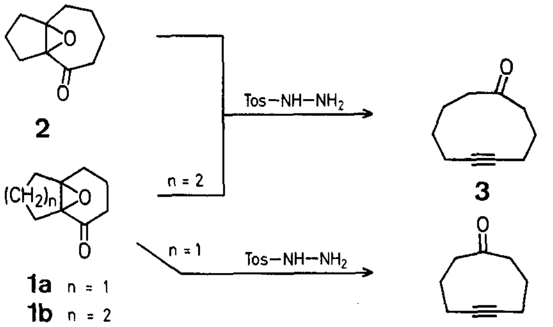
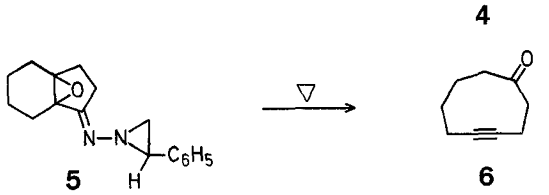
# Use of Mesitylene-2-sulphonyl Hydrazide in the Synthesis of Medium-Ring Cycloalkynones by the Eschenmoser Fragmentation Reaction

Colin B. Reese*, H. Paul Sanders

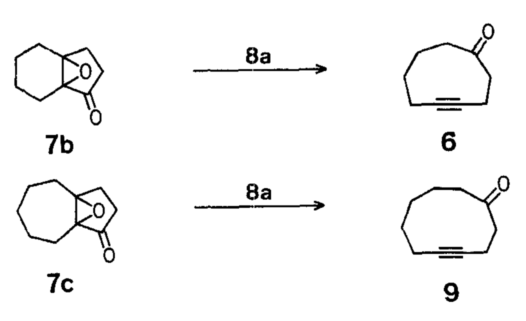
Department of Chemistry, King's College, Strand, London WC2R 2LS, England

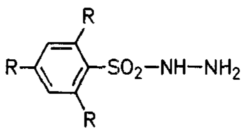
The Eschenmoser fragmentation reaction[1] has been used successfully in the synthesis of nine- and ten-membered cycloalkynones. For example, 1-cyclodecyn-6-one (**3**) was obtained by Eschenmoser et al.[2] by treating either **1b** or **2** with toluene-*p*-sulphonyl (tosyl) hydrazide; compound **3** was also prepared from **1b** and tosyl hydrazide by Tanabe et al.[3]. The more strained 1-cyclononyn-6-one (**4**) was prepared[4] in satisfactory yield from **1a** and tosyl hydrazide and the isomeric 1-cyclononyn-5-one (**6**) was obtained[5] in 38% yield by the pyrolysis of the *N*-(2-phenylaziridino)-imine **5** (a hydrazone of ketone **7b**) at 230 °C.





Several years ago, we originally observed[6] that mesitylene-2-sulphonyl and 2,4,6-triisopropylbenzenesulphonyl hydrazides (**8a** and **8b**, respectively) underwent base-catalyzed decomposition in deuteriomethanol solution at, respectively, ~16 and 380 times the rate of tosyl hydrazide. We attributed[6] this rate enhancement to the greater release of steric compression in the decomposition of *ortho*-substituted arenesulphonyl hydrazides and later exploited it in the development of a convenient nitrile synthesis[7]. Bond et al.[8] have demonstrated the advantages of using 2,4,6-triisopropylbenzenesulphonyl hydrazones in the Shapiro[9] and Bamford-Stevens[10] reactions. We now report that the epoxy-ketones **7b** and **7c**, which both contain a carbonyl group in a five-membered ring, readily undergo fragmentation to give the expected products (**6** and **9**, respectively) when they are treated with mesitylene-2-sulphonyl hydrazide (**8a**) but that products **6** and **9** are not obtained when the same epoxy-ketones (**7b** and **7c**) are treated with tosyl hydrazide.

