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A Novel Approach to Substituted α-Carbamoyl Phosphonates: Useful Reagents for the Horner–Wadsworth–Emmons Olefination

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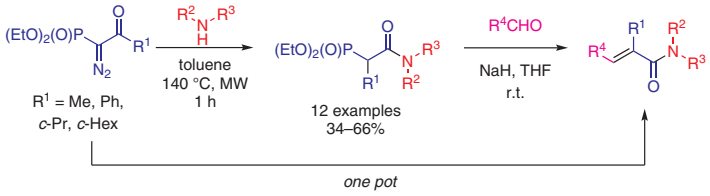

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Abstract α-Carbamoyl phosphonates are useful reagents for the Horner–Wadsworth–Emmons olefination of aldehydes en route to medicinally relevant polysubstituted acrylamides. A new synthetic approach to these reagents has been developed. The methodology relies on the microwave-promoted Wolff rearrangement of α-acyl-α-diazophosphonates with trapping of the ketene intermediate in situ with various amines.

Key words Michael acceptors, α-diazo-β-oxophosphonates, Wolff rearrangement, ketene trapping, Horner–Wadsworth–Emmons olefination, one-pot procedure

The so-called 'Michael acceptors' (electron-deficient olefins capable of reacting with nucleophiles via conjugate or Michael addition) are often regarded as cautionary structural features in bioactive compound design because of their potentially nonspecific reactivity towards nucleophilic centers in proteins, which can generate false positive response in biological assays.[1] At the same time, the reactivity of Michael acceptors towards cysteines has been successfully exploited in medicinal chemistry, particularly for the design of targeted covalent inhibitors.[2] It is also notable that in the natural product domain, unrivaled by its success as a source of drug leads, Michael acceptor motifs are frequently encountered[3] and could be responsible for the antineoplastic activity displayed by such naturally occurring compounds.[4] The selective cytotoxic activity displayed by Michael acceptors towards cancer cells could be attributable to their interaction with the components of critical cell survival mechanisms (such as ubiquitin proteasome system[5] or thioredoxin system[6]).

In our medicinal chemistry program[7] directed at developing anticancer small-molecule inhibitors of thioredoxin reductase (TrxR), a redox defense enzyme overexpressed in cancer cells, we required a convenient entry into simple substituted acrylamides **1** (or 'piper-amides' i.e., α,β-unsaturated amides bearing resemblance to the components of plant genus *Piper*[8]), which would allow for a flexible variation of the peripheral diversity elements ($R^{1/2}$, R^3, and R^4). Such a facility in substituent variation is required to fine-tune the electrophilicity of **1** from electronic as well as steric perspectives and to achieve selective targeting of the catalytic selenocysteine (Sec-SeH) residue (ionized at physiological pH) of TrxR over cysteines (Cys-SH) abundantly present in proteins.[9] Retrosynthetically, acrylamides **1** can be disconnected, with the Horner–Wadsworth–Emmons (HWE) olefination in mind, to 2-phosphonamides **2** (Scheme 1).[10] The latter, in turn, can be obtained either via amidation of β-phosphono-*N*-hydroxysuccinimidyl esters **3**[11] or through a somewhat cumbersome sequence comprising the Arbuzov reaction of α-bromoacetamide **4** and subsequent α-alkylation with R^1Hal.[12] For our purposes, however, we considered an entirely different disconnection of **2**; namely, down to their diazo precursors **5**, the simplest of which (**5a**, R^1 = Me) is known as the Ohira–Bestmann reagent.[13] Such a disconnection was inspired by our recent success involving closely related α-diazo-β-oxosulfones in thermally promoted Wolff rearrangement in the presence of aromatic amines, which gave rise to α-sulfonyl acetanilides.[14] Indeed, the Wolff rearrangement of α-diazo phosphonates has been realized under Rh(II)-catalyzed[15] as well as thermally promoted[16] conditions, with O-nucleophile trapping of the resulting ketene intermediate **6**. This provided an additional encouragement for us to investigate the new approach to phosphonamides **2** (intended for the use in the Horner–Wadsworth–Emmons olefination of aldehydes) from α-diazo phosphonates **5** under practically convenient, catalyst-free conditions (Scheme 1). Herein, we would like to provide the details of this investigation.

