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A New Synthesis of Fused Heterocyclic and Carbocyclic Compounds via the Reaction of the Vinylphosphonate with Imide and Ketone Enolate Anions[1)]

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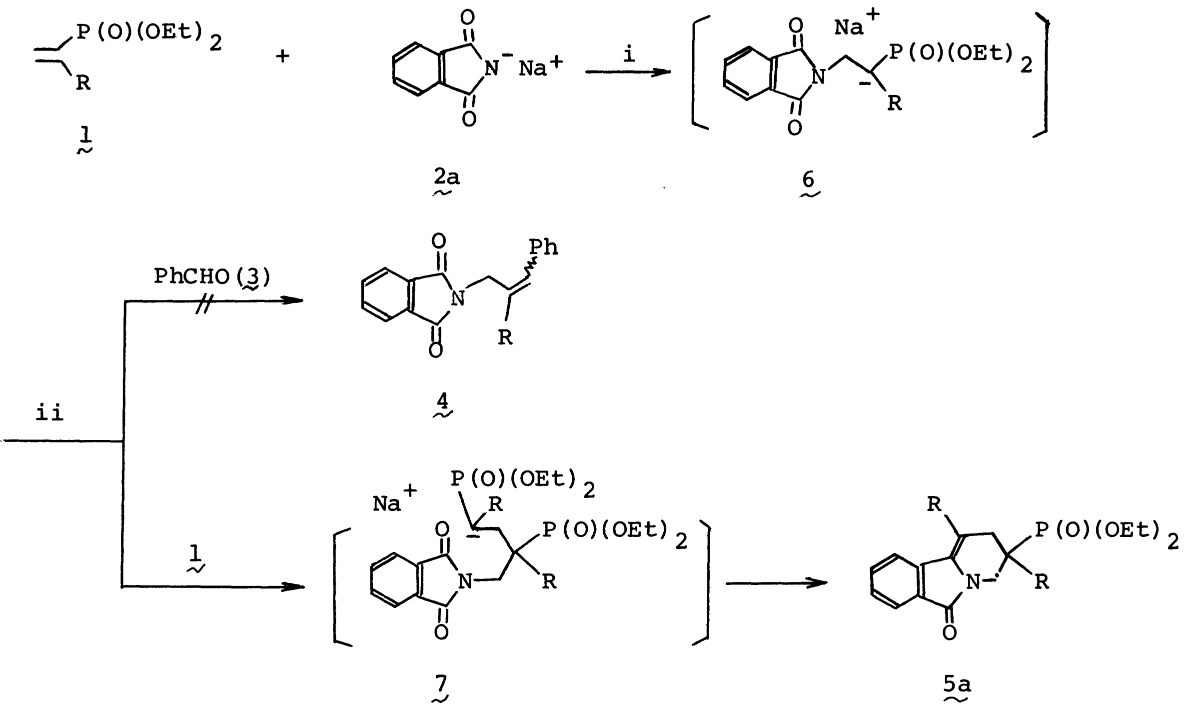
The reaction of diethyl (α-ethoxycarbonylvinyl)phosphonate with various imide and ketone enolate anions gave functionalized heterocyclic and carbocyclic, and spirocarbocyclic compounds containing the phosphorus residue in good yields.

A variety of allyl amines has been stereoselectively synthesized via the reaction of vinylphosphonium salts and phthalimide with aldehydes, followed by hydrolysis.[2)] In order to synthesize the N-(2-ethoxycarbonylallyl)phthalimide derivative as a β-amino acid synthon, we have examined similar reactions of diethyl (α-ethoxycarbonylvinyl)phosphonate (1) and sodiophthalimide (2) with aldehydes.

