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1-(*N*-Acylamino)-1-triphenylphosphoniumalkylphosphonates: General synthesis and prospects for further synthetic applications

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Dedicated to the memory of Professor Jerzy Suwiński (1939–2017).

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ABSTRACT

A general approach for the synthesis of 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates from readily accessible alkyl imidate hydrochlorides has been developed. The three-step synthesis involves acylation of the imidate hydrochloride with an acyl chloride, the Michaelis–Becker-like addition of diethyl phosphite to the *N*–acylimidate and subsequent nucleophilic substitution of the ethoxy group of the 1–ethoxyphosphonate derivative with triphenylphosphonium tetrafluoroborate. 1-(*N*–Acylamino)-1-triphenylphosphoniumalkylphosphonates were demonstrated to be promising intermediates for further synthetic transformations toward α-functionalized derivatives of α–aminophosphonic acids and α,β-dehydro-α-aminophosphonates.

Introduction

α-Aminophosphonic acids **1**, as phosphorus analogues and mimetics of α-amino acids, exhibit a variety of important biological activities [1–4]. In the last decade our research group has developed effective methods for the synthesis of 1-(*N*-acylamino) alkylphosphonium salts **2** and demonstrated their efficiency as highly reactive α-amidoalkylating agents in reactions with a variety of nucleophiles [5–7]. 1-(*N*-Acylamino)-1-triphenylphosphoniumalkylphosphonates **4** can be considered both as a subclass of 1-(*N*-acylamino)alkylphosphonium salts **2** and phosphonium derivatives of α-aminophosphonic acids **1**, as they include both the triphenylphosphonium group of phosphonium salts **2** and the phosphonate group of compounds **1** (Fig.1). It could be assumed that nucleophilic substitution of the triphenylphosphonium group at the α–position of compounds **4** would enable the simple synthesis of variously α-functionalized α–aminophosphonic acid derivatives. It could also be expected that the Wittig reaction of phosphonium salts **4** with a proton at the α-position ($R^2 = H$) would enable the direct synthesis of important α,β-dehydro-α-aminophosphonic acid derivatives. The elimination of triphenylphosphonium tetrafluoroborate from phosphonium salts **4** with a proton at the β–position ($R^2 = R^6R^7CH$) represents another pathway towards α,β-dehydro-α-aminophosphonic acid derivatives.

Recently, we reported a method for the synthesis of hitherto unknown diethyl 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4** by electrochemical oxidative α-methoxylation of diethyl 1-(*N*-acetylamino)alkylphosphonates **6** to 1-(*N*-acetylamino)-1-methoxyalkylphosphonates **7**, followed by substitution of the methoxy group with triphenylphosphonium tetrafluoroborate (Scheme 1) [8]. We also showed the usefulness of these compounds in the synthesis of α-aminobisphosphonates **5** as well as their phosphonyl-phosphinyl and phosphonyl-phosphinoyl unsymmetrical analogues [8]. However, the reaction scope for the synthesis of compounds **4** was proven to be limited. Electrochemical α-methoxylation of 1-(*N*-acetylamino)alkylphosphonates was possible only in the case of compounds **6** with small substituents at the α-position (R^2 = H or Me). Attempts to extend this method to 1-(*N*-acetylamino)alkylphosphonates with more bulky substituents at the α-position (R^2 = Ph or *i*Pr) failed, as electrochemical oxidation in methanol gave intractable mixtures of many compounds in these cases.

