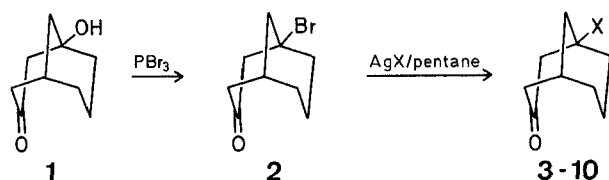


Bridgehead Substitution. Facile Replacement of Bromine in 1-Bromobicyclo[3.3.1]nonan-3-one

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Bridgehead substituted derivatives of bridged bicyclic ring systems are of considerable theoretical interest¹. In connection with an N.M.R. study of 'rigid' β -substituted cyclohexanone derivatives, we needed a series of bicyclo[3.3.1]nonan-3-ones substituted at the bridgehead position. It has been shown on closely related systems such as gibberellic acid synthons² that acetylation of a bridgehead hydroxy group could not be realized with standard reagents. Since alcohol **1**³ was found to be inactive towards esterification procedures, the direct replacement of a reactive group during a S_N1 reaction was envisaged. The ease of bromination of **1** to yield **2**⁴ seemed to be a valuable indication for reactivity at the bridgehead position in bicyclo[3.3.1]nonan-3-ones.



As summarized in the Table, the reaction of 1-bromobicyclo[3.3.1]nonan-3-one (**2**) leads, in the presence of various silver salts at room temperature, to the products **3-8**. Pentane was chosen as a solvent to avoid possible side reactions⁵.

It should be mentioned that the substitution of bromine in **2** is not restricted to the presence of silver salts. The

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Table. 1-Substituted Bicyclo[3.3.1]nonan-3-ones 1–10

Product ^a No. X	Reaction time [h]	Yield [%]	Purity ^b [%]	m.p. ^c	Molecular formula ^d	I.R. (CHCl ₃) ν_{\max} [cm ⁻¹]	¹ H-N.M.R. (CDCl ₃ /TMS) δ [ppm] H ₂ C-2	M.S. <i>m/e</i>
1 ³ OH	—	80	97	184–185°	C ₉ H ₁₄ O ₂ (154.2)	1700; 3440, 3610 (OH)	2.5 (m)	154 (M ⁺ , 18 %), 97 (100 %)
2 ⁴ Br	—	87	98	82–84°	C ₉ H ₁₃ BrO (217.1)	1705	3.08 (s)	218, 216 (M ⁺ , 9 %), 137 (100 %)
3 F	48 ^e	83 ^f	98	150–152°	C ₉ H ₁₃ FO (156.2)	1710, 1070 (C–F)	2.78 (broad s)	156 (M ⁺ , 50 %), 97 (100 %)
4 O—CO—CH ₃	24–30	84 ^f	100	61–62°	C ₁₁ H ₁₆ O ₃ (196.2)	1705, 1730 (ester)	2.98 (s)	196 (M ⁺ , 20 %), 97 (100 %)
5 O—CO—CF ₃	1	82 ^g	100	—	C ₁₁ H ₁₃ F ₃ O ₃ (250.2)	1710, 1780 (ester)	3.05 (AB m)	250 (M ⁺ , 1 %), 97 (100 %)
6 O—CO—C ₆ H ₅	18–22	82 ^g	—	55–57°	C ₁₆ H ₁₈ O ₃ (258.3)	1705	3.16 (s)	258 (M ⁺ , 7 %), 97 (100 %)
7 O—SO ₂ —C ₆ H ₄ —CH ₃ -4	1–2	95 ^g	—	—	C ₁₆ H ₂₀ O ₄ S (308.4)	1705	3.03 (m)	308 (M ⁺ , 12 %), 94 (100 %)
8 ONO ₂	2	96 ^g	90	—	C ₉ H ₁₃ NO ₄ (199.2)	1710; 1630, 1290 (NO ₂)	3.06 (AB m)	199 (M ⁺ , 0.7 %), 97 (100 %)
9 OCH ₃	1–2	84 ^h	100	—	C ₁₀ H ₁₆ O ₂ (168.2)	1705	2.3–2.6 (m)	168 (M ⁺ , 16 %), 111 (100 %)
10 CN	48	87 ^{f, h}	—	149–151°	C ₁₀ H ₁₃ NO (163.2)	1715, 2240 (CN)	2.75 (s)	163 (M ⁺ , 81 %), 120 (100 %)

^a Compounds 3–8 prepared by reaction 2 + AgX in pentane; 9 by 2 + NaOCH₃ in pentane; 10 by 2 + NaCN under phase transfer catalysis (triethylbenzylammonium chloride/ether/water).

