

Synthesis of 2-Arylimino Thiazol [4,5-e] (1,4) Diazepines

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Benzodiazepines possess a variety of useful biological activities, pharmaceutical properties and therapeutic applications. Their discovery has opened a new era in the research of drugs acting on the central nervous system. Their clinical importance and commercial success tempted us to synthesize 1,4-diazepine type compounds.

Key Words: 1,4-Diazepines, Benzodiazepines, Synthesis

INTRODUCTION

Diazepines exhibit various biological activities¹⁻⁵ such as antipyretic, analgesic, sedative, antiasthmatic and antidepressant. 1,4-Benzodiazepines are useful in psychotherapy and possess an impressive armoury in synthetic routes^{6, 7}. Some of the benzodiazepines have shown anticancer and anticonvulsant activity. Benzodiazepines can be used as anxiolytic, hypnotic, sedative and muscle relaxant⁸. The discovery of benzodiazepine has opened a new era in the research of central nervous system and the drugs acting on it.

In view of the useful biological activities, pharmacological properties and therapeutic applications of benzodiazepines, various methods have been developed for their synthesis. The clinical importance and commercial success of 1,4-benzodiazepines has led to extensive synthetic studies of these compounds.

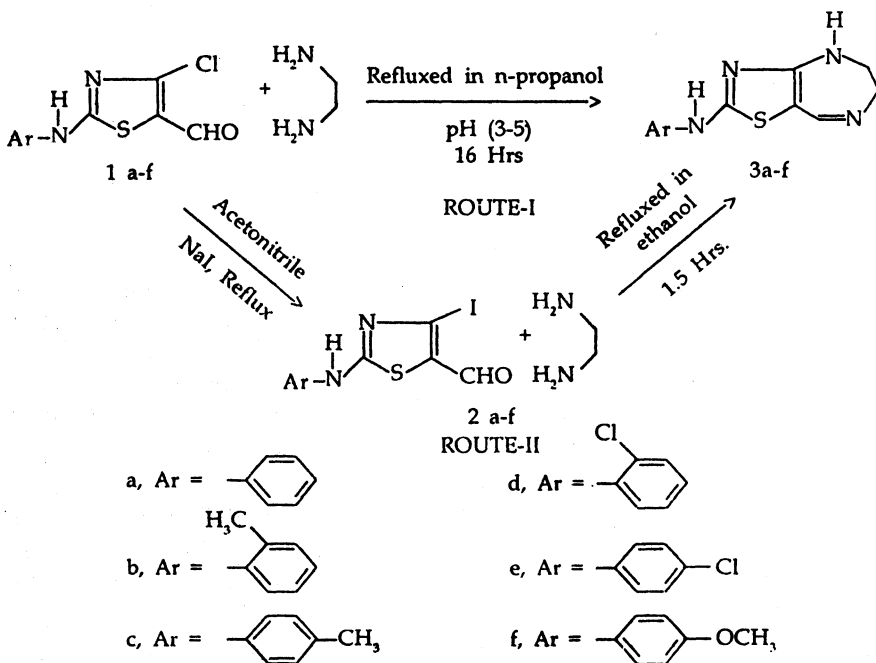
In view of these reports and in continuation of our work⁹⁻¹¹ in the synthesis of fused five, six and seven-membered heterocyclic diazepines, we report the synthesis of 1,4-diazepine type of compounds.

RESULTS AND DISCUSSION

We used synthones (1a-f) to prepare 2-arylimino thiazol [4,5-e] (1,4) diazepines (3a-f) by two different routes as visualised in Scheme-I.

Route I: The method described by Mosher *et al.*¹² was used for the conversion of (1a-f) into 3(a-f). The carboxaldehydes (1a-f) were synthesised as per literature¹³. A suspension of (1a-f) in *n*-propanol was added to equimolar amount of ethylenediamine maintaining acidic pH of the solution by adding formic acid and refluxing the reaction mixture for 16 h. The extraordinary conditions such as pH control and refluxing the reaction mixture for longer duration is required because formation of seven-membered rings is rather difficult as both strain and distance factors become worse¹⁴. Even after using much extraordinary conditions the yields were only in the range of 49 to 59% (Table-1).

