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Uncatalyzed Three-Component Synthesis of α-Hydrazido Phosphonates

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Various α-hydrazido phosphonates have been easily prepared on the basis of the nucleophilic addition of diphenyl phosphite to reactive, preformed *N*-acylhydrazones and a three-component (aldehydes, *N*-benzoylhydrazide and diphenyl phosphite) coupling reaction through a non-catalyzed process. An unprecedented and promising enantioselective example of this reaction is also reported.

Introduction

The hydrophosphonylation of aldehydes and imines (Pudovik reaction)[1] is the most general, straightforward and widely applied method for construction of P–C bonds.[2] The main interest in phosphonyl compounds and related derivatives resides in their important biological activity as antibiotics,[3] herbicides,[4] insecticides,[5] fungicides,[6] antiviral agents[7] and in their wide range of applications with respect to enzyme inhibition,[8] including HIV protease.[9] In particular, the nucleophilic addition reaction of dialkyl phosphites to imines has been used as one of the most convenient methods in the synthesis of α-amino phosphonic acids as structural analogues of α-amino acids (Figure 1);[10] this has a broad scope because a large variety of substrates can be employed.[11]

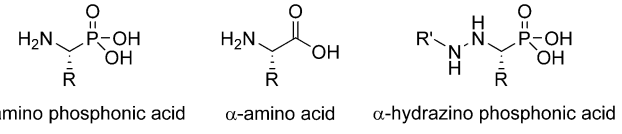

Figure 1. α-Amino phosphonic acids as analogues of α-amino acids.

For this purpose, Lewis acids have been conveniently used as promoters of such a hydrophosphonylation;[12] however, these methods show a few limitations since these catalysts are either expensive or somewhat difficult to prepare. In addition, many imines are hygroscopic and are not sufficiently stable to be isolated, particularly, those derived from aliphatic aldehydes. *N*-Acylhydrazones have been broadly used as imine surrogates,[13] since they are versatile electrophiles, more stable than imines, and are capable of reacting with a great number of nucleophiles towards the synthesis of nitrogen-containing compounds. In spite of its interest, to the best of our knowledge, the hydrophosphonylation of *N*-acylhydrazones with dialkyl phosphites has been overlooked in the literature,[14] and only a few examples of the synthesis of α-hydrazino phosphonic acids have been reported.[15] For a long time, it has been known that treatment of *N*-tosylhydrazones with dialkyl phosphites gives rise to a nucleophilic addition reaction[16] that provides interesting α-hydrazino phosphonates (Figure 1). Moreover, other few examples of activated *N*-tosylhydrazones have been reported, but in all these cases, a large excess of dialkyl phosphite or strong Brønsted acids were necessary to perform the process.[17] Preparation of α-hydrazino phosphonates has also been developed with less-reactive *N*,*N*-dialkylhydrazones but under strong reaction conditions or by adding catalysts to promote the reaction.[18] α-Hydrazino phosphonic acids and their derivatives are of potential biological importance as mentioned above.[3–9,19] We want to present here a novel and easy procedure for the hydrophosphonylation of hydrazones in the absence of catalysts and in a multicomponent process.

Results and Discussion

Firstly, we initiated the study of reactivity by testing the less-reactive *N*,*N*-dialkylhydrazones **1**–**3** against nucleophilic addition of dialkyl phosphite **4a** by a Lewis and Brønsted acid catalyzed process.[20] Unfortunately, the reaction does not work, perhaps because of the high tendency of these hydrazones to act as nucleophiles instead of as electrophiles (Scheme 1).[21]

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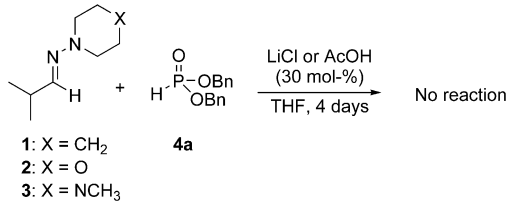
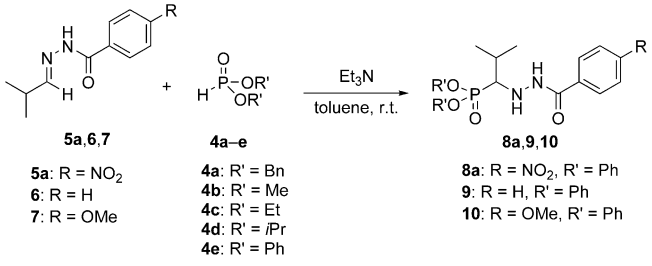


Scheme 1. Screening with *N*,*N*-dialkylhydrazones.

