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Phosphonamidation Reactions

Investigation of Reactive Intermediates and Reaction Pathways in the Coupling Agent Mediated Phosphonamidation Reaction

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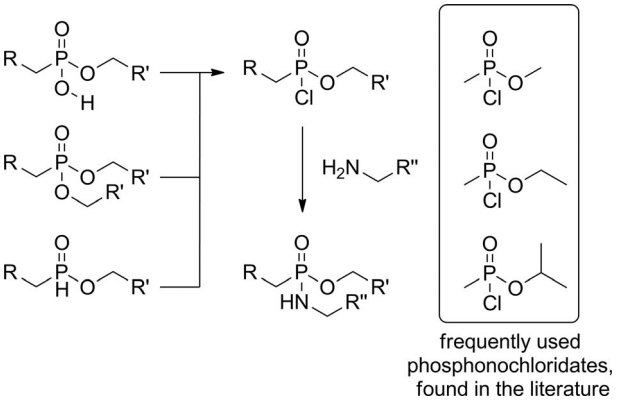
Abstract: The preparation of carboxamides through the coupling agent mediated reaction of carboxylic acids and amines is one of the most frequently employed reaction types of modern organic synthesis and has largely replaced older methods of amide formation based on reactive acyl chloride intermediates. However, the preparations of analogous phosphonamidates still rely on the use of phosphonochloridate intermediates – a method that is incompatible with sensitive functional groups. Herein, we present a comprehensive study in which different coupling agents are tested in the phosphonamidation reaction. The procedures, parallel to those typically applied to the preparation of carboxamides, were generally unsuccessful with regard to the coupling reactions of monoesters of phosphonic acids and amines, with the exception of those mediated by (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP). The implementation of a preactivation period in the absence of the amine coupling partner allowed for efficient phosphonamidate formation with coupling agents such as (1-cyano-2-ethyoxy-2-oxoethylideneaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), [ethyl cyano(hydroxyimino)acetato-O^2]tri-1-pyrrolidinylphosphonium hexafluorophosphate (PyOxim), dicyclohexyl carbodiimide (DCC), *N*,*N*′-diisopropylcarbodiimide (DIC), and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU). The reactive intermediates observed by ^{31}P NMR analysis were individually synthesized and examined to understand their influence on the reaction.

Introduction

Amide bond-forming reactions are among the most important tools in a synthetic organic chemist's toolbox. Carboxamides are, by far, the most studied among the different classes of amides and are frequently encountered in organic compounds that range from complex natural products to high-strength polymer fibers. Unlike the rapidly interconverting, pseudoplanar geometry of carboxamides, the geometry of phosphonamidates, in which the nitrogen atom is bonded to a phosphorus(V) instead of a carbon atom, is tetrahedral, making the phosphorus atom a stereogenic center. Phosphonamidates have attracted interest in various areas of organic chemistry for their potential as structural scaffolds in medicinal chemistry, and in many cases, the tetrahedral geometry around the phosphorus atom is of key importance.[1] The commonly employed strategy for the formation of such phosphonamidates involves the aminolysis of phosphonochloridates, which in turn are available from either phosphonates (mono- or diesters of phosphonic acid) or phosphites (Scheme 1).[1d,2] Although this strategy has been successfully used to prepare phosphonochloridates from simple starting materials, the reaction conditions are commonly incompatible with sensitive functional groups or labile stereogenic centers. In addition, caution must be exercised when preparing lower molecular weight phosphonochloridates to avoid the formation of highly neurotoxic substances, structurally similar to chemical warfare agents.[3]



Scheme 1. Preparation of phosphonamidates by employing phosphonochloridates.

Phosphonamidates can also be prepared from phosphorus(III) species through a late-stage oxidation to give phosphorus(V).[4] Reports detailing phosphonamidate formation mediated by coupling agents are scarce. To the best of our knowledge, Burger and Anderson reported in as early as 1957 the first successful coupling agent mediated phosphonamidation reaction between monoesters of phosphonic acids and amines by using dicyclohexyl carbodiimide (DCC) as the coupling agent.[5] Nevertheless, this report appears to have been overlooked by most researchers in the field, which may partly ex-

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plain the lack of successful phosphonamidation reactions. Regrettably, we became aware of this article at a late stage of our study. In Burger and Andersons work, DCC was reportedly capable of generating activated species such as pyrophosphonates, and notably, the order of addition of the reagents was found to be critical.[6] Years later, and perhaps unaware of the work by Burger and Andersons,[5] Imoto and co-workers were unsuccessful in their attempt to use DCC to facilitate a phosphonamidation reaction.[7] Martell and co-workers experienced similar difficulties with the use of DCC to mediate a P–N bond formation.[8]

With the introduction of tris(alkylamino)phosphonium coupling agents, Dumy and co-workers demonstrated that both (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) could facilitate a phosphonamidation reaction.[9] Coste and co-workers adopted their method a few years later in a publication primarily directed towards the synthesis of mixed phosphonates.[10] Notably, the approach shared by the two reports, encompasses a narrow substrate scope, and only four products were isolated in the moderate yields of 60–65 %.

