One-Step Bridgehead Acetamidation of Polycycloalkanes through Bromine Oxidation

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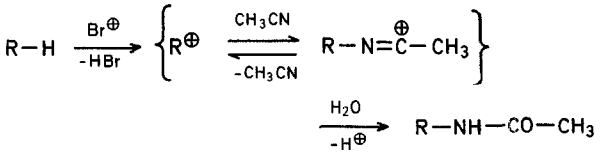
Functionalization reactions of bridged polycycloalkanes via carbocation intermediates are by far the most effective method for the preparation of bridgehead derivatives of these hydrocarbons. Selectivity to and, sometimes, yield of the desired derivatives are better in cationic reactions than in radical and anionic substitutions. In addition, selectivity is often shown even among different bridgeheads within a molecule.

Generation of bridgehead carbocations from polycycloalkanes necessarily involves as the key step "oxidation" of the corresponding bridgehead hydrides. The well-known ionic brominations of adamantane[1] and other compounds[2] can be regarded as oxidation by bromonium ion. Some recent examples of successful ionic oxidizing agents are chromium trioxide[3], electrolysis[4], lead(IV) acetate[5], and iodine tris[triflate][6].

Worthy of particular mention is the oxidation by other carbocations (most frequently by *t*-butyl cation)[7], which would rather be referred to as intermolecular hydride transfer than as oxidation. The target cation in this method, similarly as in anodic oxidation in acetonitrile[4], was produced *in situ* in the presence of a nucleophile (e.g., carbon monoxide[7,8,9], halide ions[10], or vinylidene chloride[11]), and the derivatives corresponding to the nucleophiles were obtained in one-step from the polycycloalkanes. We describe here another versatile one-step functionalization reaction leading to acetamido derivatives which comprises *in situ* oxidation by bromine in sulfuric acid in the presence of acetonitrile as the nucleophile. The method is superior to the corresponding stepwise synthesis (bromination followed by Ritter reaction) in that a much smaller amount of bromine is used, giving better yield of the amide with simpler experimental procedures.



A polycycloalkane was dissolved in a solution of 95% sulfuric acid in acetonitrile, and bromine was added to the mixture. The reaction mixture was stirred at ambient temperature and gradually decolorized as the bromine was reduced to hydrogen bromide and escaped out of the reaction. Dilution with ice/water followed by the usual work-up gave the acetamide derivative.

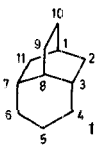
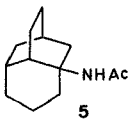
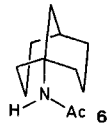
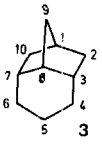
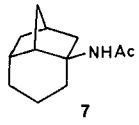
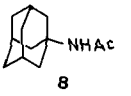
Optimum amounts in bromine and sulfuric acid with respect to a maximum yield in the amide were observed in this synthetic procedure. Results are shown in Table 1 for the reaction of 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane, **1**)[12]. A rise in reaction temperature resulted in an increase in the amount of tarry materials. Use of sulfuric acid is indispensable in the present synthesis. Only 3% of **5** was obtained from **1** with 5 mol of bromine and acetonitrile. Other oxidizing agents, e.g., potassium pyrosulfate ($K_2S_2O_7$), chromium trioxide, or *t*-butyl chloride, are not well compatible with the sulfuric acid/acetonitrile system, giving below 5% yield of **5**.

Table 1. Acetamidation of 4-Homoisotwistane (**1**)[a]

Br_2 (mol)	H_2SO_4 (ml)	Product (**5**) Yield (%)[b]
0.01	7.5	5[c]
0.03	7.5	63[c]
0.05	7.5	96
0.10	7.5	–[d]
0.05	0	3[c]
0.05	1.5	37[c]
0.05	5.0	82
0.05	15.0	–[d]

[a] 1.5 g (0.01 mol) of **1** in 30 ml of acetonitrile at room temperature for 24 h.
[b] Calculated from V.P.C. peak areas.
[c] A reaction time of 3 days.
[d] Formation of tarry materials.

