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A Carbodiimide-Mediated P–C Bond-Forming Reaction: Mild Amidoalkylation of *P*-Nucleophiles by Boc-Aminals

Paraskevi Kokkala, Thayalan Rajeshkumar, Anastasia Mpakali, Efstratios Stratikos, Konstantinos D. Vogiatzis,* and Dimitris Georgiadis*

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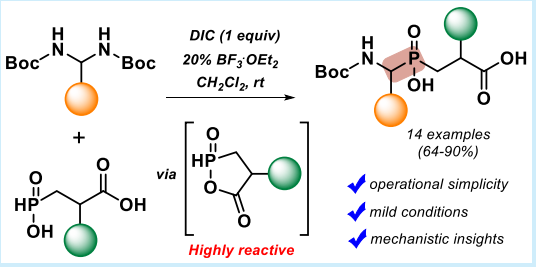
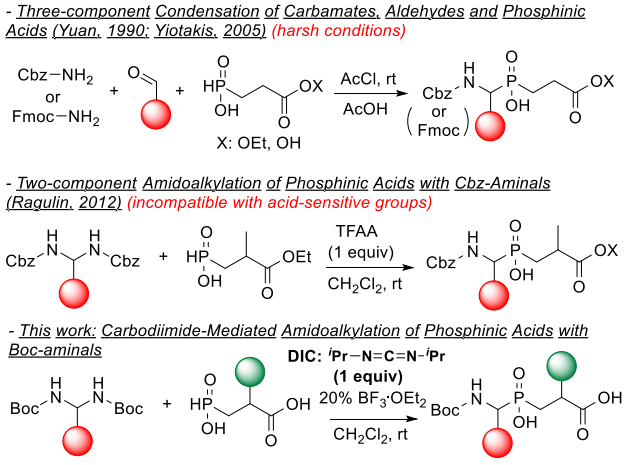
ABSTRACT: The first example of a carbodiimide-mediated P–C bond-forming reaction is described. The reaction involves activation of *β*-carboxyethylphosphinic acids and subsequent reaction with Boc-aminals using acid-catalysis. Mechanistic experiments using ^{31}P NMR spectroscopy and DFT calculations support the contribution of unusually reactive cyclic phosphinic/carboxylic mixed anhydrides in a reaction pathway involving ion-pair "swapping". The utility of this protocol is highlighted by the direct synthesis of Boc-protected phosphinic dipeptides, as precursors to potent Zn-aminopeptidase inhibitors.



Phosphinic peptides constitute a class of bioactive compounds that exhibit remarkable inhibitory properties against Zn-metallopeptidases.[1] Proper tuning of their structural features has successfully led to highly potent and selective inhibitors of medicinally relevant carboxypeptidases,[2] aminopeptidases,[3] and endopeptidases.[4] Synthetic approaches toward these structures fall into two main categories: the NP + C approach which allows diversification of the *C*-terminus (P_1' position) and the less common N + PC approach which offers the possibility to assemble the *N*-terminus (P_1 position) at a late stage of the synthesis.[1c,5] For the latter case, the main tool to achieve such a transformation is the Birum–Oleksyszyn reaction,[6] as it was modified by the research groups of Yuan, Coward, Yiotakis, and Ragulin (Scheme 1), which involves a condensation between *H*-phosphinic acids, aldehydes, and carbamates.[7] The main drawback of these protocols is the harsh conditions employed that are incompatible with acid-sensitive substrates.[7e] Aiming to address this issue, in this report we present a general, mild methodology which is based on the *first use of carbodiimides for the formation of a P–C bond.*