In the context of solid phase synthesis, another successful P–N bond formation mediated by *N*,*N*′-diisopropylcarbodiimide (DIC), also a carbodiimide coupling agent, in the presence of 1-hydroxy-7-azabenzotriazole (HOAt) as an additive has been reported by Kitamura and Ishibashi.[11] Notably, their attempts to use PyBOP among other coupling agents gave poor results.[12]

It is surprising to observe the limited number of successful coupling agent mediated preparative methods for phosphonamidates in the literature. The few available reports appear to have focused on the synthesis of target molecules rather than investigating the scope and limitations of the described methods. This observation prompted us to undertake a systematic study of the phosphonamidate coupling reaction to gain insight into its key features and reactive intermediates that are involved in its mechanism. Furthermore, these results would benefit the development of a more general protocol for the synthesis of phosphonamidates by using standard peptide coupling reagents.

Results and Discussion

In the course of our studies, we examined several types of coupling agents in the phosphonamidation reaction between monoalkyl esters of benzylphosphonic acid and amines, including carbodiimides DCC and DIC[13] and the 1-hydroxybenzotriazole (HOBt)-based coupling agents PyBOP and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU)[14] as well as [ethyl cyano(hydroxyimino)acetato-*O*^{2}]tri-1-pyrrolidinylphosphonium hexafluorophosphate (PyOxim), and (1-cyano-2-ethyoxy-2-oxoethylideneaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU),[15] – two recently reported coupling agents based on ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma, Figure 1).[16] The initial phosphonamidation reactions were carried out with readily available starting materials in procedures that are typically employed for analogous carboxylic acids.

To our surprise, only PyBOP efficiently mediated the conversion of phosphonic acid derivative **1a** into the corresponding product, whereas the reactions with the other coupling agents resulted in either trace amounts of product or no conversion (Table 1).

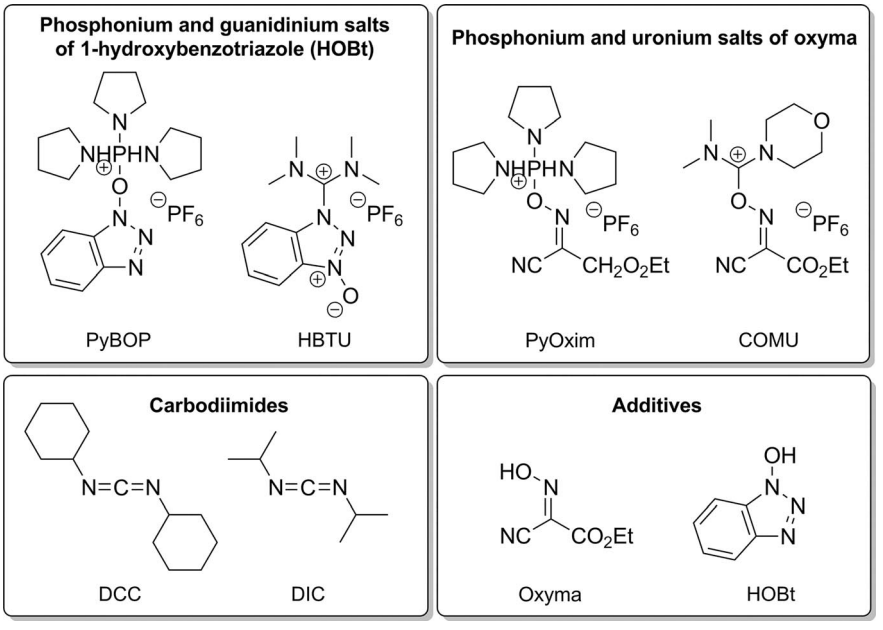
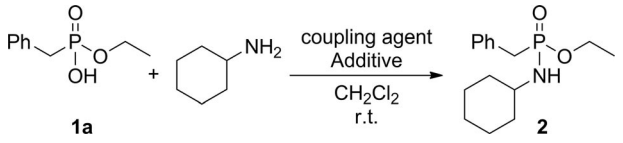


Figure 1. Coupling agents and additives investigated in this work.

Table 1. Screening of coupling agents in the phosphonamidation reaction by using literature procedures.

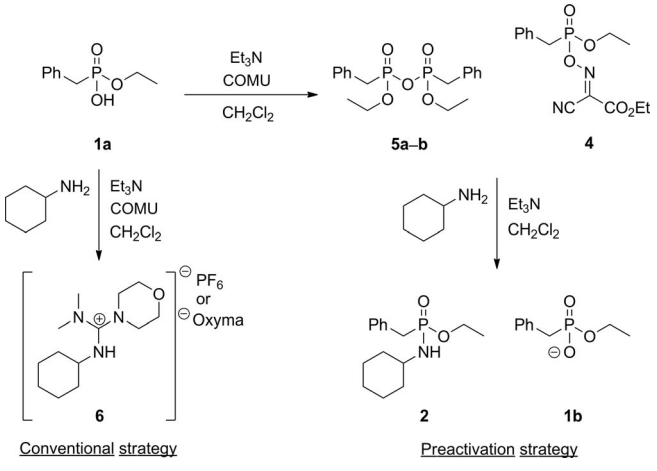


1a 2

Entry	Coupling agent [1.15 equiv.]	Additive [0.5 equiv.]	Conversion [%][a]
1[b]	PyBOP	–	>95
2	HBTU	–	trace
3	DCC	–	0
4	DIC	–	0
5	DCC	HOBt	0
6[b]	COMU	–	trace
7	PyOxim	–	trace

[a] Conversion was measured by ^{31}P NMR analysis of the crude reaction mixture. [b] Similar results were obtained when cyclohexylamine was replaced with $BnNH_2$.

Notably, in the attempted COMU-mediated coupling reaction, the major isolated product was stable guanidinium salt **6** rather than phosphonamidate **2**. The direct reaction between the coupling agent and the amine had occurred instead (Scheme 2).[17] The extent of formation of this byproduct suggests that the amine is significantly more reactive than phosphonic acid derivative **1a** towards COMU.



