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AN INTRAMOLECULAR BAYLIS-HILLMAN REACTION

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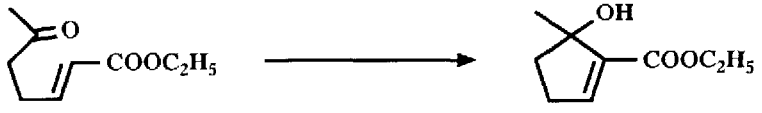
Abstract: *By means of an intramolecular Baylis-Hillman reaction the cyclopentene derivative 1 has been formed from 2. Asymmetric induction is low (entry 12, table 1). In the sixmembered ring example 9 → 10 the yield is only 17% - 23% (entries 1 and 2, table 2).*

In the course of a synthetic program we required the cyclopentenol derivative 1. It seemed to us that an intramolecular Baylis-Hillman reaction of the α,ß-unsaturated-ε-keto ester 2 would be a possible route. An intramolecular variant of this reaction[1] has not been described up to now.



2 1

The results of the experiments in which we tried to transform 2[2] into 1 are compiled in table 1. Under the most common conditions, i.e. with DABCO as a catalyst[1], neat or in THF (entry 1) only the formation of cis-2 has been observed. Sodium ethoxide (entry 2) gave a 40% yield of the ethylate-addition-Michael-reaction product, whereas with lithium-tetramethylpiperidide (entry 3) the starting material 2 with shifted double bond among others has been formed in low yield. Quinidine (entry 4) was completely inactive as catalyst, and lithium-quinidinate (entry 5) gave a mixture of not identified compounds.

Contrary to these N-bases, phosphines turned out to be useful in this reaction[4]. Tributylphosphine (entry 6) and dimethylphenylphosphine (entry 7 and entry 8) gave comparable results of a mixture consisting of ca. 30% 2 and ca. 70% 1[5]. Isobutylmethylphenylphosphine is still active but very slow (entry 9) and methyldiphenylphosphine is completely inactive (entry 10).

The last two entries (11 and 12) deal with chiral catalysts. (-)PAMP, which is an alkyl diaryl phosphine, was completely inactive, in agreement with the results in entry 10. However, (-)CAMP catalysed the reaction and in 10 days the equilibrium (vide infra) has been reached. The product 1 thus formed showed however, a disappointingly low e.e. of 14%.

At least one reason for the low e.e. in our experiment and also in earlier attempts [1b,6] is the reversibility of the ring-closure, or more generally of the C-C-bond formation[9]. That is, when 1 is treated

Table 1 Cyclisation experiments 2 → 1

Entry	Catalyst, Solvent[a]	Time	Mol%cat.	%2	%1	Remarks
1	DABCO	32d	15	81	-	19% cis-2
	DABCO, THF	30d	37	80	-	20% cis-2
2	$NaOC_2H_5$, C_2H_5OH, (-30° → rt)	2h	100	10	-	40% 4[7]
3	LiTMP[b], ether (-50° → rt)	1d	3	10	-	a.o. 5[7]
4	Quinidine, C_2H_5OH, THF	10d	10	100	-	
5	Li-quinidinate, HMPA	5h	25	0	0	mixture of unidentified products
6	$(n\text{-}Bu)_3P$	1d	25	25	75(GLC)	isolated 39% 1
7	$(CH_3)_2(C_6H_5)P$	1d	25	35	65(GLC)	
8	" CH_3CN	5d	30	70	30(GLC)	
9	$(i\text{-}Bu,CH_3,C_6H_5)P$	30d	25	50	50	
10	$CH_3(C_6H_5)_2P$	40d	25	100	-	
11	(-)PAMP(6, 78%ee)[8]	20d	20	100	-	
12	(-)CAMP(7, 62%ee)[8]	10d	18	25	75(GLC)	isolated 40% 1 (14%ee)[c]

a) if not otherwise mentioned, reactions were carried out without solvent at room temperature; b) Lithium-2,2,6,6-tetramethylpiperidide; c) NMR, optishift, CH_3-triplet of the ester group separated, $[\alpha]_D^{20}$ 0° (c=1,EtOH).

Table 2 Cyclisation experiments[a] 9 → 10

Entry	Catalyst	Conditions	9	10(%)	Remarks
1	$(CH_3)_2(C_6H_5)P$	6d,	83	17 (GC)	
2	Li-quinidinate	2h, HMPA		23 (isolated)	6% e.e.[b][c]
3	Li-(R)-3-hydroxy-quinuclidine	30 Min, HMPA, 0°C		8 (isolated)	0% e.e.
4	DABCO	1d	100		
5	Li OC_2H_5	HMPA	0	0	
				<~10	other products

a) If not otherwise mentioned, all reactions at ambient temperature and with 25 Mol% of catalyst. b) 6% of the isomer of 10 with ß,γ-positioned double bond has also been isolated. c) NMR, optishift, CH_3-triplet of the ester group separated, $[\alpha]_D^{20}$ 0° (c=1,EtOH).

with 0,25 equivalents of dimethylphenylphosphine at ambient temperature during 3 hours an equilibrium mixture consisting of 65% 1 and 35% 2 (GLC) is formed[10,11]. Treatment of 1 with DABCO (see also table 1 entry 1) resulted in a very slow formation of 2(16d, 14% 2).

