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Preliminary communication

[3 + 3] Cycloaddition of trimethylenemethane to activated aziridines: palladium-catalysed synthesis of piperidines

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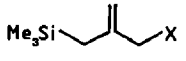
Abstract

The zerovalent palladium complex $[Pd(PPh_3)_4]$ catalyses the cycloaddition of trimethylenemethane to activated aziridines to give a high yield of 5-methylenepiperidines.

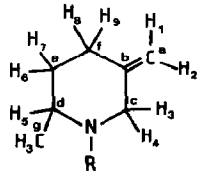
Interest in metal complexes of trimethylenemethane (tmm) [1], and transition metal mediated cycloaddition of tmm to C=C, C=O [2], and C=N [3], double bonds prompts us to report the first metal-catalysed cycloaddition of tmm to the aziridine ring system.

Nucleophilic ring opening of activated aziridines by carbon nucleophiles is well documented [4–9] and in view of the nucleophilic character of the catalytic species $[M(\eta^3\text{-tmm})(PPh_3)_2]$ (M = Ni or Pd) [1–3] we decided to investigate cycloaddition reactions of the tmm equivalents (1) in the presence of d^{10} metal complexes.



(1) a; X = OCOMe
b; X = OS(O)$_2$Me
c; X = I

(2) a; R = S(O)$_2$C$_6$H$_4$Me-p
b; R = C(O)C$_6$H$_4$NO$_2$-p



(3) a; R = SO$_2$C$_6$H$_4$Me-p
b; R = C(O)C$_6$H$_4$NO$_2$-p

The reactions of the acetate (**1a**) with the aziridines (**2**) in the presence of $[Pd(PPh_3)_4]$ gave the piperidines (**3**) * in high yield. However, no cyclo-adduct was isolated from the reactions of the mesylate (**1b**) and iodide (**1c**), and none of the tmm equivalents (**1**) afforded the piperidines (**3**) in the presence of $[Ni\{P(OEt)_3\}_4]$ as catalyst. The general reaction is shown in Scheme 1.

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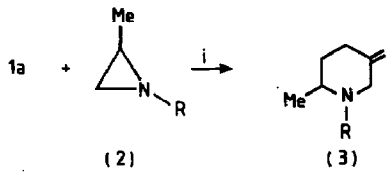
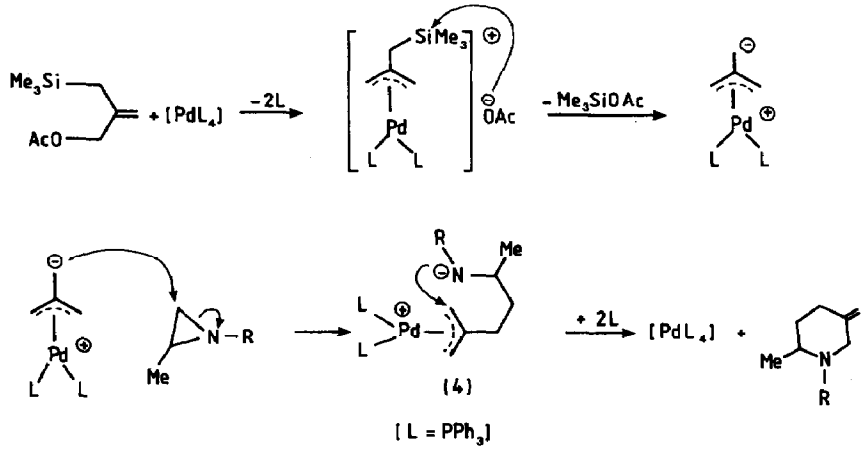


Scheme 1. Reagents i, cat., $[Pd(PPh_3)_3]$ 5 mol.%, tetrahydrofuran or toluene, reflux 16 h.

The reactions involved mixing the acetate (**1a**) and the aziridine in a molar ratio of 1.5 with 5 mol% of $[Pd(PPh_3)_4]$ in tetrahydrofuran or toluene and refluxing the solution under nitrogen. Interestingly, although addition of 1% of bis(diphenylphosphino)ethane to the $[Pd(PPh_3)_4]$ produces a more effective catalyst [2], for the addition of tmm to alkenes this catalyst system only marginally increased the yield of **3a**.

The mechanism for the reactions of **1a** with **2** presumably proceeds via a zwitterionic intermediate **4** as illustrated in Scheme 2. The cycloaddition of tmm to the aziridines (2) shows excellent regioselectivity, ring opening occurring at the methylene carbon, as normally observed in nucleophilic ring opening of activated aziridines [4–9].

The [3 + 3] cycloaddition of tmm to activated aziridines provides an attractive route to the piperidine ring system, which is present in a number of pharmaceutically active compounds [10]. Attempts to catalyse the cycloaddition of tmm to



Scheme 2.

* Selected NMR and mass spectroscopic data (J in Hz): **3a** ^{1}H (300 MHz; $CDCl_3$; room temp.) δ 7.7 (d, 2H, *o*-H, phenyl), 7.25 (d, 2H, *m*-H, phenyl), 4.79 (bs. 1H, H^1), 4.70 (bs, 1H, H^2), 4.15 (m, AB spin system, 2H, H^3, H^5), 3.68 (d, AB spin system, J 14.7, 1H, H^4), 2.44 (s, 3H, *p*-Me, MeC_6H_4), 2.28–2.22 (m, 1H, H^6), 2.04 (dt, 1H, H^7), 1.62–1.4 (m, 2H, H^8), 1.20–1.18 (d, 3H, Me). ^{13}C (DEPT), (75.4 MHz) δ 118.0 (C^b), 110.3 (C^a), 48.3 (C^d), 46.1 (C^c), 30.5 (C^e), 27.0 (C^f), 16.28 (C^g); ^{13}C NMR data of *p*-tosyl group omitted. m/z (M^+) 265.

electrophilic cyclopropanes, such as diethyl cyclopropane-1,1-dicarboxylate, have not been successful.

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