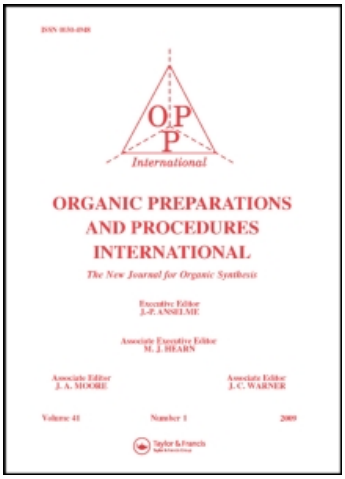

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PREPARATION OF 2-PHENYLPERHYDROAZEPINE

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PREPARATION OF 2-PHENYLPERHYDROAZEPINE

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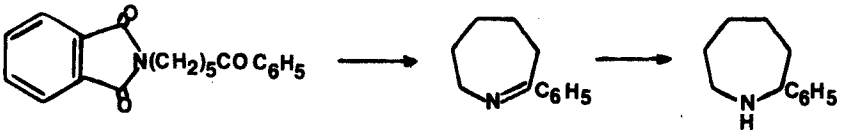
Research on the preparation of aminimides from 2-phenylperhydroazepine(III) required large amounts of its precursor 7-phenyl-3,4,5,6-tetrahydro-2H-azepine(II). The three methods reported for the preparation of II from ε-caprolactam were investigated with respect to yield and adaptability to a large scale preparation. The addition of phenylmagnesium bromide in tetrahydrofuran to ε-caprolactam or O-methylcaprolactim in benzene-ether gave 6% and 32% yield of II respectively. The overall yield from ε-caprolactam in the latter reaction was 19%. The literature reports,[2,3] using ether as a solvent, an 8% and 22.6% respectively. In the first case the unsaturated azepine was not isolated but was reduced with LAH to III.

The third method studied was based upon the condensation of ε-caprolactam with phthalic anhydride.[4,5] The resulting ε-phthalimidocaproic acid, obtained in a 69% yield, was



I II III

converted through its acid chloride by a Friedel-Crafts reaction to ε-phthalimidocaprophenone(I) in an 80% yield.[6] Conversion of I to II in 65% yield was accomplished by hydrazinolysis with hydrazine followed by treatment with alkali. The overall yield of II from ε-caprolactam was 36% and the reactions involved were more adaptable to large scale manipulations than those involving the Grignard reagent. II was reduced to III in 94% yield with sodium borohydride.

EXPERIMENTAL

Boiling points are uncorrected. The NMR spectra were determined with a Varian A60 spectrometer.

2-Phenyl-3,4,5,6-tetrahydro-2H-azepine(II).-A solution of ε-phthalimidocaprophenone(I)[6] (79 g, 0.25 mole) in ethanol (350 ml) at reflux was treated with 85% hydrazine hydrate (28.9 g, 0.49 moles) dropwise over a 45 min. period. The reaction mixture was heated at reflux for an additional 50 hrs. The resulting mixture, which contained precipitated phthalhydrazide, was cooled and acidified with 6N hydrochloric acid. The mixture was filtered and the precipitate was washed with water. The filtrate was distilled under reduced pressure to remove the ethanol, water was added and the mixture was filtered. The filtrate was basified with 10% NaOH and extracted with two 100 ml portions of ether. Removal of the ether gave 38 g of a brown oil which gave 28 g of 7-phenyl-3,4,5,6-tetrahydroazepine(II), bp. 108°/0.6 mm, lit.[2] bp. 139-141°/9 mm. NMR(CCl_4): δ ppm 1.20-1.99 (6H, m, 3,4,5-CH_2), 2.50-2.89 (2H, m, 6-CH_2), 3.58-3.92(2H,

m, 6-CH_2), 3.58-3.92(2H, m, 2-CH_2), 6.98-7.43(3H, m, m, p-aromatic protons) and 7.48-7.95(2H, m, o-aromatic protons).

2-Phenylperhydroazepine(III).-A stirred mixture of sodium borohydride (12.9 g, 0.34 mole) in ethanol (410 ml) at 0-5° was treated dropwise with 7-phenyl-3,4,5,6-tetrahydro-2H-azepine(II) (59 g, 0.34 mole) over the course of one hour. The temperature of the mixture was maintained between 25-30°. The resulting solution was stirred at room temperature for an additional 12 hrs. and then heated at reflux for 3 hrs. The reaction mixture was acidified with 6N HCl (350 ml), heated on a steam bath to decompose the complex then concentrated under reduced pressure. After basification of the concentrate with 6N NaOH, the mixture was extracted with one 200 ml portion of methylene chloride and two 100 ml portions of methylene chloride. Removal of the methylene chloride followed by a distillation at reduced pressure gave 55.7 g of 2-phenylperhydroazepine(III), bp. 89°/0.7 mm, lit.[3] bp. 130-132°/14 mm. NMR(CCl_4): δ ppm 0.97-2.15(9H, m, 3,4,5,6-CH_2 and NH), 2.30-3.03(2H, m, 7-CH_2), 3.33-3.73(1H, m, 2-CH) and 6.57-7.67(5H, m, aromatic protons).

The use of one equivalent of hydrazine gave only an 18% yield of III. A portion of the hydrazine is apparently involved in hydrazone formation and is not available for hydrazinolysis of I.

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