

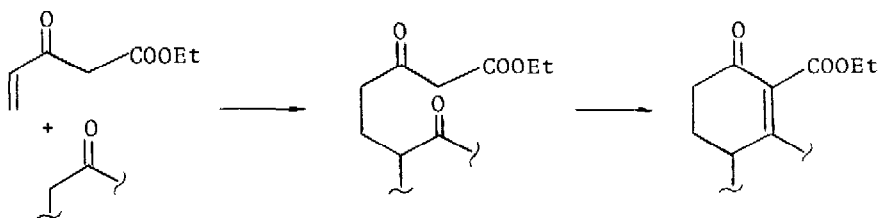
A NEW EFFICIENT SYNTHESIS OF SUBSTITUTED NAZAROV REAGENTS.  
A WITTIG-HORNER-EMMONS APPROACH

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*Summary* A highly stereoselective synthesis of terminally substituted ethyl 3-oxo-4-pentenoates **3** from  $\gamma$ -phosphorylated ethyl acetoacetate **2** and diverse carbonyl compounds was accomplished.

Continuously growing interest in the chemistry of biologically active and naturally occurring compounds possessing cyclic structures has resulted in the development of a number of simple and effective annulation methods<sup>1</sup>. Recent years have witnessed the introduction of numerous novel synthetic approaches to carbocyclic compounds as well as various refinements of the approaches already known. Among others, the efficacy of a particularly useful Robinson annulation involving in its classical form a reaction of an enolate with methyl vinyl ketone<sup>2</sup> has been considerably improved by replacing the latter component with ethyl 3-oxo-4-pentenoate known as the Nazarov reagent<sup>3-8</sup>.

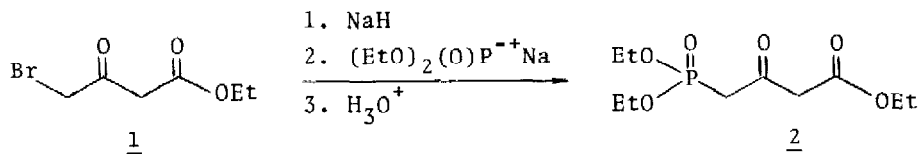


The substitution pattern of the final products formed in both kinds of annulation is essentially the same and it depends mainly on the structural variation of the enolate used.

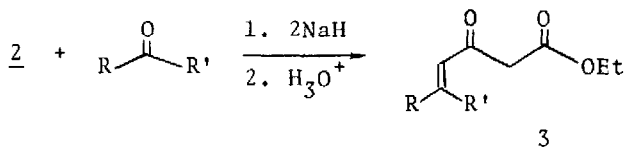
Considering the applicability of the Robinson reaction to the synthesis of carbocyclic systems with various substitution patterns we came to the conclusion that the utilization of substituted ethyl 3-oxo-4-pentenoates would provide especially attractive possibilities. In this communication we wish to present a simple method for the preparation of a series of Nazarov-type reagents containing one or two substituents at a terminal carbon atom.

According to the literature, a crucial step in the synthesis of the parent ethyl 3-oxo-4-pentenoate which involves formation of a conjugated double bond required elimination of either alcohol<sup>3,4,7,9</sup> or sulfoxide<sup>8</sup> elements from the corresponding ethyl 3-oxopentanoate derivatives. Considering the extreme usefulness of the Wittig-Horner-Emmons reaction in olefin syntheses<sup>10</sup> we hoped, that replacement of the elimination step with this type of reaction would result in obvious preparative advantages.

$\gamma$ -Phosphorylated ethyl acetoacetate 2 was chosen as a new substrate. This ester was obtained by the reaction of sodium diethyl phosphite with sodium ethyl  $\gamma$ -bromoacetoacetate 1 in THF (50%, b.p. 120°/0.4 Torr, <sup>31</sup>P NMR (CHCl<sub>3</sub>)  $\delta$  = 18.6 ppm)<sup>11</sup>.



The ester 2, in the presence of two equivalents of sodium hydride in THF at 20°-60°C, reacted regiospecifically during the Wittig-Horner-Emmons reaction using selected aliphatic, aromatic and  $\alpha,\beta$ -unsaturated aldehydes as well as aliphatic, alicyclic and aromatic ketones.



