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Base-mediated reactions of *N*-alkyl-*O*-acyl hydroxamic acids: synthesis of 3-oxo-2,3-dihydro-4-isoxazole carboxylic ester derivatives

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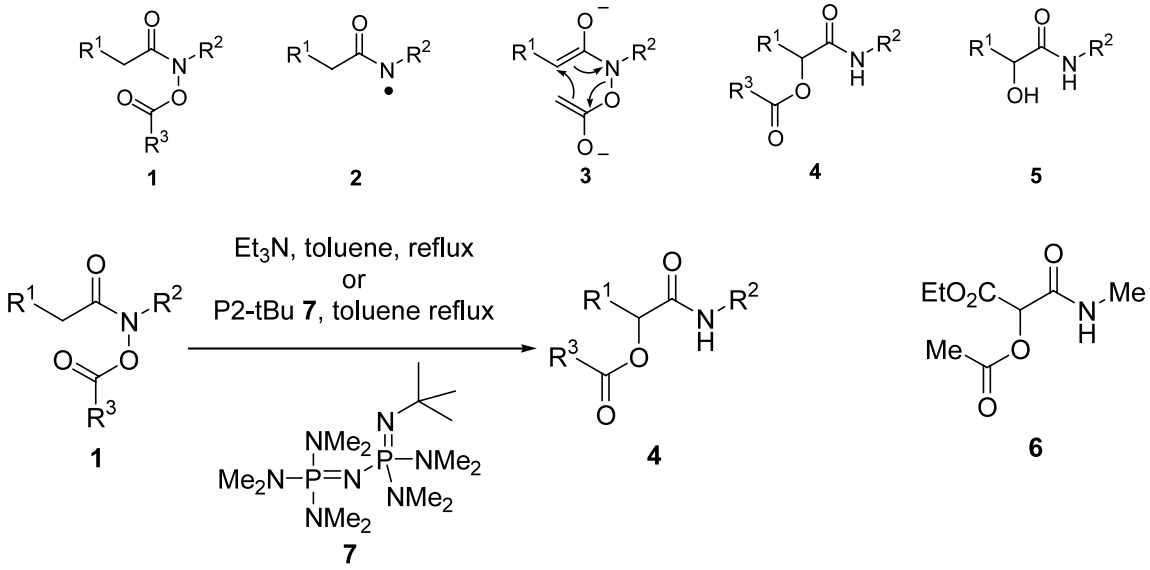
Abstract—Treatment of malonyl derived *O*-acyl hydroxamic acid derivatives **10a**–**h** with the phosphazene super base P-2-*t*-Bu **7** gives 2,3-dihydro-4-isoxazole carboxylic ester derivatives **11a**–**h**. The rate and yield of the reaction is dependent upon the *O*-acyl substituent.

Hydroxamic acids have been studied for over 100 years.[1] However, the reactivity and chemistry of *O*-acylated hydroxamic acids **1** have been little explored.[2–4]

Recent studies have included the cleavage of the weak N–O bond to generate amidyl radicals **2**,[2] the base-mediated [3,3]-sigmatropic reactions of their corresponding bis-enolates **3**,[3] and their base-catalysed rearrangement to give 2-acyloxyamides **4**.[4] Deprotection of the *O*-acyl group in **4** gives rise to 2-hydroxyamides **5** which are versatile synthetic intermediates.[4b] The rearrangement (**1** to **4**, Scheme 1) was found to be heavily dependent upon the nature of the group R^1. Thus, when R^1 was an aryl or alkenyl group the reactions were easy occurring with Et_3N at room temperature, but when R^1 was an alkyl group, harsher conditions using strong phosphazene bases[5] were required (Scheme 1). Thus, the ease of the reactions was linked to the acidity of the protons adjacent to the



Scheme 1.

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amide carbonyl group. As part of a programme towards the synthesis of 2-acyloxy malonamide derivatives (e.g. **6**) we decided to investigate the base-mediated rearrangement of the malonate derived hydroxamic acid derivatives **1**, $R^1 = CO_2Et$. We anticipated that rearrangement would be easy due to the activating effect of the ester group.

