SYNTHESIS OF DIAZEPINO-FUSED HETEROCYCLES: REACTIONS WITH 4-CHLOROBUTYL ISOCYANATE

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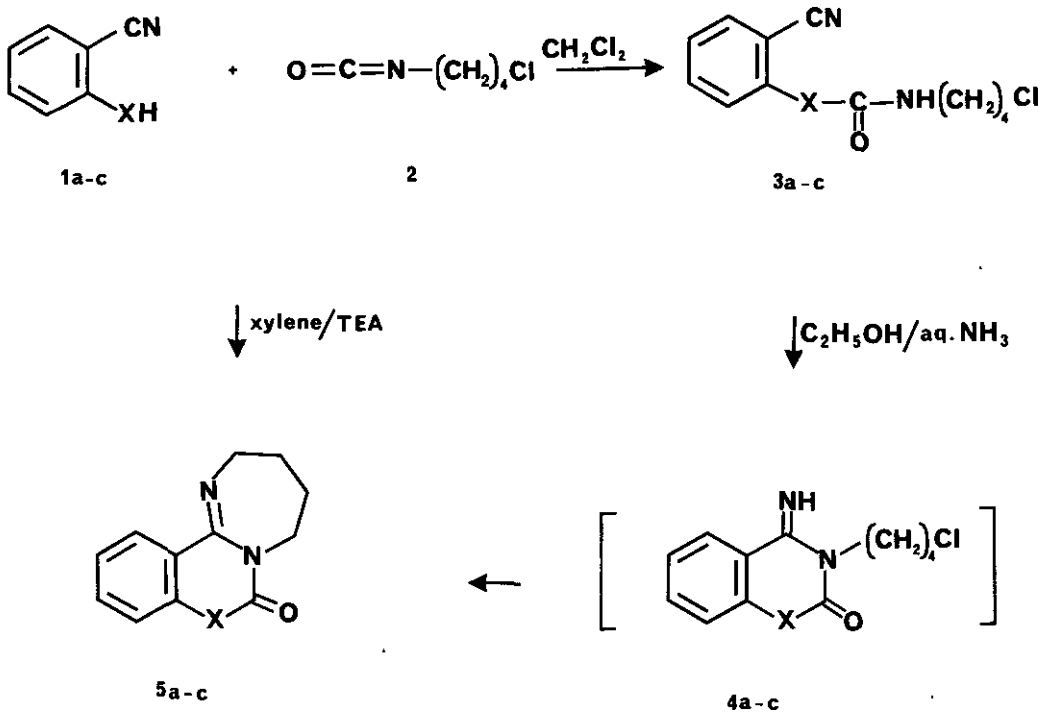
Abstract - The reaction of anthranilonitrile with 4-chlorobutyl isocyanate gives urea 3, which undergoes a double cyclization to form 2,3,4,5-tetrahydro[1,3]-diazepino[1,2-c]quinazolin-7(8H)-one, upon heating or treatment with a base. Similarly, the reaction of 2-hydroxybenzonitrile with 4-chlorobutyl isocyanate and upon cyclization affords 2,3,4,5-tetrahydro[1,3]diazepino[1,2-c][1,3]-benzoxazin-7-one.

Though 1,4-benzodiazepines[1,2] have received intensive study since the early 1960s because of their value in psychotherapy, 1,3-diazepines[3] have received rather less attention even than their 1,2-isomers[4]. Our interest in fused quinazolinones[5,6] and 1,3-benzoxazinones[7] have led to the synthesis of 1,3-diazepines fused to quinazolinones and 1,3-benzoxazinones with a view to unravelling their biological profiles. Further, very few isolated reports[8] have appeared in literature on 1,3-diazepines fused to other heterocyclic rings compared to an impressive armoury of synthetic routes for fused 1,4-benzodiazepines[9,10]. This paper describes the reactions of anthranilonitriles 1a and 2-hydroxybenzonitrile 1c with 4-chlorobutyl isocyanate 2 which lead to the formation of the 1,3-diazepino[1,2-c]quinazoline and 1,3-diazepino[1,2-c][1,3]benzoxazine ring systems respectively in a remarkably convenient and efficient manner.

Reaction of 1a with 2 in an aprotic solvent, such as diethyl ether, dichloromethane and benzene yields the expected urea, 2-[3-(4-chlorobutyl)ureido]benzonitrile 3a in essentially quantitative yield. On heating, 3a melts and its treatment with potassium bicarbonate (10% solution) gives 2,3,4,5-tetrahydro-[1,3]diazepino[1,2-c]quinazolin-7(8H)-one 5a. This product is also obtained when 3a is treated with aqueous ammonia in ethanol. The most probable intermediate 4 could not be isolated, may be on account of the spontaneous formation of the tetrahydrodiazepino ring. Finally, the second ring closure leads to a tricyclic ring system 5 by an intramolecular nucleophilic substitution involving the imino nitrogen atom of the initial cyclization product 4.