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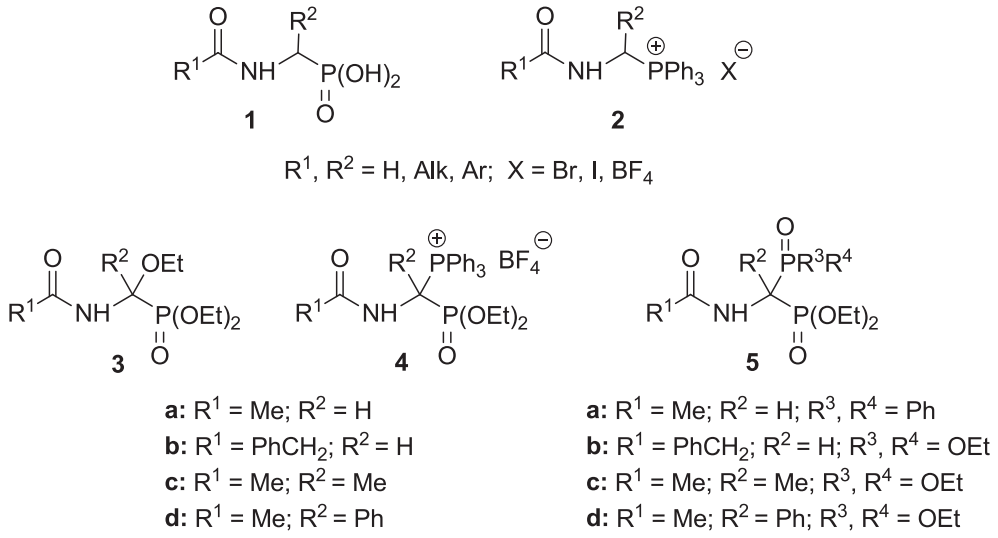
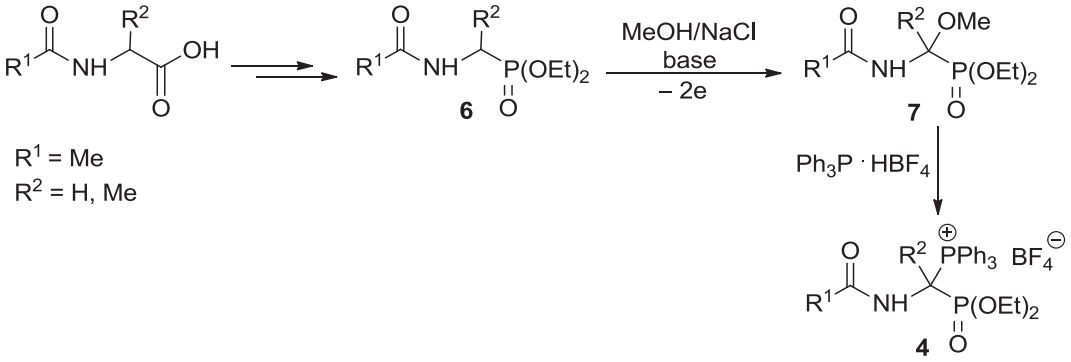
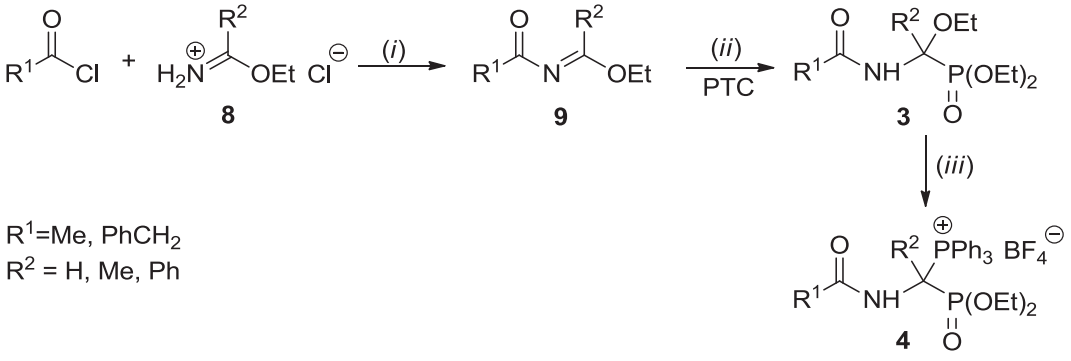


Fig. 1. General structures of α-aminophosphonic acids **1** and their α-functionalized derivatives **3**, **5** as well as 1-(*N*-acylamino)triphenylphosphonium salts **2** and 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4**.



Scheme 1. Synthesis of 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4** *via* electrochemical α-methoxylation of 1-(*N*-acylamino)alkylphosphonates **6** followed by substitution of the methoxy group with triphenylphosphonium tetrafluoroborate [8].

Herein, we report a more general strategy for the synthesis of 1-(*N*-acylamino)-1-triphenylphosphoniumphosphonates **4** based on *N*-acylimidates **9** as starting compounds (Scheme 2). The oxidation state of the imine carbon in *N*-acylimidates **9** and in the α–carbon in 1-(*N*-acylamino)-1-triphenylphosphoniumphosphonates **4** are the same, thus the difficult oxidation step in the discussed syntheses has been omitted. The second part of this paper demonstrates the potential applications of 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates as new reagents for the synthesis of variously α–functionalized α-aminophosphonic acid derivatives.



Scheme 2. Synthesis of 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4** from imidate hydrochlorides **8** *via* 1-(*N*-acylamino)-1-ethoxyalkylphosphonates **3**. Reagents and conditions: (*i*) acyl chloride, Et_3N, Ar atmosphere, 0–20 °C, 2–18 h, 76–87%; (*ii*) $HP(O)(OEt)_2$, K_2CO_3, 18-crown-6, 20 °C, 4–120 h, 38–78%; (*iii*) $Ph_3P{\cdot}HBF_4$, 20–85 °C, 0.1–6 h, 82–96%.