Scheme 2. A preactivation strategy was necessary to avoid the side reaction between the amine and COMU.

We were intrigued by the apparent significance of the activator group (i.e., phosphonium, guanidinium, and uronium) of a given coupling agent on the outcome of the reaction and especially by the difference in the results obtained by PyBOP (Table 1, Entry 1) and HBTU (Table 1, Entry 2).[18] After the initial activation steps, both PyBOP and HBTU should give rise to the same benzotriazolylphosphonates **3a** and **3b** (Figure 2), which in turn should undergo aminolysis to furnish phosphonamidate **2**. Notably, only PyBOP gave the product in appreciable yields, and, therefore, the difference in the outcome of the two reactions may indicate a mechanistic difference in the activation steps. In light of this observation, we decided to evaluate PyOxim (Table 1, Entry 7) as an alternative to COMU (Table 1, Entry 6) to investigate whether the outcome of these reactions could be affected by the choice of the activator group (i.e., phosphonium vs. guanidinium/uronium) rather than by the identity of the leaving group [OBt or Oxyma anion, Figure 1]. PyOxim and PyBOP are both activated by the tripyrrolidinophosphonium group, but they were expected to generate different activated phosphonates after the initial activation steps. PyBOP should give OBt-phosphonate **3a** and **3b**, and PyOxim is expected to give Oxyma-phosphonate **4** (Figure 2).[19] This change, however, had no significant effect on the outcome of the phosphonamidation reaction, and the result obtained by PyOxim was comparable to that with COMU (Table 1, Entries 6 and 7). This indicates that the structure of the activator group alone cannot fully explain the results presented in Table 1. As for the DCC- and DIC-mediated phosphonamidation reactions, no product formation was observed in either the presence or absence of HOBt.[20]

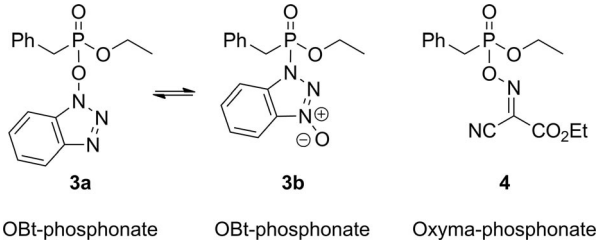


Figure 2. Different activated phosphonates; OBt = benzotriazolyl)oxy).

As our initial results suggest, the structures of both the activator and leaving groups of the coupling agents are important, but their roles are not easily rationalized. In this context, it is important to acknowledge that the development of coupling agents has focused on amidation reactions of carboxylic acids and not of other acids, such as phosphonic acids. Phosphonic acids are stronger acids than their carboxylic acid counterparts, and subsequently the phosphonic acid anion formed upon deprotonation should be less nucleophilic than a carboxylate. In addition, the phosphonic acid anion is sterically congested, which may contribute to its low nucleophilicity.[21]

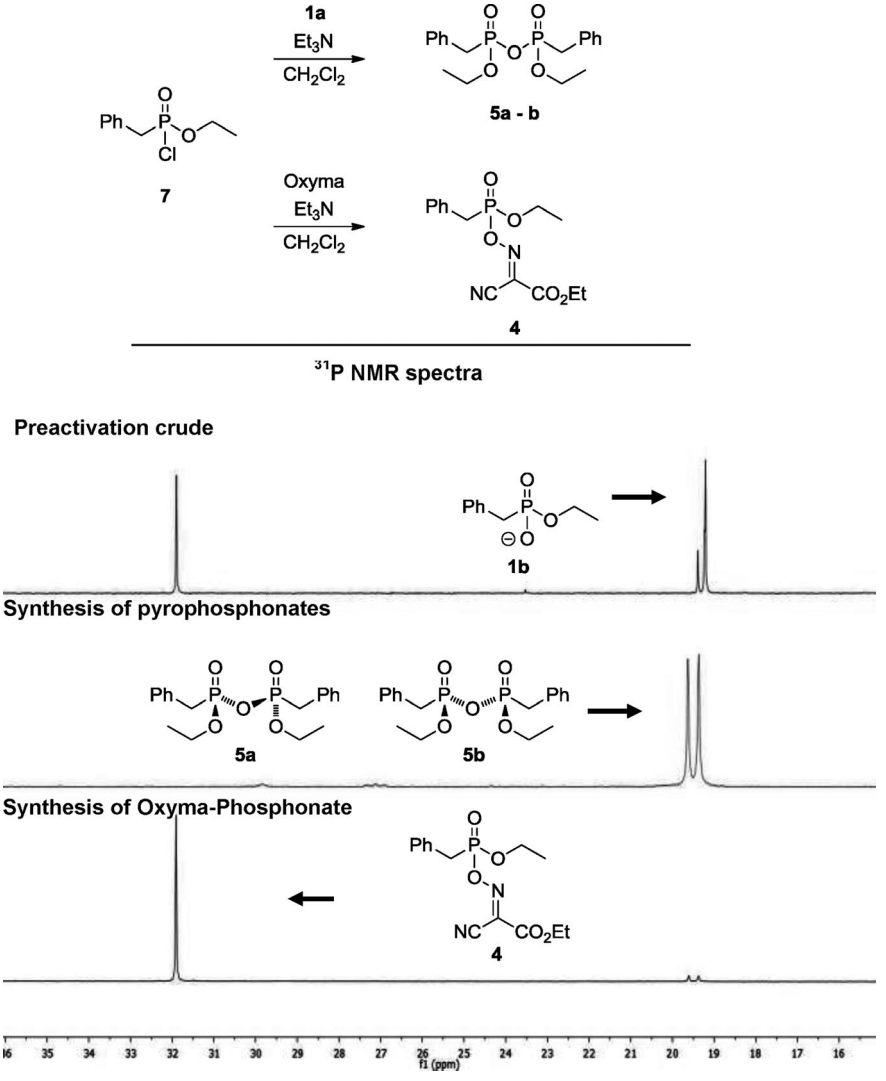
The inability of most of the examined coupling agents to facilitate the phosphonamidation reaction led us to investigate the reaction further. Thus, we sought to explore the possibility of using a non-hydroxybenzotriazole-based coupling agent to facilitate the reaction because of the intrinsic risks associated with this class of compounds.[22] Both COMU and PyOxim fulfill this requirement, as their structures contain the less hazardous Oxyma oxime (Figure 1).[16]

