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Review Article **Medicinal chemistry**

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RECENT TRENDS IN THE CHEMISTRY OF PRIVILEGED SCAFFOLD: 1,4-BENZODIAZEPINE

NAVJEET KAUR

Department of Chemistry, Banasthali University, Banasthali-304022 (Rajasthan), India

ABSTRACT

Intention in this review is to present a picture of 1,4-benzodiazepine with particular attention to their reactions and uses in synthetic organic chemistry. Some of these reactions have been applied successfully to the synthesis of biologically important compounds. The main purpose of this review is to present a survey of the literature on 1,4-benzodiazepine chemistry.

KEYWORDS: 1,4-Benzodiazepines, Privileged scaffold, Reactions.

NAVJEET KAUR
Department of Chemistry, Banasthali University, Banasthali-304022 (Rajasthan),

**Corresponding author*

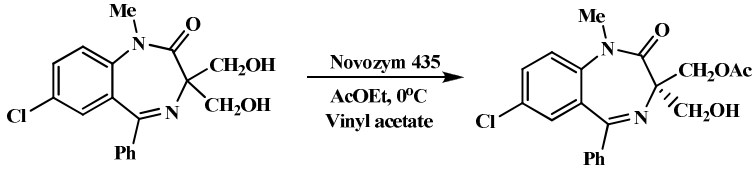
INTRODUCTION

The chemistry and applications of 1,4-benzodiazepines have recently received much attention due to their usefulness as synthetic intermediates and their biological importance. The wide range of biological activities displayed by benzodiazepine derived compounds makes benzodiazepine scaffolds, particularly 1,4-benzodiazepine systems, among the most important privileged structures. The benzodiazepine nucleus is a pharmacophoric scaffold and represents a class of heterocycles with a wide range of biological applications. Many of them are widely used as anticonvulsant, anti-anxiety, sedative, anti-depressive, hypnotic, and neuroleptic agents. Some heterocycles containing benzodiazepines moiety are reported to possess anti inflammatory, antiviral, anti-HIV, antimicrobial, and antitumor activities.[1,2]A vast number of 1,4-benzodiazepines have been synthesized by a variety of methods and extensive data on their pharmacological activity have been accumulated. Since the discovery of benzodiazepines in 1960, extensive research efforts in the field led to the development of a variety of modified derivatives. Many 1,4-benzodiazepines have been identified as intermediates in synthesis, consequently studies of their properties and reactions have become obligatory. This ring system has demonstrated considerable utility in drug design, with derivatives demonstrating a wide range of biological activities.

Recent years been the subject matter of a number of reviews of synthetic methods of 1,4-benzodiazepines, but little attention has been made on their reactions. In this review therefore, an attempt has been made to bring together the known chemistry of the 1,4-benzodiazepines. It is not claimed, that this review is exhaustive nor that it refers to all known reactions but rather that the general reactions of these compounds are discussed.

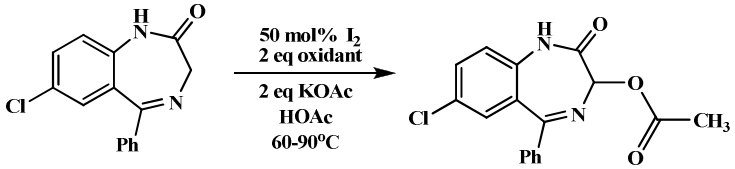
Acetylation

Avdagic and co-workers[3] enantioselectively acetylated a series of chiral 3-(hydroxyalkyl)-1,4-benzodiazepin-2-ones using the enzyme Novozym 435 (scheme-1).



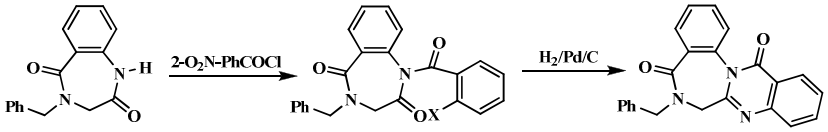
Scheme-1

Several possible reagents efficiently act as stoichiometric oxidants in the model iodine-(50 mol %)-catalyzed acetoxylation of 1,4-benzodiazepines in the presence of potassium acetate in glacial acetic acid at elevated temperatures (scheme-2).[4]



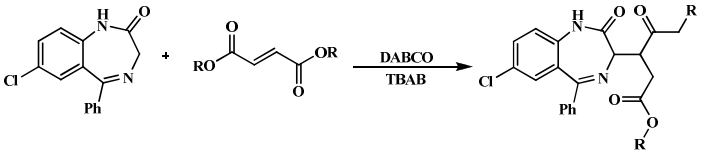
Scheme-2

Acylation: Acylation with *o*-nitrobenzoyl chloride furnished a labile 1,4-benzodiazepinedione derivative, which upon reduction afforded *N*-benzylsclerotigenin (scheme-3) in high yield.[5]



