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Synthesis of 4-phosphono-β-lactams via phosphite addition to acyliminium salts

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Abstract—4-Aryl-4-phosphono-β-lactams are prepared by acylation of iminium salts with chloroacetyl chloride followed by phosphite addition and ring closure using sodium hydride as a base. Deacylation of the iminium salt is in competition with the desired addition of phosphites to acyliminium salts, which lowers the yield of the reaction.

α-Aminophosphonic acids have received a lot of attention since they mimic transition states of peptide hydrolysis and thus affect several physiological activities of the cell.[1] Therefore, aminophosphonic acids are often active as enzyme inhibitors, such as the α-aminophosphonic acid alaphosphin,[2] which inhibits alanine racemase. Also inhibition of thrombin by synthetic aminophosphonates has been reported.[3] Others are active as herbicides (e.g. glyphosate) or as neurotransmitters[4,5] (e.g. (*R*)-CPP and CGS 19755). Aminodiphosphonates on the other hand, can be used for the treatment of disorders of calcium metabolism. In view of the wide range of their physiological activities, efforts have been made by several research groups to develop efficient strategies for the synthesis of aminophosphonate derivatives with a diverse substitution pattern.

In our efforts to evaluate heterocyclic aminophosphonates for agricultural applications,[6–8] the phosphono-β-lactams seemed an interesting class of compounds. Further, the β-lactams still hold a lot of attention due to the importance of β-lactams in the field of elastase inhibitors[9] and monobactam antibiotics.[10] Since the discovery of penicillin, numerous penicillin derivatives have been prepared and examined for antibacterial activity. A variety of new β-lactam containing ring systems have been reported to show antibacterial properties, including the penams, carbapenems, cephalosporins, clavulanic acids and oxapenams.[11,12] Several phosphonylated penicillin-like derivatives have also been evaluated in this area, although these compounds did not possess promising antibacterial properties.[13–15] A classical method for the synthesis of 4-phosphono-β-lactams is via the Arbuzov reaction of 4-acetoxy-β-lactam and a trialkylphosphite.[2,15] An asymmetric synthesis of azetidine 2-phosphonic acids, starting from β-amino alcohols, was reported recently.[16] This synthesis involved an *N*-alkylation with a methylene phosphonate moiety, chlorination of the alcohol and stereoselective ring closure with LiHMDS. Due to this very recent publication, the preliminary publication of our work in this area was initiated.

In order to develop a new strategy to synthesise 4-aryl phosphono-β-lactams, aromatic aldehydes were condensed with primary amines in the presence of magnesium sulfate leading to the corresponding imines in good yields (82–99%).

In order to make the precursors **5** of the phosphono-β-lactams, two methodologies can be applied. The first one consists of the addition of a phosphite to the imine followed by acylation of the corresponding aminophosphonate. A second option involves the acylation of the imine with the formation of an iminium salt, followed by the addition of a trialkyl phosphite.

Evaluating the first approach, the addition of dialkyl phosphites, activated by silylation (trimethylsilyl chloride) or by deprotonation (sodium hydride), to imines, proved to be a very slow reaction. In the cases of quite stable imines, the reaction could be performed either at reflux (Ar = Ph; R^1 = Bn, reflux 4–12 h; 69%) or at room

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temperature over 2 weeks (88% yield). However, using sensitive imines (e.g. Ar = pyridyl; R^1 = Bn; 2 weeks; rt; 99% yield), the reaction had to be performed at room temperature leading to very long reaction times, making this approach less practical. Furthermore, synthesising the aminophosphonate first also resulted in problems in the acylation afterwards. The low reactivity results from the low nucleophilicity of the nitrogen atom (e.g. Ar = pyridyl; R^1 = naphthyl) because of the strong electron withdrawing effect of the phosphonate group. Therefore, we became interested in the evaluation of a new approach trying to use the addition of a phosphorus nucleophile onto an acylated iminium salt (Scheme 1).