Table 2. Acetamidation of Polycycloalkanes[a]

Substrate	Product	Reaction time	Yield[b] [%]	m.p. (Lit. m.p.)
 **1**	 **5**	1 day	90	125–126°[c] (125–126°)[9]
 **2**	 **6**	3 days	87	89–90° (85–86°)[5]
 **3**	 **7**	6 days	85	114–115° –[c]
 **4**	 **8**	8 days	92	150–151° (148–149°)[1,5]

[a] 0.01 mol of the reactant, 8.0 g (0.05 mol) of bromine, 7.5 ml of 95% sulfuric acid, and 30 ml of acetonitrile at 15–20°.
[b] Yield of the isolated, purified product.
[c] See experimental procedure.

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The present acetamidation reaction is also successfully applicable to various bridged compounds such as bicyclo-[3.3.1]nonane (**2**), 4-homobrendane (tricyclo[5.2.1.$0^{3,8}$]decane, **3**)[13], and adamantane (**4**), as indicated in Table 2. However, the method is particularly effective for those compounds, e.g., 4-homoisotwistane (**1**), which give relatively unstable (reactive) bridgehead bromides[8]. Isolation of these unstable bromides often led to appreciable lowering in yields. Hydrocarbons (**2–4**), which gave relatively unreactive, stable bromides, also showed a low reactivity in this method. Longer reaction times (up to 8 days) were required in order to obtain good yields of the acetamido derivatives.

3-Acetamido-4-homoisotwistane (5):
In a solution of 95% sulfuric acid (7.5 ml) in acetonitrile (30 ml) is dissolved at room temperature (15–20°) 4-homoisotwistane[12] (**1**: 1.5 g, 0.01 mol). Bromine (8.0 g, 0.05 mol) is added dropwise to the solution within 10 min. The reaction mixture is stirred at ambient temperature overnight. The mixture is poured into ice/water (200 ml) and unreacted bromine is decomposed by the addition of a 2% sodium hydrogen sulfite solution. The precipitate is collected by filtration and triturated with a small amount of *n*-pentane. Recrystallization from ether gives pure **5**: yield: 1.8 g (90%); m.p. and mixture m.p. 125–126° (Lit.[9], m.p. 125–126°).

3-Acetamido-4-homobrendane (7):
A sample of 4-homobrendane[13] (**3**; 1.35 g, 0.01 mol) is treated similarly as for 4-homoisotwistane described above with the same amounts of the reagents. Recrystallization from acetone gives pure **7**; yield: 1.53 g (85%); m.p. 114–115°.

$C_{12}H_{19}NO$	calc.	C 74.57	H 9.91	N 7.25
(193.3)	found	74.45	9.93	7.42

I.R. (Nujol): ν_{max} = 3350; 3040; 1630; 1540 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.1–1.8 (m, 15H); 1.86 (s, 3H, $COCH_3$); 5.25 ppm (br s, 1H, NH).

^{13}C-N.M.R. ($CDCl_3$): δ = 17.28 (t); 24.43 (q); 26.38 (t); 31.57 (t); 32.48 (t); 34.04 (d); 34.29 (d); 39.11 (t); 42.36 (t); 47.43 (d); 59.46 (s); 169.06 ppm (s).

M.S.: *m/e* (relative intensity) = 193 ($M^{\oplus}$, 37); 150 (11); 135 (18); 134 (100); 119 (22); 106 (15); 105 (15); 96 (13); 93 (18); 92 (25).

The ^{13}C-N.M.R. spectrum unambiguously demonstrated the compound to be asymmetrical (ten signals for skeletal carbon atoms) with a substituted bridgehead (singlet at δ = 59.46 ppm). The 3-acetamido derivative **7** is the only structure that corresponds to the spectrum.

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