During the course of our studies on aminopeptidase inhibitors,[3a,c] we became interested in a synthetic protocol that would offer possibilities for the late-stage P_1-diversification of Boc-protected building blocks. Our initial efforts were focused on the amidoalkylation of phosphinic acid **2a** (Table 1) by using Boc-NH_2 and various aldehydes. However, application of existing protocols using different combinations of AcCl, Ac_2O, and acidic catalysts led consistently to low yields and byproducts related to Boc-cleavage and subsequent *N*-acetylation. In 2012, Ragulin et al. reported that milder conditions can be achieved by replacing the carbamate/aldehyde dyad with the respective aminals (Scheme 1).[8] Inspired by the work of Maruoka who introduced Boc-aminals as imine equivalents in acid-catalyzed Mannich reactions,[9,10] we envisioned that Boc-aminals could tolerate Ragulin's conditions. Indeed, by using TFAA the yields were significantly improved, however side-acylation was not completely suppressed (Table 1, entries 1,2). These observations prompted us to explore nonacylating conditions for the reaction, based on the absence of any acylated P(III)-species in the ^{31}P NMR

Scheme 1. Amidoalkylation of Phosphinic Acids



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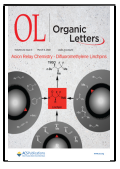

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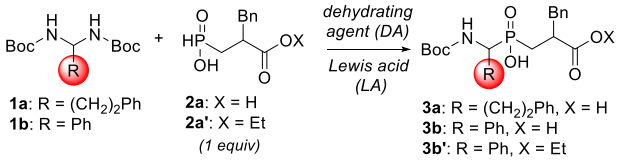
Table 1. Optimization Experiments[a]



entry	1	2	DA (equiv)	LA (equiv)	time (h)	NMR yield[b,c] (%)
1	**1a**	**2a**	TFAA (1)	-	24	32 (24)
2	**1a**	**2a**	TFAA (2)	-	4	48 (35)
3	**1a**	**2a**	DCC (1)	-	24	41[d,e]
4	**1b**	**2a**	DCC (1)	-	3.5	10
5	**1b**	**2a**	DCC (1)	-	72	87
6	**1a**	**2a**	DCC (1)	$Cu(OTf)_2$ (0.1)	24	12[f]
7	**1a**	**2a**	DCC (1)	TMSOTf (0.5)	1	67[g]
8	**1a**	**2a**	DCC (1)	$BF_3{\cdot}OEt_2$ (0.8)	4	65
9	**1a**	**2a**	DIC (1)	$BF_3{\cdot}OEt_2$ (0.8)	4	71
10	**1b**	**2a**	DIC (1)	$BF_3{\cdot}OEt_2$ (0.1)	4	84
11	**1b**	**2a**	DIC (1)	$BF_3{\cdot}OEt_2$ (0.2)	1.3	92
12	**1b**	**2á**	DIC (1)	$BF_3{\cdot}OEt_2$ (0.2)	24	10

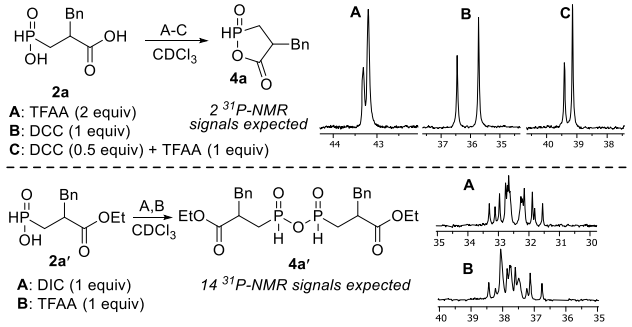
[a]Substrates **1** and **2** (0.2−0.4 mmol, 0.3 M), $CDCl_3$, inert atmosphere. [b]Conversion to side-acylation byproducts in parentheses. [c]Determined by ^{31}P NMR of the reaction mixture. [d]Solvent: CH_2Cl_2. [e]Determined by ^{31}P NMR after aqueous workup. [f]13% Boc-cleavage, [g]33% silylation byproducts.