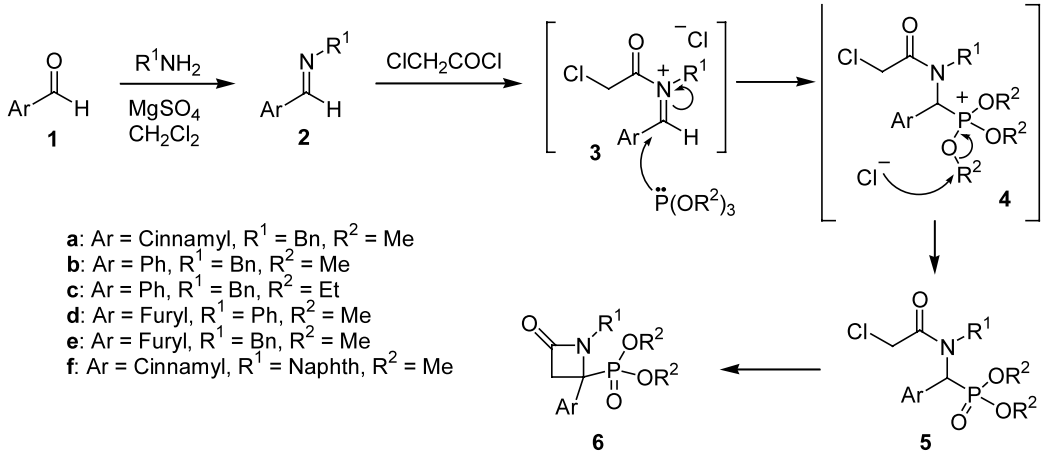
First, attempts were made to isolate the iminium salts after treatment of the aromatic imines **2** with chloroacetyl chloride. Unfortunately, due to the very hygroscopic character of these iminium salts **3**, they could hardly be isolated and could not be characterised properly. Therefore, after formation of the salts in toluene at −40°C, which can be followed visually by precipitation of the salts, the reaction mixture was stirred for one additional hour, followed by addition of the trialkyl phosphite. The best results were obtained using trimethyl phosphite. Triethyl phosphite can be used as well, however resulting in a lower yield. Triisopropyl phosphite proves to be too sterically hindered for the addition. The aim of the reaction is the addition of the phosphite to the activated iminium salt, generating a phosphonium salt which is then dealkylated by the liberated chloride (Arbuzov type dealkylation).[17] Using trimethyl phosphite, methyl chloride is formed in the reaction and bubbles out of the reaction mixture (CAUTION: the reaction should be performed in a properly working hood), so that theoretically only the desired aminophosphonate **5** is present in the mixture.

However, a competing reaction complicated the addition and made the yields drop to 24–56% due to the formation of some side products, which could not be isolated in pure form. Examination of the ^{31}P NMR spectra of several compounds, revealed that two doublets are always present. These were attributed to the phosphoryl phosphonate **11** formed from chloroacetyl chloride. The mechanism for this reaction was described by Britelli[18] and involves a Perkow reaction followed by a Michaelis–Arbuzov reaction (Scheme 2).

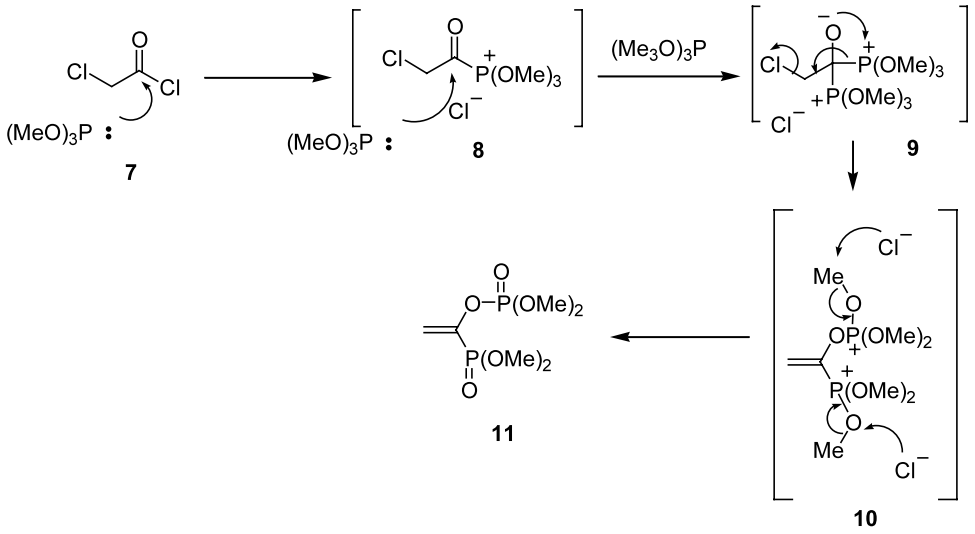
In order to prove this hypothesis, an experiment was done with chloroacetyl chloride and trimethyl phosphite. Comparison of the ^{31}P NMR spectrum obtained with those from the side product confirmed our presumption. Mechanistically, two possibilities for the formation of the phosphonate **11** had to be considered. The acylation reaction was not completed and the phosphite reacted with the excess of acid chloride, or the phosphite is able to abstract the acyl group from the iminium salt. To investigate this last case, a very small amount of the iminium salt was isolated free of chloroacetyl chloride under an N_2 atmosphere and reacted with trimethyl phosphite. Again, phosphonate **11** was found in the reaction mixture. This indicates that the formation of the side product is not due to the presence of an excess of acid chloride in the reaction mixture. Therefore, it will be necessary to alter the reaction conditions in order to minimize the abstraction of the acyl group and to maximize the addition to the iminium salt in further investigations.

The subsequent ring closure reactions were performed with NaH in THF and the β-lactams were obtained in good yields (71–99%). The formation of the β-lactam ring via a C_3–C_4 bond is not exploited in detail, since most lactams are prepared by a [2+2] cycloaddition.[19,20] However, the cycloaddition approach is not applicable for the phosphono-β-lactams. These promising results in the ring closure stimulate us to spend more time on the optimisation of the addition reaction of phosphite to the iminium salts.

