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Rearrangement of unactivated *N*-alkyl-*O*-benzoyl hydroxamic acid derivatives with phosphazene bases

Andrew J. Clark,[a,*] Yassair S. S. Al-Faiyz,[a] Divya Patel[a] and Michael J. Broadhurst[b]

[a]*Chemistry Department, University of Warwick, Coventry CV4 7AL, UK*
[b]*Roche Discovery Welwyn, Welwyn Garden City, Hertfordshire AL7 3AY, UK*

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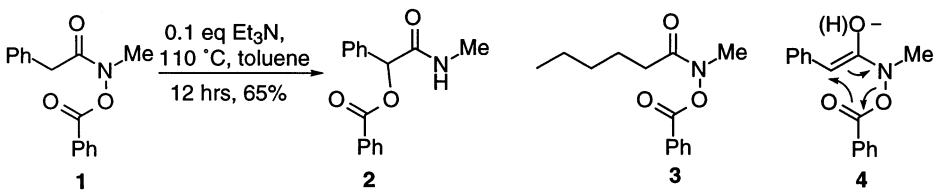
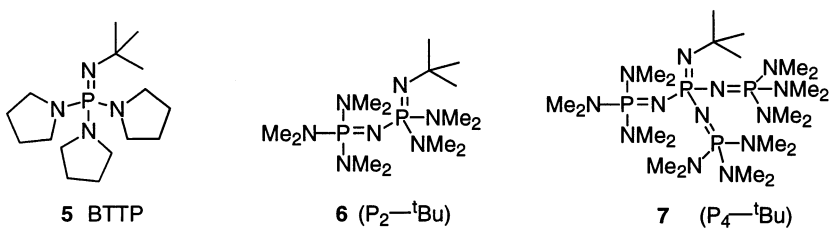
Abstract—The phosphazene super bases BTPP **5**, P-2-^{t}Bu **6**, and P-4-^{t}Bu **7** mediate the rearrangement of unactivated *N*-alkyl-*O*-benzoyl hydroxamic acid derivatives **8**, **11a–f**, **13** and **16** to give 2-benzoyloxy amides **9**, **12a–f**, **14** and **17**. The rate of reaction was found to be dependant upon the steric nature of the *N*-alkyl substituent.

We recently reported that *N*-alkyl-*O*-acyl hydroxamic acid derivatives **1** containing suitably acidic α-protons undergo smooth rearrangement to give 2-acyloxyamides **2** upon heating with catalytic organic bases such as Et_3N (Scheme 1).[1–3] After deprotection of the acyl protecting group the reaction furnishes secondary 2-hydroxyamides which are versatile synthetic intermediates.[3,4] The reaction failed however when no activating group (e.g. Ph) able to stabilise a negative charge or enol form was present in the substrate. Thus, it was not possible to rearrange the substrate **3** even when strong inorganic bases such as KHMDS or LDA were utilised.[3,5] In fact even the activated systems (e.g. **1**) failed to react when these inorganic bases were used suggesting that the presence of a coordinating metal may switch the conformation of the hydroxamic acid to an unreactive one. We initially postulated that the rearrangement took place via a [3,3]-sigmatropic rearrangement of the enolate or enol form **4** and were interested to read the report of Hartley et al.[6] that indicated that organic phosphazene super bases **5**–**7**[7] were useful alternatives to conventional inorganic bases in [3,3]-sigmatropic Cope rearrangements.



Scheme 1.



* Corresponding author.

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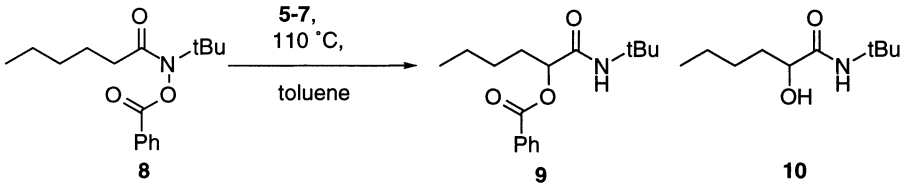


Scheme 2.

