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Inter- and intramolecular Horner–Wadsworth–Emmons reactions of 5-(diethoxyphosphoryl)-1-acyl-2-alkyl(aryl)-2,3-dihydro-4-pyridones

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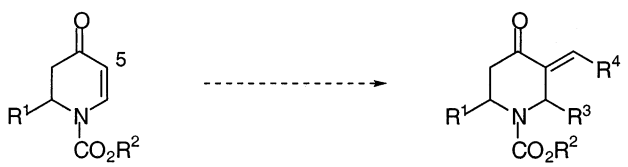
Abstract—Dihydropyridones of the type **1** were converted to their C-5 alkylidene derivatives **2** by a reaction sequence involving phosphorylation, conjugate reduction or addition to provide piperidones **4**, and then olefination via a Horner–Wadsworth–Emmons reaction. An intramolecular version of this method was used to prepare *trans*-bicyclic enone **13**.

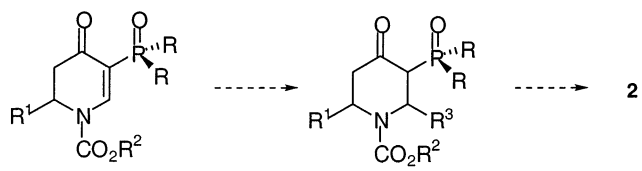
N-Acyldihydropyridones of the type **1** are versatile building blocks for piperidine, indolizidine, quinolizidine, perhydroquinoline and other alkaloid ring systems.[1] These heterocycles (**1**) can be conveniently prepared in racemic[2] or enantiopure[3] form using 1-acyl-4-methoxypyridinium salt chemistry.[4] To enhance the scope of dihydropyridones **1** as synthetic intermediates, we are developing methods to add substituents at various positions of the heterocyclic ring in a regio- and stereocontrolled fashion.[5] In support of total synthesis efforts in our laboratories, we have been examining ways to regioselectively introduce an alkylidene group at the C-5 position of **1** to provide enones **2**.



1 **2**

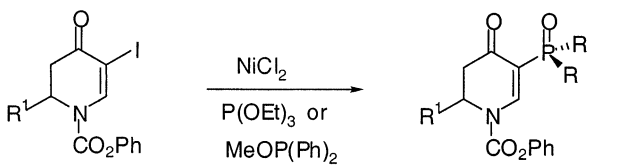
The route we chose to investigate first is depicted in Scheme 1. The plan called for preparation of phosphorus derivatives **3**, conjugate reduction or addition to provide piperidones **4**, and then olefination via a modified Wittig reaction to give the desired enones **2**.

The preparation of dihydropyridones of the type **3** was accomplished as shown in Scheme 2. The iododihydropyridones **5** were prepared by C-5 iodination of the corresponding dihydropyridones using our previously described procedures.[6] To convert **5** to the desired phosphorus derivatives, we examined Kazankova's method[7] for converting vinyl halides to phosphonates and phosphine oxides using a metal-catalyzed cross-



3 **4**

Scheme 1.



5 R^1 = Ph, *i*-Pr

6, R = OEt, R^1 = Ph, *i*-Pr
7, R = Ph, R^1 = Ph

Scheme 2.

* Corresponding author.

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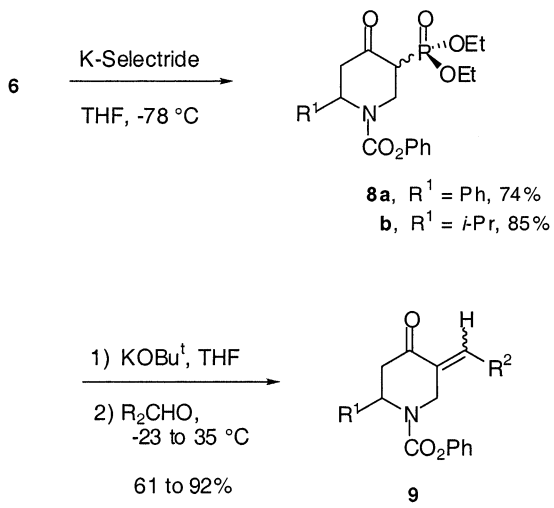


Scheme 3.

