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Triple (Grob) Fragmentation. Retro-Mannich Reactions of 1-Aza-adamantane Derivatives

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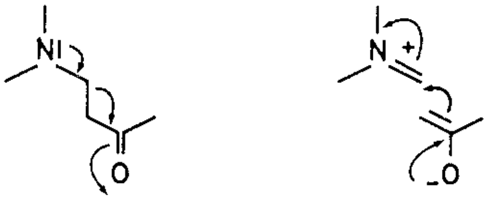
Key Words: Triple Grob Fragmentation; Retro-Mannich Reaction; 1-Aza-adamantanes; Phloroglucinols; 5-Chloro-resorcinols.

Abstract: *The first triple (Grob) fragmentation is described. The process (mechanism) involves retro-Mannich reactions. Easily accessible 1-aza-adamantane derivatives 1 are converted to substituted 5-chloro-resorcinols 5.*

Most heterolytic fragmentation reactions [1,2] (Grob fragmentations) produce a carbenium ion, an alkene, and a leaving group X^-. However, when a carbonyl group is involved in this reaction, acting as an electron acceptor, only two fragmentation products are formed. In scheme 1, we demonstrate that certain Grob fragmentations of this type, generating an iminium ion, are retro-Mannich reactions. The resulting enolate regenerates the carbonyl group upon hydrolysis.



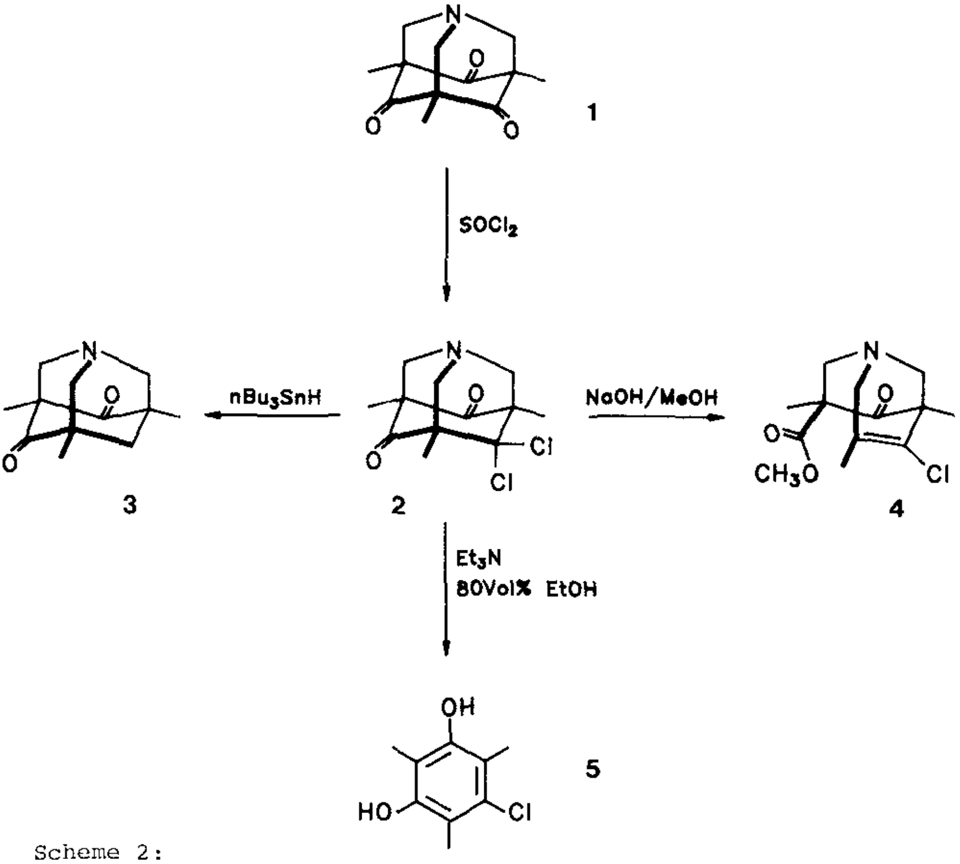
Grob fragmentation **Mannich reaction**

Scheme 1:
Comparison of the Mannich reaction and the Grob fragmentation (retro-Mannich reaction).

