Reinvestigation on the Catalytic Isomerisation of Carbon–Carbon Triple Bonds

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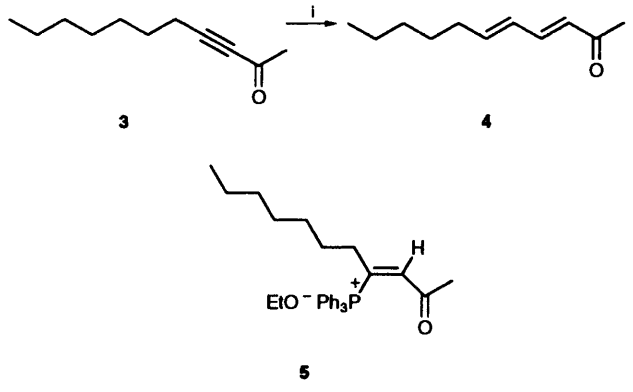
Based on the discovery that phosphines could catalyse the isomerisation of triple bonds, the isomerisation of acetylenic derivatives was differentiated into two types: phosphine-catalysed and transition metal-catalysed.

We have reported[1–12] the isomerisation of a variety of acetylenic derivatives, in which we used transition metal complexes containing or with phosphines as catalysts. In an experiment connected with a recently found novel deoxygenation–isomerisation reaction of 4-hydroxy-2-ynoic esters (**1**; R^1 = alkoxy) and γ-hydroxy-α,β-ynones (**1**; R^1 = alkyl) mediated by triphenylphosphine (Scheme 1),[13] isomerisation

1 **2**

Scheme 1 *Reagent:* PPh_3 (1 mol equiv.)

product **4** was obtained instead of the expected phosphonium salt **5** when ynone **3** was subjected to reaction with triphenylphosphine (Scheme 2). This result prompted us to undertake a reinvestigation of the catalytic isomerisation of triple bonds to see whether the transition metal is necessary. The results are listed in Tables 1 and 2.



3 **4** **5**

Scheme 2 *Reagents, conditions and yields:* i, Ph_3P (100 mol%), EtOH (100 mol%), benzene, reflux, 35 h, 72%

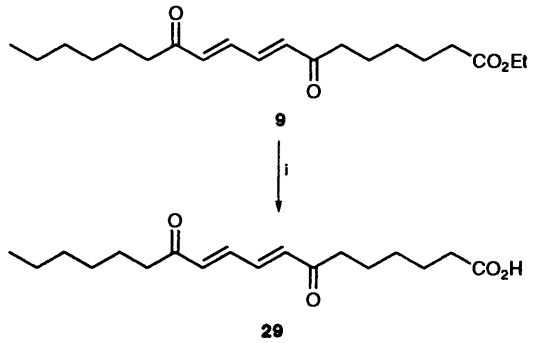
From Table 1, we can see that ynones **3**, **6**, **8** and **10** isomerised smoothly in the presence of a catalytic amount of triphenylphosphine even at 25 °C, and that ynoates **14** and **16** isomerised when subjected to the more nucleophilic Bu_3P. Ynamide **18** also underwent isomerisation effected by Bu_3P but in lower yield even at higher temperature. The reactivity order is ynone > ynoate > ynamide (entries 1, 7, 9 and 10) and Bu_3P > Ph_3P (entries 5 and 6). The requirement of an electron-withdrawing group is clearly illustrated by the reactivity order of the substrates and the fact that the yne-hydroxy compounds with electron-non-deficient triple bonds did not undergo isomerisation in the presence of a phosphine alone (Table 2, entries 11, 14, 17 and 20). This result is consistent with Trost's report,[14] which showed that yne-carbonyl compounds such as **3**, **14**, **16** and **18** could isomerise under the catalysis of triphenylphosphine with no effect whatsoever on the non-conjugated acetylene.

Enynone **12** did not isomerise in the presence of triphenylphosphine even at 110 °C (entry 5) while trienone **13** was obtained in 77–82% yield by using $Pd(OAc)_2$ (5 mol%)/Ph_3P (35 mol%) as the catalytic system (100 °C in toluene). By using the more nucleophilic Bu_3P, compound **12** also isomerised without addition of the palladium complex (entry 6).

While no isomerisation occurred for ynols (Table 2, entries 11, 14, 17 and 20) in the presence of a phosphine, they could all isomerise under the catalysis of transition metal complexes (Table 2).[8–12] In these reactions, the presence of a metal is crucial.

In summary, the isomerisation of acetylenic derivatives is briefly differentiated into two types: (a) The reaction can be catalysed by a phosphine alone (for yne-carbonyl compounds); (b) a transition metal is necessary (for yne-hydroxy compounds). Thus, the phosphine and the transition metal show different utility in the isomerisation of different types of acetylenic derivatives.

