268. A New α,β-Enone → Alkynone Fragmentation. Syntheses of Exaltone® and (±)-Muscone

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(27.IX.79)

Summary

p-Toluenesulfonylhydrazones of α,β-unsaturated ketones undergo an alkynone fragmentation in high yield when treated with electrophiles under basic conditions. With N-bromosuccinimide in alcohols, the *p*-tosylhydrazones **4a** and **4b** yielded in a one-pot reaction the cyclic 4-alkyn-1-ones **5a** and **5b**; these were converted to Exaltone® (**1a**) and muscone (**1b**) on catalytic hydrogenation.

The synthesis of Exaltone® (**1a**) and muscone (**1b**), published in 1967 by *Ohloff, Eschenmoser et al.* [1] [2], represent the first examples of a C_3 ring-expansion sequence using cyclododecanone as an easily available and inexpensive starting material. Recently, this strategy has been reapplied to furnish many new pathways for these macrocyclic ketones [3] as well as for lactones [4], subsequently leading to industrially applicable processes for manufacturing Exaltone® (**1a**), (±)-muscone (**1b**) and Exaltolide® [5].

The ring-enlarging step in this synthesis involves an α,β-epoxyketone → alkynone fragmentation (*Scheme 1*, **3** → **5**) *via* the corresponding *p*-tosylhydrazone. This reaction has proved useful in many fields of organic chemistry [6], and proceeds particularly well for β-substituted cyclic α,β-epoxyketones[2]).

Unfortunately, the formation of epoxyketones from sterically crowded enones is often difficult. For example, the epoxidation of bicyclo[10.3.0]pentadec-1(12)-en-13-one (**2a**) with $NaOH/H_2O_2$ gives only a 60% yield of epoxyketone **3a** [2b]. Under the same conditions, enone **2b** does not give any reaction, and epoxide **3b** must be prepared indirectly *via* epoxidation of the corresponding allylic alcohol [2]. Once formed, the epoxides **3a** and **3b** then smoothly undergo the fragmentation reaction and yield the acetylenic ketones **5a** and **5b** in 84% and 70% yield respectively [2].

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[2]) For improvements of the *Eschenmoser* fragmentation and its extension to both β-unsubstituted cyclic and acyclic α,β-epoxyketones, see [7].

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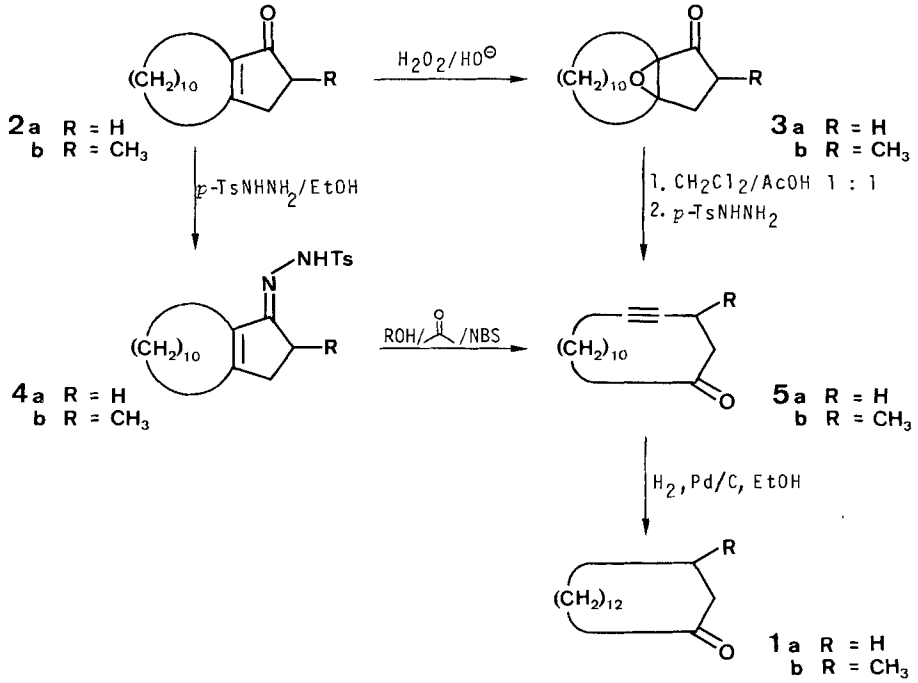
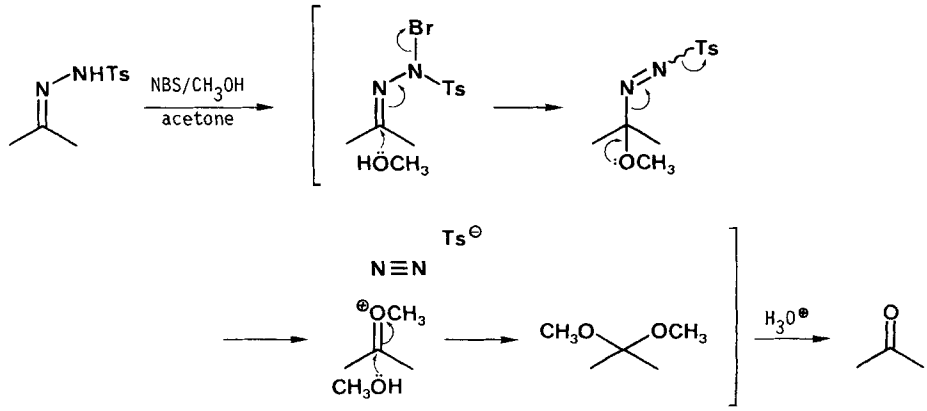
Scheme 1. *Fragmentation starting from α,β-unsaturated ketones*