The product 5a can also be obtained directly by the reaction of 1a and 2 in refluxing xylene and equimolar amount of triethylamine.



1a-c 2 3a-c

5a-c 4a-c

a , X = NH : b , X = NCH_3 : c , X = O

The analogous reactions of 1b and 1c with 2 lead to formation of 8-methyl-2,3,4,5-tetrahydro[1,3]diazepino[1,2-c]quinazolin-7(8H)-one 5b and 2,3,4,5-tetrahydro[1,3]diazepino[1,2-c][1,3]benzoxazin-7-one 5c, respectively. These are hitherto unknown ring systems and their structures are supported by microanalytical, IR, NMR and mass spectral data. Structures 5a-c are compatible with the absence of a C≡N stretching band in the IR spectra.

EXPERIMENTAL

Melting points were taken using Buchi melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 283B spectrophotometer in a KBr pellet. ^1H NMR spectra were measured with a JEOL FX-90 Fourier transform spectrometer from $CDCl_3$ solution[11] using internal TMS. Mass spectra were recorded on a VG 7070H mass spectrometer at 70 eV.

2-[3-(4-Chlorobutyl)ureido]benzonitrile, 3a

General Procedure:

To a solution of anthranilonitrile 1a (2.36 g, 0.02 mol) in dichloromethane (20 ml) was added a solution

of 4-chlorobutyl isocyanate 2 (2.67 g, 0.02 mol) in dichloromethane (10 ml) dropwise with stirring at room temperature. After completion of the addition the stirring was continued for 4 h. The dichloromethane is then removed in vacuo and the residue is left for 30 h at room temperature to give the crude product 3a, which on recrystallisation from ethanol yielded the colourless crystals (4.5 g, 89%), mp 135-138°C (melts partially and then resolidifies); IR, 3330, 3300, 2200, 1645, 1610 cm^{-1}; ^1H NMR, 1.7-2.0m, 3.1t, 3.5t, 6.9-8.3m, 9.6s (D_2O exchangeable) MS, m/z 251 M^+).

3b : yield, 92%, mp 122-124°C; IR, 3335, 3295, 2215, 1640, 1610 cm^{-1}; MS, m/z 265.

2-[(4-Chlorobutyl)aminocarbonyloxy]benzonitrile, 3c: yield 87%, mp 105-108°C; IR, 3310, 2210, 1710 cm^{-1}; ^1H NMR: 2.0m, 3.3t, 3.8t, 5.9s, 7.0-7.6m.

2,3,4,5-Tetrahydro[1,3]diazepino[1,2-c]quinazolin-7(8H)-one, 5a

General Procedure A:

Thermal decomposition of 3a (1.0 g) in an oil bath at 200°C gave solid material which was treated with aqueous potassium bicarbonate solution (10% solution) to yield 5a (0.8 g, 94%), mp 250°C. Recrystallization from ethanol gave colourless crystals, mp 282-284°C (with decomposition); IR 3425, 1730, 1610 cm^{-1}; ^1H NMR: 1.9m, 3.4t, 3.6t, 6.9-8.0m, 10.1s (D_2O exchangeable), MS, m/z 215.

General Procedure B:

A mixture of 3a (2.0 g) in ethanol (30 ml) and aqueous ammonia (30%, 15 ml) was refluxed for 30 min on a water bath. On cooling and diluting with water the precipitate separated was filtered and dried to yield 5a (1.5 g, 88%) which was recrystallized from ethanol as colourless crystals, mp 282-283°C (with decomposition).

General Procedure C:

A mixture of 1a (2.36 g, 0.02 mol), xylene (10 ml), 2 (2.67 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) was refluxed for 30 h. Then xylene was removed under vacuo and the precipitate separated was filtered and washed with water to yield 5a (3.8 g, 88%). The pure compound was obtained by recrystallization from methanol as colourless crystals of 5a, mp 282-284°C.

The product 5a obtained by procedure B and C exhibited superimposable IR spectra to the product obtained by procedure A. Compounds 5b and 5c were also obtained by employing the aforesaid procedures.

5b: yield 85%, mp 273-275°C; IR, 3420, 1725, 1610 cm^{-1}; MS, m/z 229 (M^+).

5c: yield 87%, mp 140-143°C; IR, 1730, 1640 cm^{-1}; ^1H NMR: 1.9m, 3.6t, 3.9t, 6.9-7.8m; MS, m/z 216 (M^+).

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11. Compounds which were not soluble in $CDCl_3$; a drop of d_6-DMSO was added.

Received, 4th November, 1986