Table 1. HWE olefination of **8** with various aldehydes to give **9**

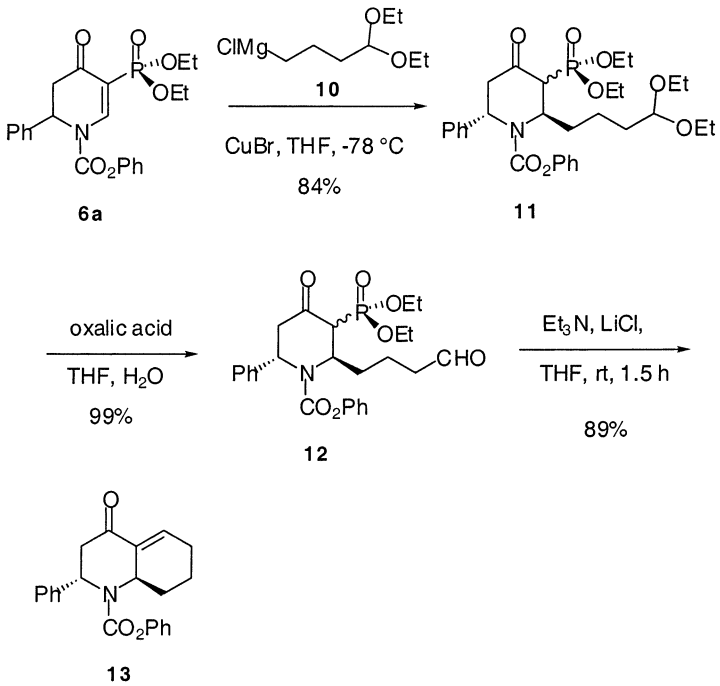
Entry[a]	8	Aldehyde	9, Yield (%)[b]	*E*/*Z* ratio[c]
1	**8a**	Benzaldehyde	92	8.3/1
2	**8a**	Hydrocinnamaldehyde	75	6.4/1
3	**8a**	Cinnamaldehyde	64	3.1/1
4	**8a**	Hexanal	80	8.8/1
5	**8b**	Benzaldehyde	84	11.6/1
6	**8b**	Hydrocinnamaldehyde	74	1.2/1
7	**8b**	Cinnamaldehyde	61	3.6/1
8	**8b**	Hexanal	76	12.3/1

[a] The reactions were performed on a 1.5–3.0 mmol scale.
[b] Yield of **9** obtained from radical PLC (silica gel, EtOAc/hexanes) as a mixture of *E*,*Z* isomers.
[c] Isomer ratios were determined by HPLC.

coupling reaction. Initial attempts using triethyl phosphite and $NiCl_2$ catalyst in various solvents were not successful. Fortunately, when the reaction was performed without solvent at 150°C, excellent yields of the vinyl phosphonates **6** were obtained (**6a**, R^1 = Ph, 97%; **6b**, R^1 = *i*-Pr, 87%). We also could prepare the phosphine oxide **7** in high yield (81%) using **5a** (R^1 = Ph), methyl diphenylphosphinite, and cat. $NiCl_2$ in refluxing toluene. Product **7** was difficult to purify, however, so subsequent studies were performed with phosphonates **6**.

The double bond in **6** was reduced with K-Selectride to give phosphonates **8**.[8] The Horner–Wadsworth–Emmons (HWE) reaction was examined to convert **8** and various aldehydes to enones **9** (Scheme 3).[9] Anion formation with KOBu^t in THF, followed by addition of the aldehyde, and raising the reaction temperature to 35°C gave good yields of the desired enones as shown in Table 1.

An intramolecular HWE olefination sequence was also carried out as shown in Scheme 4. Dihydropyridone **6a** was added to Grignard reagent **10**[10] and CuBr·SMe_2 in THF to provide an 84% yield of the *trans*-piperidone **11**. The stereoselectivity was opposite of that anticipated, as 2-substituted *N*-acyl-2,3-dihydro-4-pyridones generally give *cis*-addition with organocuprates.[11] The combination of the C-2 phenyl and C-5 phosphonate groups on **6a** must hinder axial attack via chair conformation **A**. Axial attack via the higher energy chair conformation **B** leads to the observed product (Fig. 1). Hydrolysis of the acetal **11** was carried out using aqueous oxalic acid/THF at rt to afford the crude aldehyde **12** in near quantitative yield. Attempted purification of **12** by chromatography on silica gel resulted in partial cyclization to bicyclic enone **13**. The



Scheme 4.

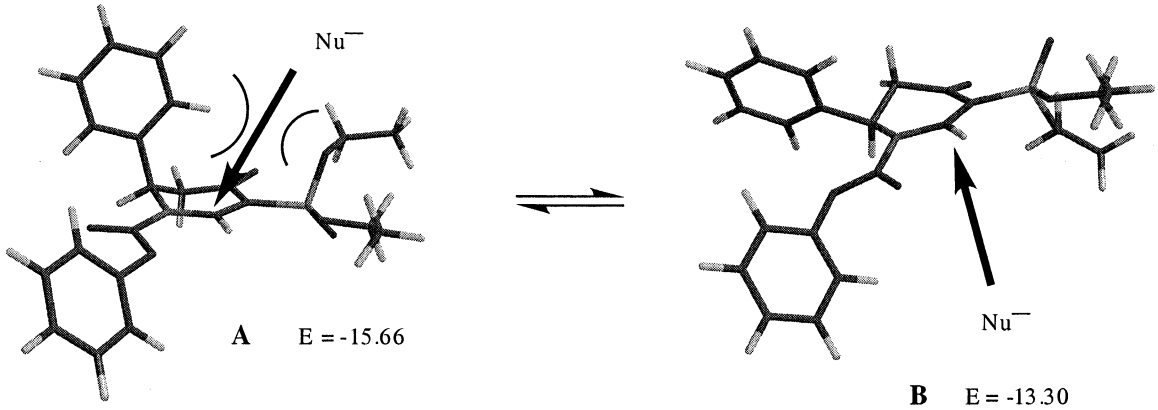


Figure 1. Axial attack on chair conformations **A** and **B**.[14]

SiO_2-mediated cyclization could not be improved, and only 20% of **13** was obtained by this procedure.