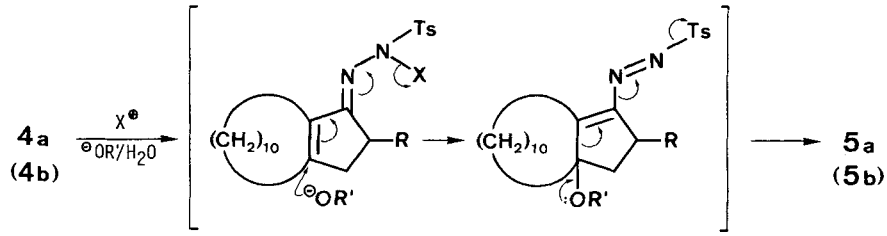
Considering the difficulties of epoxidizing the enones **2a** and **2b**, and the ease of preparing the bicyclic ketones **2a** [8] and **2b** [1], we decided to study a new type of arenesulfonyl hydrazone fragmentation to alkynones thus avoiding the epoxidation step (*Scheme 1*, **4** → **5**).

By taking inspiration from the existing methods for the regeneration of aldehydes and ketones from their arenesulfonyl hydrazones [9] [10] *(Scheme 2)*, we

Scheme 2. *Example of a hydrazone cleavage* [10]



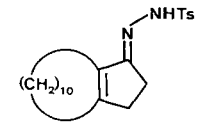
Scheme 3. *Vinylogous fragmentation reaction*



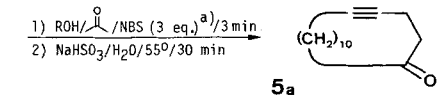
argued that the analogous enone hydrazones **4a** or **4b** would undergo a vinylogous fragmentation to afford the ynones **5a** and **5b** respectively *(Scheme 3)*.

It is evident that the success of such a fragmentation depends on the possibility of directing the course of the reaction in favour of the 1,4-addition of the nucleophile as opposed to the 1,2-addition. Examination of several reaction systems using various electrophiles (*e.g.* NaOCl, H_2O_2, peracids, NCS, NBS, Br_2, I_2, Na_2O_2) in the presence of a nucleophilic species (*e.g.* H_2O, ROH, CH_3COOH) demonstrated that the hydrazone **4a** completely decomposed under all basic conditions. However, treatment of hydrazone **4a** with excess *N*-bromosuccinimide in methanol/acetone 1:1 at 0° gave the desired fragmentation product **5a** in 53% yield after chromatographic purification together with ketone **2a** (31%). It has already been reported by *Rosini* [10] that these conditions converted *N*-tosyl-hydrazone to the parent ketones although similar conditions had failed to regenerate enones from their corresponding enone-hydrazones, only unidentified product mixtures being formed. To improve the selectivity in favour of the fragmentation product **5a** we investigated the effect of a change in nucleophile combined with a