Treatment of the easily accessible 1-aza-adamantane **1** [3] with thionyl chloride yields the geminal dichloride **2** as the single product (92 %) [4]. The relative geometry of the aza-tricyclic skleleton and the leaving groups are in good agreement with Grob's rules for optimum fragmentation pathways [5].

nBu_3SnH is known as a versatile reagent for deoxygenation [6,7] and dehalogenation [8] processes. Reaction of the above with **2** proceeds by double dechlorination, yielding the diketone **3** (70 %). This reaction involves radical intermediates and this is why no fragmentation products are observed.

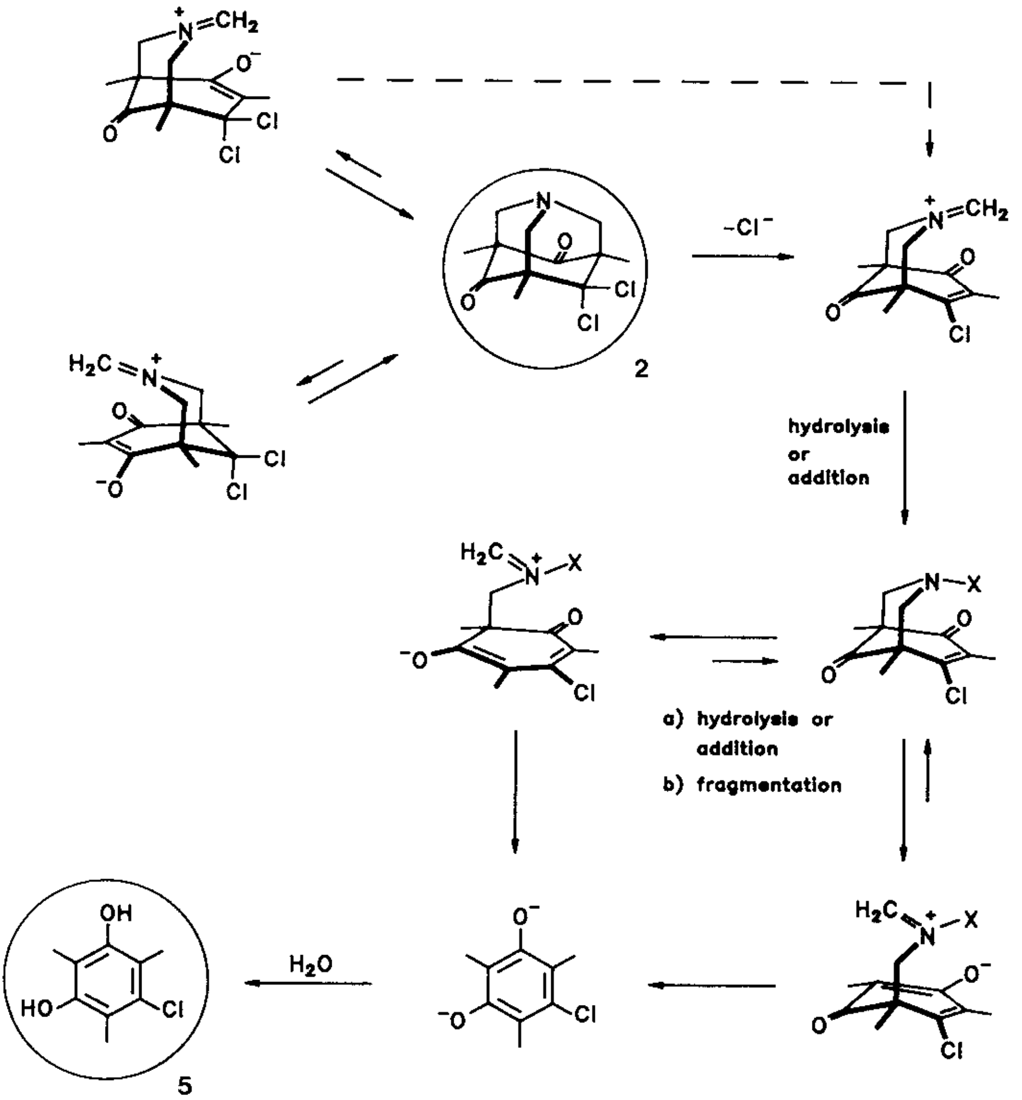
However, refluxing 2 with NaOH/methanol for 2 hours, followed by work up with hydrochloric acid, the formation of the fragmentation product 4 (71 %) is observed [9] (initiated by the nucleophilic attack of methanol to the carbonyl group).