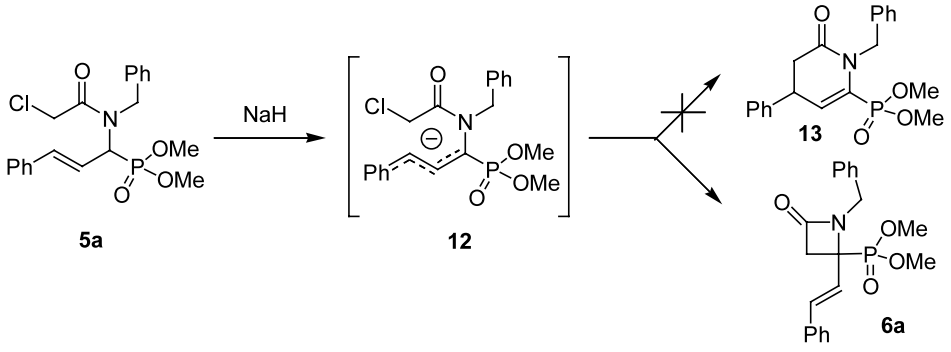
A further remarkable observation that still needs some computational background, is the ring closure of dimethyl 1-[benzyl(chloroacetyl)amino]-3-phenyl-2-propenyl phosphonate **5a**. Using sodium hydride as a base, the highly stabilised anion **12** formed, ring closes exclusively to the four membered ring **6a** instead of to the expected less strained six-membered ring **13** (Scheme 3).



Scheme 1.



Scheme 2.



Scheme 3.

This is in accordance with some earlier observations[21] and will be looked at in more detail.

In conclusion, a straightforward synthesis of 4-phosphono-β-lactams has been developed which leads to interesting building blocks for the synthesis of functionalised amino phosphonates. The optimization of the addition reaction using other types of imines and the biological testing of the new compounds are currently under investigation.

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17. Representative experimental procedure: To a dry round-bottom flask, 0.97 g (5 mmol) of *N*-(benzylidene)-benzylamine was added to 9 ml of dry toluene. The solution was stirred and cooled to −40°C under an N_2 atmosphere. Then, a solution of 0.62 g of chloroacetyl chloride in 2 ml of dry toluene was added dropwise. A white precipitate was formed in the reaction mixture. The mixture is stirred for 10 min at −40°C and then a solution of 0.68 g of trimethyl phosphite in 2 ml of dry toluene was added. After the addition, the precipitate dissolved again due to the dealkylation which is kept at 80°C for 3 h. Finally, the solvent was evaporated and the dimethyl 1-[benzyl (chloroacetyl)amino]benzyl phosphonate was obtained pure using flash chromatography (80/20 EtOAc/petroleum ether; Rf = 0.28; yield = 56%).
Spectral data:
^{1}H NMR δ (270 MHz, $CDCl_3$, ppm): 3.68 (3H, d, J_{H-P} = 10.9 Hz, OMe); 3,80 (3H, d, J_{H-P} = 10.9 Hz, OMe); 3.84 (1H, d, J_{AB} = 12.5 Hz, $C\underline{H}_A H_B Cl$); 3.93 (1H, d, J_{AB} = 12.5 Hz, $CH_A\underline{H}_B Cl$); 4.84 (1H, d, J_{AB} = 18.2 Hz, $NC\underline{H}_A H_B Ph$); 5.02 (1H, d, J_{AB} = 18.2 Hz, $NCH_A\underline{H}_B Ph$); 6.31 (1H, d, J_{H-P} = 22.8 Hz, NCHP); 6.8–6.9 (2H, m, CH_{arom}); 7.1–7.2 (3H, m, CH_{arom}); 7.3–7.4 (3H, m, CH_{arom}); 7.6–7.7 (2H, m, CH_{arom}).
^{13}C NMR δ (68 MHz, $CDCl_3$, ppm): 41.85 (CH_2Cl); 49.40 ($N\underline{C}H_2Ph$); 53.19 (OMe, J_{C-P} = 7.3 Hz); 53.84 (OMe, J_{C-P} = 7.3 Hz); 54.16 (NCH, J_{C-P} = 158.6 Hz); 125.59; 127.19; 127.31; 128.34; 128.39; 128.68; 128.98 (2×); 130.37; 130.49 (CH, Ph); 132.61 (C_{quat}, Ph, J_{C-P} = 2.4 Hz); 136.51 (C_{quat}, Ph); 167.98 (C = O, J_{C-P} = 3.7 Hz).
^{31}P NMR δ (109 MHz, $CDCl_3$, ppm): 22.48.
IR (NaCl, cm^{-1}): 1662, 1254.
MS (*m*/*z*, %): 381 (M^+, 5); 274 (26); 215 (11); 202 (8); 201 (90); 197 (15); 196 (10); 95 (8); 93 (8); 91 (100).
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