones (entries 11–16) in 50–88% isolated yield.

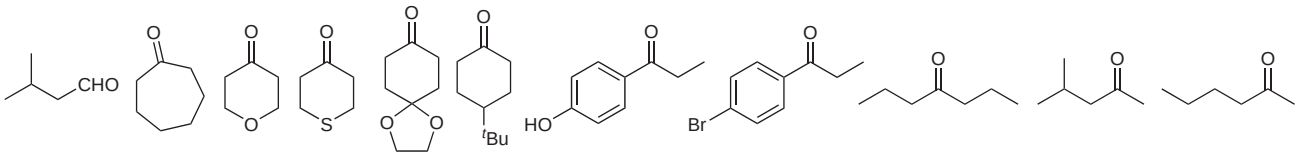


Figure 2 Carbonyl substrates used in this study

The reaction with aldehyde substrates was complete in less than four hours at room temperature providing the products **40** and **41** (entry 1: 88%; entry 2: 59%). The reaction also proceeded at room temperature for both 6- (entries 4–10) and 7-membered (entry 3) rings and was tolerant of a variety of functional groups including ethers, sulfides and ketals. With the substituted cyclohexanone **34** the thermodynamic *cis*-isomers **49** and **50** were prepared in an excellent 76% and 84% yield, respectively (entries 9 and 10). With acyclic substrates it was necessary to warm the reaction mixture up to 50 °C in order to achieve reasonable reaction times of less than 24 hours (entries 11–16). For example, 4-hydroxypropiophenone (**35**) underwent reaction with the carbamoylation reagent **18** in 79%. This highlights that the reactions proceed not only in the presence of moisture and air, but also in the presence of unprotected phenol groups, thereby adding to the applicability of this process. The reagents were ineffective in the α-functionalisation of primary centres under a variety of reaction conditions which allowed for the regiospecific functionalisation of the non-symmetrical substrates **38** and **39** (Figure 2). 4-Methylpentan-2-one (entry 15) and hexan-2-one (entry 16) gave the products **54** (64%) and **55** (50%) with the dimethyl reagent **17**, where reaction had taken place exclusively at the secondary centre.

In summary, we have developed the first method for the direct α-oxycarbamoylation of carbonyl compounds. The reagents are easily prepared in three high-yielding steps from *N*-methyl hydroxylamine hydrochloride and are bench-stable solids that can be stored for prolonged periods. The reaction proceeds readily at either room temperature for aldehydes and cyclic ketones or at 50 °C in the case of acyclic ketones. The transformations are operationally simple, without any specialised reaction techniques, proceed in the presence of both moisture and air and are tolerant of a variety of functional groups. We are currently investigating alternative reagents for the formation of C–N and C–S bonds to add to this structural class and will report on our findings shortly.

Typical Experimental Procedure for the Preparation of Reagent

N-Boc-*N*-methyl-hydroxylamine (**15**, 500 mg, 3.7 mmol), Et_3N (512 μL, 3.7 mmol) and a catalytic amount of dimethylaminopyridine (45 mg, 10 mol%) were dissolved in CH_2Cl_2 (8 mL) and cooled to 0 °C in an ice-water bath. A solution of diphenylcarbamoyl chloride (860 mg, 3.7 mmol) in CH_2Cl_2 (2 mL) was then added dropwise to the reaction over a period of 5 min. After warming to r.t. and stirring for 16 h, the reaction was concentrated to dryness and triturated with PE to precipitate triethylamine hydrochloride, which was subsequently removed by filtration. After concentration in vacuo the resultant crude reaction mixture was purified by flash chromatography (20% Et_2O–PE) to furnish *N*-Boc-*N*-methyl-*O*-diphenylcarbamoyl hydroxylamine as white needles (1.12g, 92%); mp (Et_2O–PE) 112–114 °C. IR (CH_2Cl_2): 2976, 1754, 1721, 1592, 1492, 1339, 1149 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.09 (m, 10 H), 3.19 (s, 3 H), 1.43 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2 (s), 153.3 (s), 141.8 (s), 129.2 (d, 2 C), 126.8 (d), 82.2 (s), 37.9 (q), 28.3 (q). MS (APCI): *m/z* = 343 $[M + H]^+$. HRMS: *m/z* calcd for $C_{19}H_{23}N_2O_4$ $[M + H]^+$: 343.1652; found: 343.1655.

N-Boc-*N*-methyl-*O*-diphenylcarbamoyl hydroxylamine (500 mg, 1.46 mmol) was dissolved in 4 M HCl–dioxane solution (1.83 mL, 7.3 mmol) and stirred at r.t. for 6 h. The resultant precipitate was collected by filtration, and washed with 25 mL ice-cold Et_2O before drying in vacuo to yield *N*-methyl-*O*-diphenylcarbamoyl hydroxylamine hydrochloride (**18**) as green microcrystals (402 mg, 99%); mp (Et_2O–PE) 124–126 °C. IR (nujol): 2974, 1760, 1545, 1152 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.8 (br s, 2 H), 7.34–7.28 (m, 4 H), 7.23–7.18 (m, 6 H), 2.75 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.8 (s), 141.7 (s), 129.8 (d), 127.7 (d), 127.5 (d), 37.5 (q). MS (APCI): *m/z* = 243 $[M + H]^+$. HRMS: *m/z* calcd for $C_{14}H_{16}N_2O_2Cl$ $[M + H – HCl]^+$: 243.1128; found: 243.1126.

Typical Experimental Procedure for the Direct α-Carbamoylation of Carbonyl Compounds

Cyclohexanone (56 μL, 0.54 mmol) and *N*-methyl-*O*-diphenylcarbamoyl hydroxylamine hydrochloride (**18**, 150 mg, 0.54 mmol) were dissolved together in DMSO (1 mL) and stirred at r.t. for 16 h. After this period, the reaction broth was diluted with EtOAc (50 mL) and washed sequentially with brine (50 mL) and H_2O (2 × 50 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo to yield the crude product as a yellow oil. This residue was subjected to flash chromatography (5% Et_2O–CH_2Cl_2) to furnish 2-oxocyclohexyl diphenylcarbamate (**22**) as salmon-pink microcrystals (121 mg, 79%); mp (Et_2O–PE) 146–148 °C. IR (CH_2Cl_2): 2084, 1750, 1718, 1570, 1093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.05 (m, 10 H), 5.15–5.06 (m, 1 H), 2.43–2.27 (m, 2 H), 2.21–2.11 (m, 1 H), 2.01–1.89 (m, 1 H), 1.84–1.76 (m, 1 H), 1.70–1.41 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.1 (s), 153.9 (s), 142.6 (s), 128.8 (d), 127.1 (d), 126.1 (d), 78.0 (d), 40.6 (t), 32.9 (t), 27.0 (t), 23.7 (t). MS (APCI): *m/z* = 310 $[M + H]^+$. HRMS: *m/z* calcd for $C_{19}H_{20}NO_3$ $[M + H]^+$: 310.1438; found: 310.1439.

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(8) All compounds prepared were characterised by mp, IR, ^{1}H NMR, ^{13}C NMR, MS and HRMS.