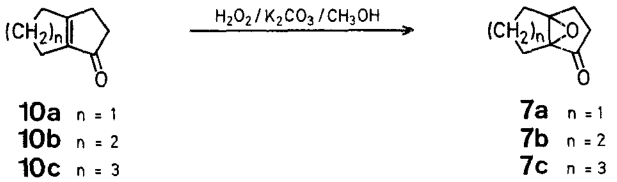




**8a** R = $CH_3$
**8b** R = $i$-$C_3H_7$

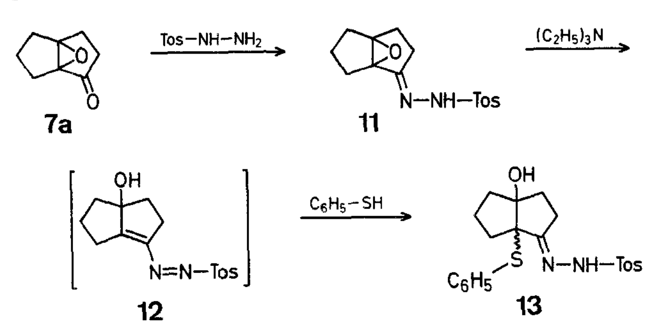
$R_3C_6H_2$–$SO_2$–NH–$NH_2$

1,6-Epoxybicyclo[4.3.0]nonan-7-one (**7b**) was prepared by treating the corresponding $\alpha,\beta$-unsaturated ketone[11] (**10b**) with aqueous hydrogen peroxide (50% w/w) and potassium carbonate in methanol and was isolated as a colourless oil (~95% pure) in 60% yield.



When epoxyketone **7b** was treated with 1.1 equiv of mesitylene-2-sulphonyl hydrazide (**8a**) in dichloromethane/acetic acid (1/1) at room temperature, a yellow coloration developed and effervescence was observed immediately. Work-up after 20 min gave 1-cyclononyn-5-one (**6**) as a colourless oil (~95% pure) in 43% yield. The latter compound (**6**) was characterized on the basis of spectroscopic data and as its crystalline, analytically pure 2,4-dinitrophenylhydrazone. We confirmed the previous report[5] that **6** cannot be prepared by the action of tosyl hydrazide on **7b**. As indicated above, pyrolysis of the *N*-(2-phenylaziridino)-imine **5**[5] gives **6** in 38% yield of isolated product. When 1,7-epoxybicyclo[5.3.0]decan-8-one (**7c**) was treated in the same way with 1.1 molecular equivalents of mesitylene-2-sulphonyl hydrazide (**8a**) at room temperature, fragmentation occurred smoothly and, after 20 min, 1-cyclodecyn-5-one (**9**) was isolated from the products in ~69% yield. We were unable to detect **9** in the products of the reaction between **7c** and tosyl hydrazide.

It was of interest to determine whether the Eschenmoser fragmentation reaction could be used in the synthesis of cyclooctyne derivatives. When 1,5-epoxybicyclo[3.3.0]octan-2-one (**7a**), prepared from the unsaturated bicyclic ketone **10a**[12] by the procedure described above, was treated with a slight excess of **8a** in dichloromethane/acetic acid (1/1) at room temperature, a rapid reaction ensued (as evidenced by an immediate yellow coloration and effervescence) but no 1-cyclooctyn-5-one could be detected in the products. Treatment of **7a** with tosyl hydrazide gave the tosylhydrazone **11** as an isolable product. When **11** was allowed to react with triethylamine (2 molecular equivalents) and thiophenol (~1.1 molecular equivalents) in tetrahydrofuran at −20 °C, compound **13** was obtained as a crystalline product in 95% yield. This suggests that the first step of the fragmentation reaction occurred readily in the presence of triethylamine, presumably to give the tosylazoalkene intermediate **12** which



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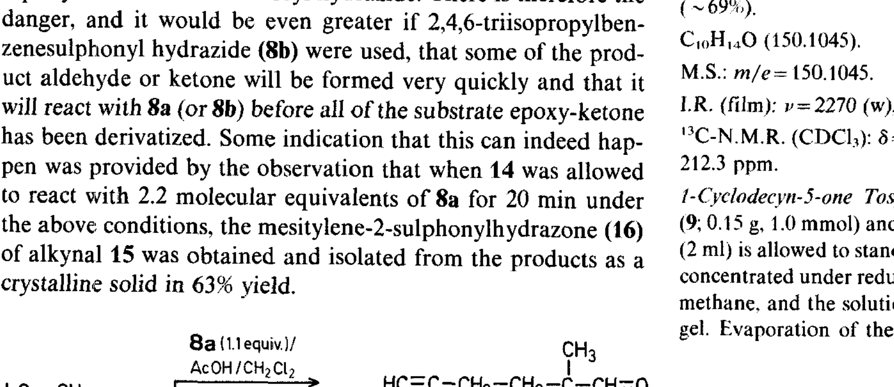
then reacted with benzenethiolate ion to give **13**. The fragmentation of **12** (or its conjugate base) to give the very strained 1-cyclooctyn-5-one would seem to be unfavourable and apparently does not occur even when mesitylene-2-sulphinate ion is the leaving group [i.e. when **7a** is treated with mesitylene-2-sulphonyl hydrazide (**8a**) rather than with tosyl hydrazide].

