JOC Note

Four-Component Reaction for the Preparation of α-Amino Phosphonates from Methyleneaziridines

Peter M. Mumford,[†] Gary J. Tarver,[‡] and Michael Shipman*

Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, United Kingdom, and Schering Plough Corporation, Newhouse, Scotland, ML1 5SH, United Kingdom

m.shipman@warwick.ac.uk

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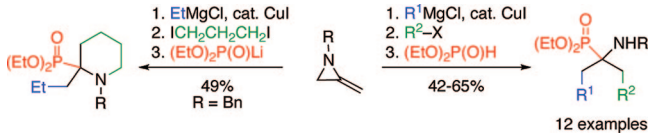
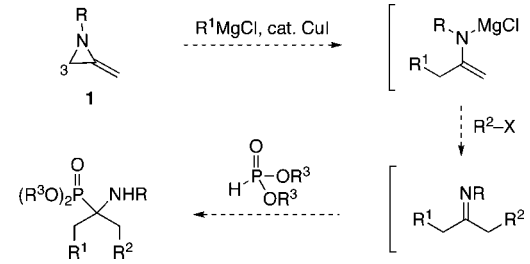


α-Amino phosphonates can be rapidly assembled in moderate to good yields (42−65%) via a "one-pot" process that brings together four components through the construction of three new intermolecular bonds.

α-Amino phosphonic acids and their derivatives act as analogues of α-amino acids, and as such they constitute important motifs in medicinal chemistry.[1,2] They display a range of biological activities including use as antibiotics,[3] herbicides,[4] and fungicides.[5] The most general and straightforward preparative route to these compounds involves hydrophosphonylation of imines (Pudovic reaction).[6] This transformation has broad substrate scope and has been successfully extended to the synthesis of enantiopure derivatives through the application of asymmetric catalysis.[7]

The Kabachnik−Fields reaction[8,9] combines imine formation, through condensation of an amine with an aldehyde (or ketone), with the hydrophosphonylation step. In this way, the preparation of α-amino phosphonates can be realized through a more direct multicomponent reaction (MCR). As four-component reactions (4CRs) are generally more useful in diversity-oriented synthesis and library generation than 3-CRs,[10] we thought that the development of a 4-CR for the synthesis of α-amino phosphonates would be of considerable value to medicinal chemists. In this Note, we describe what we believe is the first 4-CR for the synthesis of α-amino phosphonates and outline its scope and limitations.

SCHEME 1. MCR Approach to α-Amino Phosphonates



In previous studies, we have devised a 3-CR for the synthesis of ketimines from 2-methyleneaziridines both in solution[11] and on solid phase.[12] The reaction involves opening of methyleneaziridine at C-3 by using a Grignard reagent under Cu(I) catalysis, and capture of the resulting metalloenamine with a carbon-based electrophile (R^2-X). By further manipulation of the resulting ketimines, a range of compound classes including ketones,[11,12] amines,[13] α-amino nitriles,[14] hydantoins,[15] and β-lactams[16] can be made in "one-pot". By combining this approach to ketimines with hydrophosphonylation,[6] we reasoned that it should be possible to develop a flexible approach to α-amino phosphonates (Scheme 1). Notably, this 4-CR would create three new intermolecular bonds and generate up to four points of chemical diversity in a single transformation.

Methyleneaziridines **1a**−**c** used in this study were prepared according to published methods.[17] Treatment of **1a** in THF with EtMgCl (2.5 equiv) and CuI (20 mol %) induced ring-opening of the aziridine at C-3 to generate the metalloenamine, which was alkylated with BnBr (1.5 equiv). Subsequent addition of diethylphosphite (2.5 equiv) yielded α-amino phosphonate **2a** in 65% yield after silica gel column chromatography (Scheme

[†] University of Warwick.
[‡] Schering Plough.