The reaction of the phosphonate carbanion 6, generated from the Michael addition of 2 (2 mmol) to 1 (0.47 g, 2 mmol) in a mixed solvent of THF (10 ml) and DMF (2 ml), with benzaldehyde (3) (0.21 g, 2 mmol) at 65 °C for 5 h gave an annelation product, 1,3-diethoxycarbonyl-3-diethoxyphosphinyl-2,3,4,5-tetrahydropyrido[2,1-a]-isoindolin-6-one (5a) (0.205 g, 44%), but none of the expected phthalimide 4 was formed. The structure of 5a[3)] was readily assigned on the basis of its spectral data: IR (KBr) 1725 and 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00-1.49 (12H, m, Me), 2.75-3.27 (2H, dd, J=9.52, 17.50 Hz, CH_2), 3.40-3.83 (2H, dd, J=5.37, 12.94 Hz, NCH_2), 3.93-5.10 (8H, m, OCH_2), 7.40-8.00 (3H, m), and 8.53-8.80 (1H, br); MS 465 (M^+). As shown in Scheme 1, this result can be explained by the reaction of 6 with a second molecule of 1 to yield the phosphonate carbanion 7, followed by the intramolecular Wittig-Horner reaction to afford 5a. So, when the reaction of 2a was carried out with 2 mol equiv. of 1 in the absence of 3, the compound 5a was obtained in 92% yield.[4)]



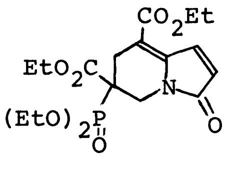
$R=CO_2Et$ i) THF/DMF, rt, 1 h ii) 65 °C, 5 h

Scheme 1.

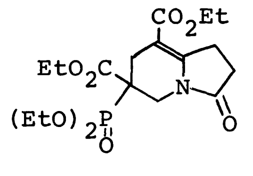
In order to apply this procedure to the synthesis of various fused heterocyclic compounds, similar treatment of 1 with imide anions such as maleimide (2b), succinimide (2c), and glutarimide anions (2d) successfully produced the corresponding indolizine 5b,c and quinolizine derivatives 5d in 19-57% yields.5)

In contrast, upon similar treatment with 2 equiv. of 1, sodioisatin (2e) afforded no corresponding 1:2 cycloadduct but the unexpected 1:3 cycloadduct 6e albeit in low yield (19%).5) The reaction of 2e with a threefold excess of 1 gave 6e in 58% yield. Thus, the yield of 6e was dependent upon the molar ratio of 1 to 2e.

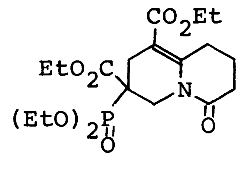
The formation of 6e suggests that the intramolecular Wittig-Horner reaction of the carbanion 8 to 5e would be presumably inhibited due to steric strain and 8 undergoes, therefore, the subsequent Michael addition to a third molecule of 1 yielding the carbanion 9, followed by the Wittig olefination (Scheme 2).