Terminally substituted ethyl 3-oxo-4-pentenoates 3 were obtained in high yields and were isolated easily by means of column chromatography or kugelrohr distillation. The corresponding data are shown in Table.

TABLE

Carbonyl substrate	Product <u>3</u>	Yield <sup>a</sup> [%]	B.p. <sup>b</sup> [°C/0.15 Torr]	Enol content <sup>c</sup> [%]	M.S.
CH <sub>3</sub> -CHO		89	50	60	156 (M <sup>+</sup> ), 141, 110, 83, 69
		96	90	65	184 (M <sup>+</sup> ), 171, 141, 113, 97, 83
		91	75	70	182 (M <sup>+</sup> ), 156, 141, 122, 83
Ph-CHO		84	150 <sup>d</sup>	75	218 (M <sup>+</sup> ), 189, 172, 145, 131
		70	90	30	170 (M <sup>+</sup> ), 155, 125, 96, 83
		65	115	30	196 (M <sup>+</sup> ), 150, 122, 108, 81
Ph-CO-CH <sub>3</sub>		60 <sup>e</sup>	245	35	232 (M <sup>+</sup> ), 217, 203, 160, 158, 115
			245	55	

<sup>a</sup> Isolated yields. <sup>b</sup> Kugelrohr distilled; oven temperature given. <sup>c</sup> In CCl<sub>4</sub>.

<sup>d</sup> M.p. 51-3°C. <sup>e</sup> Trans : cis ratio 3 : 1.

$^1\text{H}$  NMR spectra of the products were in excellent agreement with the proposed structures. Furthermore they allow a stereochemical assignment to be made. Each product 3 formed in the reactions of 2 with aldehydes was found to be a single isomer of E configuration at an alkyl or aryl substituted double bond. This was identified by the values of the corresponding coupling constants  $^3J_{\text{HC}=\text{CH}}$  equal ca. 16 Hz. The assessment of E and Z configurations for the two stereoisomeric products formed in the reaction of 2 with acetophenone was based on differential shielding effects of the phenyl substituent on the adjacent vinyl proton ( $\Delta\delta = 0.41$  ppm).

Evidently, all the products discussed are noticeably engaged in a keto-enol equilibrium 3  $\rightleftharpoons$  4. Although stabilizing effects of an intramolecular hydro-



gen bond suggest an assumption of the Z configuration for the enolic double bond in 4, spectral evidence is not unequivocal and does not permit a completely tenable analysis.

High stereoselectivity of the Wittig-Horner-Emmons reaction resulting in configurational homogeneity of most of the ethyl 3-oxo-4-pentenoates 3 described herein seems to be exceptionally valuable in the context of prospective synthetic applications of these compounds.

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#### REFERENCES AND NOTES

1. M.E.Jung, *Tetrahedron*, **32**, 3 (1976).
2. W.S.Rapson and R.Robinson, *J.Chem.Soc.*, 1285 (1935).
3. I.N.Nazarov and S.I.Zavyalov, *Zh.Obshch.Khim.*, **23**, 1703 (1953).
4. E.Wenkert, A.Adrians, B.Brendenberg, C.Kaneko and A.Tahara, *J.Am.Chem.Soc.*, **86**, 2038 (1964).
5. S.W.Pelletier, R.N.Chappell and S.Prabhakar, *ibid.*, **90**, 2889 (1968).
6. G.Stork and R.N.Guthikonda, *ibid.*, **94**, 5109 (1972).
7. J.E.Ellis, J.S.Dutcher and C.H.Heathcock, *Synth.Comm.*, **4**, 71 (1974).
8. B.M.Trost and R.A.Kunz, *J.Am.Chem.Soc.*, **97**, 7152 (1975).
9. C.Wakselman and H.Molines, *Synthesis*, 622 (1979).
10. J.Boutagy and R.Thomas, *Chem.Rev.*, **74**, 87 (1974); E.J.Corey, Z.Arnold and J.Hutton, *Tetrahedron Lett.*, 307 (1970).
11. Although compound 2 has been previously reported as a part of a reaction mixture<sup>12</sup> it has not, to our knowledge, been isolated or prepared in pure form previous to this publication.
12. V.Jagodic, *Croat.Chem.Acta*, **49**, 487 (1977), *C.A.*, **88**, 6297r (1978).

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