At this point, we decided to increase the reactivity of the hydrazone by varying the *N*-protecting group. We tested more-reactive *N*-acylhydrazones[13] **5a**, **6** and **7** against different substituted dialkyl/diphenyl phosphites **4a**–**e** as reported in Table 1. With regard to the phosphorus nucleophile, it is known that it is the phosphite and not the phosphonate form that is the real nucleophilic species.[22] This equilibrium, which under neutral conditions is completely shifted towards the unreactive phosphonate form, could be influenced by the presence of a base (Figure 2).[23]

Table 1. Hydrophosphonylation of **5a**, **6** and **7** with phosphite **4a**–**e**.[a]



Entry	Hydrazone	Phosphite	Et_3N [%]	Time [h]	Product	Yield [%]
1	**5a**	**4a**	20	24	–	n.r.[b]
2	**5a**	**4b**	20	24	–	n.r.[b]
3	**5a**	**4c**	20	24	–	n.r.[b]
4	**5a**	**4d**	20	24	–	n.r.[b]
5	**5a**	**4e**	20	24	**8a**	>99[c]
6	**5a**	**4e**	–	18	**8a**	95[d]
7	**6**	**4e**	–	48	**9**	90[d]
8	**7**	**4e**	–	24	**10**	77[d]

[a] Experimental setup: To a solution of hydrazone **5a**, **6** or **7** (1 mmol) and Et_3N (20 mol-%) in toluene (2 mL) was slowly added dialkyl/diphenyl phosphite **4a**–**e** (1.5 mmol). After the appropriate reaction time, the corresponding product **8a**, **9** or **10** was isolated by chromatography on silica gel (hexane/EtOAc, 7:3). [b] No reaction observed. [c] Calculated conversion by ^1H NMR spectroscopy. [d] Isolated yield.

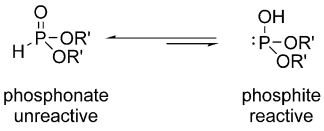


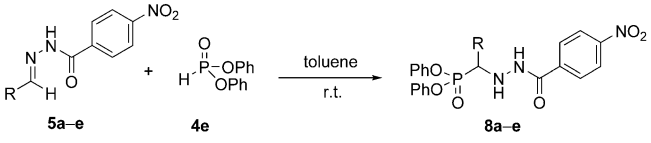
Figure 2. Equilibrium between the unreactive phosphonate and reactive phosphite forms.

In this sense, we firstly tested Et_3N as a possible Brønsted base catalyst for this process (Table 1, Entries 1–5).

Highly reactive hydrazone **5a** with an electron-withdrawing group was used in the test reaction to explore the viability of this hydrophosphonylation process. Firstly, we screened differently substituted dialkyl/diphenyl phosphites **4a**–**e** in a Brønsted base catalyzed reaction (Entries 1–5, Table 1). Only diphenyl phosphite (**4e**) showed promising reactivity when the reaction was performed at room temperature in toluene (Entry 5). This might be due to the drastic variation of pK_as for the differently substituted phosphites; diphenyl phosphite (**4e**) is the most acidic.[24] This result encouraged us to perform the reaction in the absence of the amine with the same reactive phosphite **4e**; fortunately, this assay afforded the final product with a very good yield (Entry 6). The screening with hydrazone **6** furnished product **9** with a very good yield but after a longer reaction time (Entry 7), and **7** provided hydrazide **10** with a lower yield under the same reaction conditions (Entry 8).

We further explored the scope of this hydrophosphonylation process for different compounds **5a**–**e**, under the optimized reaction conditions. The corresponding derivatives **8a**–**e** were obtained with very high yields at room temperature in toluene (Table 2, Entries 1–5). Only **5b** required a longer reaction time (Table 2, Entry 2), perhaps because of the sterically hindered *tert*-butyl group.