In addition, the isomerisation products **17** and **19**. (Table 1, entries 9 and 10) can be used as precursors to synthesize bicyclic compounds through an intramolecular Diels–Alder reaction.[15,16] Furthermore, ostopanic acid **29** was obtained by hydrolysis of ethyl ostopanoate **9** from the isomerisation of compound **8** (Table 1, entry 3), which was prepared from pent-4-ynal in three steps,[4] thus providing a novel total synthesis of this plant-derived anticancer agent (Scheme 3). Therefore, this



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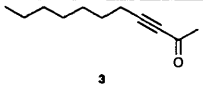
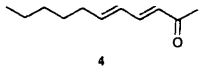
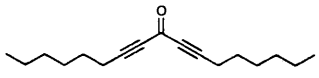
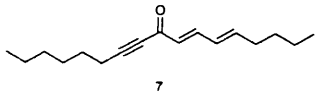
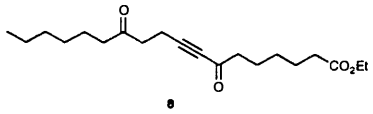
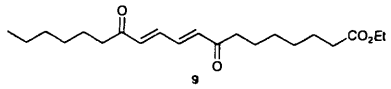
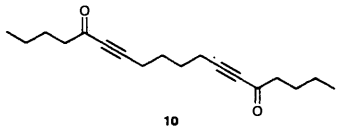
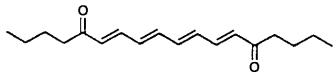
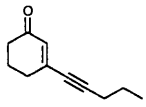
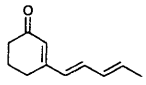
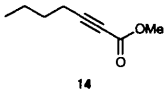
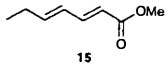
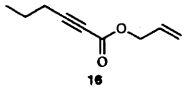
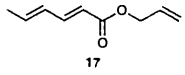
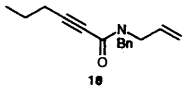
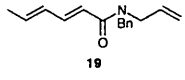
Scheme 3 *Reagents, conditions and yields:* i, LiOH, Pr^iOH–water, room temp., 95%

simple and highly stereoselective reaction catalysed by a phosphine gives a very practical approach toward the synthesis of very useful polyene carbonyl compounds.

Experimental

M.p.s and b.p.s are uncorrected. M.p.s were measured on a Thiele apparatus. ^1H NMR spectra were recorded on a Varian

Table 1 Isomerisation of yne-carbonyl Compounds[a]

Entry	Substrate	R_3P (mol %)	Temp (T/°C)/Time (t/h)	Product	Isolated yield (%)
1	 **3**	Ph_3P (10)	25/34	 **4**	84
2	 **6**	Ph_3P (10)	25/47	 **7**	89
3	 **8**	Ph_3P (10)	25/47	 **9**	86
4	 **10**	Ph_3P (20)	25/46	 **11**	83
5	 **12**	Ph_3P (100)	110/35	 **13**	0[b]
6	**12**	Bu_3P (20)	110/30	**13**	89
7	 **14**	Ph_3P (100)	25/35	 **15**	0[b]
8	**14**	Bu_3P (20)	110/24	**15**	82
9	 **16**	Bu_3P (20)	25/48	 **17**	80
10	 **18**	Bu_3P (20)	110/24	 **19**	60

[a] All reactions were performed as described in the Experimental section. [b] Starting material was recovered.

EM-360 or Varian XL-200 spectrometer for solutions in C_6D_6 or $CDCl_3$ with Me_4Si as internal standard. IR spectra were taken on a Shimadzu IR-440 spectrometer and mass spectra (MS) were run on a Finnigan 4021 GC/MS/DC instrument by electron ionisation (EI).

All reactions were carried out under argon. All solvents were dried and redistilled before use. Ynones **3**,[2] **6**,[3] and **8**,[4] ynoate **14**,[6] enynone **12**,[5] and ynols **20**,[8] **23**,[12] **25**,[11] and **27**[10] were prepared as described in our previous work. Diynedione **10**,[17] ynoate **16**,[17] and ynamide **18**[18] were prepared according to reported methods.

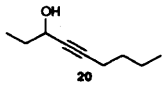
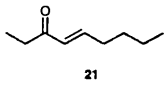
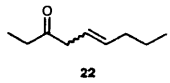
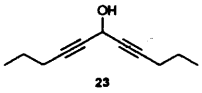
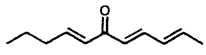
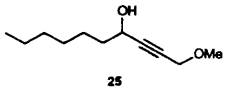
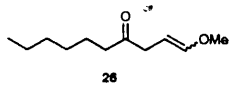
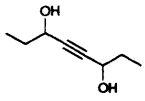
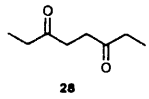
Isomerisation of Acetylenic Derivatives. General Procedure.—A mixture of acetylenic compound (1 mmol) and a phosphine (0.1–1 mmol) in benzene or toluene (5 cm^3) was stirred at 25 °C or at reflux. When the reaction was complete as monitored by TLC, the solvent was removed under reduced pressure. The residue was chromatographed on a column of silica gel to give the pure product.

