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Solvent free preparation of amidophosphonates from isocyanides

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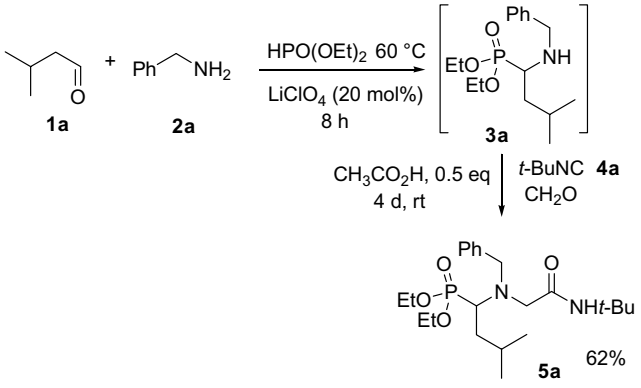
Abstract—New amidophosphonates are prepared via a two-step Mannich/Ugi one-pot procedure from isocyanides. Aminophosphonates are readily prepared from primary amines, dialkyl phosphites and carbonyl compounds under $LiClO_4$ catalysis without any solvent. After completion, addition of an isocyanide, an aldehyde and acetic acid give access to phosphono Ugi-type adducts in good to moderate yields.

Nucleophilic additions to the C=N bond of imines are of paramount importance in the synthesis of amino derivatives. Among these, three component Mannich reactions have attracted much attention due to the simplicity of the experimental procedures associated with a wide scope of possible nucleophiles.[1] Starting from primary amines, two consecutive Mannich-type additions may be observed to form tertiary amines. The selection of different nucleophiles and aldehydes in these consecutive additions together with the possible use of solvent free conditions, meet the demand for new environmental friendly reactions with high molecular diversity.

Looking for useful processes involving both phosphorus and isocyanide chemistry, we screened various catalysts in order to perform one-pot, solvent free Mannich condensations of dialkyl phosphites, followed by Ugi coupling of the intermediate aminophosphonate. We now report the use of lithium perchlorate as an efficient catalyst for this two-step procedure. An equimolar amount of isovaleraldehyde, diethyl phosphite and benzylamine was heated for 7 h at 60 °C in the presence of $LiClO_4$ (20 mol %), when complete (as shown by ^1H NMR of an aliquot) the mixture was cooled to room temperature before adding *tert*-butyl isocyanide (1 equiv), formaldehyde (1 equiv as a 40% solution in water) and acetic acid (0.5 equiv). After four days at room temperature, the amidophosphonate **5a** was obtained in 62% isolated yield (Scheme 1).



Scheme 1.

Various aldehydes, amines and isocyanides behaved similarly with diethyl phosphite and formaldehyde giving coupled products in moderate to good yields (Table 1). Simple aliphatic isocyanides, as well as amino acid derived isocyanides, are suitable starting materials. With glycine isocyanide ethyl ester (entries 9 and 10), this simple procedure allows a staightforward formation of phosphonate tripeptide analogues. Ketones are also efficiently coupled with diethyl phosphite giving further Ugi addition with formaldehyde. In these cases, thermal instability of the intermediate aminophosphonate requires room temperature additions in the first step with increased reaction time (entries 13, 14, 15 and 16).

The choice of formaldehyde is mainly dictated by the sensitivity of the Ugi coupling towards the steric hindrance around the amino function: an attempt to couple

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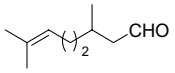
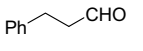
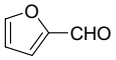
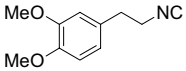
Table 1. Amidophosphonates **5a**–**p** produced via Scheme 1

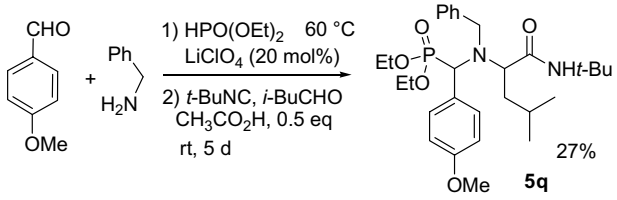
Entry	Carbonyl compound	Amine	Time (step 1)	Isocyanide	Time (step 2)	Product	Yield %
1	*i*-BuCHO	$BnNH_2$	7 h	*t*-BuNC	4 d	**5a**[8]	62
2	EtCHO	$BnNH_2$	1 d	*t*-BuNC	1 d	**5b**	15
3		$BnNH_2$	1 d	*t*-BuNC	4 d	**5c**	55
4		$BnNH_2$	1 d	*t*-BuNC	2 d	**5d**	25[c]
5	*p*-$MeOC_6H_4CHO$	$BnNH_2$	4 d[a]	*t*-BuNC	1 d	**5e**	70
6		$BnNH_2$	2 d[b]	CyNC	4 d[d]	**5f**	36
7	*p*-FC_6H_4CHO	$BnNH_2$	1 d	CyNC	4 d	**5g**	50
8	*i*-BuCHO	$BnNH_2$	1 d		4 d	**5h**	46
9	*i*-BuCHO	$BnNH_2$	1 d	$EtOOCCH_2NC$	4 d	**5i**	46
10	*p*-$MeOC_6H_4CHO$	$BnNH_2$	1 d	$EtOOCCH_2NC$	4 d	**5j**	36
11	*p*-FC_6H_4CHO	$CH_2{=}CHCH_2NH_2$	1 d	CyNC	3 d	**5k**	40
12	*p*-FC_6H_4CHO	$MeO{-}(CH_2)_2{-}NH_2$	3 d[a]	CyNC	3 d	**5l**	47
13	EtCOEt	$BnNH_2$	1 d[a]	*t*-BuNC	4 d	**5m**	35
14		$MeO{-}(CH_2)_2{-}NH_2$	4 d[a]	*t*-BuNC	3 d	**5n**	43
15		$BnNH_2$	1 d[a]	*t*-BuNC	4 d	**5o**	43
16		$MeO{-}(CH_2)_2{-}NH_2$	4 d[a]	*t*-BuNC	3 d	**5p**	55