The extension of the above reaction (2 → 1) to a sixmembered example, i.e. 9[12]→ 10 furnished only mediocre results (table 2).

9 10

DABCO (entry 4) did not catalyse the reaction at all. Dimethyl-phenylphosphine (entry 1) led to a mixture of 83% 9 and 17% 10[13]. No 9 was formed after treatment of 10 with dimethyl-phenylphosphine (0,25 equivalents,10d).

References and notes

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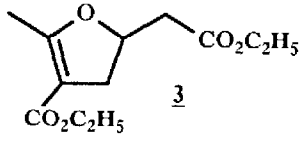
2. 2 has been prepared through alkylation of methyl-acetoacetate with ethyl-4-bromo-crotonate to 3[3] and subsequent hydrolysis and decarboxylation to 2.



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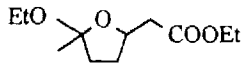
3. J.Colonge, J.P.Cayrel, Bull.Soc.Chim. France 1965, 3596.

4. Phosphine catalysts have sporadically been described for the Baylis-Hillman reaction: a) K.Morita, Z.Suzuki, H.Hirose, Bull.Chem.Soc.Jap. 41, 2815 (1968); b) T.Miyakoshi, H.Omichi, S.Saito, Nippon Kagaku Kaishi, 1980, 44; c) T.Miyakoshi, S.Saito, ibid, 1983, 1623; d) T.Imayawa, K.Uemura, Z.Nagai, M.Kawanisi, Synth.Comm.14, 1267 (1984).

5. 1-Ethoxycarbonyl-5-hydroxy-5-methyl-cyclopent-1-ene(1); ^{1}H-NMR (400 MHZ, $CDCl_3$) : 6,78 (dd; J = 2,9; 2,4; H-C(2)) 4,24 (ABX_3pattern; O-$\underline{CH_2}$-); 3,13(s;broad;OH); 2,52 and 2,57(ABXYZ-pattern; each 1H; 2H-C(3)), 2.2-2.0 (m; 2H-C(4)), 1.51 (s;CH_3-C(5)), 1.32 (t,J = 7; $\underline{CH_3}$-CH_2-); IR($CHCl_3$): 3660, 3540, 1690, 1620; MS: 269 (2; M^+-1); 156(5), 155(58), 153(3), 127(8), 125(12), 110(8), 109(100), 97(9).

6. D.Basavaiah, V.V.L.Gowriswari, P.K.S.Sarma, P.D.Rao, Tetrahedron Lett. 31, 1621 (1990).

7. 

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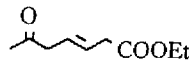

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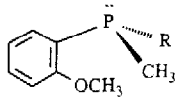
8. 

6 R = C_6H_5; (-)PAMP
7 R = c-C_6H_{11}; (-)CAMP

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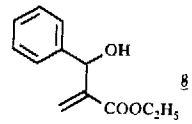
9. In addition to the reversibility of the C-C-bond formation, the possibility of pseudorotation in an intermediate oxaphospholen could be a further reason for the low e.e. observed: a) G.Buono, J.R.Llinas, J.Am.Chem.Soc. 103, 4532 (1981); b) R.R.Holmes, ibid, 100, 433 (1978); D.Gorenstein, ibid, 92, 644 (1970); D.Gorenstein, F.H.Westheimer, ibid, 92, 634 (1970).

10. When 8 is treated with 0,25 eq. DABCO during 6d an equilibrium mixture of 87% 8 and 13% benzaldehyde (NMR measurement) is formed.



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11. Our experience with different catalysts in the intramolecular reaction 2 → 1 prompted us to run a series of experiments in the intermolecular case benzaldehyde + ethylacrylate → 8. Very big differences exist in reaching the equilibrium concentration of ca. 75 - 80% 8 (neat, r.t. 5-15 Mol%cat.): DABCO (8d), triphenylphosphine (21d), (+)-Norphos (4d), $CH_3(C_6H_5)_2P$ (2.5h),$(CH_3)_2(C_6H_5)P$(2.5h), (-)CAMP[8](30 min),i-Bu(CH_3) $(C_6H_5)P$(30 min).

12. 9 has been prepared through ozonolysis of 1-methylcyclopentene (-45°, CH_3OH-CH_2Cl_2, work up with sodiumthiosulfate at pH 6, 70%) to 5-oxo-hexanal and subsequent Horner-Wittig reaction at -40°C (60%).

13. 1-Ethoxycarbonyl-6-hydroxy,6-methyl-cyclohex-1-ene(10). NMR (200MHZ, $CDCl_3$); 6.97(dd, J_1~J_2~2,4; H-C(2)),4.23(q,0-CH_2-), 4.16 (s; OH), 2.3-2.1(m, 2H-C(3)), 1.9-1.5 (m; 2H-C(4), 2H C(5)), 1.47(s, CH_3-C(6)), 1.32(t;CH_3-CH_2-). MS: 170(8,M^+), 169(50), 123(100), 110(17),95 (16), 82(24), 68(9), 55(38), 43(37).

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