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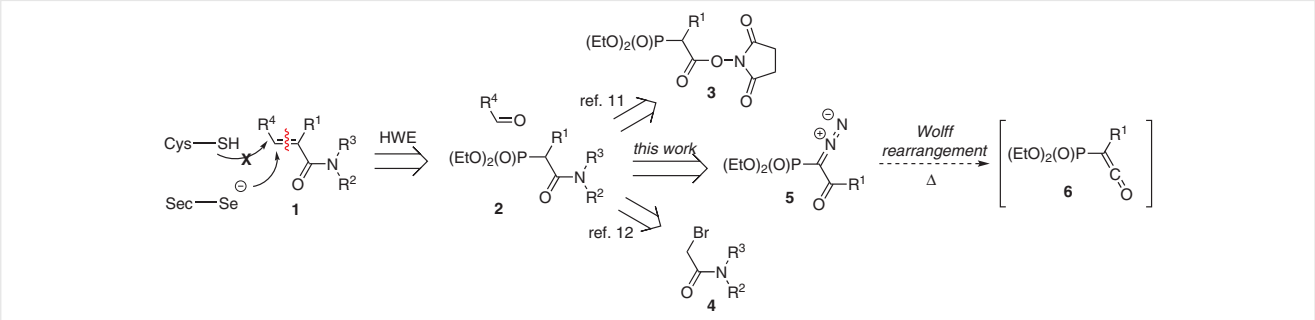
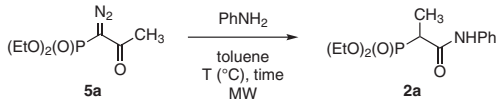


Scheme 1 'Piper-amides' **1** and retrosynthetic approaches to their phosphonamide precursors **2**

Initially, we screened the reaction conditions for the ketene generation from **5a** and trapping it with aniline under microwave irradiation.[17] As detailed in Table 1, the optimum results (entry 2) from the standpoint of the yield of product **2a**, reaction time and the reagent expenditure were obtained with 1.2 equiv of **5a** at 140 °C in toluene. The reaction could also be conducted under conventional heating (reflux in toluene, entry 3) with no detriment to the yield, albeit with markedly longer reaction time.

Table 1 Condition Screening for the Preparation of Phosphonamide **2a**[a]



5a **2a**

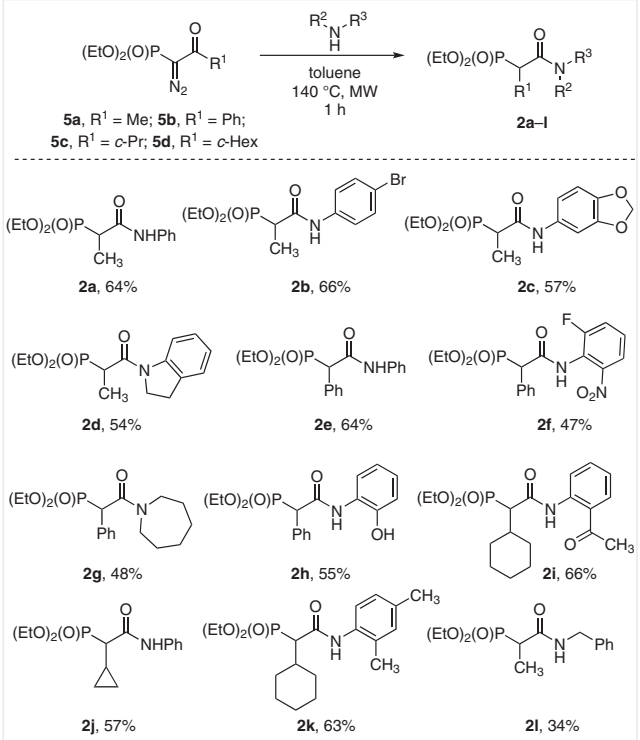
Entry	**5a** (equiv)	T (°C)	Time (h)	Yield (%)[b]
1	1.1	140	1	54
2	1.2	140	1	64
3[c]	1.2	110	6.5	63
4[d]	1.2	140	1	57
5	1.5	140	1	67
6	1.2	110	5	65
7	1.2	130	2	65
8	1.2	150	0.75	60