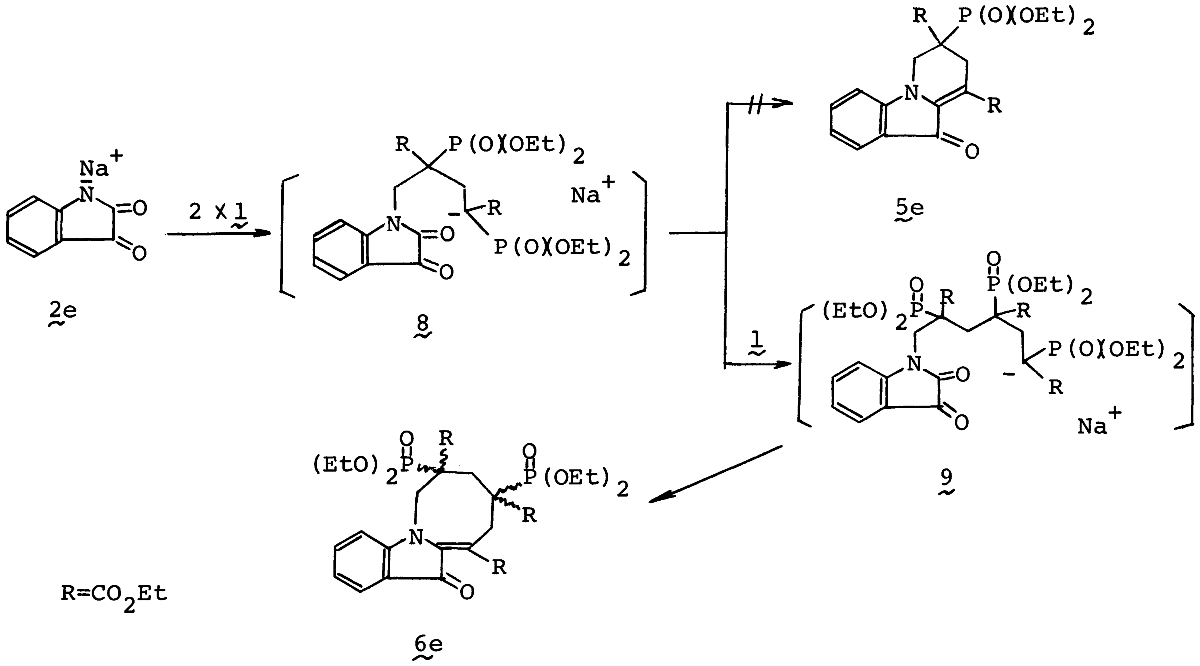
5b



5c



5d



Scheme 2.

Also, we have sought to examine the reaction of 1 with ketone enolates.6) The reaction of 1 (0.30 g, 1.26 mmol) with cyclopentanone lithium enolate (10a) (0.6 mmol), generated in-situ from cyclopentanone and lithium diisopropylamide (LDA) at -75 °C, in THF for 1 h at -75 °C and for 5 h at reflux produced a functionalized cyclohexenylphosphonate 11a7) (0.18 g, 74%) as a 1:1 mixture of two diastereoisomers.

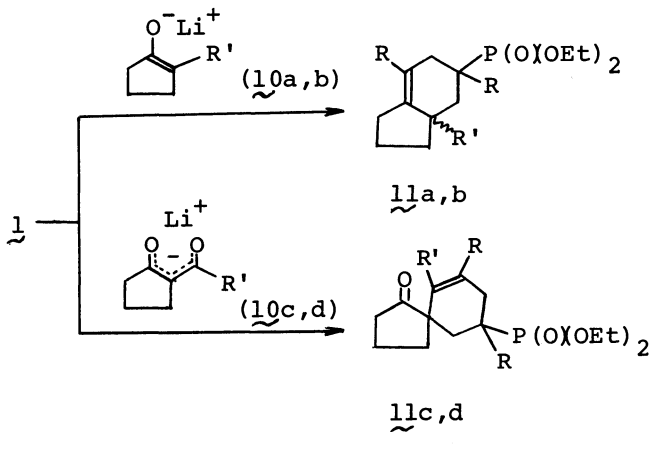


Table 1. Synthesis of Cyclohexenylphosphonates

Product	R	R'	Yield/%
11a	CO_2Et	H	74
11b	CO_2Et	CO_2Et	71
11c	CO_2Et	Me	62
11d	CO_2Et	Ph	79

Similar treatment of lithium enolates 10b-d of 2-ethoxycarbonyl-, 2-acetyl-, and 2-benzoylcyclopentanones with 1 led to the corresponding cyclohexenylphosphonates 11b-d7) in good yields (Table 1).

Thus, the above results show that the vinylphosphonate is a versatile reagent for the synthesis of fused heterocyclic and carbocyclic compounds, which have wide applicability. Synthetic application of the products is now under investigation.

References

1) Reactions of Vinylphosphonates. 4. For the preceding paper in this series, see: T. Minami, S. Tokumasu, and I. Hirao, Bull. Chem. Soc. Jpn., 58, 2139 (1985).

2) A. I. Meyers, J. P. Lawson, and D. R. Carver, J. Org. Chem., 46, 3119 (1981).

3) 5a: mp 75-76 °C. Found: C, 56.67; H, 6.11; N, 3.01%. Calcd for $C_{22}H_{28}NO_3P$: C, 56.77; H, 6.06; N, 3.01%.