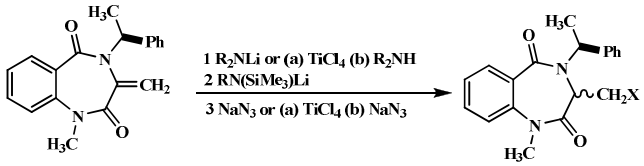
Scheme-3

Addition reaction: The addition reaction of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one with symmetrical fumaric esters was done in solvent-free thermal conditions in presence of TBAB (scheme-4) as highly efficient and green alkylating agent by using mild organic base DABCO.[6]



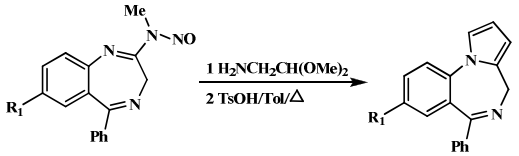
Scheme-4

1,4-addition reaction: Enone of 1,4-benzodiazepine was treated with various N-nucleophiles, in an attempt to achieve a 1,4-addition (scheme-5).[7]



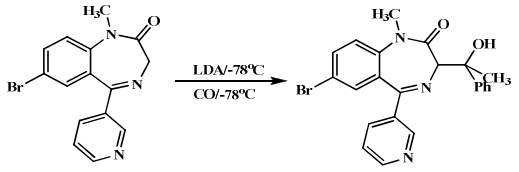
Scheme-5

Addition-elimination reaction: Treatment of *N*-nitrosoamidines with aminoacetaldehyde dimethylacetal afforded the corresponding amidines in an addition-elimination sequence. These amidine derivatives were heated in toluene at 80ºC in the presence of two equivalents of *p*-toluenesulphonic acid (TsOH) to furnish imidazo[1,2-a][1,4]benzodiazepines (scheme-6).[8]



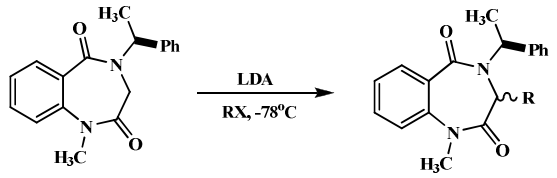
Scheme-6

Aldol condensation: Aldol reaction (scheme-7) of 7-bromo-5-pyrido-1,4-benzodiazepin-2-one with representative aliphatic and aromatic aldehydes and ketones afforded 7-bromo-3-(1-hydroxy-1-phenylmethyl)-1-methyl-5-(2-pyridyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one.9



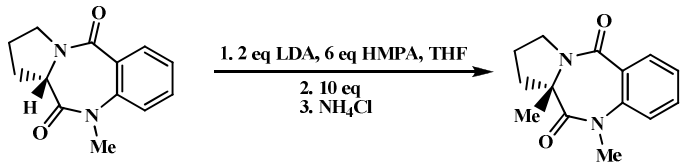
Scheme-7

Alkylation: The alkyl halide addition (at -78°C) to enolate-Li, generated by metalation of the corresponding benzodiazepinedione with LDA is as follows (scheme-8):[10]



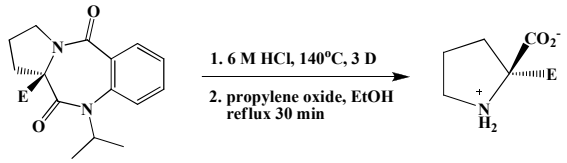
Scheme-8

α-Alkylation: After a 10 min deprotonation time at -78°C, addition of methyl iodide afforded the racemic α-methylated product (scheme-9).[11]



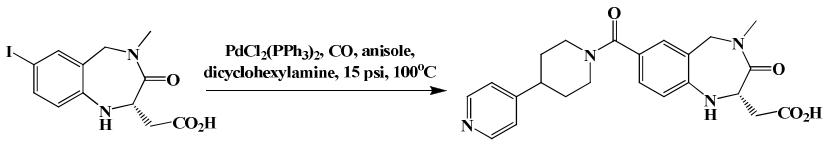
Scheme-9

Amino acid synthesis: Ala and Phe were derived from 1,4-benzodiazepin-2-ones according to the reaction given below (scheme-10):[12]



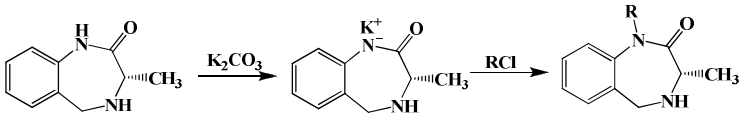
Scheme-10

Aminocarbonylation: Synthesis of lotrafiban SB-214857-A involved the key step palladium-catalyzed aminocarbonylation reaction (scheme-11).[10]



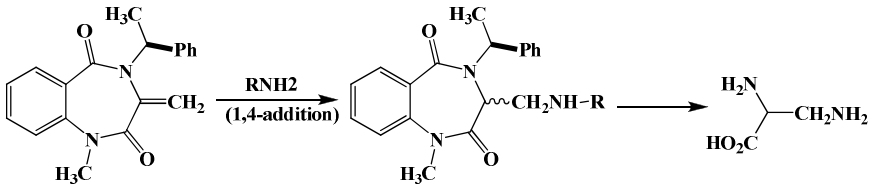
Scheme-11

Aminoethylation: The regioselective aminoethylation of 1,4-benzodiazepin-2-one can be carried out using classical heating or microwave irradiation as the source of energy to furnish either N_1 or N_4 aminoethylated products (scheme-12).[13]