[a] Reactions were performed on a 0.5 mmol scale.
[b] Yield after isolation of **2a** by flash column chromatography.
[c] Reaction was conducted under conventional heating.
[d] Reaction was conducted in 1,4-dioxane.

The optimum conditions thus identified were then applied to α-diazo-β-oxophosphonates **5a–d** (all prepared on gram scale from the respective active-methylene β-oxophosphonates by using the *s*ulfonyl-*a*zide-*f*ree or SAFE diazo transfer protocol in aqueous medium[18]) in combination with a range of aromatic as well as aliphatic amines (Scheme 2).[19]

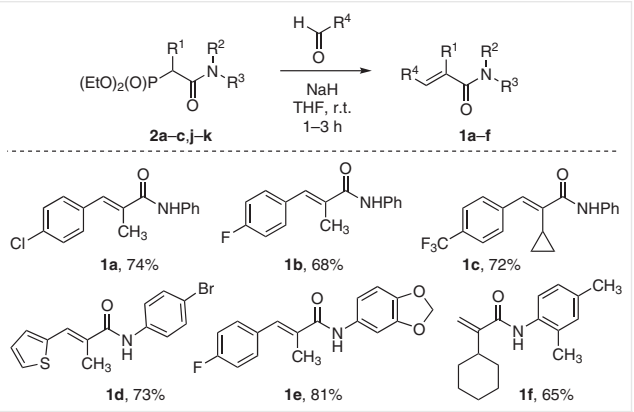
The yields of products **2a–l** were quite uniform, irrespective of the nature of the migrating group (R^1) or the trapping amine. In contrast to the similar transformation of the closely related α-diazo-β-oxosulfones, which failed for aliphatic amines,[14] products **2g** and **2l** were successfully obtained, albeit in somewhat lower yields. This could be due to the higher nucleophilicity of aliphatic amines, which can lead to degradation of the starting α-diazo-β-oxophosphonates **5** via deacylation. Also notable is the successful use of deactivated anilines (to give **2f** and **2i**) as well as of *o*-aminophenol (to give **2h**).

Having established the new approach to phosphonamides **2**, we were keen to test them in HWE olefination reactions (although this is a transformation well established for **2**[10]). To this end, reagents **2a–c** and **2j–k** were treated with a slight excess of sodium hydride in the presence of various aldehydes in THF at room temperature.[11] The reactions were complete in 1–3 hours according to the



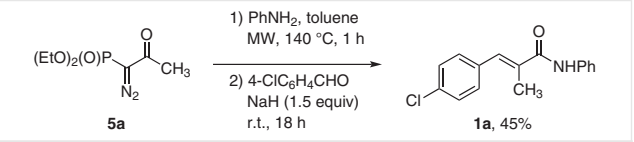
Scheme 2 Conversion of α-diazo-β-oxophosphonates **5** into phosphonamides **2**[20]

TLC analysis, and the respective (*E*)-configured piperamides **1a–f** were isolated chromatographically in good yields (Scheme 3). The (*E*)-configuration of the double bond in these products was confirmed by single-crystal X-ray crystallographic structure of compound **1a** (see the Supporting Information).