Initial work focussed upon the preparation and rearrangement of four *N*-alkyl-*O*-acyl hydroxamate derivatives **10a–d** (Table 1). Thus, to a solution of *N*-methylhydroxylamine hydrochloride in MeOH at 0°C was added potassium hydroxide and a THF solution of the corresponding acid chloride **8a–d** (prepared by treatment of the corresponding acid with oxalyl chloride). Reaction of the intermediate hydroxamic acids **9a–d** with acetyl chloride and Et_3N in CH_2Cl_2 at 0°C produced the desired precursors **10a–d** (Table 1, Scheme 2).[6]

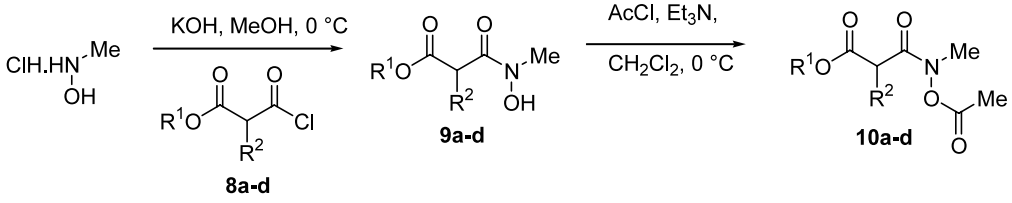
With the precursors **10a–d** in hand, attention now turned to investigating their rearrangement reactions. However, treating **10a–d** with either a catalytic (10 mol%) or stoichiometric amount of Et_3N in CH_2Cl_2 at room temperature or at reflux led only to recovered starting materials (as did heating in toluene with Et_3N at reflux for 2 days). This was surprising as previous work suggested that the presence of any activating group (e.g. **1**, $R^1 = CO_2R$) would facilitate the rearrangement reaction.[4a,b] Thus, we next tried the harsher conditions reported for deactivated substrates[4c] and heated **10a–d** with one equivalent of the phosphazene base **7** in toluene at reflux for 3 h. However, under these conditions, instead of the desired rearranged compounds **4** we isolated the 2,3-dihydro-2,5-dimethyl-3-oxo-4-isoxazole carboxylic ester derivatives **11a–c** (note: reaction of **10d** only gave recovered starting material even after 2 days). The structures of these heterocycles[7] are interesting as they are tautomeric to isoxazol-3-ols **12** which have been studied in detail as conformationally restricted analogues of GABA and glutamic acid (Scheme 3).[8]

Presumably our isoxazole derivatives **11a–c** are obtained by direct attack of the malonate derived anion onto the ester group of the *O*-acyl substituent followed by elimination of water. Having observed that this reaction did not occur for the phenyl substituted malonate derivative **10d** we briefly investigated the chemistry of a range of other derivatives where we varied the nature of the *O*-acyl substituent **10e–h** to determine the scope and limitation of the reaction (Scheme 4).

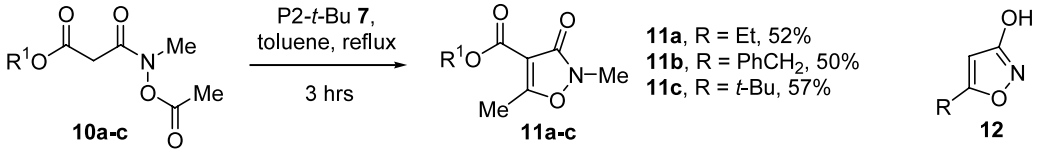
Changing the nature of the *O*-acyl substituent from an alkyl group (**10a–c,e**) to an aryl group (**10f**, **10h**) severely retarded the rate and yield of the cyclisation. Thus, while **10e** underwent cyclisation in 68% yield in only 3 h, the phenyl substituted precursor **10f** only gave **11f** in 47% yield after 27 h. The presence of the strongly electron-withdrawing *p*-nitrophenyl group **10h** also lowered the yield substantially (13%). The rest of the mass

Table 1.