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SCHEME 2. α-Amino Phosphonate Synthesis by 4-CR

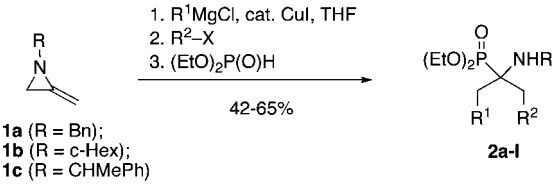
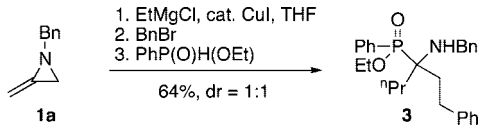


TABLE 1. 4-Component α-Aminophosphonate Synthesis

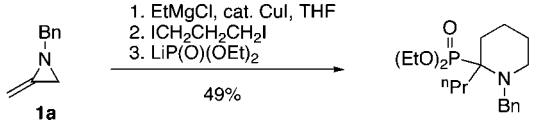
entry	SM	R^1	R^2–X	product	yield[a] (%)
1	**1a**	Et	BnBr	**2a**	65
2	**1b**	Et	BnBr	**2b**	57
3	**1c**	Et	BnBr	**2c**	54[b]
4	**1a**	Et	$THPO(CH_2)_3Br$	**2d**	60
5	**1a**	Et	$CH_2{=}CHCH_2Br$	**2e**	61
6	**1a**	Et	p-$MeOC_6H_4CH_2Br$	**2f**	62
7	**1a**	Et	$CH_3C{\equiv}CCH_2Br$	**2g**	57
8	**1a**	Et	p-$BrC_6H_4CH_2Br$	**2h**	52
9	**1a**	^{i}Bu	BnBr	**2i**	63
10	**1a**	Bn	BnBr	**2j**	62
11	**1a**	c-Hex	BnBr	**2k**	42
12	**1a**	Allyl	BnBr	**2l**	61

[a] Isolated yield after aqueous workup and column chromatography. Detailed experimental procedures and full characterization data are provided in the Supporting Information. [b] Isolated as ca. 1:1 mixture of diastereomers as judged by ^{1}H NMR spectroscopy.

SCHEME 3. Use of Ethyl Phenylphosphinate in 4-CR



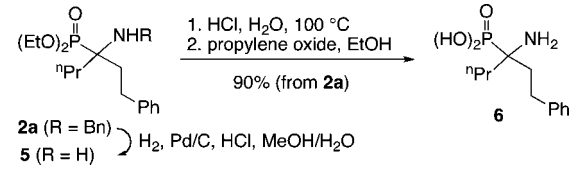
SCHEME 4. Use of Difunctionalized Electrophiles in 4-CR



2 and Table 1, entry 1). Interestingly, no additives were required to effect the final phosphite addition step, which was complete after stirring overnight at 45 °C. As Lewis acids are known to accelerate Pudovic reactions,[6,18] we speculate that the magnesium and copper salts produced in this MCR assist in the addition of the P−H bond across the imine. Good variation in the structure of the methyleneaziridine, Grignard, and electrophile component is achieved in this 4-CR (Table 1). While the chemical yields are modest (42−65%), this limitation is offset by the significant increases in molecular complexity achieved in this "one-pot" procedure. Changes in the nature of the phosphorus-containing component are also possible. For example, ethyl phenylphosphinate can be used to make **3** by use of the same general protocol (Scheme 3).

By using 1,3-diiodopropane as electrophile, the chemistry can be further extended to the synthesis of piperidines. For example, methyleneaziridine **1a** can be transformed into piperidine **4** in 49% yield (Scheme 4). In this case, higher yields were observed with use of $LiP(O)(OEt)_2$ in the addition step,[19] a finding consistent with this reaction proceeding through a cyclic iminium ion.[13,14]

SCHEME 5. Deprotection to α-Amino Phosphonic Acids



To establish if the resulting α-amino phosphonates could be converted into the corresponding α-amino phosphonic acids, deprotection of one of the products was investigated. Hydrogenolysis of **2** yielded primary amine **5**, which upon further treatment with HCl then propylene oxide gave α-amino phosphonic acid **6** in 90% overall yield (Scheme 5).

To conclude, a versatile 4-CR for the rapid synthesis of α-amino phosphonates from methyleneaziridines has been developed by the sequential formation of three new intermolecular bonds through a sequence that involves aziridine opening, C-alkylation, and hydrophosphonylation of the resulting imine. Work to produce other important classes of compounds by use of methyleneazidine MCRs is ongoing in our laboratory.