[a] The mixture was stirred at rt.
[b] The mixture was stirred at 80 °C.
[c] The Ugi reaction can be performed with benzoic acid with similar yield (27%).
[d] The mixture was stirred at 50 °C.

isobutyraldehyde and *t*-butylisocyanide to the aminophosphonate, resulting from the addition of benzylamine and 4-methoxybenzaldehyde, gave only adduct **5q**, isolated as a single diastereomer in a low 27% yield (Scheme 2).

Various catalysts and solvents were tested according to known literature on aminophosphonate formation.[2] Successful final coupling needs almost quantitative conversion in the first step. Without catalyst, aminophosphonate formation is too slow and often incomplete;[3] the use of alumina under microwave irradiation[4] followed by Ugi reaction, gives adducts in much lower yields, whereas metal triflates (Mg, Cu)[5] do not improve significantly the overall yields of the two steps. Under solvent conditions (1 M in ether, MeOH or CH_2Cl_2),[6] low yields were observed with reactions too slow to give an efficient two-step procedure.

Ugi reactions are usually performed on primary amines.[7] With secondary amines the carboxylic acid which cannot be coupled to the amino group, is liberated back to the medium allowing a substoichiometric use of acid. Various amounts (20%, 100%) as well as different acids (benzoic, trifluoroacetic acids) have been tried in order to increase the yields or to improve the kinetics without much success. Lithium perchlorate alone did not allow the Ugi reaction to proceed.



Scheme 2.

In conclusion, we have disclosed a new multicomponent two-step procedure giving access to phosphonic peptide analogues under solvent free conditions. Ugi reactions are among the most efficient tools for the formation of complex targets with high molecular diversity, their integration in multistep procedures allowing even higher diversity remains an area of intense research effort. Other results in this field will be reported soon.

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8. Typical procedure for **5a**: to isovaleraldehyde (110 μL, 1.0 mmol) was added lithium perchlorate (20 mg, 0.2 mmol), benzylamine (110 μL, 1.0 mmol) and diethyl phosphite (130 μL, 1.0 mmol). The mixture was heated at 60 °C for 7 h, followed by the addition of formaldehyde (90 μL, 1.2 mmol, as a 40% solution in water), *tert*-butyl isocyanide (115 μL, 1.0 mmol) and acetic acid (30 μL, 0.5 mmol) and then stirred for 4 days at room temperature. Extraction and purification by column chromatography on neutral alumina with AcOEt/petroleum ether gave 270 mg of **5a** as a pale yellow oil: Rf: 0.3 (AcOEt/petroleum ether, 30:70 → 100:0). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.30 (m, 5H), 7.20 (bs, 1H), 4.13 (quint., $J = 7.1$ Hz, 4H), 3.95 (dd, $J = 3.3$, 12.9 Hz, 1H), 3.76 (d, $J = 12.9$ Hz, 1H), 3.35 (s, 2H), 3.01 (ddd, $J = 4.5$, 9.3, 17.9 Hz, 1H), 1.83–1.70 (m, 1H), 1.65–1.55 (m, 1H), 1.52–1.43 (m, 1H), 1.36 (t, $J = 7.1$ Hz, 3H), 1.35 (t, $J = 7.1$ Hz, 3H), 1.30 (s, 9H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.73 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.9, 138.6, 130.0, 129.1, 128.1, 62.2 (d, $J = 7.3$ Hz), 62.0 (d, $J = 7.3$ Hz), 58.3, 57.3, 56.0 (d, $J = 142.0$ Hz), 50.8, 37.0 (d, $J = 5.1$ Hz), 29.0, 25.5 (d, $J = 10.1$ Hz), 23.6, 21.9, 17.1 (d, $J = 5.9$ Hz), 17.0 (d, $J = 5.9$ Hz).