Tosyl hydrazide has been reported[13] not to be a particularly satisfactory reagent for the synthesis of alkynals by the Eschenmoser fragmentation reaction. In confirmation of this report, we found that when the epoxy-ketone **14** was treated with 1.1 molecular equivalents of tosyl hydrazide in dichloromethane/acetic acid (1/1) for 5 h at room temperature, 2,2-dimethyl-5-hexynal (**15**) was obtained in only ~16% yield. However, when **14** was treated with 1.1 molecular equivalents of mesitylene-2-sulphonyl hydrazide (**8a**) under the same conditions, the reaction was complete in 10 min and aldehyde **15** was isolated from the products in ~42% yield. The fragmentation reaction occurs more rapidly with **8a** than with tosyl hydrazide. There is therefore the danger, and it would be even greater if 2,4,6-triisopropylbenzenesulphonyl hydrazide (**8b**) were used, that some of the product aldehyde or ketone will be formed very quickly and that it will react with **8a** (or **8b**) before all of the substrate epoxy-ketone has been derivatized. Some indication that this can indeed happen was provided by the observation that when **14** was allowed to react with 2.2 molecular equivalents of **8a** for 20 min under the above conditions, the mesitylene-2-sulphonylhydrazone (**16**) of alkynal **15** was obtained and isolated from the products as a crystalline solid in 63% yield.



**1-Cyclononyn-5-one (6):**

*1,6-Epoxy-7-oxobicyclo[4.3.0]nonane* (**7b**): Hydrogen peroxide (50% w/w; 10.0 g, 0.15 mol) is added dropwise over a period of 30 min to a stirred mixture of potassium carbonate (3.0 g, 22 mmol) and 7-oxobicyclo[4.3.0]non-1(6)-ene[11] (**10b**; 3.6 g, 26 mmol) in methanol (50 ml) at 0 °C (ice bath). The stirred reactants are then allowed to warm up to room temperature. After 16 h, more hydrogen peroxide (50% w/w; 5.0 g, 74 mmol) is added and after a further period of 24 h, the products are poured into water (200 ml) and the resulting mixture is extracted with ether (4 × 50 ml). The organic extract is dried with magnesium sulphate and concentrated under reduced pressure to give **7b** as a ~95% pure (G.L.C.) colourless oil; yield: 2.4 g (60%).

*1-Cyclononyn-5-one* (**6**): Mesitylene-2-sulphonyl hydrazide[6] (**8a**; 2.37 g, 11.0 mmol) is added to a stirred solution of **7b** (1.52 g, 10.0 mmol) in dichloromethane/acetic acid (1/1 v/v; 50 ml) at room temperature. After 20 min, the products are basified with aqueous potassium carbonate and extracted with ether (3 × 150 ml). The combined ether extracts are washed with aqueous potassium carbonate, dried with magnesium sulphate, and evaporated under reduced pressure. Distillation of the residue at 1 torr gives **6** as a 95% pure [G.L.C. (Carbowax 20M, 170 °C)] colourless oil; yield 0.61 g (~43%).

$C_9H_{12}O$ (136.0888).

M.S.: $m/e = 136.0891$.

I.R. (film): $\nu = 2210$ (w), 1705 (s) cm$^{-1}$.

$^{13}$C-N.M.R. ($CDCl_3$): $\delta = 15.3$; 18.8; 23.3; 28.8; 39.9; 45.5; 83.3; 89.4; 213.1 ppm.

*1-Cyclononyn-5-one 2,4-Dinitrophenylhydrazone:* A solution of 2,4-dinitrophenylhydrazine (0.12 g, 0.6 mmol) in ethanol/5 molar sulphuric acid (9/1 v/v; 4.8 ml) is added to 1-cyclononyn-5-one (**6**; 0.068 g, 0.5 mmol) at room temperature. After 15 min, the mixture is cooled to −20 °C and, after a further period of 1 h, the resulting precipitate is isolated by filtration and recrystallized from methanol to give the orange crystalline 2,4-dinitrophenylhydrazone; yield: 0.145 g (92%); m.p. 158.5–160.5 °C.

