Cycloaddition of Diphenylnitrilimine to 1,5-Benzodiazepines

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ABSTRACT: *The cycloaddition reaction of diphenylnitrilimine on the 1,5-benzodiazepines has been studied. New molecules of triazolobenzodiazepines type have been isolated and characterized.*

KEY WORDS: *Benzodiazepine, Diphenylnitrilimine, Heterocycle, Cycloaddition, Phase transfer catalyse*

Benzodiazepine fused to five-membered heterocycles at the 4,5-positions [1] are of great interest because of their potential pharmacological activities [2]. As part of our continuing investigation in this area [3], we recently developed the synthesis of a new homologous of 1,1'-bis-benzodiazepin methane. This type of compounds, particularly with spacer alkyl chain between the two heterocycles represent the first example of benzodiazepine derivatives with a hydrophobic-hydrophilic balance which may lead to a control of their possible activities on the nervous system. These molecules are multifunctionals, having imines and lactams groups in addition to α-carbonyl activated methylenes. Therefore they offer the possibility of access to a wide variety of more elaborate heterocyclic derivatives. In fact, the monomer 4-phenyl-1,5-benzodiazepin-2-one, has been used as pivotal precursor to various heterocyclic systems such as pyrazole, isoxazole, benzimidazole and 1,3,5-benzotriazepine derivatives. We have been interested in the possibility of the introduction of the five-membered rings at the imine functional group. In this context, it should be pointed out that the reactivity of the imine group toward the formation of a five-membered heterocycle has been already reported by *Chimiri* et al. [4], like the preparation of oxadiazolobenzodiazepine from 1,5-benzodiazepine and benzonitrile oxide. In our case, attraction was on the introduction of a triazole ring by reaction with diphenylnitrilimine. For this purpose, 1,1'-bis [4-phenyl-1,5-benzodiazepin-2-oxo-1-yl] methane 1, used as starting compound, was prepared in good yield following the synthetic procedure outlined in the scheme.

Phase-transfer catalyzed alkylation of benzodiazepin-2-one 3 [2d], with dibromomethane in benzene, in the presence of 0.5N NaOH solution and a catalytic amount (0.1 equivalent) of tetrabuthylammonium bromide afforded 1 in 70% yield. Subsequent treatment of the latter with a large excess of diphenylnitrilimine in methylene chloride and in the presence of triethylamine gave a mixture consisting mainly of the mono triaza heterocycle 4 and only traces of the desired bis-triaza heterocycle 5. The low yield of 5 may be due to the low solubility of 4 in the reaction medium. To overcome this difficulty, the condensa-

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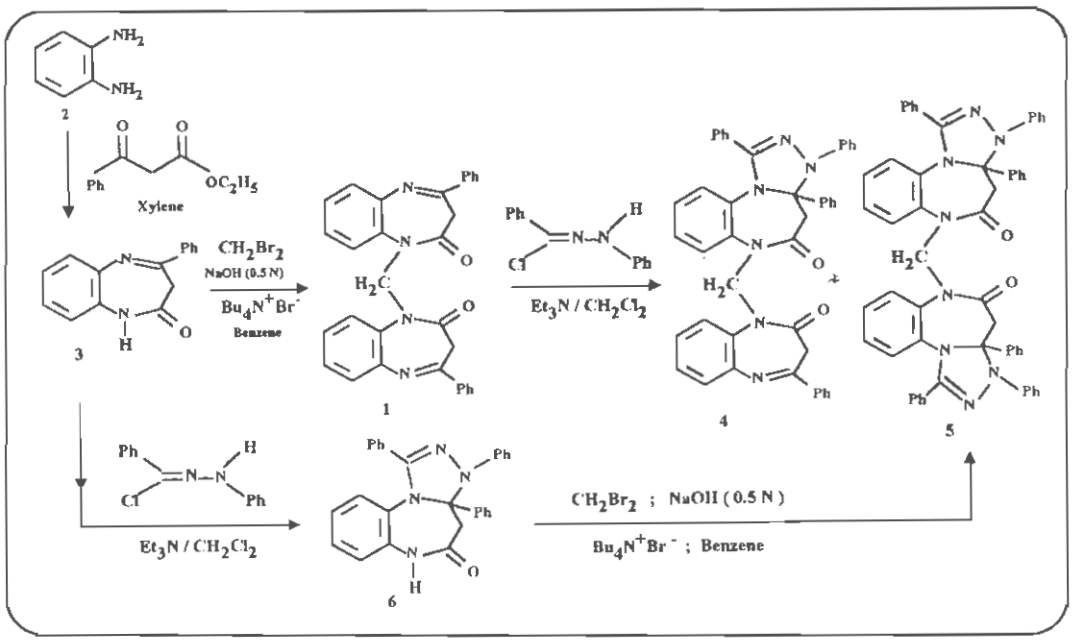
1021-9986/2000/1/16 *3/$/2.30*



tion reaction was performed on the mono imino compound **3**. The yield of the corresponding product of cyclization **6** is 57% yield. Subsequent treatment of **6** with dibromomethane, under the phase-transfer conditions, afforded the desired bis-triaza heterocycle **5** in yield up to 81%.