To avoid the aforementioned unproductive side reaction between COMU and the amine, we opted for a preactivation strategy, in which phosphonic acid derivative **1a**, the base, and COMU were stirred for 3 h prior to the aminolysis (Scheme 2). This approach increased the conversion of **1a** into product **2** from the trace amounts obtained by the original procedure to 69 % with the preactivation strategy, as measured by ^{31}P NMR analysis of the crude reaction mixture (Scheme 2).

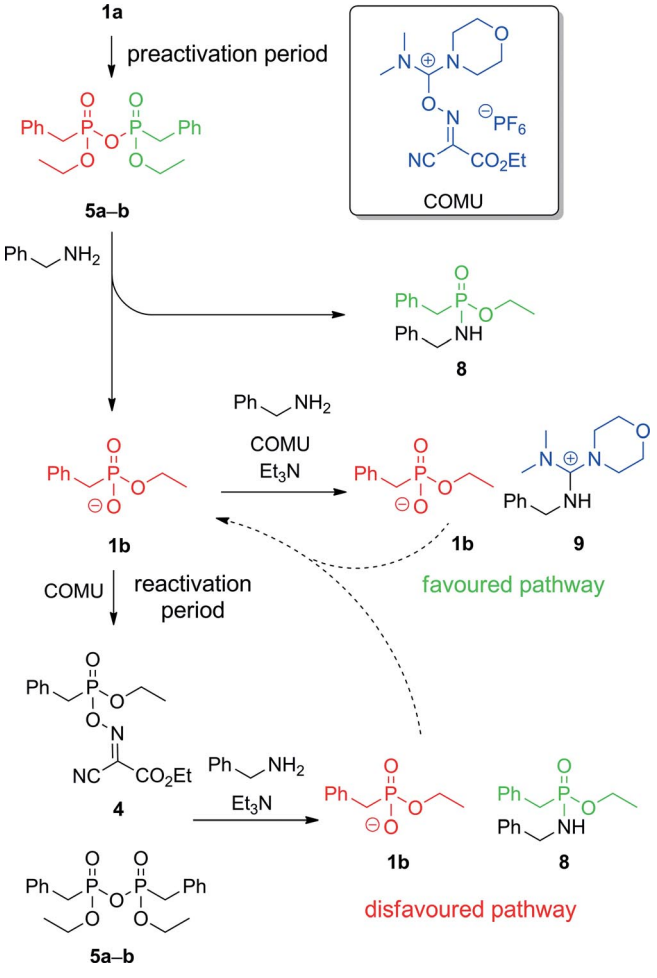
In the ^{31}P NMR spectrum of the reaction mixture from the preactivation step, three main species along with unconsumed starting material were observed (Scheme 3). The signals were confirmed to stem from Oxyma-phosphonate **4** and a diastereomeric mixture of pyrophosphonates **5a** and **5b** by comparison of the spectroscopic data with that of separately synthesized material. Compounds **4**, **5a**, and **5b** could be synthesized separately by adding either Oxyma/Et_3N or phosphonic acid derivative **1a**/Et_3N to freshly prepared batches of phosphonochloridate **7** (Scheme 3).

In a control experiment, we could demonstrate that pyrophosphonates **5a** and **5b** were capable of undergoing an aminolysis reaction with both cyclohexylamine and $BnNH_2$ in the absence of a coupling agent, additive, or base to generate phosphonamidates **2** and **8** with 42 % conversion and the simultaneous release of anion **1b**. This control experiment was deemed necessary for our study because of the existence of contradicting reports with regard to the reactivity of other pyrophosphonates towards amines.[23] When Oxyma-phosphonate **4** was subjected to an aminolysis reaction with $BnNH_2$, full conversion of **5** into both product **8** and anion **1b** was observed. Product **8** was afforded in 74 % conversion from **5**. Thus, to achieve high conversion into the desired product, it was necessary to limit the formation of pyrophosphonates **5a** and **5b** during the preactivation step. This is important because anion **1b**, which is produced from the aminolysis reaction of pyrophosphonates **5a** and **5b**, is significantly less reactive towards COMU than the amine. This leaves most of anion **1b** unable to reactivate, as the coupling agent is irreversibly consumed by the formation of guanidinium salt **9** (Scheme 4).