4) The reaction using 2a and diethyl (α-methylsulfonylvinyl)phosphonate under similar conditions led to only a 1:1 Michael adduct in 70% yield, but no expected annelation product was obtained.

5) All new compounds were fully characterized by the IR, ^{1}H NMR, and mass spectra, and gave satisfactory elemental analyses and/or high resolution mass spectra. The physical and spectral data ($CDCl_3$ solutions for ^{1}H and ^{13}C NMR) of the selected compounds are as follows.

5b: 57% yield; oil; IR (neat) 1690-1740 cm^{-1}; ^{1}H NMR δ 1.08-1.60 (12H, m, Me), 2.52-3.12 (2H, br dd, J=9.40, 18.31 Hz, CH_2), 3.28-3.72 (2H, dd, J=5.71, 13.04 Hz, NCH_2), 3.90-4.52 (8H, m, OCH_2), 6.27 (1H, d, J=6.0 Hz, olefinic H), and 7.90 (1H, d, J=6.0 Hz, olefinic H).

5c: 47% yield; oil; ^{1}H NMR δ 1.07-1.52 (12H, m, Me), 2.12-2.80 (4H, m, CH_2CH_2), 2.80-3.60 (4H, m, NCH_2, CH_2), and 3.90-4.40 (8H, m, OCH_2).

5d: 19% yield; oil.

6e: oil; IR (neat) 1725, 1710 cm^{-1}; ^{1}H NMR δ 0.80-1.60 (21H, m, Me), 2.0-2.92 (4H, m, CH_2), 3.04-4.50 (16H, m, NCH_2, OCH_2), and 6.60-7.68 (4H, m, aromatic H); MS Found: m/z 701.2351. Calcd for $C_{31}H_{45}NO_{13}P_2$: 701.2365.

6) Similar reaction using vinyltriphenylphosphonium bromide has recently been reported by Posner and Lu [J. Am. Chem. Soc., 107, 1424 (1985)].

7) 11a: oil; IR (neat) 1700-1730, 1650 cm^{-1}; ^{1}H NMR δ 1.0-1.52 (12H, m, Me), 1.60-3.40 (11H, m, CH_2, CH), and 3.84-4.48 (8H, m, OCH_2); MS Found: m/z 402.1816. Calcd for $C_{19}H_{31}O_7P$: 402.1807.

11b: oil.

11c: a 2:1 mixture of two diastereoisomers; oil; IR (neat) 1710-1740 cm^{-1}; ^{1}H NMR δ 1.33 (12H, t, J=7.03 Hz, Me), 1.80 (3H, s, Me), 1.90-3.12 (10H, m, CH_2), and 3.80-4.42 (8H, quint, OCH_2); ^{13}C NMR δ 13.8, 14.3, 16.1 (d, $^3J_{p-c}$=5.2 Hz), 16.4 (d, $^3J_{p-c}$=5.2 Hz), 18.2, 18.5, 28.1, 28.2, 31.7, 32.0, 33.4, 33.7, 35.8, 36.5, 38.0, 38.6, 46.3 (d, $^1J_{p-c}$=131.5 Hz), 46.7 (d, $^1J_{p-c}$=134.1 Hz), 54.8 (d, $^3J_{p-c}$= 11.2 Hz), 55.6 (d, $^3J_{p-c}$=12.0 Hz), 62.7 (d, $^2J_{p-c}$=6.0 Hz), 63.6 (d, $^2J_{p-c}$=6.0 Hz), 128.5 (d, $^3J_{p-c}$=12.9 Hz), 132.0 (d, $^3J_{p-c}$=10.3 Hz), 141.5, 167.9, 168.4, 168.5 (d, $^2J_{p-c}$=4.3 Hz), 169.9 (d, $^2J_{p-c}$=4.3 Hz), 216.6, and 221.1; MS Found: m/z 444.1877. Calcd for $C_{21}H_{33}O_8P$: 444.1910.

11d: oil.

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