^b By G.L.C. analysis (Carbowax 20M, 3 m column, 160°).

^c Uncorrected.

^d All new compounds except 7, 8, and 9 gave satisfactory microanalyses (C ± 0.42, H ± 0.2, N ± 0.02).

^e The reaction is complete after a second addition of AgF after 24 h.

^f Sublimed at 50–60°/12 torr.

^g Not purified.

^h Filtered on silica gel 60 (pentane/ether).

methoxy derivative 9 is easily prepared by reaction of 2 with sodium methoxide, while the reaction with sodium cyanide and the application of phase transfer catalysis conditions⁶ yields the nitrile 10. The latter reaction represents an entry to carbon substituted bicyclo[3.3.1]nonan-3-ones⁷.

1-Hydroxybicyclo[3.3.1]nonan-3-one (1):

Modification of procedure reported by Macrosson et al.³: 2-Cyclohexenone (20 g, 208 mmol), freshly distilled ethyl acetate (32.5 g, 249 mmol), and sodium methoxide (11.3 g, 209 mmol) are heated under reflux for 72 h in dry methanol (300 ml). A solution of potassium hydroxide (30 g, 534 mmol) in water (80 ml) is added at room temperature and refluxing is continued for 12 h. Most of the methanol is evaporated and the aqueous layer extracted with dichloromethane (200–300 ml) by means of a continuous extraction apparatus (24 h). The organic solution is dried (magnesium sulfate), filtered, and evaporated to give a brown, semisolid product (28 g). Vacuum sublimation at 115°/12 torr (7 days) gives a liquid fraction (1–1.5 days), which was not collected, and a solid fraction (1.5–7 days) of 1; yield: 25.7 g (80%).

1-Bromobicyclo[3.3.1]nonan-3-one (2)⁴:

1-Hydroxybicyclo[3.3.1]nonan-3-one (1; 4.62 g, 30 mmol) dissolved in dry ether (200 ml) is added (30 min) to a stirred solution of phosphorus tribromide (8.1 g, 30 mmol) in dry ether (50 ml). Stirring is continued (in some experiments the solution becomes cloudy) and the mixture is refluxed (2 h), and poured into a mixture of ice and 1 normal hydrobromic acid. The phases are separated and the aqueous layer is extracted with ether (2 × 50 ml), the ether solutions are washed (aqueous sodium hydrogen carbonate and water), dried, and evaporated at room temperature. Vacuum sublimation of the residue at 50–60°/12 torr affords 2 as a colourless, highly crystalline product, which decomposes slowly when exposed to the light; yield: 5.7 g (87%).

1-Substituted Bicyclo[3.3.1]nonan-3-ones (3–9); General Procedure:

1-Bromobicyclo[3.3.1]nonan-3-one⁴ (2; 200 mg, 0.92 mmol) is dissolved in dry pentane (10–20 ml) and the appropriate silver salt (3 mmol) or sodium methoxide (4 mmol) is added. The reaction mixture is stirred magnetically at room temperature in absence of light, the course of the reaction being followed by G.L.C. (Carbowax 20M, 160°, 3 m). The solution is filtered and the solvent evaporated. In the case of tosylate 7, the filter residue must be extracted with dry ether to isolate this reaction product. Compound 7 is hygroscopic and difficult to obtain without little amounts of 1 as an impurity.

In a larger scale experiment 2 (4.34 g, 20 mmol) is treated (24 h/room temperature) with silver acetate (5 g, 30 mmol) in pentane (150 ml) to give product 4; yield after sublimation: 2.9 g (74%).

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⁷ **Note added in proof:** Two accounts appeared recently which describe the synthesis and reactions of (1): T. Momose, O. Muraoka, *Chem. Pharm. Bull.* **26**, 288 (1978) and H. O. House, W. A. Kleschick, E. J. Zaiko, *J. Org. Chem.* **43**, 3653 (1978).