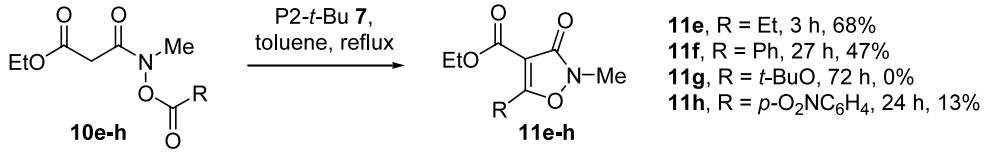
Substrate	R^1	R^2	Yield **9** (%)	Yield **10** (%)
a	Et	H	52	82
b	$PhCH_2$	H	52	97
c	*t*-Bu	H	51	95
d	$PhCH_2$	Ph	53	71



Scheme 2.



Scheme 3.



Scheme 4.

balance in both these reactions was unreacted starting material. No reaction occurred when a bulky *t*-butoxy group was present with starting material **10g** being recovered, even after 72 h.

In conclusion we have reported an easy synthesis of 2,3-dihydro-2,5-dialkyl-4-isoxazole carboxylic ester derivatives by reaction of *O*-acylated malonate derived hydroxamic acid derivatives with the strong phosphazene base **7**. The nature of the *O*-acyl substituent affected the reactions, with aromatic or bulky groups retarding the rate of cyclisation.

Acknowledgements

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6. All new compounds exhibited satisfactory spectroscopic and analytical data. Typical data ***N*-acetoxy-*N*-methyl malonamic acid *tert*-butyl ester 10c**: Yield 95%; yellow oil; R_f (hexane (60–80°C)–ethyl acetate: 1:2): 0.50; (found: C, 51.7; H, 7.4; N, 6.0%; MH^+(CI), 232.1188. $C_{10}H_{17}NO_5$ requires C, 51.9; H, 7.4; N, 6.0%; M^+H, 232.1107); ν_{max} (neat)/cm^{-1} 2938, 1802, 1745, 1694; δ_H (300 MHz; $CDCl_3$) 1.44 (9H, s), 2.17 (3H, s), 3.24 (2H, s), 3.29 (3H, s); δ_C (100.6 MHz; $CDCl_3$) 18.8 (q), 28.3 (3×q), 35.9 (q), 42.8 (t), 82.6 (s), 165.9 (2×s), 168.3 (s); *m*/*z* (CI) 232 (MH^+, 24%), 193 (100), 176 (94), 135 (72), 118 (67), 91 (17), 74 (51).
7. Compound **11a** has been previously reported: Schlewer, G.; Krogsgaard-Larsen, P. *Acta. Chem. Scand. Ser. B.* **1984**, *38*, 815. **General procedure for cyclisation**: To a solution of the substrate hydroxamic acid derivatives **10a–c** (0.50 mmol) in toluene (5 mL) was added the phosphazene base-P_2-*t*-Bu (184 μL, 0.50 mmol). The mixture was heated for 3 h at 110°C. The mixture was then washed with dilute HCl (15 mL) and dried over $MgSO_4$. Evaporation of the solvent gave the crude product, which was purified by chromatography (hexane (60–80°C)-ethyl acetate 1:2). **2,5-Dimethyl-3-oxo-2,3-dihydro-isoxazole-4-carboxylic acid *tert*-butyl ester 11c**: Yield 57%; yellow oil; R_f (hexane (60–80°C)–ethyl acetate 1:2): 0.18; (found: M^+ (EI), 213.0996. $C_{10}H_{15}NO_4$ requires M, 213.1001); ν_{max} (neat)/cm^{-1} 2987, 2926, 1739, 1703, 1617; δ_H (300 MHz; $CDCl_3$) 1.59 (9H, s), 2.54 (3H, s), 3.51 (3H, s); δ_C (75.5 MHz; $CDCl_3$) 14.6 (q), 28.6 (3×q), 33.3 (q), 82.2 (s), 104.9 (s), 161.1 (s), 165.0 (s), 175.4 (s); *m*/*z* (EI) 213 (M^+, 18%), 158 (63), 140 (100), 113 (47), 57 (34), and 43 (29).
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