spectra of reaction mixtures with 1 or 2 equiv of TFAA. We assumed that TFAA may act as a dehydrating agent, rather than an acylating one, and therefore, we reasoned that *N,N*-carbodiimides may be suitable to mediate such transformations. To our delight, with **1a** and 1 equiv of DCC, phosphinic acid **2a** furnished 41% of **3a** after 24 h (Table 1, entry 3). Moreover, aminal **1b** furnished 10% of product **3b** in 3.5 h, reaching an 87% conversion after 3 days (Table 1, entries 4,5). This unique reactivity was further enhanced by the addition of an acid catalyst, with $BF_3{\cdot}OEt_2$ rendering the most efficient choice (Table 1, entries 6−8). In addition, an impressive improvement was observed when DCC was replaced by DIC, leading to 92% conversion of **1b** in only 1.3 h (Table 1, entry 11). Interestingly, when phosphinic acid **2a′** was subjected at the same reaction conditions, only a 10% formation of product **3b′** was observed after 24 h (Table 1, entry 12), implying that the *C*-terminal of phosphinic substrates contributes to the reactivity of *P*-nucleophiles.[11]

In 1993, Campagne and co-workers proposed that phosphinic diacids may cyclize by a coupling reagent (BOP) toward mixed anhydride species.[12,13] By monitoring the reaction of diacid **2a** with 1.0 equiv DCC by ^{31}P NMR spectroscopy, we observed rapid formation of two signals, which was attributed to the two diastereoisomeric forms of proposed intermediate **4a** (Scheme 2). Interestingly, in a separate experiment the same intermediate was observed when 2 equiv of TFAA were employed. This was unambiguously confirmed by the formation of only one set of two signals when a mixture of DCC (0.5 equiv) and TFAA (1.0 equiv) was used, leading to the conclusion that the activated intermediate of the reaction is irrelevant of the condensating agent. With phosphinic acid **2a′**, TFAA (1.0 equiv) and DIC (1.0 equiv) generated a very similar ^{31}P NMR profile; only this time a multiplet was observed rather than two signals. We suggest that this multiplet corresponds to symmetric anhydride **4a′**, also a dehydration product, albeit much less reactive.[14]

Aiming to rationalize the difference in observed reactivity between proposed intermediate anhydrides, we performed

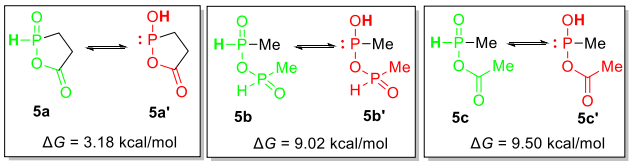
Scheme 2. Formation of Reactive Intermediates 4a and 4a′ Monitored by ^{31}P-NMR[a]



[a]^{31}P NMR signals are shifted downfield when TFAA is used due to released TFA that interacts with P═O. All ^{31}P NMR spectra are proton decoupled.

DFT calculations to estimate the Gibbs free energies (ΔG) of the prototropic P(V)/P(III) tautomerism for model compounds **5a−c** (Scheme 3). Strikingly, the tautomerism of cyclic

Scheme 3. Gibbs Free Energies (ΔG) for the Tautomerism of Model Compounds 5a−c Computed at the B3LYP-D3(BJ)/def2-TZVPP Level of Theory



anhydride **5a** is 5.8 and 6.3 kcal/mol less endothermic than the tautomerism of its symmetric (**5b**) and asymmetric (**5c**) acyclic anhydride counterparts, respectively. This observation justifies the experimentally observed increased reactivity of **4a**, as compared to **4a′**.[15] Interestingly, apart from the ability of **4a** to react even in the absence of an acid catalyst, additional