Scheme 2:

On the other hand, treatment of 2 with triethylamine (3 mol equivalents), in a mixture of ethanol and water (4:1), produces the new phloroglucinol derivative (5-chloro-2,4,6-trimethyl-resorcinol) 5 (62%) [10]. Scheme 3 shows the postulated intermediates (measurement of the kinetic data has not yet been done). The (one-pot) reaction sequence is started by a classical Grob fragmentation of the aza-tricycle, with the exo-chloride as the leaving group (irreversible). The nitrogen lone pair, which is essential for further (repetitive) fragmentations, is regenerated by addition of the solvent to the iminium ion or by hydrolysis (X = H, -CH_2O-, etc.). The next two fragmentation steps follow the retro-Mannich type reaction, discussed at the beginning.

To our knowledge the overall reaction is the first triple (Grob) fragmentation, described in the literature. Using this method, derivatives of 5-chloro-resorcinols are easily available from substituted phloroglucinols in three steps [3].



Scheme 3: Postulated intermediates of the triple Grob fragmentation of 2 [triethylamine (3 mol equivalents) in a mixture of ethanol and water (4:1); X = H, $-CH_2O-$, etc.].

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4. **2**: Mp 149°C; IR (KBr, cm^{-1}): 2990, 2940, 2870, 1725, 1695, 1465, 1450, 1380, 1255, 1140, 1080, 955, 935, 755, 640; MS (70 eV): m/z (%) = 275 (7, M^{+}), 240 (85), 212 (5), 184 (4), 156 (4), 122 (4), 91 (9), 69 (100), 57 (28), 41 (87), 28 (15); ^{13}C-NMR (CDCl$_3$, 75 MHz), δ(ppm): 11.51 (C-7^1), 14.71 (C-3^1, -5^1), 60.47 (C-3, -5), 63.79 (C-2, -10), 68.74 (C-7), 72.57 (C-8), 98.15 (C-4), 202.00 (C-6, -9); ^{1}H-NMR (CDCl$_3$, 300 MHz), δ(ppm): AB (δ_A = 3.62, ^4J = 1.6 Hz, δ_B = 2.96, $^2J_{AB}$ = 13.5 Hz; 4H, 2-, 10-CH$_2$), 3.20 (t; ^4J = 1.7 Hz; 2H, 8-CH$_2$), 1.43 (s; 6H, 3-, 5-CH$_3$), 1.21 (s; 3H, 7-CH$_3$); Anal. calcd. for $C_{12}H_{15}Cl_2NO_2$ (276.16): C 52.19 H 5.47 N 5.07. Found: C 51.95 H 5.39 N 5.15.
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10. A solution of 1 g **2** (3.6 mmol) and 1.8 g Et$_3$N (10.8 mmol) in 100 ml 80 Vol% EtOH is refluxed for 1 h. After removal of the solvent, the residue is dissolved in water and extracted with CH$_2$Cl$_2$. The combined organic layers are dried with Na$_2$SO$_4$ and concentrated in a rotary evaporator to afford 0.42 g (2.2 mmol, 62 %) **5** in form of fine orange needles; **5** : Mp 153°C; IR (KBr, cm^{-1}): 3550, 3200, 2940, 2860, 1600, 1450, 1380, 1305, 1235, 1100, 1010, 985, 860, 800, 730, 655; MS (70 eV): m/z (%) = 186 (100, M^{+}), 171 (23), 151 (72), 123 (9), 93 (11), 77 (26), 43 (31), 39 (26), 27 (16); ^{13}C-NMR (CDCl$_3$, 75 MHz), δ(ppm): 8.68 (C-2^1), 13.03 (C-4^1, -6^1), 108.30 (C-2), 113.96 (C-4, -6), 132.25 (C-5), 150.59 (C-1, -3); ^{1}H-NMR (CDCl$_3$, 300 MHz), δ(ppm): 2.25 (s; 6H, 4-, 6-CH$_3$), 2.13 (s; 3H, 2-CH$_3$); Anal. calcd. for $C_9H_{11}ClO_2$ (186.64): C 57.92 H 5.94. Found: C 58.00 H 6.09 .

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