Table 1



4a

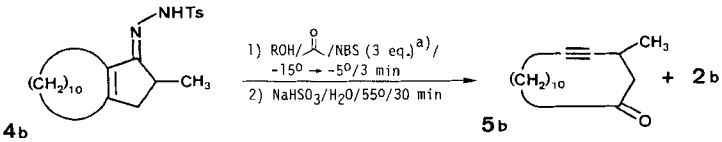


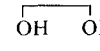
5a

Entry	Solvent/Temp.	Yield **2a** + **5a** %	Ratio of **5a** : **2a**
1	MeOH/0°	84[b])	1.7:1
2	MeOH/ – 15°	94[b])	2.6:1
3	MeOH/ – 25°	[c])	2.0:1
4	EtOH/ – 20°	[c])	2.0:1
5	 OH/ – 10° → 0°	[c])	5 :1
6	 / – 15° → – 5°	88[b]), 70[d])	9 :1
7	 / – 15° → – 5°	71[d])	19 :1

[a]) An alternative reagent is 1,3-dibromo-4,5-dimethyl-hydantoin (1.5 equiv.). [b]) After column chromatography. [c]) Not isolated. [d]) Distilled product.

Table 2



Entry	Solvent	Yield **2b** + **5b** %	Ratio of **5b** : **2b**
1	MeOH	b)	~1 :1
2		b)	2.5:1
3		b)	3.5:1
4	 /THF 1:1	b)	5 :1
5		b)	5 :1
6	 OH/THF 1:2	54c)	7 :1

a) An alternative reagent is 1,3-dibromo-5,5-dimethyl-hydantoin (1.5 equiv.). b) Not isolated. c) After distillation.

lower reaction temperature. It should be noted that the steric bulk of the nucleophile markedly influences the ratio of products **5a**:**2a** as exemplified by the case of *sec.* butyl alcohol (*Table 1*, entry 7).

For the synthesis of Exaltone® (**1a**), the bicyclic enone **2a** [8] was converted into its hydrazone **4a** (H_2NNHTs, refl. EtOH; 93.5%), which was then submitted to the new fragmentation procedure (entry 7) and afforded a 19:1 product mixture of **5a** and **2a** (71% after bulb-to-bulb distillation). Ynone **5a** was hydrogenated (H_2, Pd/C, EtOH [2]) to afford, after distillation, crystalline Exaltone® (**1a**) in 90% yield, identical to an authentic sample [1].

Finally we applied this sequence to the synthesis of (±)-muscone (**1b**). Hydrazone **4b**, obtained in a 66% yield after prolonged heating of ketone **2b** and *p*-tosylhydrazine in refluxing ethanol, underwent fragmentation to give the expected products **5b** and **2b** with a slightly inferior selectivity *(Table 2)*. The optimum results were obtained using ethylene glycol in THF/acetone.

Fragmentation of hydrazone **4b** (entry 6) gave after bulb-to-bulb distillation over K_2CO_3 at 160°/0.1 Torr a 54% yield of product mixture (**5b**:**2b** = 7:1), which was hydrogenated [2] to afford pure muscone (**1b**) (75% after bulb-to-bulb distillation at 115°/0.1 Torr) and recovered enone **2b** (12% after bulb-to-bulb distillation at 150°/0.01 Torr).

We would like to thank Drs. *K.H. Schulte-Elte, F. Näf* and *R.L. Snowden* for stimulating discussions.

Experimental Part

General. – Melting points are uncorrected. IR. spectra were recorded on a *Perkin-Elmer* A21 spectrometer (films or CCl_4 solutions; absorption maxima are given in cm^{-1}). ^1H-NMR. spectra were measured on a *Varian* A-60 instrument, using 3–4% solutions in $CDCl_3$ with $Si(CH_3)_4$ (= 0 ppm) as the internal standard. Spectra are given in ppm (δ), coupling constants are given in Hz and the multiplicities are abbreviated as follows: *s* = singlet, *m* = multiplet, *d* = doublet, br. = broad. Mass spectra (MS.) were determined on an *Atlas* CH 4 instrument, electron energy: 70 V. Abbreviations: RT. = room temperature, i.V. = *in vacuo*.

Work-up refers to: washing of the combined organic phase with H_2O and aq. sat. NaCl-solution, drying over Na_2SO_4, filtration, and evaporation of the solvent.