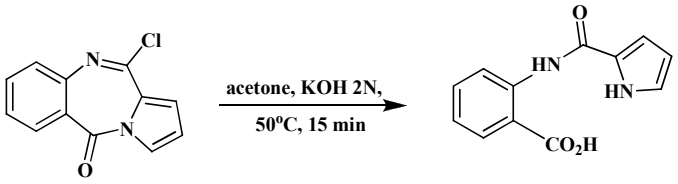
Scheme-12

α,β-Aminopropionic acid synthesis: The 1,4-addition of N-nucleophiles to methylidene derivative followed by diastereoselective protonation of the resulting enolate would afford suitable precursors of the desired α,β-aminopropionic acid (scheme-13).[14]



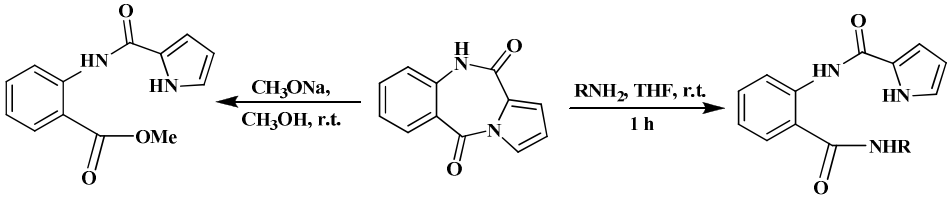
Scheme-13

Anthranilic derivative synthesis (reaction with amines): 1,4-benzodiazepine ring get opened under alkaline conditions to give the anthranilic derivative, (scheme-14) obtained in 95% yield.[15]



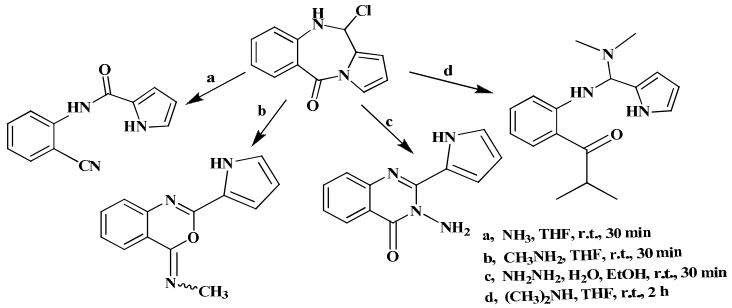
Scheme-14

The reaction with ammonia, methylamine or sodium methoxide led, respectively, to anthranilamides and methyl anthranilate (scheme-15).[15]



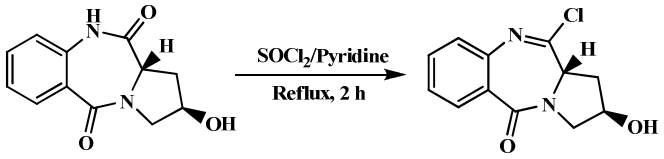
Scheme-15

The reaction with amines appeared to be more complex since rearranged products were obtained. Ammonia led to an anthranilonitrile derivative, methylamine to the 4-methyliminobenzoxazine, hydrazine to the 3-aminoquinazolin-4-one and dimethylamine to the disubstituted product (scheme-16).[15]



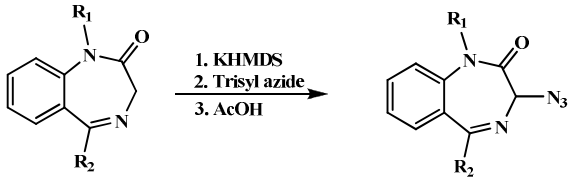
Scheme-16

Aromatization: 2-Hydroxypyrrolo[2,1-*c*][1,4]benzodiazepines were aromatized in refluxing thionyl chloride into 11-chloropyrrolo[2,1-*c*]-[1,4]benzodiazepines in high yield (scheme-17).[15]



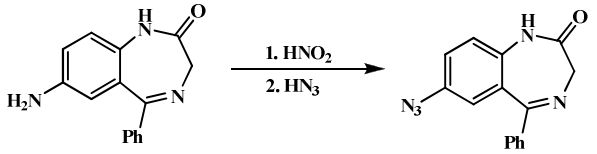
Scheme-17

Azidation: The direct azidation of 1,4-benzodiazepin-2-ones with trisyl azide provided access to 3-amino derivatives after reduction of the intermediate azide in a process that is compatible with a range of N_1 and C_5 substituents (scheme-18).[16]