Scheme 3 HWE olefination with selected phosphonamides **2**

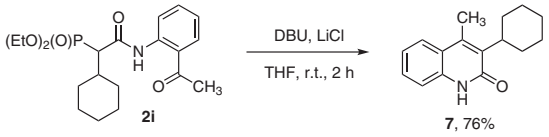
At this point we wondered whether the generation of phosphonamides **2** and their use for HWE olefination could be coupled in a one-pot sequence. To this end, we tested the preparation of acrylamide **1a** (combined yield 47% over two steps) in one-pot format by preparing phosphonamide **2a** from the Ohira–Bestmann reagent (**5a**) and performing the subsequent olefination of 4-chlorobenzaldehyde in the same toluene solution.[21] To our delight, the yield of compound **1a** obtained after chromatographic purification (45%) was comparable to that calculated over two steps (Scheme 4).



Scheme 4 One-pot preparation of compound **1a** from the Ohira–Bestmann reagent (**5a**)

Finally, we noted that compound **2i** was set for intramolecular HWE olefination involving the nearby acetyl group.[22] Indeed, treatment of this compound with DBU in THF in the presence of lithium chloride[22–23] gave hitherto unreported 2-quinolone **7** in very good yield (Scheme 5).

In summary, we have developed a new synthetic approach to α-carbamoyl phosphonates, which are useful reagents for the Horner–Wadsworth–Emmons olefination of aldehydes en route to medicinally relevant polysubstituted acrylamides. The methodology relies on the microwave-promoted Wolff rearrangement of α-acyl-α-diazophosphonates with trapping of the ketene intermediate in situ with various amines. The resulting phosphonamides can be purified chromatographically and used in the HWE reaction or the latter can be performed, with comparable yields, in one-pot format, without the isolation of the phosphonamide reagent.



Scheme 5 Preparation of 2-quinolone **7**

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707200. Included are experimental details and copies of the ^{1}H, ^{13}C and ^{31}P NMR spectra.