Bicyclo[10.3.0]pentadec-1(12)-en-13-one tosylhydrazone (**4a**). A solution of ketone **2a** (220 g, 1.0 mol) [8] and *p*-toluenesulfonylhydrazine (205 g, 1.1 mol) in 95% ethanol (1 l) was refluxed during 7 h. After cooling the reaction mixture, water (100 ml) was added and the crystalline hydrazone **4a** (346.8 g) was collected. The mother liquors yielded a further 15.8 g of product **4a** (total yield: 362.6 g, 93.5%); m.p. 164–167°. – IR.: 3200, 3030–2750, 1615, 1600, 1460, 1440, 1395, 1325, 1180, 1160, 1085, 1015. – NMR.: 1.1–1.9 (*m*, 16 H); 2.0–2.5 (*m*, ~8 H); 2.40 (*s*, ~3 H); 7.26 (*AB*, *J* = 8, 2 H); 7.77 (*s*, 1 H, exchanges with D_2O); 7.90 (*AB*, *J* = 8, 2 H). – MS.: 137 (11), 121 (10), 109 (12), 95 (19), 93 (13), 83 (13), 82 (11), 81 (55), 71 (15), 70 (10), 69 (100), 68 (11), 67 (13), 57 (24), 55 (23), 43 (22), 41 (33), 32 (99), 28 (20).

Exaltone® (Cyclopentadecanone) (**1a**). 1,3-Dibromo-5,5-dimethylhydantoin[3]) (4.30 g, 15.0 mmol) was added, in one portion, to a stirred suspension of the finely ground hydrazone **4a** (3.88 g, 10.0 mmol) in dry acetone (40 ml; dist. over K_2CO_3 and stored over molecular sieves 4 Å) and *sec.* butyl alcohol (40 ml; *Fluka* purum, stored over molecular sieves 3 Å). A vigorous gas evolution was observed and the temperature of the resulting red solution rose to −5°. After 3 min aq. 2.75N $NaHSO_3$ (10 ml) was added followed by water (50 ml). The reaction mixture was now heated at 55° during 30 min prior to the addition of petroleum ether (80–100°, 100 ml) and 10% aq. NaOH-solution (100 ml). Extraction (petroleum ether), work-up, and distillation i.V. gave 95% pure, crystalline ynone **5a** (1.56 g, 71%), whose analytical data were consistent with those previously reported [2]. Subsequent hydrogenation [2] gave Exaltone® (**1a**) (1.40 g, 90%), m.p. 53–60°, b.p. 110°/0.01 Torr, identical in all respects to an authentic sample [1].

14-Methyl-bicyclo[10.3.0]pentadec-1(12)-en-13-one tosylhydrazone (**4b**). A suspension of ketone **2b** (234 g, 1.0 mol) [1], *p*-toluenesulfonylhydrazine (200 g, 1.07 mol) and 95% ethanol (500 ml) was refluxed during 24 h. The hydrazone **4b** (267 g, 66.5%) was isolated in the usual manner (*cf.* preparation of **4a**); m.p. 134–140°. – IR.: 3230, 3030–2800, 1620, 1600, 1465, 1445, 1395, 1370, 1330, 1160, 1090, 1015. – NMR.: 1.07 (*d*, *J* = 1.7, 3 H); 1.0–1.9 (*m*, total 19 H); 1.9–2.6 (*m*, ~6 H); 2.40 (*s*, ~3 H); 2.80 (br. *d*, *J* = 5, 1 H); 7.26 (*AB*, *J* = 8, 2 H); 7.62 (*d*, 1 H, exchanges with D_2O); 7.87 (*AB*, *J* = 8, 2 H): – MS.: 119 (14), 107 (21), 106 (12), 105 (16), 94 (34), 93 (18), 92 (50), 91 (78), 81 (12), 79 (15), 77 (11), 67 (10), 65 (13), 64 (27), 55 (22), 48 (12), 45 (17), 44 (93), 43 (27), 41 (26), 39 (20), 32 (37), 31 (38), 28 (100), 27 (18).

(±)-Muscone (**1b**). *N*-bromosuccinimide (20.0 g, 0.112 mol) was added in one portion to a stirred solution of **4b** (20.1 g, 50 mmol) in acetone/THF/ethylene glycol 2:2:1 (500 ml) at −15°. A vigorous gas evolution was observed and the temperature of the resulting red solution rose to −6°. After 90 s 2.75N $NaHSO_3$ (50 ml) was added, followed by H_2O (200 ml). The reaction mixture was now heated at 55° during 30 min. Extraction, work-up and distillation (*cf.* preparation of **1a**) gave a 7:1-mixture of **5b** and **2b** (3.16 g, 54%). Subsequent hydrogenation [2] gave (±)-muscone (**1b**) (2.36 g, 75%), b.p. 115°/0.02 Torr, identical in all respects to an authentic sample, and enone **2b** (380 mg, 12%), b.p. 150°/0.02 Torr.

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[3]) For the fragmentation 1,3-dibromo-5,5-dimethylhydantoin (1.1–1.5 mol-equiv.) or *N*-bromosuccinimide (2.2–3.0 mol-equiv.) was used.

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