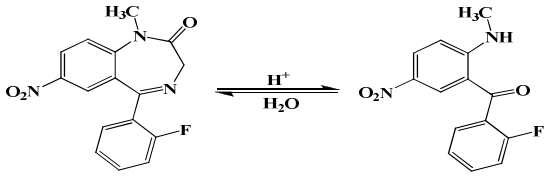
Scheme-18

The 7-azido group was introduced by diazotization of the corresponding 7-amino compounds followed by treatment with hydrazoic acid (scheme-19).[17]



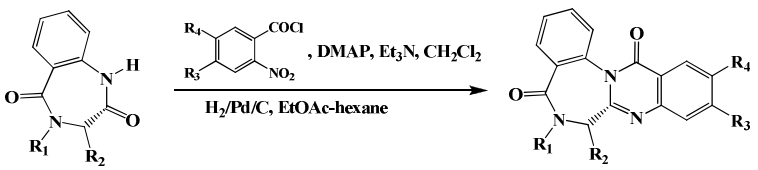
Scheme-19

Benzophenone synthesis: Flunitrazepam is a very weak base, due to the nitrogen atom in position 4 only, as the other atom in position 1 is methyl substituted. In acidic solutions hydrolysis of benzophenone occurs (scheme-20).[18]



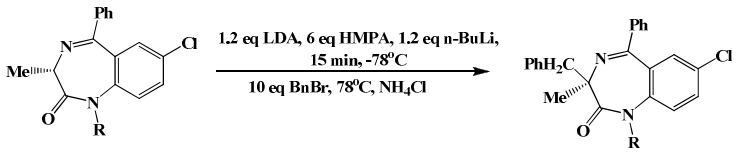
Scheme-20

Benzoylisation: 1,4-Benzodiazepines were first treated with the appropriate 2-nitrobenzoyl chlorides to afford the corresponding *N*-benzoyl derivatives, which, in turn, underwent reductive cyclization to afford the corresponding quinazolino-[1,4]-benzodiazepine (scheme-21).[19]



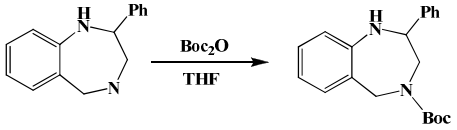
Scheme-21

Benzylation: Notably, when deprotonated and alkylated at -78°C the *N*-Me derivative affords the desired benzylated product (scheme-22).[20]



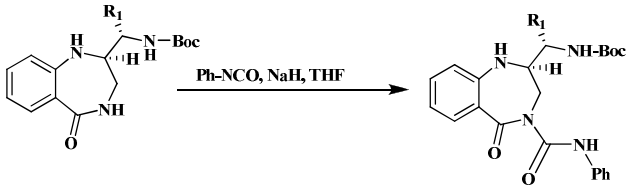
Scheme-22

Boc-protection: 2-phenyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine can be protected on the 4 position in neutral conditions while in acidic medium it slowly decompose to an unidentified product (scheme-23).[20]



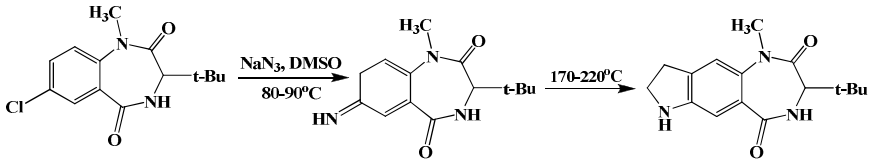
Scheme-23

Carbamoylation: The reaction with an equivalent of phenyl isocyanate in the presence of NaH gave the 4-phenylcarbamoyl derivatives (scheme-24).[21]



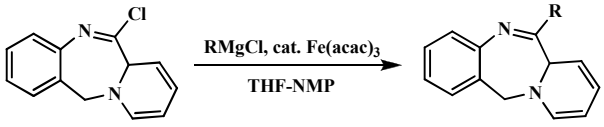
Scheme-24

Cloke rearrangement: Treatment of 5-chloro-1,4-benzodiazepin-2,5-dione with NaN_3 in DMSO effected a facile conversion directly to the imine, which underwent a Cloke rearrangement upon heating in vacuo to give the dihydropyrrolo-fused 1,4-benzodiazepin-2,5-one in good overall yield (scheme-25).[22]



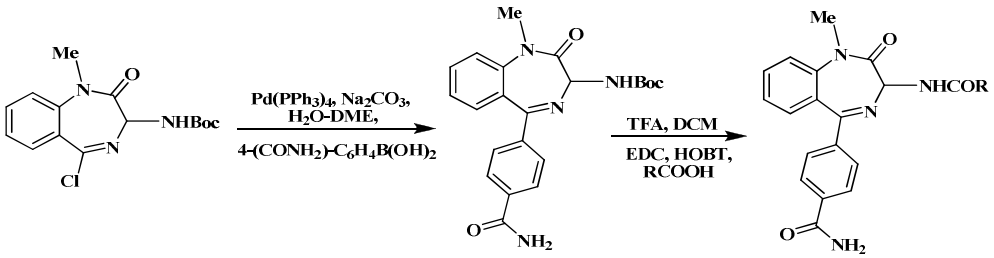
Scheme-25

Coupling reaction*:* Iron-catalyzed cross-coupling of Grignard reagents with the imidoyl chloride provided a convenient and efficient method for substituting the heterocyclic ring (scheme-26).[23]



