A novel ring enlargement reaction: Synthesis of 6, 7-benzo-2-phenyl-2, 4-bisazacycloheptane-1, 5-dione

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Abstract

Condensation of N-(tosyloxymethyl)phthalimide with aniline furnished most interestingly the title compound (III) in 20% yield instead of the hitherto known N-(N′-anilinomethyl) phthalimide (V).

Key words: Nucleophilic addition-elimination, Internal Michael addition, ring enlargement, new heterocyclic system.

1. Results and discussion

N-(tosyloxymethyl)phthalimide (II) (Fig. 1) obtained by treating the hitherto known N-(hydroxymethyl)phthalimide (I)[1–3] with tosyl chloride and pyridine, was heated with freshly distilled aniline at 110° for 10 hr under dry nitrogen atmosphere. The product, isolated after the usual work-up, was thoroughly washed with ice-cold dilute HCl, water and then dried *in vacuo*. The resulting dark brown neutral product on repeated recrystallization from ethyl acetate furnished the hitherto unknown 6, 7-benzo-2-phenyl-2, 4-bisazacycloheptane-1, 5-dione (III) as a light brown solid, m.p. 199–201°, *in ca* 20% yield (Fig. 1). That this solid (III) was different from the hitherto known N-(N′-anilinomethyl) phthalimide[4] (V), prepared by the direct displacement of the halogen of N-(bromomethyl)phthalimide (IV) by aniline[4], was evident from the following considerations.

The ring-enlarged product (III), m.p. 199–201°, depressed the melting point of the authentic sample of N-(N′-anilinomethyl)phthalimide (V), m.p. 257°, prepared according to the procedure described by Sachs[4]. Compound (III) indicated a large difference in R_f values in a comparative TLC study. The extreme insolubility of (III) in the usual solvents prevented the comparison of the IR spectrum of (III) in solution with that of the authentic sample (V) which is easily soluble in chloroform. The IR spectrum of (III) (KBr) indicated two bands at 3300 and 3150 cm^{-1}, characteristic of the NH stretching of the secondary amide while the IR spectrum of (V) (KBr) indicated an intense sharp band at 3330 cm^{-1}, quite characteristic of the free NH stretching of a secondary amine.

The IR spectrum of (III) showed, as anticipated, intense bands at 1650 and 1630 cm^{-1}, characteristic of the amide carbonyl whereas the IR spectrum of (V) (KBr) indicated intense bands at 1745 and 1680 cm^{-1} quite characteristic of the phthalimide carbonyl function. The ^1H NMR spectrum of (III) (DMSO–d_6) indicated signals at δ 3·15 (s, 2H, CH_2 at position 3) and 6·5–7·8 (m, 9H, aromatic). The signal due to the secondary amide proton (HNC = 0) was absent due to its rapid exchange with the solvent DMSO–d_6. In contrast to this, the ^1H NMR spectrum of (V) ($CDCl_3$) indicated signals at δ 5·1 (s, 2H, CH_2–N), 5·27 (somewhat broad, HN–C_6H_5) and 6·6–7·8 (m, 9H, aromatic). Moreover, the signal at δ 5·27, as anticipated, disappeared on D_2O exchange. The ^{13}C NMR spectrum (DMSO–d_6) of the ring enlarged product (III) indicated signals at δ 43·06 (t, CH_2 at 3), 116·4, 122·1, 122·3, 126·1, 130·3, 131·1 and 132·2 (doublets, the unsubstituted aromatic ring carbons), 139·3 (s, the aromatic tertiary carbons at 6, 7), 140·76 (s, the aromatic tertiary carbon directly connected to N) and 169·9 (s, the amide carbonyls[5]).

The driving force for the formation of this ring enlarged product may be due to the facile leaving nature of the tosyloxy function in (II). The probable mechanism is depicted in Fig. 1. It involves the intermediacy of (III *a*) which, on internal Michael addition, furnishes the observed product (III).

Further study with regard to the generality of this reaction with other nucleophiles is currently under progress.

