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<th>1-Benzazepines (Commemoration Issue Dedicated to Professor Eiichi Fujita on the Occasion of his Retirement)</th>
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<tr>
<td>Author(s)</td>
<td>Katayama, Hajime</td>
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<tr>
<td>Citation</td>
<td>Bulletin of the Institute for Chemical Research, Kyoto University (1985), 63(2): 120-131</td>
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<tr>
<td>Issue Date</td>
<td>1985-08-24</td>
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<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/2433/77100">http://hdl.handle.net/2433/77100</a></td>
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<tr>
<td>Type</td>
<td>Departmental Bulletin Paper</td>
</tr>
<tr>
<td>Textversion</td>
<td>publisher</td>
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REVIEW

1-Benzazepines

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Received April 10, 1985

KEY WORDS: 1-Benzazepines/ Dihydro-1-benzazepines/ Tetrahydro-1-benzazepines/ Synthesis/ Reactions

Fusion of benzene and azepine rings leads to three isomeric benzazepines. Kasperek\(^1\) reviewed the chemistry, mainly the synthesis, of these benzazepines up to 1972. In this review focussing are on the synthesis of 1-benzazepines, which appeared between 1972 and 1984, and the reactions of 1-benzazepines which are not the main theme of Kasperek’s review. 1-Benzazepine has three isomers, 1H-1-benzazepine 1, 3H-1-benzazepine 2 and 5H-1-benzazepine 3. None of these is synthesized. The manner which is used in Kasperek’s review is also used in this review for the classification of the synthesis and the reactions are surveyed according to three major compounds, tetrahydro-1-benzazepines, dihydro-1-benzazepines and 1-benzazepines.

![Diagram of 1-Benzazepines](image)

I SYNTHESIS

Synthetic methods are categorized into four parts, i.e., 1 Cyclization, 2 Nitrogen insertion, 3 Ring enlargement, 4 rearrangement.

1. Cyclization reaction

There are three types of cyclization reactions which have appeared in literatures. The first approach is the classical one and no noticeable report concerning with method (A) has reported since 1972. The major reaction which constitutes type (B) cyclization is Friedel-Crafts reaction. Intramolecular Friedel-Crafts alkylation finds its utility in the case where it is possible to generate the stable carbenium ion as the reaction intermediate.\(^1\) But Friedel-Crafts acylation for method (B) has found no solid promise

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to succeed. Intramolecular acylation of 4 was carried out by phosphoryl chloride but the yield of 5 was 24% at best. Other reagents provide no promise.2) New example is added in this area. When 6 is heated in polyphosphoric acid (PPA), double cyclization occurred and 7 was obtained in 14% yield.3) In this reaction Friedel-Crafts acylation took place at first then acid-catalyzed amino-Claisen rearrangement and subsequent cyclization into 7 followed since N-2-carboxyethyl-2-methylindole does not give any cyclization product under this reaction condition. We have also tried Friedel-Crafts acylation. When acid 8 was heated in a mix of methanesulfonic acid and phosphorous pentoxide (9: 1) at 100°C for 3 h, the cyclized product 9 was obtained in 6.3% yield after tedious separation. The structure of 9 was confirmed by reducing by Wolff–Kishner reaction and comparing with 2,3,5,6,7,8-hexahydro-1H-1-benzazepino[3, 2, 1-ij] quinoline 10 which was prepared from 2,3,4,5-tetrahydro-1H-1-benzazepine 11.4) For hydrocarbons Friedel-Crafts acylation is an effective reaction to construct fused seven-membered ring5) but the type (B) approach to form 1-benzazepine skeleton seems to be fruitless.

For type (C) reaction, Dieckmann, aldole and acyloin condensations are studied. Among them, Dieckmann condensation has been studied most extensively and the
typical application is the reaction of 12. It is possible to prepare 14 and 15 in hundreds grams scale, thus this method constitutes the major entry into 1-benzazepine chemistry. Tosyl group is essential in this reaction because no cyclization takes place when nitrogen is not protected and acetyl group is used as protecting group. 

Aldol and acyloin condensations are seldom used for type (C) reaction. Recently Vilsmeier reaction is used in this area. When 16 was subjected to Vilsmeier–Haack reaction condition, 17 was formed in good yield. Condensation of laevulinic acid with aniline is reinvestigated. The structure of the major product is corrected. The yield of 18 is poor but this reaction is simple so that it can still find application, especially when activating substituent (8-OCH₃) locates on aromatic ring (25% yield).