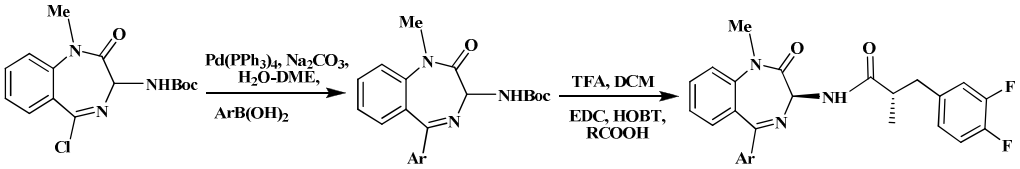
Scheme-26

Cross-coupling: Palladium-catalyzed cross-coupling with 4-carboxamidophenyl boronic acid under standard aqueous conditions followed by removal of the Boc protecting group with trifluoroacetic acid and acylation with 3-(2,4-dichlorophenyl)propionic acid gave biologically active product with IC50 33 nM (scheme-27).[24]



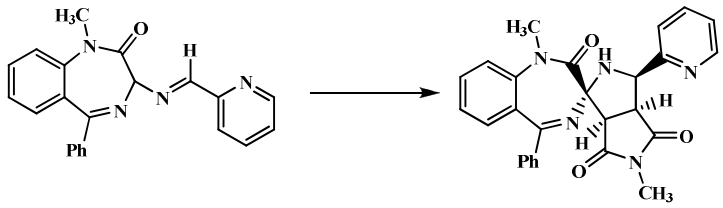
Scheme-27

Palladium-catalyzed cross-coupling with commercially available aryl boronic acids or borate esters under standard aqueous Suzuki conditions give intermediates, followed by subsequent BOC deprotection, acylation with homochiral 2-(S)-methyl-3-(3,4-difluorophenyl)propionic acid, and separation of diastereomers (scheme-28).[24]



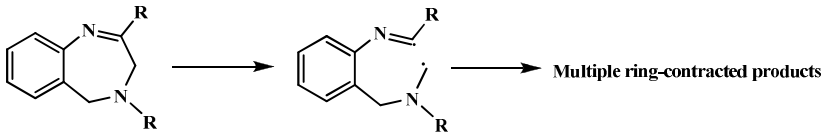
Scheme-28

Cycloaddition: Heating imines derived from 3-amino-1,4-benzodiazepin-2-ones with N-methylmaleimide in boiling toluene provided adducts derived from the stereospecific cycloaddition of the resonance-stabilized azo-methine ylide, formed by a 1,2-prototropic rearrangement (scheme-29).[25]



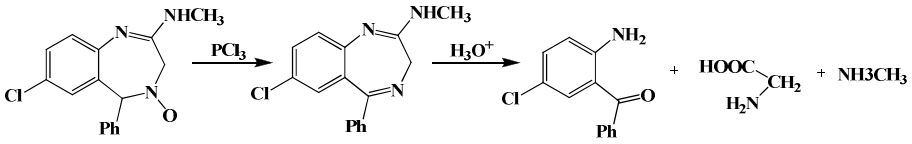
Scheme-29

Decomposition: At the much higher temperatures associated with FVP, >800^{o}C, decomposition of 2,4-dimethyl or 2,4-diphenyl-1,4-benzodiazepines occurred to produce multiple ring-contracted products that can be traced mechanistically (scheme-30).[26]



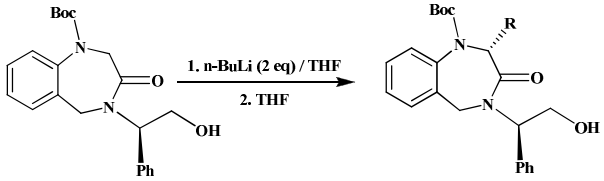
Scheme-30

Degradation: Specific degradative studies of the benzodiazepine-4-oxide shows the following sequence (scheme-31):[27]



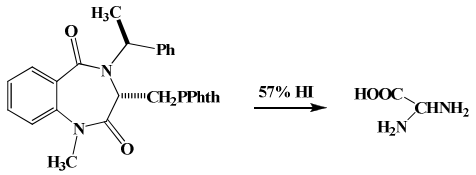
Scheme-31

Deprotonation: Highly diastereoselective alkylation at C_2 of benzo-1,4-diazepin-3-ones was accomplished using an (R)-phenylglycinol moiety at N_4 as the chirality-inducing element. The optimum conditions involve deprotonation with 2 equiv of n-BuLi at 40°C and alkylation at 78°C (scheme-32).[28]



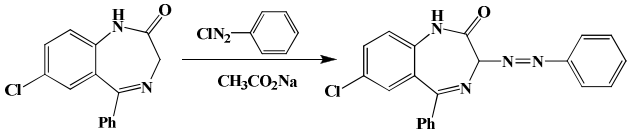
Scheme-32

α,β-Diaminopropionic acid synthesis: Acid hydrolysis of alkylated precursor was best achieved with 57% HI. Under these conditions, both amide groups were cleaved, and both the phenethyl and phthalimido groups were removed to give the desired α,β-diaminopropionic acid (scheme-33).[14]