Several other conditions were used without success to effect the intramolecular HWE reaction of **12** (e.g. NaOMe, KOBu^t, TFA, Amberlyst 15, TEA). Fortunately, Rathke's method[12] using TEA/LiCl in THF led to a high yield of the desired enone **13**. The stereochemistry of **13** was confirmed by single crystal X-ray analysis.[13]

In summary, an alkylidene group can be introduced at the C-5 position of dihydropyridones **1** using a phosphorylation, reduction, and an intermolecular HWE olefination sequence. An intramolecular version of this method allowed the facile preparation of *trans*-bicyclic enone **13** in a highly stereocontrolled fashion.[15]

Acknowledgements

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8. NMR analysis in $CDCl_3$ shows that **8** exist as a mixture of its keto and enol forms.
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13. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 159535. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
14. Molecular modeling program: MacSPARTAN Pro (1.02) by Wavefunction, Inc. Force field: MMFF. The *E* values (kcal/mol) are for the ground-state conformations shown.
15. The structure assigned to each new compound is in accord with its IR and ^1H and ^{13}C NMR spectra and elemental analysis or high-resolution mass spectra. Selected characterization data: Compound **6a**: white

solid; mp 134–135°C; IR ($CHCl_3$): 2985, 1750, 1681, 1584, 1301, 1243, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.25 (t, 3H, $J=6.6$ Hz), 1.33 (t, 3H, $J=6.6$ Hz), 2.95 (d, 1H, $J=16.5$ Hz), 3.27 (dd, 1H, $J=7.3$ and 17.1 Hz), 4.10 (m, 4H), 5.90 (d, 1H, $J=7.2$ Hz), 7.25 (m, 10H), 8.92 (d, 1H, $J=14.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.9, 17.0, 17.1, 42.8, 42.9, 57.5, 63.1, 63.1, 63.2, 63.3, 107.2, 109.7, 121.8, 126.4, 127.4, 129.3, 129.8, 130.4, 137.9, 150.8, 151.6, 152.2, 152.5, 189.7. Anal. calcd for $C_{22}H_{24}NO_6P$: C, 61.54; H, 5.63; N, 3.26. Found: C, 61.61; H, 5.74; N, 3.23.

Compound **8b**: colorless oil; IR ($CHCl_3$): 2968, 1715, 1639, 1592, 1417, 1242, 1202, 1160, 1021, 968, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.02 (d, 6H, $J=6.3$ Hz), 1.35 (t, 6H, $J=5.7$ Hz), 1.78 (br s, 1H), 2.04 (br s, 1H), 2.38 (br s, 1H), 2.44 (br s, 1H), 2.65 (d, 2H, $J=14.1$ Hz), 2.94 (dd, 1H, $J=4.3$ and 24.0 Hz), 3.06 (m, 1H), 3.22 (m, 1H), 4.15 (m, 4H), 4.44 (m, 1H), 4.68 (dd, 1H, $J=6.2$ and 14.2 Hz), 4.97 (q, 1H, $J=15.9$ Hz), 7.08–7.39 (m, 5H), 10.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.5, 18.4, 19.1, 19.7, 20.3, 29.0, 30.8, 38.0, 39.7, 40.9, 42.2, 42.7, 49.4, 51.1, 55.5, 56.4, 58.9, 59.8, 62.5, 63.1, 63.3, 121.8, 125.5, 129.5, 151.6, 154.1, 202.5. HRMS calcd for $C_{19}H_{28}NO_6P$: 398.1733 $[M+H]^+$. Found: 398.1729 $[M+H]^+$.

Compound **13**: white solid; mp 122–123°C; IR ($CHCl_3$): 3031, 2919, 2867, 1724, 1694, 1620, 1490, 1420, 1266, 1196 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.65 (m, 1H), 1.94 (m, 1H), 2.19–2.49 (m, 4H), 3.02 (dd, 1H, $J=5.6$ and 5.9 Hz), 3.13 (dd, 1H, $J=7.6$ and 7.7 Hz), 4.51 (m, 1H), 5.52 (t, 1H, $J=6.6$ Hz), 6.88 (m, 2H), 7.15 (t, 1H, $J=7.3$ Hz), 7.27–7.42 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2, 25.6, 27.7, 43.1, 54.4, 55.8, 121.8, 125.6, 126.8, 127.9, 129.0, 129.4, 137.3, 138.9, 139.9, 150.9, 154.2, 197.2. Anal. calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.06; H, 6.11; N, 3.97.