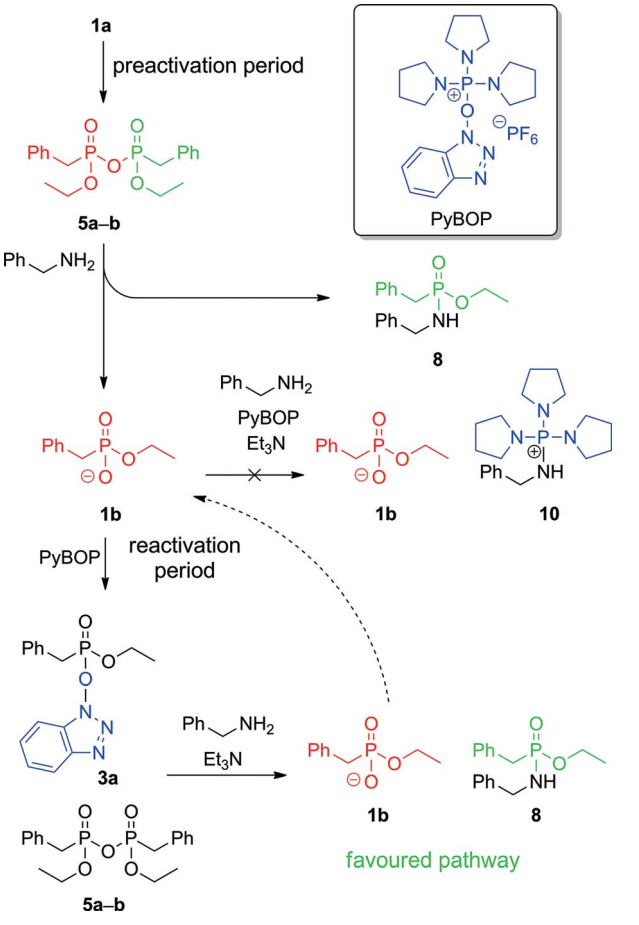
When the preactivation protocol was attempted with PyBOP instead of COMU, a higher concentration of pyrophosphonates **5a** and **5b** relative to the activated phosphonate (i.e., **4** or **3a**) was measured. When PyBOP was used, the ratio of **5a**/**5b** was approximately 1:1 prior to the aminolysis compared to a ratio of 1:0.8 with COMU. However, a significant amount of unconsumed starting material was observed in the crude reaction mixture with COMU, which suggests that a longer preactivation period is required. Unlike the phosphonamidation reaction mediated by COMU, the resulting preactivation mixture that con-



Scheme 3. All reactive intermediates observed in the crude mixture of the preactivation step were synthesized separately to confirm their presence in the reaction mixture and map their reactivity in the phosphonamidation reaction.



Scheme 4. During the preactivation period, the formation of pyrophosphonates **5a** and **5b** is undesired when using COMU. Upon aminolysis, **5a** and **5b** release anion **1b**, which has a low rate of reactivation compared to its rate of formation of guanidinium salt **9**.



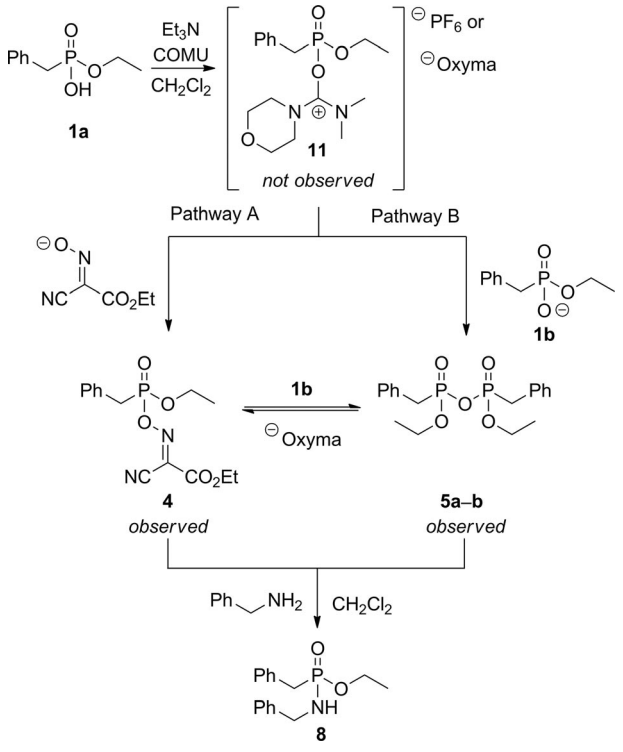
Scheme 5. PyBOP is more capable than COMU of converting the pyrophosphonates into product during the aminolysis step of the reaction.

tained PyBOP efficiently converted a majority of the reactive intermediates into product, without the side reaction between the amine and the coupling agent (Scheme 5).

The difference in reactivity between COMU and PyBOP towards the amine could be demonstrated by a series of control experiments, in which $BnNH_2$ was added to a solution of equimolar amounts of pyrophosphonates **5a** and **5b**, Et_3N, and the respective coupling agent. The ratio between the product and anion **1b** was determined by ^{31}P NMR analysis. In the presence of 2 equiv. of $BnNH_2$, a second aminolysis step is possible if the coupling agent is able to reactivate anion **1b**, which is released from the aminolysis reaction of pyrophosphonates **5a** and **5b**. An investigation into the ability of both COMU and PyBOP to reactivate anion **1b** after the initial aminolysis step was performed. For this second aminolysis to operate, anion **1b** would need to be more reactive than the amine towards the coupling agent. When 1 equiv. of COMU and Et_3N were added together with pyrophosphonates **5a** and **5b**, a conversion of 53 % was achieved, whereas the combination of **5a** and **5b** with PyBOP and Et_3N resulted in an increased conversion of 82 %. In a previous experiment, we subjected pyrophosphonates **5a** and **5b** to an aminolysis reaction with $BnNH_2$, which afforded product **8** in 42 % conversion. These experiments demonstrate that both coupling agents facilitate the phosphonamidation reaction of anion **1b** after the initial aminolysis step of pyrophosphonates **5a** and **5b**.