2. Nitrogen insertion reaction

Beckmann and Schmidt rearrangements have played major roles in this field (D). There are many reports concerning with these reactions to prepare tetrahydro-1-benzazepines. The major drawback for these reactions is the formation of by-product, the isomer of 1-benzazepines. In these reactions the introduction of electron donating group at para position of aromatic ring decreases the yield of 1-benzazepine derivative and increases the yield of 2-benzazepine derivative. Beckmann rearrangement of 1-tetralone oxime 29 took place in favor of tetrahydro-1-benzazepin-2-one but the reaction of 19 proceeded in favor of 2-benzazepine derivative 21 over 1-benzazepine derivative 20. The ratio of 2-benzazepine derivative is further increased in the reaction of 22. Similar trend is reported in Schmidt rearrangement of 1-tetralone. When Schmidt rearrangement was adopted to alcohol 25, 2-methyl-1-benzazepine
1-Benzazepines derivative 26 was formed. In this reaction alkyl substituent was introduced into C-2.\textsuperscript{10)} The preparation of 2-alkyl-tetrahydro-1-benzazepine was carried out by the oxidation of 11 with m-chloroperbenzoic acid and Grignard reaction of nitrone 27. The yield of 28 was moderate.\textsuperscript{11)}

Yamamoto et al have used diisobutylaluminum hydride (DIBAL) as the catalyst for Beckmann rearrangement as well as the reducing agent for amide in one pot procedure.\textsuperscript{12)} By this method oxime 29 was directly reduced into 11 and the purity of the product was high. But when this reaction was applied to 19, the product was a mix of 30 and 31 (1:1). The presence of methoxy group again reduced the yield of 1-benzazepine derivative 30.\textsuperscript{4)}

3. Ring enlargement reaction

Two types of ring enlargement (E) and (F) are reported for the preparation of 1-benzazepine skeleton. After 1972, the efforts are focused onto type (F) reaction and also on the behaviors of reaction products. The first report concerning with type (E) reaction is that the dibromocyclopropane ring was opened by the contact with silver nitrate or by refluxing in pyridine.\textsuperscript{13a)} Heating is also found to be effective.

When 32 was heated under reduced pressure, 33 was obtained in 65\% yield.\textsuperscript{13b)} The presence of electron releasing group on aromatic ring does not increase the yield of ring-expanded product. Product 33 polymerized when exposed to acid. The analogues of 32 with dichlorocyclopropane ring are stable enough to distill under heating.\textsuperscript{13b)} New method to introduce one carbon into quinoline A ring has appeared.\textsuperscript{14)} The reaction of ylide with N-oxide 34 produced 35 as brown crystals. The major product in this reaction is dimeric quinoline. When other quinoline N-oxide is used in this reaction no 1-benzazepine derivative is formed. The property of 35, mp 82–83°C is unique since many attempts at isolating 1H-1-benzazepines have failed due to its instability.

Type (F) reaction has attracted many chemists. A series of studies are conducted with substituted indoles 36. When a solution of 1-methylindole 36a and dimethyl acetylenedicarboxylates (DMAD) in absolute acetonitrile was refluxed for 6 days, 1-benzazepine derivative 38a was formed as one of seven products.\textsuperscript{15)} However if a solution of this mixture in benzene was irradiated at 10°C by medium-pressure Hg lamp in the presence of benzophenone as sensitizer, the smooth reaction took place and a mixture of 37a and 38a was obtained.\textsuperscript{16)} The major product 37a is deep orange oil and formed intramolecular CT complex. This product was thermally transferred into 38a while standing at ambient temperature. Irradiation of 38a gave an equilibrium

\begin{align*}
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{N}\text{R}^5\text{R}^6\text{N}^+\text{R}^7\text{R}^8\text{R}^9
\end{align*}
Sensitized photocycloaddition of 1,2-dimethylindole 36b and DMAD also gave a mixture of 37b and 38b along with the secondary product 39. Warming at 40°C readily converted 37b into 38b. Irradiation of 38b also sets an equilibrium between 37b and 38b.

Reaction of 1,3-dimethylindole 36c is complicated. When an equimolar amount of 1,3-dimethylindole 36c and DMAD was treated with excess boron trifluoride in ether at 15°C, 37c was produced. Although it was unable to isolate this product in pure state, the crude product was warmed and transformed into 38c in 10% overall yield. The adduct 40 was the major product in this reaction. The similar reaction in carbon tetrachloride at 0–4°C afforded 37c (30%), 38c (8%) and 40 (40%) after separation. In the crude product of this reaction, 38c was not detected but it was formed during the process of isolation. On heating benzene solution, 37c was ring-expanded into 38c. When an equimolar mixture of 1,3-dimethylindole 36c and DMAD in benzene was irradiated in the presence of sensitizer, 37c was formed with six other products. If two fold excess of DMAD was used at 10°C, 37c predominated in the reaction products and no 38c was formed, though 38c rather than 37c was isolated when the reaction was carried out at ambient temperature. These obser-
vations conclude that the primary photochemical process is the cycloaddition and followed by thermal ring opening. 1-Benzazepine derivative 38c in benzene at 10°C was photolyzed into 37c in 71% yield.