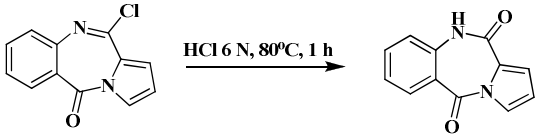
Scheme-33

Diazotization: A number of new diazonium salt derivatives of 7-chloro-5-phenyl-3-(phenyl-n-substituted)-diazo-1,3-dihydro-benzo[e][1,4]-diazepin-2-one from 7-chloro-5-phenyl-1,3-dihydro-benzo[e]-[1,4]-diazepin-2-one (III) with diazonium salts were prepared (scheme-34).[29]



Scheme-34

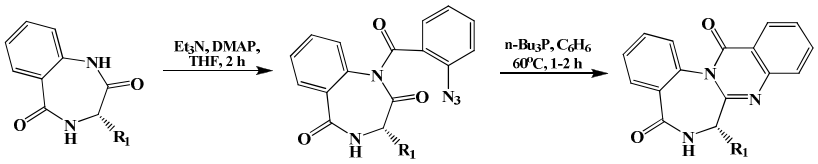
Dilactam synthesis: Exposed to air moisture for several days, 1,4-benzodiazepine compound was hydrolyzed to give the dilactam. However, in acidic conditions seemed to be much more stable and the hydrolysis of the imidoyl chloride succeeded to give the dilactam (scheme-35).[15]



Scheme-35

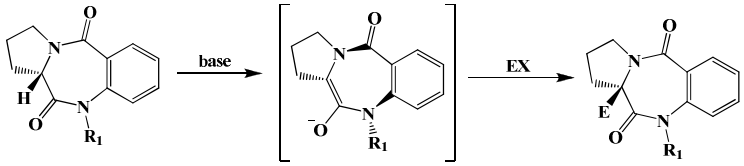
Eguchi aza-Wittig reaction: The quinazolinone annelation method has been utilized by Snider's group to provide an efficient entry to quinazolinone alkaloids fused to a benzodiazepinedione ring

such as in asperlicin C. This method together with intramolecular aza-Wittig methods is known as the Eguchi aza-Wittig protocol (scheme-36).[30]



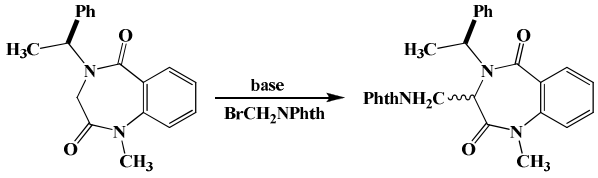
Scheme-36

Electrophilic addition: Carlier group recently demonstrated the enantioselective preparation of α-alkylated *N-i*-Pr-1,4-benzodiazepin-2-ones using a memory of chirality strategy. Deprotonation would proceed through a dynamically chiral enolate intermediate that would "memorize" the original chirality of the ring. Addition of an electrophile would lead to highly enantio pure quaternary products (scheme-37).[11]



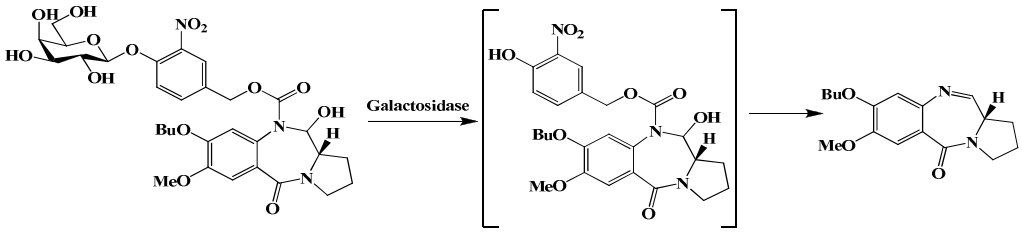
Scheme-37

The electrophilic addition of *N*-(bromomethyl)phthalimide (at -78°C) to the lithium enolate generated by metallation of the corresponding benzodiazepinedione with LDA or lithium hexamethyldisylazide (LHMDS) (scheme-38), is summarized as follows:[7]



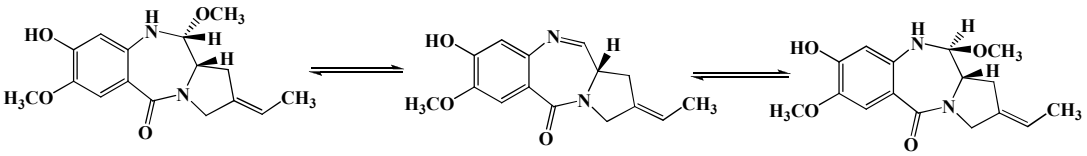
Scheme-38

1,6-elimination: Recently, Kamal and co-workers[31] (scheme-39) proposed alternative PBD prodrugs activated by E. coli-galactosidase to the 4'-position of an N_{10}-benzyloxycarbonyl PBD. The cleavage of the substrate by CPG2 releases either a 4'-hydroxy- or 4'-aminobenzyloxycarbonyl intermediate which then undergoes 1,6-elimination to release the cytotoxic PBD.



