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Controlling stereochemistry during oxidative coupling. Preparation of *Rp* or *Sp* phosphoramidates from one P-chiral precursor†

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Stereochemical outcome of oxidative coupling of H-phosphonate diesters with amines, promoted by iodine, can be controlled to obtain the corresponding phosphoramidate diesters with inversion or with retention of configuration at the phosphorus centre.

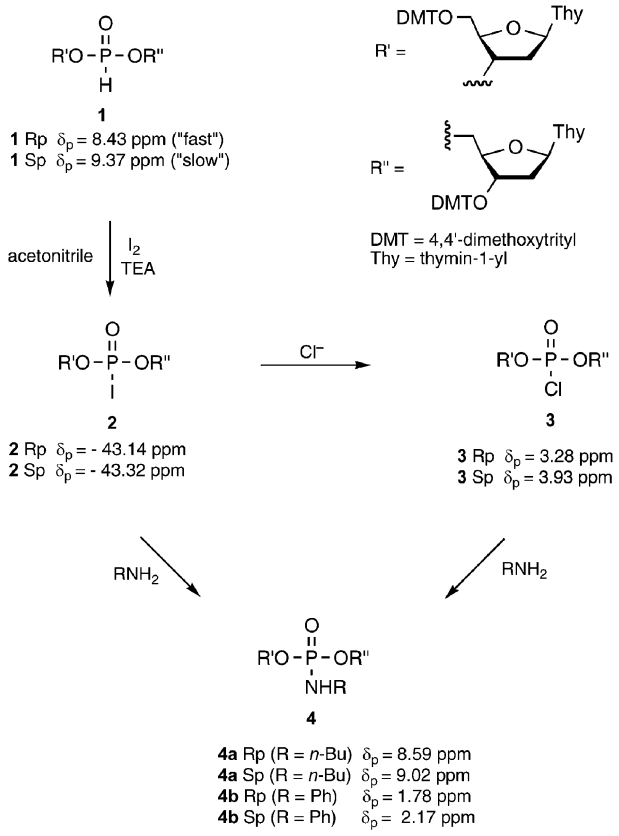
Oxidative coupling of tetracoordinate P(III) compounds consists of *in situ* generation of a reactive phosphorylating species, that upon addition of a nucleophile produces the corresponding P(V) derivatives. Since amines react efficiently with phosphorus electrophiles,[1] this procedure is most suited for the preparation of phosphoramidates.[2–4] Two protocols are usually used for the generation of reactive phosphorylating species: oxidation of H-phosphonate diesters under the Atherton–Todd conditions[3] (CCl_4 in the presence of triethylamine) to produce the corresponding phosphorochloridates, or oxidation with iodine,[5] to generate more reactive phosphoroiodidate diesters. Due to the mildness of the reaction conditions, the oxidative coupling of H-phosphonate diesters with amines is often the method of choice for the preparation of biologically important compounds bearing the P–N bond, *e.g.* nucleotide analogues,[6] phosphorylated amino acids and peptides,[4,7] phospholipid analogues.[8]

Stereochemistry of oxidation of H-phosphonate diesters with halogens or tetrahalomethanes has been thoroughly investigated[9–11] and it was shown that these transformations occur with retention of configuration at the phosphorus centre. Since the replacement of halogens in acyclic phosphorus compounds occurs stereospecifically with inversion of configuration,[11,12] the net outcome of an oxidative coupling transformation is inversion of configuration.[9,11]

In spite of its attractiveness, an inherent disadvantage of synthetic methods based on stereospecific transformations is that only one diastereomer of the substrate can be used to obtain the product with the desired (from a biological or chemical point of view) stereochemistry. Since that diastereomer is not necessarily the major one, this may severely limit the generality and efficiency of synthetic approaches based on stereospecific transformations.