(*E*,*E*)-Undeca-3,5-dien-2-one **4** (84%),[2] oil, b.p. 95 °C/1 mmHg; ethyl ostopanoate **9** (86%),[19] crystals, m.p. 86–88 °C (lit.,[19] 87–88 °C); 3-(penta-1,3-dienyl)cyclohex-2-enone **13** (89%),[5] oil, b.p. 90 °C/1 mmHg; methyl (*E*,*E*)-hepta-2,4-dienoate **15** (82%),[7] oil, b.p. 85 °C/2 mmHg; allyl (*E*,*E*)-hexa-2,4-dienoate **17** (80%),[15] oil, b.p. 68–70 °C/1 mmHg (lit.,[15] 75–85 °C/2 mmHg); (*E*,*E*)-*N*-allylbenzylhexa-2,4-dienamide **19** (60%),[16] oil, b.p. 140 °C/1 mmHg.

The spectral data of above compounds were in agreement with those reported.

(E,E)-*Heptadeca*-5,7-*dien*-10-*yn*-9-*one* **7** (89%), yellow oil, b.p. 152–154 °C/1 mmHg; δ_H 0.83 (6 H, m), 1.15 (12 H, m), 1.85 (2 H, m), 1.96 (2 H, m), 5.84 (1 H, m), 5.90 (1 H, dd, J 15.0 and 10.0), 6.21 (1 H, d, J 15.4) and 7.49 (1 H, dd, J 15.4 and 10.0); ν_{max}(neat)/cm^{-1} 2200, 1680, 1630 and 1590; m/z (%) 247 (M^+ +

Table 2 Isomerisation of yne-hydroxy compounds[a]

Entry	Substrate	Reagent[b] (mol %)	Temp (T/°C)/Time (t/h)	Product (ref.)	Isolated yield (%)
11	 **20**	Bu_3P (20)	110/42	 **21**  **22**	0[c]
12	**20**	A	110/28	**21** **22** (8)	91[d]
13	**20**	B, Pr^i_3P	80/40	**21** **22** (9)	79[d]
14	 **23**	Ph_3P (100)	110/32	 **24**	0[c]
15	**23**	B, HOAc, Ph_3P	110/30	**24** (12)	62
16	**23**	C, Ph_3P	110/30	**24** (12)	69
17	 **25**	Bu_3P (20)	110/66	 **26**	0[c]
18	**25**	A, Pr^i_3P	110/61	**26** (11)	73
19	**25**	B, Pr^i_3P	80/30	**26** (9)	82
20	 **27**	Bu_3P (20)	110/42	 **28**	0[c]
21	**27**	A	110/70	**28** (10)	81
22	**27**	B, Bu_3P	80/70	**28** (10)	72

[a] All reactions were performed as described in the Experimental section or as reported (see corresponding refs). [b] A: $IrH_5(Pr^i_3P)_2$; B: $Pd_2(dba)_3$·$CHCl_3$ (dba = dibenzylideneacetone); C: $Pd(OAc)_2$. [c] Starting material was recovered. [d] The ratio of **21** to **22** was ~4:1.

1, 9), 246 (M^+, 2), 189 (43), 137 (100), 109 (11) and 57 (25) (Found: M^+, 247.2066. $C_{17}H_{26}O + H^+$ requires M^+, 247.2062).

(E,E,E,E)-*Octadeca*-6,8,10,12-*tetraene*-5,14-*dione* **11** (83%), yellow crystals, m.p. 118–119 °C; δ_H 0.92 (6 H, t, J 6.0), 1.34 (4 H, m), 1.62 (4 H, m), 2.58 (4 H, t, J 7.0), 6.26 (2 H, d, J 15.0), 6.53 (2 H, m), 6.67 (2 H, dd, J 15.0 and 10.0) and 7.22 (2 H, dd, J 15.0 and 10.0); $\nu_{max}(CHCl_3)/cm^{-1}$ 1680, 1660, 1605 and 1565; m/z (%) 275 (M^+ + 1, 13), 274 (M^+, 24), 217 (10), 189 (28), 137 (6), 85 (87) and 57 (100) (Found: C, 78.7; H, 9.5. $C_{18}H_{26}O_2$ requires C, 78.79; H, 9.55%).

Ostopanic acid **29** (95%)[19] was prepared *via* the procedure of Gunn;[20] ethyl ostopanoate **9** was hydrolysed to give the acid **29** as a solid, m.p. 132–133 °C (lit.,[19] 132–133 °C); the spectral data were in agreement with those reported.[19]

Acknowledgements

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