In conclusion, we have demonstrate that cycloaddition of diphenylnitrilimine on the imino group of 1,5-benzodiazepine readily occurs in spite of steric hindrance by the phenyl group. This opens a new way for the synthesis more elaborate heterocycles starting from compound bearing 1,5-benzodiazepine unit.

EXPERIMENTAL

Melting points, not corrected, were measured on Kofler bench. ^{1}H NMR spectra were recorded on a Brucker AC 200 spectrometer. Mass spectra (MS) were recorded on JEOL JMS D100 spectrometer and IR spectra on a Perkin Elmer 577 spectrometer.

2,3- Dihydro-1H-4- phenyl-1,5- benzodiazepin-2- one (3)

o-Phenylenediamine **2** (2 g , 19 mmol) is heated for 10 min in refluxed xylene (20 mL). A solution of ethyl benzoylacetate (3 g , 16 mmol) in xylene (4 mL) is then added dropwise to the reaction media. After continuous stirring and heating for one h , the cooled reaction mixture affords a precipitate which is filtered, washed with 40 mL of cold xylene and dried under reduced pressure to give a crystalline material in 68% yield. m.p. 196-198°C (diethylether-benzene: 1/1), lit. [2p]: 198-200°C, ^{1}H NMR; $CDCl_3$; δ_H : 9.37 (s, 1H, NH); 8.35-7.15(m, 9H, Ar-H); 3.66(s, 2H, CH_2-CO). MS, m/z: 236.

bis-[2,3- Dihydro-1H-4-phenyl-1,5- benzodiazepin-2-one]-methane (1)

A mixture of compound **3** (10 mmol), dibromomethane (5 mmol) in benzene/ 0.5 N NaOH (1:1) is heated at reflux during 4 h in the presence of 1 mmol of tetrabutylammonium bromide. The cooled reaction media is extracted with benzene and the organic phase is washed by water and dried over magnesium sulphate and evaporated to dryness to give a crystalline material in 70% yield. m.p. 214-216°C (diethylether-benzene: 1/1). ^{1}H NMR; $CDCl_3$; δ_H : 8.35-7.15 (m, 18H, Ar-H); 6.35(s, 2H, -N-CH_2-N-), 3.50(s, 4H, CH_2-CO), MS, m/z: 484, Anal. Calcd for $C_{31}H_{24}N_4O_2$: C, 76.86; H, 4.96; N, 11.57; Found: C, 76.70; H, 4.90; N, 11.50.

Condensation of 2,3- dihydro- 1H-4- phenyl- 1,5-

benzodiazepin-2-one (3) by diphenylnitrilimine (6)

Benzodiazepine **3** (10 mmol) and diphenylnitrilimine (10 mmol) are dissolved in methylene chloride (40 mL) and 3 mL of triethylamine are added. The reaction mixture is slowly heated to 50°C and maintained at this temperature for 24 h. The precipitated triethylammonium chloride is then filtered without precooling the reaction mixture. Evaporation of the filtrate gave a residue which is chromatographed on silica to give a crystalline material in 57% yield.
m.p. 200-201°C (ethanol). ^{1}H NMR; $CDCl_3$; δ_H : 9.1 (s, 1H, NH), 8.3-6.6(m, 19H, Ar-H); 3.50(s, 2H, CH_2-CO). MS, m/z: 484. IR(KBr); $\nu(cm^{-1})$: 1600 (C=N), 1660(C=O), 3230(NH).

Condensation of bis-[2,3-dihydro-1H-4-phenyl-1,5-benzodiazepin-2-one]-methane (1) by diphenylnitrilimine (4)

Treatment of **1** with diphenylnitrilimine as described for **6** gave the triaza **4** as a crystalline material in 51% yield. m.p. 180-182°C (CH_2Cl_2). ^{1}H NMR; $CDCl_3$; δ_H : 8.3-6.5(m, 28H, Ar-H), 6.0(s, 2H), 4.7(d, 2H), 3.8(d, 2H), 3.5(d, 2H), 3.0(d, 2H). MS, m/z: 678. IR(KBr), $\nu(cm^{-1})$: 1680(C=O), 1600(C=N).

Action of dibromomethane on 6 (5)

Treatment of **6** with dibromomethane as described for **1** gave the bis-triaza **5** as a crystalline material in 81% yield. m.p. 78-80°C (ethanol). ^{1}H NMR; $CDCl_3$; δ_H : 8.3-6.5(m, 38H, Ar-H); 6.0(s, 2H), 3.5(s, 4H). MS, m/z: 872. IR(KBr), $\nu(cm^{-1})$: 1680(C=O), 1600 (C=N).

Received, 29th May 1999; Accepted, 21st November 1999

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