Our goal was thus to develop a synthetic protocol that would overcome this problem and enable conversion of both P-diastereomers of a substrate into a product with either *Rp* or *Sp* stereochemistry. For this purpose we designed a synthetic scheme which featured phosphoroiodidate **2** as a key, bifurcated intermediate (Scheme 1). In acetonitrile, the reaction step leading to phosphoroiodidate **2** (Scheme 1) should occur with retention of configuration and thus a direct reaction of amines with this intermediate would produce phosphoramidates **4** with inverted configuration at the phosphorus centre. However, if the generated phosphoroiodidate **2** were to be subjected to an additional $S_N2(P)$ reaction before treatment with an amine, then phosphoramidate **4** would be formed with net retention of configuration. As a viable $S_N2(P)$ step for this purpose we considered a reaction of phosphoroiodidate **2** with a chloride anion, which should produce the corresponding phosphorochloridate **3** with inversion of configuration. Thus, if one diastereomer of **1** were subjected to a direct oxidative coupling with amine, and the other diastereomer of **1**, *via* a pathway involving the intermediacy of phosphorochloridate **3**, one should obtain the same diastereomeric product **4**. Alternatively, if the reaction pathways for the diastereomers of **1** were to be changed (*i.e.* the diastereomers that reacted directly with **2**, now will react *via* a pathway involving phosphorochloridate **3**, and *vice versa*), then the other diastereomer of phosphoramidate **4** could be produced. Critical to a successful execution of the above reaction scheme seemed to be the transformation of phosphoroiodidate **2** into phosphorochloridate **3**, that supposed to be quantitative in order to provide stereochemically pure products.

We chose for these studies an iodine promoted oxidative coupling of separate diastereomers of dinucleoside H-phosphonate **1**[11,13] with two kinds of amines, *n*-butylamine and aniline. First, stereochemistry of a direct oxidative coupling of H-phosphonate diesters **1** was investigated (Scheme 1). To this end, separate diastereomers of **1** in acetonitrile were subjected to reaction with *n*-butylamine (3 equiv.) or aniline (3 equiv.), in the presence of iodine (1.5 equiv.). All the reactions were clean, rapid (< 5 min), and completely stereospecific as revealed by ^{31}P NMR spectroscopy. Thus, *R*p diastereomer of **1** (δ_P = 8.43 ppm) afforded



Scheme 1

† Electronic supplementary information (ESI) available: synthesis and characterisation of phosphoramidates **4**. See http://www.rsc.org/suppdata/cc/b4/b411451e/

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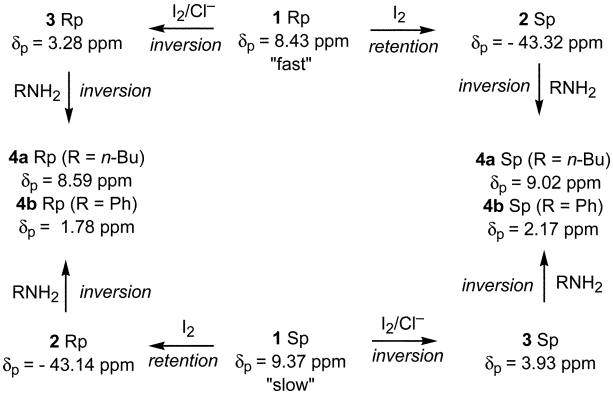

Scheme 2

phosphoramidate **4a** *Sp* (δ_P = 9.02 ppm) or **4b** *Sp* (δ_P = 2.17 ppm), while **1** *Sp* (δ_P = 9.37 ppm), gave phosphoramidate **4a** *Rp* (δ_P = 8.59 ppm) or **4b** *Rp* (δ_P = 1.78 ppm), exclusively. Since under the reaction conditions the rate limiting step is apparently the formation of phosphoroiodidate **2**, this intermediate could not be observed by ^{31}P NMR spectroscopy.[14]

To check chemical and stereochemical aspects of transformation of phosphoroiodidates **2** into phosphorochloridates **3**, separate diastereomers of dinucleoside H-phosphonate **1** were treated in acetonitrile with iodine (1.5 equiv.), in the presence of triethylamine (TEA, 6 equiv.) and triethylammonium hydrochloride ($TEAH^+Cl^-$, 3 equiv.). These produced rapidly (<1 min) phosphoroiodidates **2**,[15] that underwent stereospecific halogen exchange reaction to afford the corresponding phosphorochloridates **3** (completion within 5 min) without detectable epimerisation (^{31}P NMR). The reactions were monitored by ^{31}P NMR spectroscopy and a stereospecific conversion of H-phosphonate **1** *Rp* into phosphorochloridate **3** *Rp* (δ_P = 3.28 ppm) with intermediacy of phosphoroiodidate **2** *Sp* (δ_P = −43.32 ppm), and of H-phosphonate **1** *Sp* into phosphorochloridate **3** *Sp* (δ_P = 3.98 ppm) with intermediacy of phosphoroiodidate **2** *Rp* (δ_P = −43.14 ppm), was clearly established.[16] Addition of amines (*n*-butylamine or aniline, 3 equiv.) to these mixtures resulted in clean and stereospecific formation of the corresponding *Rp* and *Sp* diastereomers of phosphoramidates **4a** or **4b**, respectively (Scheme 1).