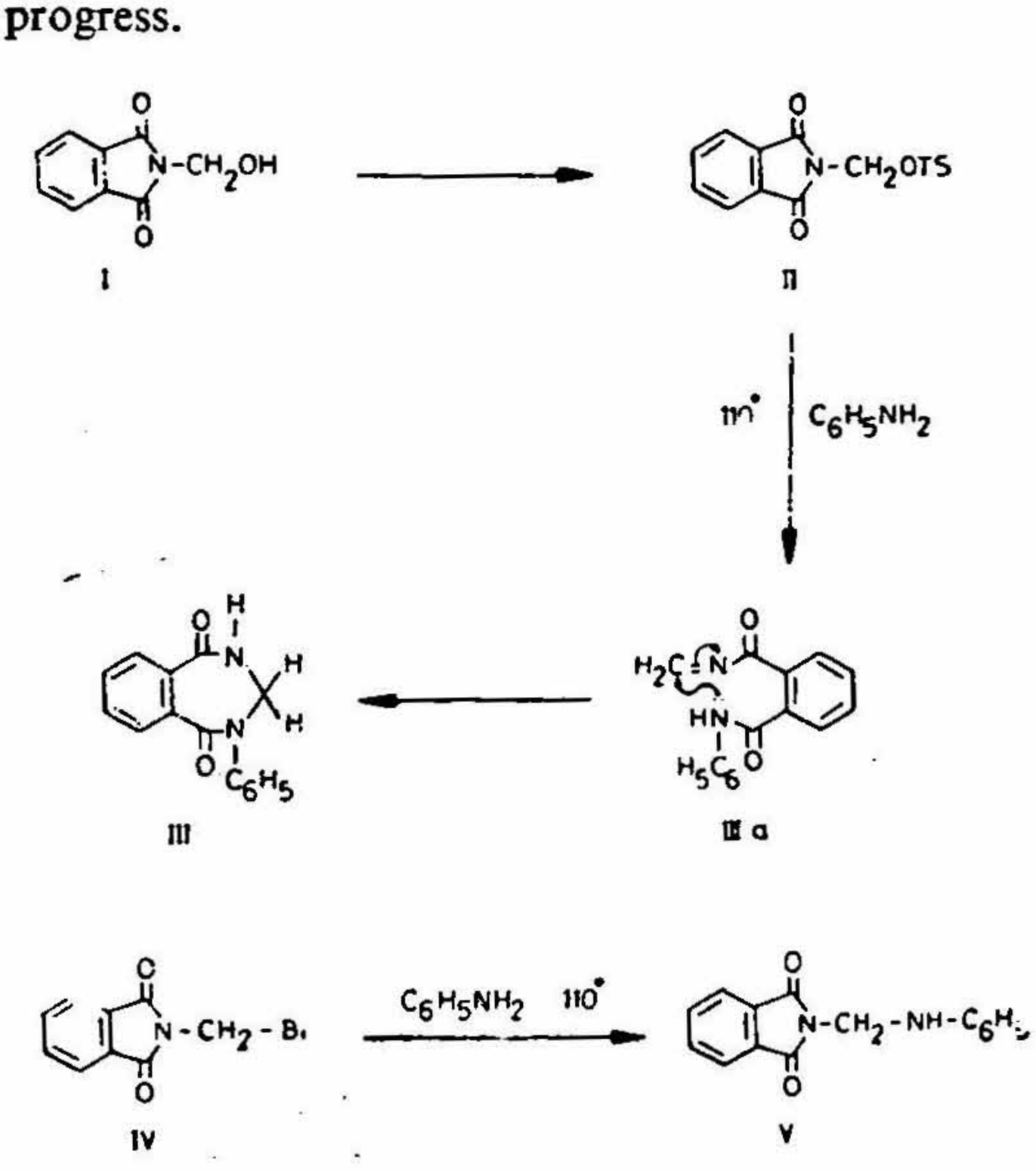

FIG. 1

2. Experimental

Melting points mentioned herein are uncorrected. IR spectra were recorded using a Perkin-Elmer spectrophotometer, Model 257. ^1H NMR and ^{13}C NMR spectra were recorded on Varian XL–100 spectrometer using TMS as an internal standard; the chemical shifts are reported as 'δ' values, for both the proton-noise decoupled and off-resonance decoupled spectra. Multiplicities of the signals observed in the off-resonance decoupled spectrum are indicated in the text in brackets. Micro analysis was carried out at Central Drug Research Institute, Lucknow. TLC plates (0·05 mm thickness) were prepared in the usual manner using 'Silica gel' (E. Merck, West Germany). Iodine was employed to develop the plates.