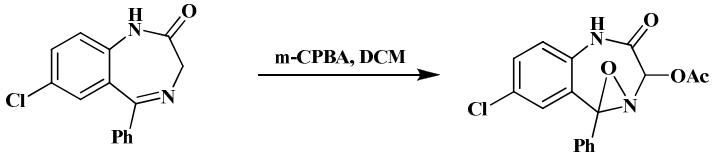
Scheme-39

Epimerization: Tomaymycin derivative of 1,4-benzodiazepine shows epimerization according to the mechanism given below (scheme-40):[32]



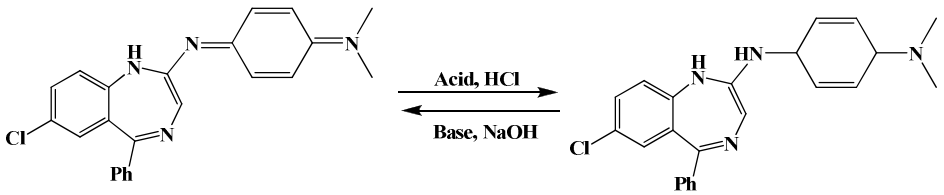
Scheme-40

Epoxidation: 1,4-benzodiazepine epoxidation of the double bond (scheme-41):[33]



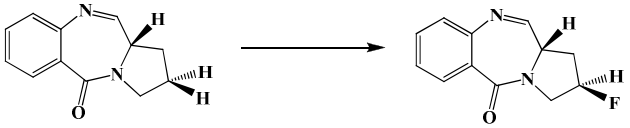
Scheme-41

Fluorescence: Dimethylaminoaniline is the only working aniline and formed by this route the 2-amino derivative (scheme-42). It is violet in alkaline media and turns yellow, after the addition of acid. This novel compound might be useful as an organic dye in fluorescence screening assays for analgesics.[34]



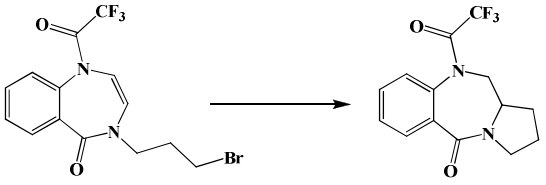
Scheme-42

Flourination: O'Neil and co-workers[35] (scheme-43) had synthesized three novel C_2-fluorinated pyrrolobenzodiazepines to verify if the replacement of hydrogen with a fluorine atom in the C_2-position of the PBD ring system could lead to a significant increase in cytotoxicity.



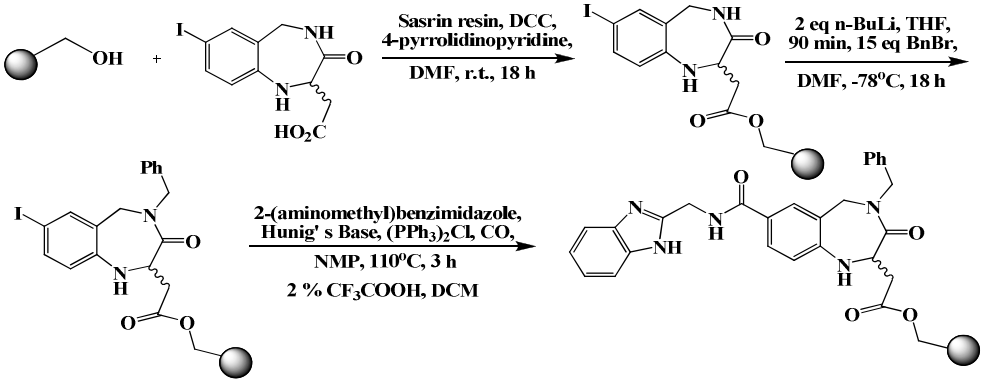
Scheme-43

Free radical reaction: The C_2-C_3 olefin of a 1,4-benzodiazepin-5-one regiospecifically captured an alkyl radical intramolecularly in a 5-exo-trig-process that is the critical step in an approach to the construction of the fused tricyclic system found in the pyrrolo[2,1-c][1,4]benzodiazepine class of antitumor antibiotic (scheme-44).[36]



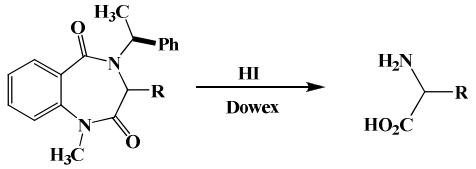
Scheme-44

Heck reaction: An efficient solid phase regioselective alkylation at the N_4 position of a 3-oxo-1,4-benzodiazepine template exemplified by 4-H-2,3,4,5-tetrahydro-7-iodo-3-oxo-1H-1,4-benzodiazepine-2-acetate-polymer ester is described (scheme-45). Further chemical elaboration at position 7, utilizing a modified Heck reaction,[37] allows the incorporation of amides from primary or secondary amines.