A stereochemical correlation diagram for the reactions investigated is depicted in Scheme 2. It shows, that both diastereomeric phosphoramidates **4** are accessible from any diastereomers of **1**. The efficacy of this approach to control stereochemistry during oxidative coupling was assessed by synthesising on a preparative scale phosphoramidates **4a** *Sp* and **4b** *Sp* on two pathways: one involving a direct oxidative coupling of H-phosphonate **1** *Rp* with the corresponding amine, and the other one, from **1** *Sp* diastereomers and using the pathway with intermediacy of phosphorochloridate **3** (Scheme 2, reaction pathways to the right). Analogously, phosphoramidates with opposite configurations, **4a** *Rp* and **4b** *Rp*, were synthesised from both diastereomers **1** (Scheme 2, reaction pathways to the left). In all the reactions investigated, the corresponding phosphoramidates **4** were obtained without detectable epimerisation and in comparable isolated yields (70–80%). These indicate that both reaction pathways, that of a direct oxidative coupling with intermediacy of phosphoroiodidate **2**, and that in which **2** is *in situ* converted into phosphorochloridate **3**, occur with a similar efficiency.

In conclusion, we designed a synthetic scheme for oxidative coupling of H-phosphonate diesters with phosphoroiodidate **2** as bifurcated intermediate (Scheme 1) that enables either synthesis of *Rp* or *Sp* phosphoramidates from one P-chiral precursor, or the conversion of both diastereomers of the starting H-phosphonate diester into one diastereomer (*Rp* or *Sp*) of the product.

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14 When oxidation of H-phosphonate **1** with iodine was carried out in the absence of amine, the formation of phosphoroiodidate **2** was observed by ^{31}P NMR spectroscopy. Thus, from **1** *Rp* diastereomer, phosphoroiodidate **2** *Sp* (δ_P = −43.32 ppm) was produced, and from **1** *Sp*, phosphoroiodidate **2** *Rp* (δ_P = −43.14 ppm). These, upon addition of *n*-butylamine or aniline afforded the same diastereomers of **4a** and **4b** as those observed when the oxidative couplings were carried out in the presence of these amines; During oxidation of H-phosphonate **1** into phosphoroiodidate **2** (Scheme 1), a substituent of the lowest priority according to the CIP rules (the hydrogen atom bound to phosphorus) is replaced by a substituent of the highest priority (iodine), and thus the notation changes from **1** *Rp* to **2** *Sp* (and *vice versa*), although the reactions occur with retention of configurations. On the other hand, in the reaction of phosphoroiodidate **2** or phosphorochloridate **3** with amines, a substituent of the highest priority (iodine or chlorine atom) is replaced by a substituent of the lowest priority (nitrogen atom), and thus the stereochemical notation does not change, *i.e.* **2** *Rp* affords **4a** *Rp* or **3** *Sp* affords **4a** *Sp*, even though these reactions occur with inversion of configuration at the phosphorus centre.
15 When the formation of phosphoroiodidate **2** was complete (<1 min), 3 equiv. of ethanethiol was added to decompose excess of iodine. If this step was omitted, formation of a side products (signal at δ_P = 8.4 ppm; *ca.* 10% after 20 min) was observed. In a separate experiment we showed that the addition of ethanethiol affected neither the stereochemical course of the halogen exchange reaction nor the subsequent reaction of the produced phosphorochloridate **3** with amines.
16 Diastereomerically pure phosphorochloridates **3** were independently synthesised from dinucleoside H-phosphonate **1** using the Atherton–Todd reaction. This oxidation, which is known to occur with retention of configuration, produced phosphorochloridate **3** *Sp* (δ_P = 3.93 ppm) from H-phosphonate **1** *Rp*, and phosphorochloridate **3** *Rp* (δ_P = 3.28 ppm), from H-phosphonate **1** *Sp*. These findings substantiate the assumed inversion of configuration in the investigated halogen exchange reaction.