Table 2. Uncatalyzed hydrophosphonylation of **5a**–**e** with phosphite **4e**.[a]



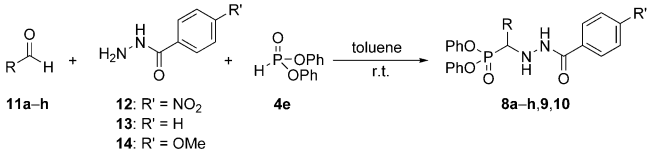
Entry	Hydrazone	R	Time [h]	Product	Yield [%][b]
1	**5a**	*i*Pr	24	**8a**	95
2	**5b**	*t*Bu	48	**8b**	83
3	**5c**	*n*Pr	24	**8c**	90
4	**5d**	*i*Bu	20	**8d**	87
5	**5e**	$PhCH_2CH_2$	20	**8e**	95

[a] Experimental setup: To a solution of hydrazone **5a**–**e** (1 mmol) in toluene (3–4 mL) was slowly added **4e** (1.5 mmol). After the appropriate reaction time, the products **8a**–**e** were isolated by chromatography on silica gel (hexane/EtOAc, 7:3). [b] Isolated yield.

In the last years, multicomponent strategies have attracted more attention in the scientific community, which allows the obtaining of high levels of atom efficiency.[25] Three-component condensation reactions are interesting and important, not only because two bonds are formed in one pot, but also because the methodology is useful for making a broad variety of compound libraries. Moreover, in these multicomponent processes, only a single reaction solvent, workup procedure and purification step is required to obtain a product that would otherwise require more

steps. In this context, we focused on the development of an uncatalyzed one-pot reaction or a multicomponent reaction for the synthesis of α-hydrazido phosphonates with in situ generated hydrazones. We tested different solvents at room temperature in the test reaction depicted in Table 3 for product **8a**, in order to improve the in situ formation of hydrazone as a possible rate-determining step for further nucleophilic attack of diphenyl phosphite (**4e**). Among them THF (49%), $CHCl_3$ (40%) and CH_2Cl_2 (15%) had a negative influence on the reactivity, on the other hand, the use of toluene (60%) gave a better and promising result.

Table 3. Multicomponent hydrophosphonylation of **11a**–**h** and **12**–**14** with phosphite **4e**.[a]



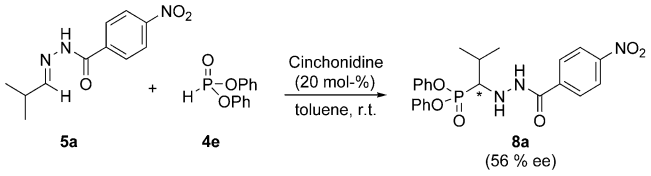
Entry	Aldehyde	R	Hydrazide	Time [h]	Product	Yield [%][b]
1	**11a**	*i*Pr	**12**	18	**8a**	95
2	**11a**	*i*Pr	**13**	24	**9**	70
3	**11a**	*i*Pr	**14**	24	**10**	60
4	**11b**	*t*Bu	**12**	72	**8b**	62
5	**11c**	*n*Pr	**12**	24	**8c**	70
6	**11d**	*i*Bu	**12**	24	**8d**	62
7	**11e**	$PhCH_2CH_2$	**12**	24	**8e**	50
8	**11f**	*s*Bu	**12**	18	**8f**	89
9	**11g**	*c*-hexyl	**12**	48	**8g**	65
10	**11h**	*c*-pentyl	**12**	24	**8h**	71
11[c]	**11a**	*i*Pr	**12**	30	**8a**	72

[a] Experimental setup: To a solution of **12**–**14** (1.1 mmol) in toluene (2 mL) was slowly added **11a**–**g** (1 mmol). After half an hour, dialkyl phosphite **4e** (1.5 mmol) and toluene (2 mL) was added, and the mixture was stirred at room temperature. After the appropriate reaction time, the final product was isolated by chromatography on silica gel (hexane/EtOAc, 7:3). [b] Isolated yield. [c] Reaction performed on a 1-g scale.

After checking the ratio of substrates, concentration and reaction time for the formation of hydrazone, the scope of the reaction was explored by using a variety of aliphatic aldehydes. In all cases, the reaction proceeded smoothly at room temperature to provide the desired products **8a**–**h**, **9** and **10**. The results are presented in Table 3. These data indicate that the reaction is highly efficient for all types of aliphatic substrates, and the final products are stable solids.