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|---|---|---|---|---|
| $C_{15}H_{16}N_4O_4$ | calc. | C 56.96 | H 5.10 | N 17.71 |
| (316.3) | found | 57.3 | 5.1 | 17.65 |

**1-Cyclodecyn-5-one (9):**

*1,7-Epoxy-8-oxobicyclo[5.3.0]decane* (**7c**): Prepared from 8-oxobicyclo[5.3.0]dec-1(7)-ene[14] (**10c**; 6.0 g, 40 mmol), potassium carbonate (4.2 g, 30 mmol), and hydrogen peroxide (30%, w/v; 15.0 g, 0.12 mol) in methanol (80 ml) by the procedure described for **7b**; yield of **7c**; 4.3 g (65%) of a colourless oil.

*1-Cyclodecyn-5-one* (**9**): Mesitylene-2-sulphonyl hydrazide (**8a**; 1.19 g, 5.5 mmol) is added to a stirred solution of **7c** (0.83 g, 5.0 mmol) in dichloromethane/acetic acid (1/1 v/v; 25 ml) at room temperature. After 20 min, the mixture is worked up as described for the preparation of **6**. The crude oily product is subjected to Kugelrohr distillation to give **9** as a ~95% pure [G.L.C. (Carbowax 20M, 170 °C)] colourless oil; yield 0.54 g (~69%).

$C_{10}H_{14}O$ (150.1045).

M.S.: $m/e = 150.1045$.

I.R. (film): $\nu = 2270$ (w), 2220 (w), 1710 (s) cm$^{-1}$.

$^{13}$C-N.M.R. ($CDCl_3$): $\delta = 16.2$; 19.2; 23.2; 24.2; 24.6; 39.9; 42.2; 80.5; 84.8; 212.3 ppm.

*1-Cyclodecyn-5-one Tosylhydrazone:* A solution of 1-cyclodecyn-5-one (**9**; 0.15 g, 1.0 mmol) and tosyl hydrazide (0.186 g, 1.0 mmol) in methanol (2 ml) is allowed to stand at room temperature. After 6.5 h, the mixture is concentrated under reduced pressure, the residue redissolved in dichloromethane, and the solution filtered through a very short column of silica gel. Evaporation of the filtrate and crystallization of the residue from aqueous ethanol gives the tosyl hydrazone as colourless crystals; yield: 0.182 g (57%); m.p. 132–133 °C.

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|---|---|---|---|---|---|
| $C_{17}H_{22}N_2O_2S$ | calc. | C 64.12 | H 6,96 | N 8.80 | S 10.07 |
| (318.4) | found | 64.2 | 7.1 | 8.8 | 9.9 |

**5-Hydroxy-1-phenylthiobicyclo[3.3.0]octan-2-one Tosylhydrazone (13):**

*1,5-Epoxy-2-oxobicyclo[3.3.0]octane* (**7a**): Prepared from 2-oxobicyclo[3.3.0]oct-1(5)-ene[12] (**10a**; 4.0 g, 32.8 mmol), potassium carbonate (3.5 g, 25 mmol), and hydrogen peroxide (30% w/v; 12.0 g, 96 mmol) in methanol (50 ml) by the procedure described for **7b**; yield of **7a** as a semi-crystalline solid: 2.2 g (50%).

*1,5-Epoxybicyclo[3.3.0]octan-2-one Tosylhydrazone* (**11**): A solution of ketone **7a** (0.138 g, 1.0 mmol) and tosyl hydrazide (0.186 g, 1.0 mmol) in tetrahydrofuran (10 ml) is allowed to stand at room temperature. After 4 h, the mixture is concentrated under reduced pressure and the residue is triturated with ether to give the tosyl hydrazone as a colourless crystalline solid; yield: 0.227 g (74%); m.p. 110.5–111.5 °C (dec).

*5-Hydroxy-1-phenylthiobicyclo[3.3.0]octan-2-one Tosylhydrazone* (**13**): To a stirred suspension of tosylhydrazone **11** (0.17 g, 0.55 mmol) in tetrahydrofuran (10 ml) at −20 °C is added thiophenol (0.06 ml, 0.066 g, 0.6 mmol) followed by triethylamine (0.15 ml, 0.11 g, 1.1 mmol). After a further period of 10 min at −20 °C, water (50 ml) is added to the clear solution of products. The mixture is extracted with ether (3 × 30 ml) and the combined extracts are washed with dilute hydrochloric acid and aqueous sodium carbonate and then dried with magnesium sulphate. The solvent is evaporated and the residual viscous oily product crystallized from dichloromethane/hexane; yield of **13**: 0.237 g (95%); m.p. 92.5–93.5 °C.

| | | | | |
|---|---|---|---|---|
| $C_{21}H_{24}N_2O_3S_2$ | calc. | C 60.55 | H 5.81 | N 6.73 |
| (416.5) | found | 60.7 | 5.7 | 6.9 |

I.R. (Nujol): $\nu = 1590$ (m), 3220 (m), 3480 (m) cm$^{-1}$.