In an effort to reduce the formation of pyrophosphonates during the preactivation step of the COMU-mediated phosphonamidation reaction, several changes to the original reaction conditions were explored. During the first step of the COMU-mediated coupling of phosphonic acid derivative **1a**, activated phosphonate **11**, for the sake of this discussion, can proceed to react by two pathways, **A** or **B** (Scheme 6).

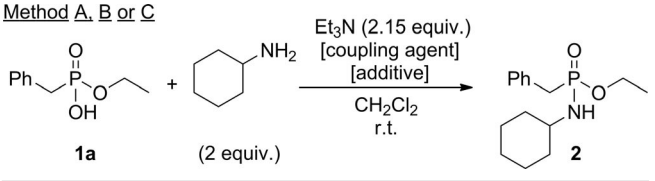
By starting from **11**, the ratio of formation of Oxyma-phosphonate **4** relative to pyrophosphonates **5a** and **5b** is expected to depend on the relative concentration of the Oxyma anion and that of anion **1b**. As the Oxyma anion is released into solution as COMU is consumed, its concentration is negligible at the beginning of the reaction compared to that of anion **1b**. During this period, Pathway B, which leads to pyrophosphonates **5a** and **5b**, is considered the dominant pathway until the concentration of the Oxyma anion increases. Thus, we sought to change the reaction conditions to favor Pathway A. This pathway should be favored if additional Oxyma is added prior to the preactivation period or by changing the order of addition



Scheme 6. During the preactivation steps, activated phosphonate **11** can proceed to react by two pathways, A or B. The relative concentration of anion **1b** and Oxyma is thought to determine which pathway is preferred.

of the reactants. The results of these changes are displayed in Table 2.

Table 2. A comparison of the conversions obtained when varying the method and reagents of the phosphonamidation reaction.



Entry	Method	Coupling agent [1.5 equiv.]	Additive [0.5 equiv.]	Conversion [%][a]
1	A[b]	COMU	–	trace
2	B[c]	COMU	–	69
3	B[c]	COMU	Oxyma	75
4	C[d]	COMU	Oxyma	89
5	C[d]	PyOxim	Oxyma	72
6	C[d]	COMU	–	75
7	C[d]	PyOxim	–	19

[a] Percent conversion was determined by ^{31}P NMR analysis of the crude reaction mixture. [b] Standard conditions were employed for Method A.[15b] [c] Preactivation for Method B: coupling agent (1.5 equiv.), additive (0 or 0.5 equiv.), phosphonic acid derivative **1a**, and Et_3N (2.15 equiv.) were mixed for 2 h before the amine was added. [d] Preactivation Method C: dropwise addition of phosphonic acid derivative **1a** and Et_3N (2.15 equiv.) into a solution of COMU or PyOxim (1.5 equiv.) and Oxyma (0.5 equiv.) in CH_2Cl_2. After approximately 5.5 h, the amine was added dropwise over 2 h.

In the presence of 1 equiv. of Oxyma during the preactivation step, we observed a slight increase in the conversion from 69 to 75 % (Method B, Table 2, Entry 3). To further increase the concentration of Oxyma relative to phosphonic acid derivative **1a** during the preactivation period, a solution of **1a** and Et_3N was added dropwise (0.4 mmol h^{-1} by an automated syringe pump) to a solution of COMU and Oxyma (Method C, Table 2, Entry 4). This improved the conversion from 75 to 89 % when cyclohexylamine was the substrate. A virtually identical result was observed when a solution of Oxyma, **1a**, and Et_3N was added dropwise to COMU.

When COMU was replaced with PyOxim (Table 2, Entry 5), a decrease was observed for the conversion. To further investigate whether the presence of 0.5 equiv. of Oxyma had any effect on the outcome of the reaction under Method C, experiments were conducted in the absence of Oxyma (Table 2, Entries 6 and 7). In both experiments, the lack of added Oxyma resulted in a reduced conversion, and thus supports our claim that a higher concentration of Oxyma during the preactivation step is beneficial.

Among the amines evaluated, primary amines normally resulted in conversions between 85 and 91 % with a few exceptions, such as allylamine and glycine ethyl ester hydrochloride (Table 3, Entries 8 and 10). The COMU-mediated coupling reactions with secondary amines, however, were less successful (Table 3, Entries 1, 11, 13, and 14) and afforded significantly lower conversions that those with the primary amines.

Because the ^{31}P NMR analysis of the crude reaction mixture from the preactivation step shows significant formation of active phosphonate **4**, we suspect that the reduced conversions for the reactions with secondary amines results from events occurring during the aminolysis of **4**. This was confirmed by two separate experiments, in which activated phosphonate **4** was subjected to an aminolysis reaction with $BnNH_2$ and morpholine. The $BnNH_2$ reaction reached 74 % conversion, whereas the reaction with morpholine reached 42 % conversion.