The behaviors of 1,2,3-trimethylindole 36d under these reaction conditions are much more simple. When a mixture of 36d and DMAD (molar ratio 1:1) was treated with a few drops of boron trifluoride etherate, 37d was formed in 82% yield which was thermally transformed into 38d in 83% yield.

Ikeda et al have established the general method for the preparation of 1-benzazepines starting from indoles. Indole and 2-methylindole are used after protecting NH bond with either benzoyl or benzyl groups. Yield for each step is good except decarboxylation stage. It requires heating up to more than 300°C to transfer 43 into 44 thermally. So, effective reaction condition for this conversion was investigated in details. The addition of silver tetrafluoroborate lowered the reaction temperature considerably and allowed to form an equilibrium between 43 and 44. The equilibration is also attained by the irradiation of 44. Interesting rearrangements occurred when 45 was heated in the presence of tetrafluoroborate. The reaction mechanisms for these reactions are proposed. Since the conrotatory ring opening of cyclobutene ring is prohibited by ring strain, biradical mechanism is considered to be most plausible under thermal condition. However, the participation of nitrogen lone pair and subsequent disrotatory ring opening is not totally ruled out. For the rearrangement of 45, the initial coordination of silver cation on nitrogen and subsequent N–C bond cleavage to form cyclobutenyl cation are proposed.

4. Rearrangement

When triene 49 was exposed under light of low-pressure coil at —78°C, a mixture of 50, 51 and 52 was formed. The isolated product 51 rearranged into 53 when 52.
heated at 180°C and also was dehydrogenated into 54 when treated with o-chloranil at ambient temperature. The catalytic hydrogenation of 54 saturated two double bonds in azepine ring. Paquette has reported the thermal rearrangement of 55 and 57. Reaction mechanism involves initial valence tautomerization for 55 then 1,5-shift of nitrogen and Cope rearrangement.21) The reaction of nitroene 59 with allene in a sealed tube gave three products 60, 61 and 62. 1-Benzazepine derivative 62 is the major product. Both 61 and 62 are derived from the addition isomer of 60 via diradical intermediate.11) Among the approaches to construct 1-benzazepine skeleton by type (E) method, Wagner–Meerwein rearrangement should be explored more and this approach should reserve more promise than the methods known due to its versatilities.

II REACTIONS

Reactions of 1-benzazepines are surveyed basing upon three compounds, tetrahydro-1-benzazepine, dihydro-1-benzazepine and 1-benzazepine. Novel and unique reactions are center of discussion.

1. Tetrahydro-1-benzazepines

2,3,4,5-Tetrahydro-1-benzazepine 11 is stable and gave nitroene 27 by the oxidation with m-chloroperbenzoic acid, vide supra. Dehydrogenation of 11 with 40% Pd–C gave a mixture of quinoline and methylquinolines.22) Amide 63 opens lactam ring by acid treatment but if double bond is present in lactam ring this reaction becomes severer. 2,3,4,5-Tetrahydro-1-benzazepin-5-one 15 is readily available and its chemistry is most widely studied. The ketone 15 is colored yellow but this color disappears if nitrogen lone pair is trapped by tosyl group and the reactivity of carbonyl group increases. Thus the controlled bromination of 14 allowed the selective substi-
tution of active methylene but bromination of 15 gave a mixture of the products which were brominated at aromatic ring and active methylene. Reaction of 15 with excess bromine gave a single product 64. When a solution of 64 in ethanol was refluxed with sodium bicarbonate, debrominated products 65 and 66 were formed. Heating 65 with lithium chloride in dimethylformamide (DMF) yielded 67 instead of dehydrobromination product. Many attempts at introducing double bond by dehydrobrominating 68 and 69 failed and the starting materials were recovered. When 64 was treated with lithium chloride in DMF, 70 was formed in 33% yield. This product was also the product when 65 was oxidized with manganese dioxide. Dehydrobrominating agents are ineffective to 65. The alkylation of 14 takes place at active methylene and that of 15 occurs at nitrogen. Ester groups of 73 and 75 were hydrolyzed by sodium hydroxide but the carboxyl group of 76, β-ketoacid, remained. Sodium borohydride in ethanol reduced both ketone and ester groups of 13 and gave dialcohol 77 in good yield. Enolate of 13 generated with sodium methoxide reacted with DMAD and gave 79 via 78 in high yield. β-Ketoesters are in equilibrium with
enol form so that 80 was methylated by diazomethane.\textsuperscript{28) 26} Carbonyl group of 82 is quite reactive and was readily converted into ketal 83 by warming in ethanol, although dechlorinated ketone does not have this reactivity.\textsuperscript{29)}