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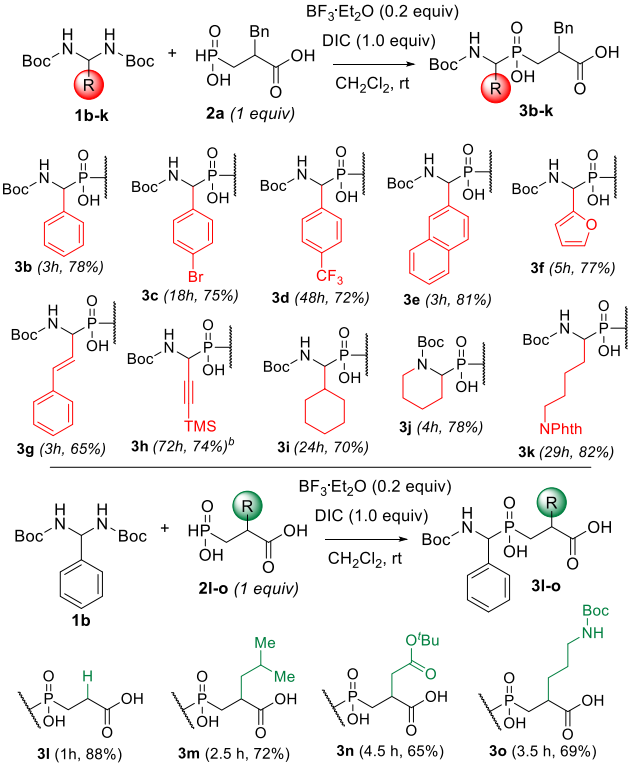
evidence of its high reactivity is its tendency to rapidly oxidize upon contact with air.

In order to explore the scope of this new P−C bond-forming reaction, we synthesized a series of derivatives (**3b−3k**) by using the corresponding Boc-aminals (**1b−1k**) that incorporate diverse aryl, alkenyl, alkynyl, as well as cyclic or acyclic alkyl substituents (Scheme 4). In all cases, the reaction

Scheme 4. Substrate Scope for the DIC-Mediated Amidoalkylation Reaction[a,c]

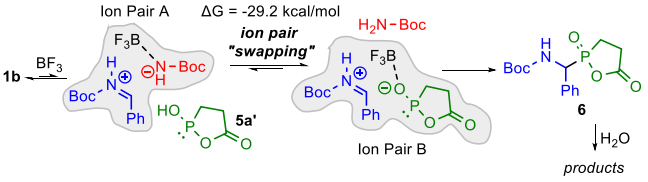


[a]DIC was added at 0 °C in a mixture of **1** and **2a** in CH_2Cl_2, followed by the addition of the catalyst, and then the mixture was stirred at rt. All reactions were performed under Ar atmosphere. Isolated yields are shown. [b]0.5 equiv of BF_3·Et_2O was used. [c]In all cases, except **3l**, the final products were obtained as a ∼1:1 mixture of diastereoisomers.

performed well affording compounds of type **3** in good to high yields after chromatographic purification. A noteworthy observation is that alkynyl derivative **1h** was found to be the least reactive among tested aminals, contrary to reactivity patterns reported by Maruoka et al. in Mannich-type reactions involving Boc-aminals.[9b] Presumably, mechanistic differences between these reactions may underlie the observed deviations. Finally, Gly (**3l**), Leu (**3m**), Asp (**3n**), and Orn (**3o**) amino acid surrogates were efficiently prepared, emphasizing the compatibility of the reaction with different side-chains and acid-sensitive protecting groups.

Concerning the reaction mechanism and in accordance with previous observations by Maruoka et al.,[9] we were also unable to identify accumulation of imine or iminium ions by monitoring the reaction by NMR spectroscopy. We envisioned that the unfavorable BF_3-catalyzed dissociation of Boc-aminal **1b** would form ion pair **A** that could participate in a second equilibrium with ion pair **B** (Scheme 5). The latter would involve the release of Boc-NH_2 through a hydrogen transfer process which allows an overall "swapping" between the

Scheme 5. Ion Pair "Swapping" Mechanistic Hypothesis



anionic parts of ion pairs **A** and **B**. By performing DFT calculations, we computed the Gibbs free energy of this exchange, and we found that the process was highly exothermic (ΔG = −29.2 kcal/mol). This stabilization may be partially attributed to the lower acidity of Boc-NH_2 as compared to phosphinic intermediate **5a′**. Upon removal of Boc-NH_2 from the equilibrium, the *P*-nucleophile is positioned in close proximity to the iminium ion, an arrangement that can be further stabilized by a bridging effect of BF_3 (see Supporting Information). Ion pair **B** is expected to collapse rapidly to intermediate **6**, allowing the formation of a stable P−C bond which cannot further dissociate. Further theoretical and experimental confirmation of proposed mechanistic hypothesis is currently underway.