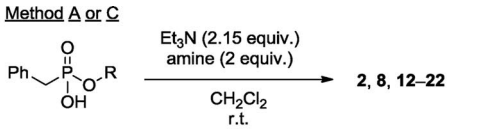
Despite our efforts, we were unable to isolate any byproducts from the crude mixture for the reaction between **4** and morpholine, which could suggest a possible mechanism for the decomposition of activated phosphonate **5** into starting material **1b**. PyBOP (Table 3, Entries 4, 12, and 16), on the other hand, achieved complete conversion of both primary and secondary amines without special considerations, such as the need for preactivation or the dropwise addition of the reagents. A reduced conversion into the product was only observed in the reaction with allylamine (Table 3, Entry 9).

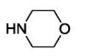
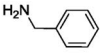
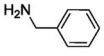
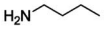
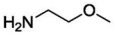
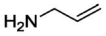
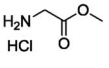
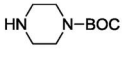
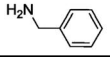
Differences were observed by changing the alkoxy group of **1a** as in the methyl or isopropyl ester of benzylphosphonic acid. The isopropyl and ethyl esters of benzylphosphonic acid gave comparable results, whereas the corresponding methyl derivative displayed a reduced stability, which was evident in the preactivation step by the presence of two additional byproducts.

With the knowledge acquired from coupling reactions with COMU, we wanted to investigate whether a coupling reaction with HBTU could be improved by applying the same modifications as described earlier (Table 4).

When HBTU and phosphonic acid derivative **1a** were subjected to the preactivation conditions for 1.5 h and subsequently treated with cyclohexylamine, a 42 % conversion into

Table 3. A comparison of the conversions obtained when varying the method and reagents of the phosphonamidation reaction.

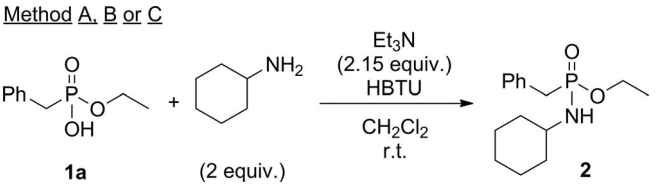


Entry	Method	R	Amine	Prod.	Conv. [%][c]	Yield [%][d]
1	A[a]	*i*Pr		**12**	29	7
2	A[a]	*i*Pr		**13**	85	45
3	A[a]	Et		**2**	89	66
4	B[b]	Et		**2**	>95	n.d.
5	A[a]	Et		**8**	90	56
6	A[a]	Et		**14**	91	49
7	A[a]	Et		**15**	87	55
8	A[a]	Et		**16**	34	13
9	B[b]	Et		**16**	45	n.d.
10	A[a][e]	Et		**17**	64	18
11	A[a]	Et		**18**	65	34
12	B[b]	Et		**18**	>95	n.d.
13	A[a]	Et		**19**	53	13
14	A[a]	Et		**20**	48	22
15	A[a]	Me		**21**	50	15
16	B[b]	Me		**21**	>95	n.d.
17	A[a]	Me		**22**	54	18

[a] Conversion was determined by ^{31}P NMR spectroscopic analysis. [b] Yields were determined after column chromatography and Kugelrohr distillation. [c] Preactivation for Method A: dropwise addition of the phosphonic acid derivative and Et_3N (2.15 equiv.) into a solution of COMU (1.5 equiv.) and Oxyma (0.5 equiv.) in CH_2Cl_2. After approximately 5.5 h, the amine was added dropwise over 2 h. [d] PyBOP (2.0 equiv.) was used under the literature conditions.[9] [e] Et_3N (3.15 equiv.) was used.

the product was observed by ^{31}P NMR analysis (Table 4, Entry 2). Analysis of the crude reaction mixture from the preactivation step showed only pyrophosphonates **5a** and **5b** and no activated phosphonate, as expected from the previous experiments with COMU and PyBOP. The presence of 0.5 equiv. of HOBt during the preactivation step combined with the slow addition of the reagents surprisingly gave only anion **1b** (Table 4, Entry 3). It is most likely that the water from the wet HOBt together with the Et_3N caused the reactive intermediates to hydrolyze into the starting material.

Table 4. A comparison of the conversions obtained when varying the method and reagents of the HBTU-mediated phosphonamidation reaction.

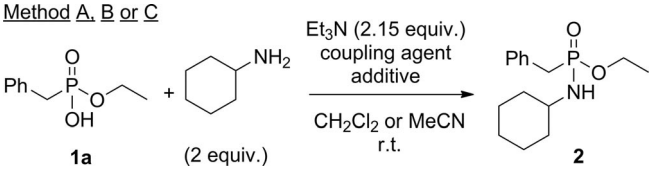


Entry	Method	Coupling agent [2.0 equiv.]	Additive [0.5 equiv.]	Conversion [%][a]
1	A[b]	HBTU	–	0
2	B[c]	HBTU	–	42
3	C[d]	HBTU	HOBt	0[e]
4	C[d]	HBTU	–	36

[a] Conversions were determined by ^{31}P NMR spectroscopic analysis. [b] The standard literature procedure was employed. [c] Preactivation for Method B: HBTU (2.0 equiv.), phosphonic acid derivative **1**, and Et_3N (2.15 equiv.) were mixed for 2 h before the addition of cyclohexylamine. [d] Preactivation Method C: dropwise addition of acid derivative **1** and Et_3N (2.15 equiv.) into a solution of HBTU (2 equiv.) and the additive (0 or 0.5 equiv.) in CH_2Cl_2. After approximately 5.5 h, the cyclohexylamine was added dropwise over 2 h. [e] The yield is likely the result of hydrolysis of the activated species from the wet HOBt.

