1-Aza-adamantanes

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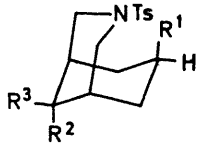
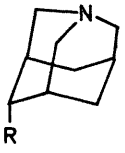
Summary A simple procedure for the synthesis of 1-aza-adamantanes is reported.

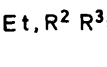
A simple, efficient preparation of 1-aza-adamantane[1] (**1**) and some of its derivatives *via* a novel method is reported. The procedure is based upon the condensation of ethyl α-bromomethylacrylate or its precursor, the corresponding ββ′-dibromoisobutyrate with the pyrrolidine enamine of *N*-toluene-*p*-sulphonylpiperid-4-one to afford the bicyclic intermediate[2] (**2**). Although acetalisation experiments with ketone (**2**) were not successful—no reaction occurred upon use of glycol, while the dichloroethoxy-derivative (**3**)† was formed when chloroethanol[3] was employed—the $NaBH_4$ reduction gave a mixture of two alcohols (**4a**) and (**4b**) in a ratio of 4 : 1. $LiAlH_4$ reduction of alcohol (**4a**) gave a diol (**5**), m.p. 174—176°, which smoothly underwent detosylation upon treatment with HCl–AcOH, to give 4-hydroxy-aza-adamantane (**6**). The remarkable ease of this N–S fission suggests a direct participation of the $-CH_2X$ group in the elimination process. (**6**) was purified *via* ion-exchange (IRA 400) and sublimation, m.p. (sealed capillary) 279—282° (yield 92%). N.m.r. (D_2O) δ 1·9—2·4 (m, 7H), 3·1—3·5 (m, 6H), 4·33 (s, C*H*OH).

Alternatively, the keto-ester (**2**) could be converted into its thio-acetal (**7**), m.p. 190—192°, on treatment with BF_3–ethanedithiol, and the latter acetal desulphurized (Raney Ni) to yield the methylene ester (**8**), m.p. 133—134°. $LiAlH_4$ reduction of (**8**) gave a single alcohol (**9**), m.p. 140—143°, which upon HCl–AcOH treatment afforded





(**1**) R = H
(**6**) R = OH
(**13**) R = NH_2

(**2**) $R^1 = CO_2Et, R^2, R^3 = O$
(**3**) $R^1 = CO_2Et, R^2 = R^3 = -OCH_2 \cdot CH_2Cl$
(**4a**) $R^1 = CO_2Et, R^2 = OH, R^3 = H$
(**4b**) $R^1 = CO_2Et, R^2 = H, R^3 = OH$
(**5**) $R^1 = CH_2OH, R^2 = OH, R^3 = H$
(**7**) $R^1 = CO_2Et, R^2\ R^3 =$ 
(**8**) $R^1 = CO_2Et, R^2 = R^3 = H$
(**9**) $R^1 = CH_2OH, R^2 = R^3 = H$
(**10**) $R^1 = CO_2Et, R^2R^3 = NOH$
(**11**) $R^1 = CO_2Et, R^2 = NH_2, R^3 = H$
(**12**) $R^1 = CH_2OH, R^2 = NH_2, R^3 = H$

† Satisfactory C and H analyses were obtained for all crystalline compounds. The spectral data—mass, n.m.r., and i.r.—for each compound were in agreement with its structure.

1-aza-adamantane, m.p. (sealed capillary) 265—267°, yield 78%. N.m.r. (C_6D_6) δ 1·42 (s, –CH), 1·78 (s, C–CH_2–C), 3·06 (s, N–CH_2); integrated intensities 1 : 2 : 2.

Finally, reaction of the keto-ester (**2**) with hydroxylamine–HCl gave the oxime (**10**), m.p. 230—233°. Catalytic hydrogenation (PtO_2–HOAc) of the oxime function proceeded with some difficulty, although the amino-ester (**11**), m.p. 169—174°, was obtained in 40% yield, together with minor quantities of the corresponding stereoisomer. $LiAlH_4$ reduction of the ester (**11**) afforded the amino-alcohol (**12**), m.p. 173—175°. Direct chemical reduction of both the oxime and ester functions gave no satisfactory results, presumably because of concomitant cleavage of the *N*-toluene-*p*-sulphonyl group. Detosylation of (**12**) (HCl–AcOH) gave 4-aminoaza-adamantane (**13**), purified *via* ion exchange (IRA 400) and sublimation, m.p. 204—208° (sealed capillary), as an extremely hygroscopic material.

Our method allows a direct investigation on the chemical and physico-chemical properties of the aza-adamantane molecule in comparison to those of its intriguing homocyclic counterpart.[4] Potentially, it can also be adapted for the synthesis of a variety of derivatives of the parent system. Experiments have been carried out in which the utility of these systems as substituents or building-blocks in various natural products is evaluated.

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