Aldehydes **11a**–**h** smoothly reacted with *N*-acylhydrazides **12**–**14** over 18–72 h and required only a small excess of diphenyl phosphite (1.5 equiv.) to reach complete conversion. Adducts **8a**–**h** were formed in moderate to excellent yields (Table 3, Entries 1 and 4–10).[26,27] The procedure is also general for different *N*-acylhydrazide derivatives, although lower yields are obtained with **13** and **14** (Table 3, Entries 2 and 3).[28] When the reaction was performed on a 1-g scale, the product was successfully obtained in a 72% yield (Table 3, Entry 11). This multicomponent strategy leads to better results in terms of overall yields than the use of preformed hydrazones (Table 2) if the amount of product lost in the corresponding purification of the starting material is taken into account. An X-ray analysis served to confirm the structure of the final products, and single crystals were obtained for adducts **8b** and **8c** (see Supporting Information).[29]

It is not surprising that the absolute configuration for different phosphonyl compounds strongly influences their biological properties.[30] In this context, the chiral version of this reaction is of great interest, and, to the best of our knowledge, there is no previously reported example of such a process. A very preliminary screening of different chiral organocatalysts showed that the use of commercially available Cinchonidine provided the final product **8a** with an unprecedented and promising 56% enantioselectivity in good yield (Scheme 2).



Scheme 2. Enantioselective organocatalytic hydrophosphonylation of **5a**.

Conclusions

The present study reveals a mild and efficient method for the preparation of α-hydrazido phosphonate derivatives, suitable for a variety of aliphatic aldehydes. This procedure seems superior to other studies from an atom-economy point of view, since neither a catalyst nor a high excess of diphenyl phosphite is necessary, even if longer reaction times are required. Applications of this methodology for preparing enantiomerically enriched α-hydrazido phosphonates by an organocatalytic procedure are currently in progress in our laboratory.

Experimental Section

General Procedure for the Synthesis of Aldehyde *N*,*N*-Dialkylhydrazones 1–3 and *N*-Benzoylhydrazones 5a–e, 6 and 7: To a solution of the corresponding benzohydrazide or hydrazine (12 mmol) in CH_2Cl_2 (10 mL) were added Na_2SO_4 and the corresponding aldehyde **11a**–**e** (10 mmol). The mixture was stirred at room temperature and for 1 d until total consumption of the starting material. It was then filtered and concentrated. Starting material, yields and spectroscopic data for compounds **1**–**3**, **5a**–**e**, **6** and **7** are described in the Supporting Information.

General Procedure for the Synthesis of α-Hydrazido Phosphonates 8a–e: To a solution of preformed hydrazone **5a**–**e** (1 mmol) in toluene (3–4 mL) was added diphenyl phosphite (**4e**) (290 μL, 1.5 mmol), and the reaction mixture was stirred until total consumption of the starting material (20–48 h). After this reaction time, the crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3) to afford products **8a**–**e**. The amount of reagents, yields, and spectra for adducts **8a**–**e** are reported in the Supporting Information.

Multicomponent Synthesis of α-Hydrazido Phosphonates 8a–h, 9 and 10: To a solution of **12**–**14** (1.1 mmol) in toluene (2 mL) was added **11a**–**h** (1 mmol). After 0.5 h, diphenyl phosphite (**4e**) (1.5 mmol) was slowly added in toluene (2 mL). The mixture was stirred at room temperature until total consumption of the hydrazone. After the corresponding reaction time (see Table 3), the crude product was directly isolated by chromatography on silica gel (hexane/EtOAc, 7:3) to afford products **8a**–**h**, **9** and **10**. The amount of reagents, yields, and spectra for **8a**–**h**, **9** and **10** are reported in the Supporting Information.

Organocatalytic Enantioselective Hydrophosphonylation of 5a: To a solution of **5a** (0.2 mmol, 47 mg) and Cinchonidine (0.04 mmol, 11.8 mg) in toluene (0.5 mL), was added **4e** (0.3 mmol). The mixture was stirred at room temperature. After 72 h, the crude product was directly isolated by chromatography on silica gel (hexane/EtOAc, 7:3) to afford product **8a** in a 62% yield and 56% *ee*. $[a]_D^{22}$ = +54.5 (*c* = 0.835, $CHCl_3$, 56% *ee*). HPLC setup: Daicel Chiralpak IA column (hexane/EtOAc, 7:3, flow rate 1 mL/min, UV 254.4 nm, τ_{minor} = 16.5 min, τ_{major} = 20.0 min).

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization data for compounds **2**, **3**, **5a**–**e**, **6**, **7**, **8a**–**h**, **9** and **10** and ^{1}H NMR, ^{13}C NMR and HRMS spectra for all new compounds are presented.

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[28] The same moderate results were obtained when Et_3N (20 mol-%) was used as catalyst; **13** (71%) and **14** (63%).
[29] CCDC-753258 (**8b**) and -753259 (**8c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The

graphic views showed in Figures S1 and S2 (Supporting Information) were made with ORTEP3 software (Copyright by Farrugia, L. J. University of Glasgow, 1997–2000).

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