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(19) **Synthesis of 2a–l; General Procedure:** Diazo ketophosphonate **5** (1.2 mmol) and amine (1 mmol) were dissolved in anhydrous toluene (2 mL) and placed in a 5 mL microwave vial. The solution was then irradiated at 140 °C for 1 h. The resulting mixture was concentrated in vacuo and subjected to flash column chromatography on SiO_2 (*n*-hexane/acetone, gradient from 85:15 to 60:40) to afford phosphonamide **2**.
(20) Characterization data of selected compounds:
Compound 2d: Yield: 168 mg (54%); light-brown solid; mp 39.0–40.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.2 Hz, 1 H), 7.24–7.15 (m, 2 H), 7.08–6.99 (m, 1 H), 4.63–4.52 (m, 1 H, NCH_2CH_2), 4.25–4.12 (m, 4 H, OCH_2CH_3), 4.11–4.00 (m, 1 H, NCH_2CH_2), 3.37–3.14 (m, 3 H, NCH_2CH_2, CH), 1.53 (dd, *J* = 18.1, 6.9 Hz, 3 H, CH_3), 1.36 (t, *J* = 6.2 Hz, 3 H, OCH_2CH_3), 1.32 (t, *J* = 6.1 Hz, 3 H, OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.0 (d, *J* = 4.2 Hz), 142.9, 131.7, 127.4, 124.5, 123.9, 117.5, 63.1 (d, *J* = 6.6 Hz), 62.5 (d, *J* = 6.9 Hz), 48.6, 39.3 (d, *J* = 132.7 Hz), 27.9, 16.5 (d, *J* = 2.4 Hz), 16.4 (d, *J* = 2.5 Hz), 12.5 (d, *J* = 6.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.17. HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{15}H_{22}NNaO_4P$: 312.1359; found: 312.1359.
Compound 2g: Yield: 170 mg (48%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.45 (m, 2 H), 7.38–7.26 (m, 3 H), 4.48 (d, *J* = 22.8 Hz, 1 H, CH), 4.31–4.19 (m, 2 H, OCH_2CH_3), 4.1–3.94 (m, 2 H, OCH_2CH_3), 3.62–3.31 (m, 4 H, NCH_2), 1.81–1.42 (m, 7 H), 1.39–1.25 (m, 4 H, OCH_2CH_3, $NCH_2CH_2CH_2$), 1.20 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.11 (d, *J* = 3.1 Hz), 132.30 (d, *J* = 9.6 Hz), 129.46 (d, *J* = 6.0 Hz), 128.58 (d, *J* = 2.9 Hz), 127.64 (d, *J* = 3.5 Hz), 63.41 (d, *J* = 6.5 Hz), 62.51 (d, *J* = 7.2 Hz), 50.57 (d, *J* = 143.8 Hz), 48.68, 46.28, 28.92, 27.40, 26.82, 26.43, 16.41 (d, *J* = 6.1 Hz), 16.26 (d, *J* = 6.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.32. HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{18}H_{28}NNaO_4P$: 376.1648; found: 376.1645.
Compound 2i: Yield: 261 mg (66%); yellowish solid; mp 118.9–120.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.87 (s, 1 H, NH), 8.78 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.57 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1 H), 7.15 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1 H), 4.29–4.09 (m, 4 H, OCH_2CH_3), 2.77 (dd, *J* = 20.5, 9.7 Hz, 1 H, CH), 2.69 (s, 3 H, CH_3), 2.29–2.17 (m, 2 H), 1.87–1.74 (m, 2 H), 1.74–1.61 (m, 2 H), 1.40–1.26 (m, 8 H), 1.26–1.13 (m, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 167.7 (d, *J* = 4.1 Hz), 140.6, 135.1, 131.6, 122.6, 122.0, 120.9, 62.5 (d, *J* = 7.1 Hz), 62.3 (d, *J* = 6.6 Hz), 56.6 (d, *J* = 130.9 Hz), 37.6 (d, *J* = 3.8 Hz), 31.9 (d, *J* = 3.3 Hz), 31.8 (d, *J* = 7.9 Hz), 30.89, 28.5, 26.0, 25.9, 16.38, 16.33. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 23.22. HRMS-ESI: *m*/*z* [M + H] calcd for $C_{20}H_{30}NNaO_5P$: 396.1934; found: 396.1936.
Compound 2j: Yield: 181 mg (58%); white solid; mp 97.4–99.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (s, 1 H, NH), 7.60–7.54 (m, 2 H), 7.33–7.28 (m, 2 H), 7.13–7.06 (m, 1 H), 4.27–4.20 (m, 2 H, OCH_2CH_3), 4.16 (m, 2 H, OCH_2CH_3), 2.19 (dd, *J* = 21.6, 10.5 Hz, 1 H, CH), 1.44–1.25 (m, 7 H, OCH_2CH_3, CH_2CHCH_2), 0.82–0.67 (m, 2 H, CH_2CHCH_2), 0.55–0.40 (m, 2 H, CH_2CHCH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.9, 138.0, 128.9, 124.2, 119.8, 63.4 (d, *J* = 6.8 Hz), 62.8 (d, *J* = 7.0 Hz), 52.20 (d, *J* = 130.1 Hz), 16.51 (d, *J* = 5.8 Hz), 16.40 (d, *J* = 6.0 Hz), 9.4 (d, *J* = 4.6 Hz), 4.42, 4.27. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.01. HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{15}H_{22}NNaO_4P$: 334.1179; found: 334.1181.
(21) **One-Pot Procedure for the Preparation of 1a from 5a**: β-Ketophosphonate **5a** (1.2 mmol) and aniline (1 mmol) were dissolved in toluene and placed in a 5 mL microwave vial. The solution was irradiated at 140 °C for 1 h. Upon cooling to r.t., NaH (1.5 mmol, 60% suspension in mineral oil) was added portionwise. After the evolution of hydrogen gas stopped, 4-chlorobenzaldehyde (1 mmol) was added. The reaction mixture was stirred at r.t. overnight and washed with ice-cold water (10 mL). The aqueous phase was back-extracted with Et_2O (2 × 10 mL) and the combined organics was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was subjected to flash column chromatography.
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