Some Reactions of 2-Azabicyclo[2.2.1]hept-5-enes with Diphenylketene: Preparation of Polysubstituted Piperidin-2-ones

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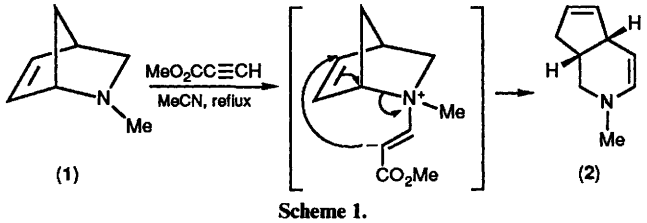
The azanorbornenes (**1**) and (**3**) reacted with diphenylketene to give the 3-azabicyclo[4.3.0]-nonanones (**7**) and (**5**) respectively, while the spiro compound (**9**) afforded the cyclopentenol derivative (**10**) on reaction with the same ketene.

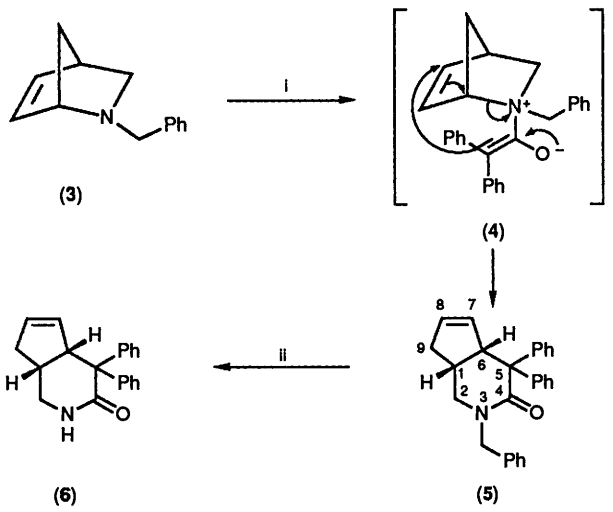
In recent reports, the use of zwitterionic amino-Claisen rearrangements as an approach to yohimbane[1] and reserpine[2] ring systems was studied. The strategy involves the addition of propiolate esters to various isoquinuclidines; the resultant zwitterionic intermediates then undergo an amino-Claisen rearrangement to furnish the D and E ring skeletons of the natural products. Also quoted was one example of an analogous reaction on 2-methyl-2-azabicyclo[2.2.1]hept-5-ene (**1**) which resulted in a poor yield of the corresponding hydropyrindine (**2**) (Scheme 1).

During the course of our work on 2-azabicyclo[2.2.1]hept-5-enes we have found that it is possible, calling on a similar mechanism, to form bicyclic piperidones by the addition of a ketene to the azanorbornene.

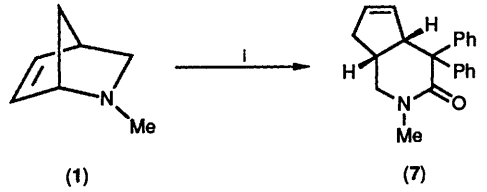


Scheme 1.

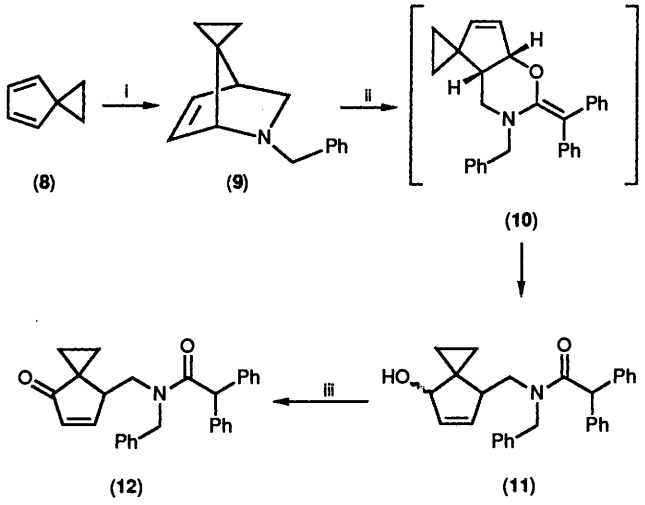
The reaction of the *N*-benzylazanorbornene (**3**)[3] with isolated diphenylketene[4] afforded the piperidone (**5**) in 59% yield, *via* the zwitterionic enolate (**4**). The reaction was carried out by refluxing in benzene for 6 days. It was possible to



Scheme 2. *Reagents and conditions:* i, $Ph_2C{=}CO/C_6H_6$, either reflux 6 days, 59% or ultrasound 12 h, 61%; ii, $Na/NH_{3(l)}$ THF 15 min, 96%.



Scheme 3. *Reagents and conditions:* i, $Ph_2C{=}CO$/THF, 0 °C–room temp, 13 h, 53%.



Scheme 4. *Reagents and conditions:* i, $PhCH_2NH_3Cl$, 37% aqueous formaldehyde, H_2O, room temp. stir, 8 h, 62%; ii, $Ph_2C{=}CO$, dropwise addition, anhydrous $CHCl_3$, −50 °C 10 min, then methanol/H_2O, 51%; iii, pyridinium chlorochromate, activated 4Å molecular sieve powder, anhydrous CH_2Cl_2, 0 °C, 83%.

increase dramatically the reaction rate by immersing the flask in an ultrasonic bath, resulting in completion of reaction in 12 h and formation of the product in 61% yield[5] (Scheme 2).