$^1$H-N.M.R. (CDCl$_3$, 90 MHz): $\delta = 1.2$–2.1 (m, 10H); 2.44 (s, 3H); 3.10 (s, 1H); 6.9–7.6 (m, 10H); 7.91 ppm (d, 2H, $J = 8.5$ Hz).

**2,2-Dimethyl-5-hexynal (15):**

*2,3-Epoxy-4,4-dimethylcyclohexanone* **(14)**: Prepared from 4,4-dimethyl-2-cyclohexenone[15] (6.0 g, 48 mmol), potassium carbonate (4.0 g, 29 mmol), and hydrogen peroxide (30% w/v; 25.0 g, 0.20 mol) in methanol (100 ml) by the procedure described for **7b**. Product **14** is purified by distillation; yield: 3.0 g (44%); b.p. 87–90 °C/15 torr.

*2,2-Dimethyl-5-hexynal* **(15)**: 2,3-Epoxy-4,4-dimethylcyclohexanone (**14**; 1.4 g, 10 mmol) is added to a stirred solution of mesitylene-2-sulphonyl hydrazide (**8a**; 2.35 g, 11 mmol) in dichloromethane/acetic acid (1/1 v/v; 25 ml) at room temperature. After 10 min, when the evolution of nitrogen has ceased, the mixture is worked up as above in the preparation of **6**, and the product subjected to Kugelrohr distillation to give **15** as a ~ 90% pure [G.L.C. (Carbowax 20M, 120 °C)] colourless oil; yield 0.6 g (~ 42%).

I.R. (film): $\nu = 2110$ (w), 1725 (s) cm$^{-1}$.

$^{13}$C-N.M.R. (CDCl$_3$): $\delta = 14.0$; 21.2; 36.0; 45.4; 69.4; 83.9; 204.9 ppm.

*2,2-Dimethyl-5-hexynal 2,4-Dinitrophenylhydrazone:* 2,2-Dimethyl-5-hexynal (**15**; 0.124 g, 1.0 mmol) is treated with 2,4-dinitrophenylhydrazine (0.218 g, 1.1 mmol) in ethanol/5 molar sulphuric acid (9/1 v/v; 8.8 ml) at room temperature. After 15 min, the precipitate is collected by filtration and recrystallized from methanol to give the hydrazone as orange needles; yield: 0.245 g (81%); m.p. 115–116 °C.

| | | | | |
|---|---|---|---|---|
| $C_{14}H_{16}N_4O_4$ | calc. | C 55.26 | H 5.30 | N 18.41 |
| (304.3) | found | 55.3 | 5.2 | 18.3 |

$^1$H-N.M.R. (CDCl$_3$, 90 MHz): $\delta = 1.22$ (s, 6H); 1.7–2.0 (m, 3H); 2.1–2.4 (m, 2H); 7.43 (s, 1H); 7.91 (d, 1H, $J = 9.7$ Hz); 8.32 (dd, 1H, $J = 2.6$ and 9.7 Hz); 9.12 (d, 1H, $J = 2.6$ Hz); 10.97 ppm (br s, 1H).

**2,2-Dimethyl-5-hexynal Mesitylene-2-sulphonylhydrazone (16):**

2,3-Epoxy-4,4-dimethylcyclohexanone (**14**; 1.4 g, 10 mmol) is added to a stirred solution of mesitylene-2-sulphonyl hydrazide (**8a**; 4.7 g, 22 mmol) in dichloromethane/acetic acid (1/1 v/v; 100 ml) at room temperature. After 20 min, the mixture is worked up as described in the preparation of **6**. The crude product **16** is recrystallized from ether/hexane to give pure **16** as colourless crystals; yield: 2.0 g (63%); m.p. 81.5–82 °C.

| | | | | | |
|---|---|---|---|---|---|
| $C_{17}H_{24}N_2O_2S$ | calc. | C 63.72 | H 7.55 | N 8.74 | S 10.01 |
| (320.5) | found | 63.75 | 7.5 | 8.6 | 9.8 |

$^1$H-N.M.R. (CDCl$_3$, 90 MHz): $\delta = 0.96$ (s, 6H); 1.4–1.9 (m, 5H); 2.30 (s, 3H); 2.66 (s, 6H); 6.92 (s, 2H); 7.00 (s, 1H); 7.82 ppm (s, 1H).

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* Address for correspondence.

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