2. Dihydro-1-benzazepines

Benzylalcohol 84 is quite susceptible to dehydration and gave 85 in good yield.\textsuperscript{24) 26} Reduction of amide 18 also afforded 2,3-dihydro-1-benzazepine derivative 86. Amides 18 was prepared by condensation reaction.\textsuperscript{8, 30) 26} Dehydrogenation with dichlorodicyanobenzene (DDQ) is effective for the preparation of unsaturated amide when methyl group of 18 is substituted with phenyl group.\textsuperscript{31}) It is also possible to locate double bond by enol ester formation as shown by the transformation of 66 into 87.\textsuperscript{24) 26}

Manganese dioxide does not work on alcohol of 84 but on amine of 84. Thus
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84 produced 88 in good yield. Preparation of 2,3-dihydro-1-benzazepin-5-one from saturated ketone has been unsuccessful. Reactions used are oxidation with selenium dioxide, dehydrobromination with amines or lithium chloride and dehydration with phosphorous pentoxide. However the preparation of 2,3-dihydro-1-benzazepin-2, 5-dione system has no problem and 90 was prepared from 89 by bromination and dehydrobromination reactions and 92 was obtained from 91 by oxidation. Diketone 93, which is available from 14 or 68, has unique reactivity. When 93 was purified by chromatography, enol ether 94 is formed. The bromination of 93 gave 68. Unsaturated ketoamide 95 is directly available by Schmidt reaction of 2-methyl-1,4-naphthoquinone and rearranged into 96 when 95 was heated in aqueous acid.

Different approach is used for the preparation of 1,2-dihydro-1-benzazepine-3-ones. Starting from 97, 100 was synthesized in good yield. When protecting group of 100 is removed by sodium methoxide, bright purple product, possibly 101, was formed. But it was unable to isolate 101 and the product isolated was 102 in poor yield after workup. The treatment of 100 with sodium hydride afforded dimeric product. Double bond of 100 does not react with osmium tetroxide nor with potassium permanganate.

3. 1-Benzazepines

Preparation methods and some of properties of 1-benzazepines are described in previous section. Notable among them is the equilibrium between 1H-1-benzazepines
and 2a,7b-dihydrocyclobut[b]indoles 37. When 103 was heated to more than 300°C, rearrangement took place and 104 was formed in high yield. Benzyl group in place of benzoyl group does not allow this rearrangement. Azepine ring is not aromatic and accepts nucleophilic attacks. Thus indole and methanol attack 38a and gave the adduct 105 in 89% and 32% yields respectively. Contrary to 54, 38a is not susceptible to catalytic hydrogenation but double bonds were reduced selectively. Sodium amalgam reduced 38a to give 4,5-dihydro-1-benzazepine derivative and reduction with zinc powder in acid afforded 2,3-dihydrogenated product. Two double bonds in azepine ring is in conjugation so that Diels–Alder reaction of 38a with DMAD gave the cycloadduct 106 in 75% yield. Catalytic hydrogenation of 107 reduced one of double bonds and gave 108. On the other hand aqueous acid hydrolyzed one of two enamines of 107 and produced 109.

Number of 3H-1-benzazepines is scarce and their chemical behaviors are little studied. Acidic hydrolysis of 110 gave 111 and basic hydrolysis afforded 112 in 88% yield. In order to prepare 3H-1-benzazepine derivative, amide 113 was treated with phosphoryl chloride. The reaction products were dimeric 114 and 115. The structures of these products were determined by X-ray analysis and the reaction mechanism is also discussed.

As 5H-1-benzazepine derivative, 116 is prepared by the oxidation of 64 with manganese dioxide. Further oxidation of 116 produces 117 which was converted in 118 with phosphoryl chloride. Similarly the reaction of 119 with Meerwein reagent...
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gave 120. This product has no ring current according to NMR analysis.37) Diketo-
amide 121 has yellow green color and is hardly soluble in organic solvent. However
its IR spectrum indicates that it has no enol isomers such as 122 and 123.32)

LITERATURES


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