Experimental Section

Synthesis of α-Amino Phosphonates: General Procedure. Copper(I) iodide (20 mol %) in a round-bottomed flask was flame-dried under vacuum and then purged with nitrogen (three cycles performed). THF (2 mL) was added and the mixture was cooled to −30 °C, whereupon the Grignard reagent (2.5 equiv) was added. After 10 min, methyleneaziridine **1** in THF (1 mL) was added and the reaction mixture was stirred at room temperature for 3 h. Upon cooling to 0 °C, the electrophile (1.5 equiv) was added dropwise, and the mixture was heated at 45 °C. After 3 h, the phosphite (2.5 equiv) was added dropwise and heating was continued at 45 °C overnight. Upon cooling to room temperature, the mixture was diluted with Et_2O (20 mL) and washed with a saturated aqueous solution of NH_4Cl (2 × 20 mL), 50% NaOH solution (2 × 20 mL), and brine (2 × 20 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the α-aminophosphonate was achieved by column chromatography with silica pretreated with Et_3N.

Diethyl [3-(Benzylamino)-1-phenylhexan-3-yl]phosphonate (2a). α-Amino phosphonate **2a** was prepared from CuI (26 mg, 0.14 mmol), ethylmagnesium chloride (2 M in THF, 880 μL, 1.76 mmol), **1a** (102 mg, 0.70 mmol), benzyl bromide (130 μL, 1.09 mmol), and diethyl phosphite (230 μL, 1.79 mmol) according to the general procedure. Workup followed by column chromatography (30% ethyl acetate in petroleum ether) afforded **2a** (185 mg, 65%) as a pale yellow oil. IR (film) 2958, 1603, 1453, 1230, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.23 (10H, m), 4.24 (4H, dt, J = 7.6, 14.6 Hz), 3.97 (2H, s), 2.91−2.76 (2H, m), 2.13−1.99 (2H, m), 1.93−1.75 (2H, m), 1.62−1.55 (3H, m), 1.41 (6H, t, J = 6.9 Hz), 1.01 (3H, t, J = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6 (C), 141.1 (C), 128.43 (CH), 128.41 (CH), 128.40 (CH), 128.2 (CH), 126.9 (CH), 125.8 (CH), 61.7 (CH_2, d, J_{CP} = 7.6 Hz), 59.7 (C, d, J_{CP} = 135.7 Hz), 47.6 (CH_2, d, J_{CP} = 2.8 Hz), 35.9 (CH_2, d, J_{CP} = 4.0 Hz), 35.8 (CH_2, d, J_{CP} = 4.4 Hz), 29.7 (CH_2, d, J_{CP} = 5.4 Hz), 16.7 (CH_3, d, J_{CP} = 5.6 Hz), 16.5 (CH_2, d, J_{CP} = 7.6 Hz), 14.7 (CH_3) ppm; ^{31}P NMR (161 MHz, $CDCl_3$) δ 30.6 ppm; MS (ES^+) m/z 404 ($[M + H]^+$, 100); HRMS (ES^+) calcd for $C_{23}H_{35}NO_3P$ $(M + H)^+$ 404.2349, found 404.2345.

Diethyl [3-(Benzylamino)-1,5-diphenylpentan-3-yl]phosphonate (2j). α-Amino phosphonate **2j** was prepared from CuI (26 mg, 0.14 mmol), benzylmagnesium chloride (2 M in THF, 890 μL, 1.78 mmol), **1a** (103 mg, 0.71 mmol), benzyl bromide (130 μL,

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(19) $LiP(O)(OEt)_2$ has been used previously in additions to ketimines. See, for example: Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757–1760.

1.09 mmol), and diethyl phosphite (230 μL, 1.79 mmol) according to the general procedure. Workup followed by column chromatography (30% ethyl acetate in petroleum ether) afforded **2j** (205 mg, 62%) as a white solid. Mp 69−70 °C; IR (film) 2923, 1601, 1451, 1221, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.17 (15H, m), 4.22 (4H, dt, J = 7.3 Hz, 14.5 Hz), 3.96 (2H, s), 2.92−2.76 (4H, m), 2.21−2.03 (4H, m), 1.70 (1H, br s), 1.37 (6H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5 (C), 141.0 (C), 128.6 (CH), 128.5 (CH) 128.3 (CH), 127.1 (CH), 126.0 (CH), 62.0 (CH_2, d, J_{CP} = 7.4 Hz), 59.7 (C, d, J_{CP} = 136.4 Hz), 47.4 (CH_2, d, J_{CP} = 3.2 Hz), 35.9 (CH_2, d, J_{CP} = 4.6 Hz), 29.8 (CH_2, d, J_{CP} = 5.4 Hz), 16.8 (CH_3, d, J_{CP} = 8.6 Hz) ppm; ^{31}P NMR (161 MHz, $CDCl_3$) 30.2 ppm; MS (ES^+) m/z 466 ($[M + H]^+$, 100); HRMS (ES^+) calcd for $C_{28}H_{37}NO_3P$ $(M + H)^+$ 466.2506, found 466.2519. Anal. Calcd for $C_{28}H_{36}NO_3P$: C, 72.23; H, 7.79; N, 3.01. Found: C, 72.56; H, 7.78; N, 2.95.