Initial studies concentrated on the effect of the various bases **5**–**7** upon the reaction of the unactivated substrate **8**.[8] Hence, heating **8** at 110°C in refluxing toluene with 0.2 equivalents of phosphazene base **6** for 18 h furnished the desired rearrangement compound **9** in 75% yield (Scheme 2). No reaction occurred under the same conditions when Et_3N was used as base. Table 1 clearly indicates that the nature of the base is crucial for successful rearrangement. Interestingly the most basic phophazene compound **7** did not lead to any reaction and only starting material was recovered. In some reactions deprotection of the secondary hydroxyl was observed, presumably due to hydrolysis in the work-up stage.

Effect of the *N*-alkyl substituent

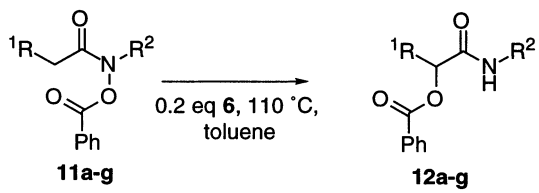
Having established that it was possible to mediate the rearrangement of an unactivated precursor next we briefly examined the scope of the reaction utilising the most successful base, that being the P2-*t*Bu base **6**. It became rapidly apparent that the efficiency of the rearrangement was heavily dependent upon the steric hindrance at the nitrogen substituent. The reaction of the *t*-Bu derived precursor **8** was facile giving **9** in 75% yield in only 18 h. The rates of reaction with the less sterically hindered *s*-Bu and *i*-Pr derivatives **11a**–**b** were much slower leading to lower 30% yields of **12a**–**b** (the rest of the mass balance being unreacted starting material) after extended reaction times. Interestingly, it was not possible to rearrange the primary substituted precursor **11c** with starting material being recovered even after 3 days at 110°C (Table 2). The same trend was found for the related series of precursors **11d**–**f** with the most efficient rearrangement being that of **11d** (Scheme 3).

The nature of the *N*-acyl substituent was briefly investigated. Branching in the side chain **13** was tolerated although the reaction was less efficient and significant amounts of the deprotected 2-hydroxyamide **15** were isolated. The presence of other functional groups (such as an alkene **16**) was also tolerated although the yield of the reaction was low (30%).

In conclusion, we have shown that the use of strong phosphazene bases can mediate the rearrangement of *N*-alkyl-*O*-acyl hydroxamic acid derivatives to 2-acyloxy amides. The rate and yield of the reaction was heavily dependant upon the steric nature of the *N*-alkyl substituent.

Table 1. Rearrangement of **8** with bases **5**–**7**

Entry	Base	Equivalent	Yield **9** (%)	Yield **10** (%)
1	Et_3N	1	0	0
2	**5**	0.2	46	0
3	**6**	1	50	30
4	**6**	0.2	75	20
5	**7**	1	0	0



Scheme 3.

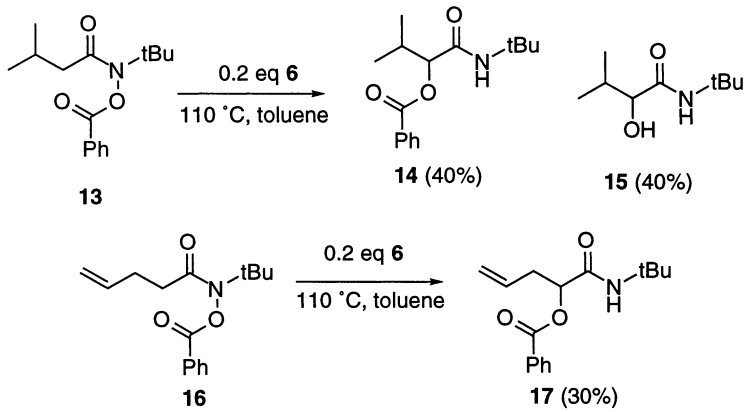


Table 2. Effect of *N*-substituent upon yield

Entry	Substrate	R^1	R^2	Time (h)	Yield **12** (%)
1	**8**	*n*-Bu	*t*-Bu	18	75
2	**11a**	*n*-Bu	*s*-Bu	72	30
3	**11b**	*n*-Bu	*i*-Pr	18	30
4	**11c**	*n*-Bu	Me	72	0
5	**11d**	Me	*t*-Bu	72	76
6	**11e**	Me	*s*-Bu	110	21
7	**11f**	Me	*i*-Pr	168	19
8	**3**	Me	Me	168	0

Acknowledgements

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8. All new compounds exhibited satisfactory spectroscopic and analytical details.