By applying the preactivation strategy to DCC- and DIC-mediated phosphonamidation reactions, we were able to obtain product **2** with acceptable conversions (Table 5, Entries 3 and 4). Notably, the addition of Oxyma to the preactivation mixture significantly improved the conversion into the product (Table 5, Entries 5, 6, and 7). No differences were observed when the reaction solvent was changed to MeCN.

Table 5. A comparison of the conversions obtained when varying the method and reagents of the carbodiimide mediated phosphonamidation reaction.



Entry	Method	Coupling agent [1.5 equiv.]	Additive [1.0 equiv.]	Conversion [%][a]
1	A[b]	DCC	–	0
2	A[b]	DIC	–	0
3	B[c]	DCC	–	50
4	B[c]	DIC	–	50
5	B[c]	DCC	Oxyma	74
6	B[c]	DIC	Oxyma	74
7	C[d]	DIC	Oxyma	78

[a] Conversions were determined by ^{31}P NMR spectroscopic analysis of the crude reaction mixture. [b] Standard liquid-phase conditions were employed. [c] Preactivation for Method B: DCC or DIC (1.5 equiv.), phosphonic acid derivative **1**, Oxyma (0 or 1.0 equiv.), and Et_3N (2.15 equiv.) were mixed for 0.5 h before cyclohexylamine was added. [d] Preactivation Method C: dropwise addition of acid derivative **1** and Et_3N (2.15 equiv.) into a solution of DIC (2 equiv.) and additive (1.0 equiv.) in CH_2Cl_2 or MeCN. After approximately 5.5 h, the cyclohexylamine was added dropwise over 2 h.

In examples where no preactivation strategy was employed, no conversion into the product was observed (Table 5, Entries 1 and 2). These observations are in agreement with previous find-

ings of carbodiimide-mediated phosphonamidation reactions that show the order of addition of reagents is crucial to obtain significant conversion into product. As mentioned above, this had already been established in 1957 by Burger and Anderson[5] and implemented, but not specifically discussed, by Ishibashi and Kitamura in 2009.[11]

Conclusions

Herein, we have presented a comprehensive study of the coupling agent-mediated phosphonamidation reaction by primarily using the non-hydroxybenzotriazole-based coupling agents COMU and PyOxim to mediate the coupling of monoesters of phosphonic acids and amines. The realization that the reaction required a preactivation period without the amine coupling partner was of crucial importance, as the amine irreversibly consumes the coupling agent in an unproductive pathway. The implementation of this preactivation step allowed for successful phosphonamidate reactions that used other well-established coupling agents such as DIC, DCC, and HBTU. All major reactive intermediates that were observed during the preactivation period of the COMU-mediated phosphonamidation were synthesized separately to confirm their identity and evaluate their reactivity. Furthermore, by limiting the formation of pyrophosphonates in the preactivation step and assuring a low concentration of the phosphonic acid derivative relative to that of the coupling agent and Oxyma, we have shown that a higher conversion into the desired phosphonamides can be achieved. Employing this strategy, we were able to obtain comparable results to those obtained by the hydroxybenzatriazole-based coupling agent PyBOP in the reaction of the phosphonic acid derivative and several primary amines. A decrease in the conversion into the phosphonamides was observed with secondary amines, which was traced back to the aminolysis of the Oxyma-phosphonate. No byproducts could be isolated to account for the low conversion into the product. When the monomethyl ester of benzylphosphonic acid was used, a similar reduction in the yield was observed. Analysis of the crude reaction mixture from the preactivation step showed that the reduced conversion could be traced back to byproducts that originated from the preactivation step rather than the aminolysis of the activated phosphonate, as was observed in the case of secondary amines.

Experimental Section

COMU-Mediated Phosphonamidation Procedure for Compounds 2, 8, and 12–22: COMU (650 mg, 1.5 mmol) and Oxyma (72 mg, 0.5 mmol) were placed in a reaction vial with a magnetic stir bar, and CH_2Cl_2 (dried, 1 mL) was added. The heterogeneous mixture was then added dropwise (0.9 mL h^{-1} by using an automated syringe pump) to a solution of the monoalkyl ester of benzylphosphonic acid (1 mmol) and Et_3N (0.3 mL, 2.15 mmol) in CH_2Cl_2 (2 mL) with vigorous stirring. The resulting mixture was aged for an additional 2 h to primarily afford the corresponding Oxyma-phosphonate with trace amounts of the pyrophosphonates and the anion of the phosphonic acid derivative. The solution of the amine (2 mmol) dissolved in CH_2Cl_2 (0.5 mL) was then added dropwise (by using an automated syringe pump) over 1 h. The reaction mixture was stirred for an additional 3 h, and then the volatiles were removed under reduced pressure. Analysis of the crude mixture by ^{31}P NMR analysis was used to determine the conversion into the product. The crude mixture was diluted with CH_2Cl_2 (30 mL), and the resulting solution was washed with water (5 × 10 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography [2.5 cm (diameter) × 10 cm (height of silica); CH_2Cl_2/MeOH/Et_3N, 100:0:0 to CH_2Cl_2/MeOH/Et_3N, 100:1:0.5; see Supporting Information for additional details]. The product fraction overlapped with that of *N*,*N*-dimethylmorpholino-urea, which was later removed by kugelrohr distillation (125 °C, 6–9 Torr, 2 h, product stays, urea is removed).

Supporting Information (see footnote on the first page of this article): Syntheses of relevant compounds and experimental setup.

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Keywords: Synthetic methods · Phosphonamidation · Reaction mechanisms · Reactive intermediates · Phosphorus · Amines

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