Diethyl (3-Amino-1-phenylhexan-3-yl)phosphonate (5). Palladium (10 wt % on activated carbon; 52 mg), was added to α-amino phosphonate **2a** (346 mg, 0.86 mmol) in methanol (10 mL), water (10 mL) and concentrated hydrochloric acid (5 mL). The resulting mixture was stirred at room temperature under a hydrogen atmosphere for 14 h. After filtration through Celite, the mixture was concentrated in vacuo. Purification by column chromatography (10% methanol in dichloromethane) afforded **5** (267 mg, 99%) as a clear colorless oil. IR (film) 2959, 1603, 1454, 1224, 1020 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOD) δ 7.31−7.16 (5H, m), 4.21 (4H, dt, J = 7.3, 14.6 Hz), 2.82−2.69 (2H, m), 2.00−1.84 (2H, m), 1.80−1.62 (2H, m), 1.60−1.46 (2H, m), 1.39 (6H, t, J = 7.1 Hz), 0.99 (3H, t, J = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, d_4-MeOD) 143.6 (C), 129.5 (CH), 129.3 (CH), 127.0 (CH), 64.0 (CH_2, d, J_{CP} = 7.8 Hz), 63.9 (CH_2, d, J_{CP} = 8.0 Hz), 56.1 (C, d, J_{CP} = 145.7 Hz), 39.3 (CH_2, d, J_{CP} = 3.1 Hz), 39.1 (CH_2, d, J_{CP} = 2.6 Hz), 30.8 (CH_2, d, J_{CP} = 5.2 Hz), 17.6 (CH_2, d, J_{CP} = 5.4 Hz), 16.9 (CH_3, d, J_{CP} = 5.4 Hz), 15.1 (CH_3) ppm; ^{31}P NMR (161 MHz, d_4-MeOD) δ 31.1 ppm; MS (ES^+) m/z 314 ($[M + H]^+$, 100); HRMS (ES^+) calcd for $C_{16}H_{29}NO_3P$ $(M + H)^+$ 314.1880, found 314.1890.

(3-Amino-1-phenylhexan-3-yl)phosphonic Acid (6). α-Amino phosphonate **5** (203 mg, 0.65 mmol) in concentrated hydrochloric acid (20 mL) was refluxed for 14 h. On cooling to room temperature, the solvent was removed in vacuo. The residue was dissolved in the minimum amount of hot ethanol (ca. 1 mL) and cooled to room temperature, then excess propylene oxide (20 mL) added. After the mixture was stirred for 3 h, the precipitated phosphonic acid **6** (152 mg, 91%) was isolated by filtration as a white solid. Mp 204−206 °C; IR (film) 2961, 2872, 1603, 1525, 1496, 1454, 1147 cm^{-1}; ^1H NMR (400 MHz, d_4-AcOD) δ 7.32−7.19 (5H, m), 2.91−2.77 (2H, m), 2.36−1.99 (4H, m), 1.67−1.52 (2H, m), 1.00 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, d_4-AcOD) δ 141.1 (C), 128.4 (CH), 128.1 (CH), 126.0 (CH), 58.5 (C, d, J_{CP} = 145.0 Hz), 35.1 (CH_2), 34.8 (CH_2), 29.3 (CH_2), 16.1 (CH_2, d, J_{CP} = 4.5 Hz), 13.5 (CH_3) ppm; ^{31}P NMR (161 MHz, d_4-AcOD) δ 17.1 ppm; MS (ES^+) m/z 258.0 ($[M + H]^+$, 100); HRMS (ES^+) calcd for $C_{12}H_{21}NO_3P$ $(M + H)^+$ 258.1254, found 258.1255.

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Supporting Information Available: Characterization data and ^1H and ^{13}C NMR spectra for compounds **2a**−**l**, and **3**−**6**, and experimental procedures for their preparation. This material is available free of charge via the Internet at http://pubs.acs.org.

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