Apart from its simplicity and efficiency, the proposed protocol may provide facile access to P_1-diversified Zn-aminopeptidase inhibitors after standard TFA-deprotection. To this regard, samples of **3b,c**, and **i** were deprotected and tested for their inhibitory potency against M1 aminopeptidase IRAP,[16] leading to IC_{50} values of 0.16, 4.17, and >10 μM, respectively (see Supporting Information). By this technique, SAR data can be rapidly collected: for example, by comparing inhibitors derived from **3b** and **3i** it is concluded that IRAP may easily accommodate aromatic rings (phenylglycine surrogates) but not aliphatic rings in its P_1 position. Taken together, the expansion of structural variety that can be achieved by the proposed protocol and the direct access to P_1-diversified candidate inhibitors, this approach is expected to facilitate drug discovery efforts involving medicinally important Zn-peptidases.

In summary, we have developed a carbodiimide-mediated P−C bond-forming reaction between Boc-aminals and phosphinic diacids of type **2**, based on the observation that amidoalkylation is driven by condensing rather than acylating conditions. Moreover, to the best of our knowledge this is the first example of a carbodiimide-mediated reaction where the reagent activates the nucleophile and not the electrophile, as it is usually the case. Based on our mechanistic experiments, the unique reactivity of cyclic mixed anhydride intermediates of type **2a** is attributed to their highest propensity to tautomerize, as compared to symmetric anhydrides that are proposed to mediate amidoalkylation of esters of type **2a′**. The reaction is operationally simple, compatible with acid-labile groups and applicable to a wide range of substrates, facilitating the late-stage P_1-diversification of phosphinic peptides. Finally, a mechanistic hypothesis is formulated which involves a thermodynamically favorable ion pair "swapping" process. Further mechanistic studies and application of the proposed protocol to the discovery of Zn-aminopeptidase inhibitors are currently in progress.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00155.

Detailed experimental procedures and characterization data for all new compounds, enzymatic data, computational details for the DFT calculations; Cartesian coordinates for all optimized structures (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Dimitris Georgiadis − *Department of Chemistry, Laboratory of Organic Chemistry, National and Kapodistrian University of Athens, 15784 Athens, Greece;* orcid.org/0000-0002-9656-0701; Email: dgeorgia@chem.uoa.gr

Konstantinos D. Vogiatzis − *Department of Chemistry, University of Tennessee Knoxville, Knoxville, Tennessee 37996, United States;* orcid.org/0000-0002-7439-3850; Email: kvogiatz@utk.edu

Authors

Paraskevi Kokkala − *Department of Chemistry, Laboratory of Organic Chemistry, National and Kapodistrian University of Athens, 15784 Athens, Greece*

Thayalan Rajeshkumar − *Department of Chemistry, University of Tennessee Knoxville, Knoxville, Tennessee 37996, United States*

Anastasia Mpakali − *National Centre for Scientific Research Demokritos, 15341 Athens, Greece;* orcid.org/0000-0003-0869-9680

Efstratios Stratikos − *National Centre for Scientific Research Demokritos, 15341 Athens, Greece; Department of Chemistry, Laboratory of Biochemistry, National and Kapodistrian University of Athens, 15784 Athens, Greece;* orcid.org/0000-0002-3566-2309

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00155

Author Contributions

D.G. conceived and supervised the project. P. K. performed the synthesis, data analysis, compound characterization, mechanistic studies. A.M. and E.S. performed enzymatic kinetic experiments. T.R. and K.D.V. designed and performed computational analysis. D.G. wrote the manuscript with the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Prof. Athanasios Yiotakis, on the occasion of his 79th birthday.

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