2.1. *Preparation of N–hydroxymethylphthalimide (I)*

This was prepared in accordance with the published procedures[1–3]. Thus, phthalimide (60 g), 40% formalin (30 ml), water (225 ml) gave N-hydroxymethylphthalimide (66 g), m.p. 138–140°, in 91% yield (reported[1–3] m.p. 138–141°; 95% yield).

2.2. *Preparation of N–bromomethylphthalimide (IV)*

This was prepared in accordance with the procedure reported by Pucher and Johnson[6]. Thus, N-hydroxymethylphthalimide (20 g), constant boiling hydrobromic acid (48%) (38 ml), conc. H_2SO_4 (1 ml) at 50–60° gave (IV) (16 g), m.p. 145–147° (reported[6] m.p. 148°).

2.3. *Preparation of N (N'–anilinomethyl)phthalimide (V)*

This was prepared according to the procedure reported by Sachs[4]. Thus, N-(bromomethyl) phthalimide (5 g), freshly distilled aniline (2 g) gave the expected product (V) (4 g), as a deep yellow solid, m.p. 254–256°, in 90% yield (reported[4] m.p. 157°, 90% yield). This compound (V) dissolves in $CHCl_3$ on slight warming.

2.4. *Preparation of 6, 7–benzo–2–phenyl–2, 4–bisazacycloheptane–1, 5–dione (III)*

To a solution of N-hydroxymethylphthalimide (I) (5 g) in benzene (20 ml) were added freshly crystallized sample of *p*-toluenesulphonyl chloride (5·5 g) and a few drops of pyridine. The mixture was stirred at room temperature for 5 hr. After this period, the solvent was evaporated under reduced pressure. The resulting product was treated with freshly distilled aniline (2 ml) and again the mixture was heated under reflux for 10 hr (bath–temp. 110–120°) in an atmosphere of dry nitrogen. The reaction mixture on cooling was treated with water (20 ml) and extracted with a mixture of ether-ethyl acetate (1 : 1) (3 × 30 ml). The organic extract was washed quickly with ice-cold dil. HCl followed by water. The dried organic extract on evaporation furnished a dark

brown solid (1·5 g) (20%), m.p. 199°. Repeated recrystallization from hot ethyl acetate (using a little Norit) gave a light brown solid, m.p. 199–201° which indicated a single spot in TLC (benzene with a few drops of ethyl acetate); this product is insoluble in CCl_4 and $CHCl_3$ but soluble in DMSO and hot ethyl acetate. (Found: C, 71·02; H, 4·46 and N, 11·01. $C_{15}H_{12}N_2O_2$ requires C, 71·42; H, 4·76 and N, 11·11%.)

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References

1. BUEHLER, C. A. AND PEARSON, D. E. — *Survey of Organic Synthesis*, Wiley-Interscience Inc. (USA), 1970, p. 931.
2. BUC, S. R. — *J. Am. Chem. Soc.*, 1947, **69**, 254.
3. SACHS, F. — *Ber. Dtsch. Chem. Ges.*, 1898, **31**, 1231.
4. SACHS, F. — *Ber. Dtsch. Chem. Ges.*, 1898, **31**, 3230.
5. LEVY, G. C. AND NELSON, G. L. — *Carbon*-13, *Nuclear Magnetic Resonance for Organic Chemists*, Wiley-Interscience, New York, 1972.
6. PUCHER, G. W. AND JOHNSON, T. B. — *J. Am. Chem. Soc.*, 1922, **44**, 817.