The *N*-methylazanorbornene (**1**) was found to be much more reactive to the ketene, the corresponding rearrangement product (**7**) being formed at 0 °C over 13 h (Scheme 3); the rate enhancement is probably due to steric factors.

The structure of compound (**5**) was elucidated by NMR spectroscopy (*vide infra*) and by debenzylation (using sodium in liquid ammonia) to provide the δ-lactam (**6**). The identity of the *N*-methyl derivative (**7**) was also elucidated from the ^1H NMR data: δ_H(250 MHz; C_6D_6) 2.00 (1 H, dm, *J* 16.6 Hz, 9-H), 2.20 (1 H, dd, *J* 13 and 1.2 Hz, 2-H), 2.34 (1 H, m, *J* 9.7, 9.6, 4.9, 4.1, and 1.2 Hz, 1-H), 2.50 (1 H, m, *J* 16.6, 9.7, and 3 × 2.3 Hz, 9-H), 2.70 (3 H, s, CH_3), 2.95 (1 H, dd, *J* 13 and 4.9 Hz, 2-H), 3.77 (1 H, dm, *J* 9.6, 3.5, 3 × 2.3 Hz, 6-H), 5.26 (1 H, m, *J* 6 and 3 × 2.3 Hz, 7-H or 8-H), 5.55 (1 H, m, *J* 6 and 3 × 2.3 Hz, 7-H or 8-H), and 7.0–7.7 (10 H, m, ArH), and by an INADEQUATE ^{13}C coupling experiment.

In contrast to the amino-Claisen rearrangement of (**1**) and (**3**) with diphenylketene, the spirocyclopropylazanorbornene (**9**) prepared by the method of Grieco *et al.*[3] from spirocyclopropylcyclopentadiene (**8**)[6] behaved quite differently, reacting very rapidly with the ketene at −50 °C to give a 51% yield of the ring-opened hydroxy amide (**11**) as a 2:1 inseparable mixture of epimers (Scheme 4). Presumably a compound of type (**10**) is formed in the reaction which subsequently undergoes hydrolysis by a selective S_N2' process on work-up. The structure of compound (**11**) was elucidated by NMR spectroscopy and by pyridinium chlorochromate oxidation which furnished the α,β-unsaturated ketone (**12**): δ_H(250 MHz; $CDCl_3$) 1.0–1.2 [4 H, m, $(CH_2)_2$], 2.95 (1 H, dd, *J* 13 and 10.5 Hz CH_2N), 3.41 (1 H, m, CH), 3.82 (1 H, dd, *J* 13 and 5.5 Hz, CH_2N), 4.35 (1 H, d, *J* 17.5 Hz, CH_2Ph), 4.70 (1 H, d, *J* 17.5 Hz, CH_2Ph), 5.15 (1 H, s, $CHPh_2$), 6.32 (1 H, dd, *J* 6 and 1.7 Hz, =CH), 7.25 (15 H, m, 3 × Ph), and 7.62 (1 H, dd, *J* 6 and 2.5 Hz, =CH); ν_{max}($CDCl_3$ soln) 3 069, 3 033, 2 935, 1 695, 1 644, and 1 493 cm^{-1} ($M + H^+$, 422.2120).

Experimental

Synthesis of the Piperidone (**5**).—A solution of compound (**3**) (7.7 g, 40 mmol) and diphenylketene (9.0 g, 46 mmol) in benzene (50 ml, distilled from sodium–benzophenone) was refluxed under nitrogen for 6 days. The reaction was then quenched with methanol, and the solvent removed under reduced pressure. The resulting dark oil was diluted with ethyl acetate (25 ml) and the product precipitated by adding diethyl ether (100 ml). The resulting tan crystals were filtered off at the pump and the filtrate was then evaporated and twice re-treated with ether. The combined crops of products were recrystallised (ethyl acetate–light petroleum) to give (**5**) in 59% yield as a colourless, crystalline solid (R_F 0.34, 30% Et_2O–70% light petroleum, on silica gel); m.p. 135–136 °C; ν_{max}(CH_2Cl_2) 3 033, 2 939, 1 650, and 1 480 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.90 (1 H, dm, *J* 16.5 Hz, 9-H), 2.63–2.88 (3 H, m, 1-H, 2-H, 9-H), 3.08 (1 H, dd, *J* 13 and 4.8 Hz, 2-H), 4.08 (1 H, dm, *J* 8 and 4 × 2 Hz, 6-H), 4.46 (1 H, d, *J* 14.5 Hz, CH_2Ph), 4.77 (1 H, d, *J* 14.5 Hz, CH_2Ph), 5.30 (1 H, m, *J* 5.8 and 3 × 2 Hz, 7-H or 8-H), 5.70 (1 H, m, *J* 5.8 and 3 × 2 Hz, 7-H or 8-H); δ_C(62.9 MHz; $CDCl_3$) *inter alia* 172.2, 132.1, and 131.8 (Found: C, 85.3; H, 6.8; N, 3.95. $C_{27}H_{25}NO$ requires C, 85.45; H, 6.64; N, 3.69%; M^+, 379.1971).

The reaction was also carried out on a 5.4 × 10^{-4} mol scale in dry tetrahydrofuran by immersing the sealed reaction flask in a Gallenkamp UL-150 ultrasonic water-bath for 12 h, to give a 61% yield of (**5**).

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