In order to increase the percentage yield and to simplify reaction conditions it was decided to develop a convenient and less time consuming method for the said compounds which could then be generalised. For this purpose it was first decided to synthesise iodocarboxaldehydes (2a-f) from (1a-f). The chlorocarboxaldehydes (1a-f) possess chlorine as the poor leaving group which was replaced by better leaving group iodine. The intermediate iodocarboxaldehydes (2a-f) can be cyclised into seven-membered heterocyclic diazepines by refluxing with equimolar quantities of ethylenediamine in ethanol.



Scheme-I

EXPERIMENTAL

Melting points are uncorrected. IR spectra (nujol) were taken on Perkin-Elmer 337 spectrophotometer. The PMR spectra were recorded in CDCl₃ on Jeol F × 90Q instrument.

2-Arylimino thiazol [4,5-e] (1-4) diazepines (3a-f) (Route-I)

A mixture of (1a-f) (0.005 mole) and ethylenediamine (0.005 mole) in *n*-propanol (10 mL) was refluxed in a water bath for 16 h. The pH was maintained 3-5 by adding formic acid. The excess of solvent was removed by distillation. The reaction mixture was then slowly added to crushed ice with constant stirring which yielded solid products (3a-f) (Table-1).

The compounds (3a-f) synthesized by Route-I and Route-II are the same. It is confirmed by their melting points, colour, elemental analysis and IR spectra.

TABLE-I
PROPERTIES OF 2-ARYLIMINO THIAZOL [4,5-E] (1,4) DIAZEPINES (3a-f)

Compd. No.	m.f.	Colour	m.p. (°C)	Yield (%)		Analysis (%), found (calcd.)		
				Route-I	Route-II	C	H	N
3a	C ₁₂ H ₁₂ N ₄ S	Dark brown	170	49	61	58.86 (59.01)	5.12 (4.19)	22.70 (22.95)
3b	C ₁₃ H ₁₄ N ₄ S	Brown	198	54	68	60.26 (60.46)	5.31 (5.43)	21.85 (21.70)
3c	C ₁₃ H ₁₄ N ₄ S	Dark brown	104	58	78	60.65 (60.46)	5.66 (5.43)	21.58 (21.70)
3d	C ₁₂ H ₁₁ N ₄ SCl	Yellow	162	50	63	51.60 (51.71)	3.80 (3.95)	20.15 (20.10)
3e	C ₁₂ H ₁₁ N ₄ SCl	Dark yellow	194	57	72	51.82 (51.71)	4.09 (3.95)	19.82 (20.10)
3f	C ₁₃ H ₁₄ N ₄ SO	Brown	255	59	64	56.72 (56.93)	5.02 (5.11)	20.24 (20.43)

Preparation of 4-iodo-2-arylimino thiazole-5-carboxaldehydes (2a-f) (Route-II)

Sodium iodide (2 g), 55% w/v aq. solution of HCl (0.5 mL) and acetonitrile (20 mL) were taken in a round-bottom flask. To this mixture chlorocarboxaldehyde (1a-f) (0.005 mole) was added and refluxed for 4.5 h. Most of the solvent was removed by distillation and saturated aqueous solution of Na₂CO₃ was added to render the mixture alkaline. The crude products were recrystallised with ethanol to afford (2a-f).

Preparation of 2-aryliminothiazol [4, 5-e] (1, 4) diazepines (3a-f)

A mixture of (2a-f) (0.002 mole) and ethylenediamine (0.002 mole) in anhydrous ethanol (8 mL) was refluxed for 1.5 h. The excess of solvent was removed by distillation. The reaction mixture was then poured into crushed ice with constant stirring. The crude products were recrystallised from aqueous ethanol to afford (3a-f).

Conclusion

By comparing the % yields of the products, the time required for the synthesis and reaction conditions, we conclude that route-II should be the preferred method for the synthesis of the above mentioned compounds.

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