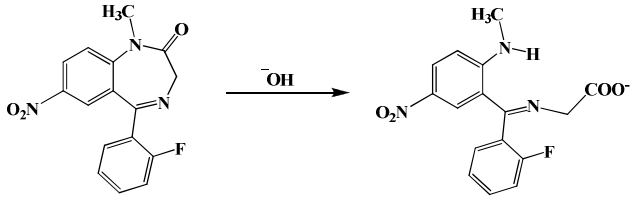
Scheme-45

Hydrolysis: Although hydrolysis was not successful upon treatment with 6 N HCl excellent results were achieved with 57% HI (scheme-46). Under these conditions, both amide groups were cleaved, and the phenethyl group was removed to give the desired amino acids in excellent yields.[38]



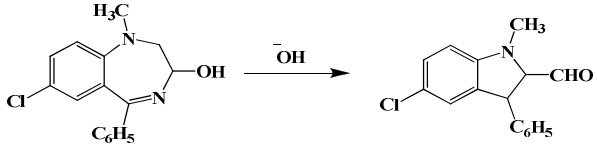
Scheme-46

When the methanolic solution of flunitrazepam reacts with aqueous NaOH 8.5% solution, an intense yellow colour occurs, due to iminic derivative hydrolysis, as follows (scheme-47):[18]



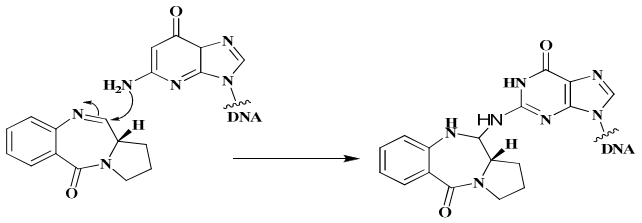
Scheme-47

Indole synthesis: Numerous rearrangements of 1,4-benzodiazepines to other heterocyclic systems have been reported. The complex rearrangement had been reported for the formation of indoles (scheme-48).[39]



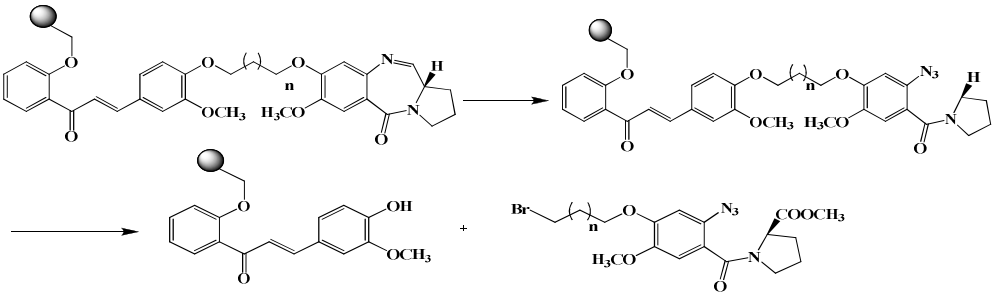
Scheme-48

Interaction with DNA: A number of naturally occurring and synthetic compounds based on PBD ring system, such as anthramycin, tomaymycin, DC-81 (scheme-49) and its dimers have shown varying degrees of DNA binding affinity and anti-cancer activity. Their interaction with DNA has been extensively investigated and it is considered unique since they bind within the minor groove of DNA forming a covalent aminal bond between the C_{11}-position of the central B-ring and the N_2 amino group of guanine base.[40]



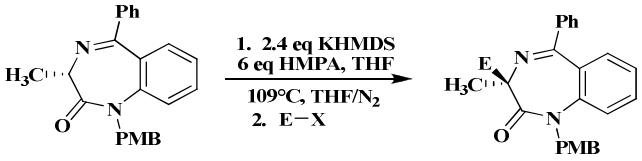
Scheme-49

Intramolecular aza-Witting reductive cyclization: The PBD-chalcone conjugates were prepared by employing the resin-bound compound and bromo-substituted azidobenzoyl proline methyl esters which were then coupled in the presence of K_2CO_3 to the corresponding solid-supported compounds, involved aldol condensation and intramolecular aza-Witting reductive cyclization process (scheme-50).[40]



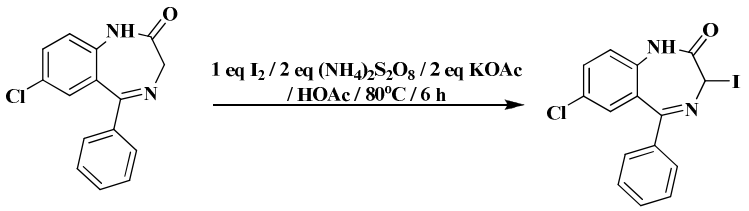
Scheme-50

Inversion trapping: It was apparent that even with short deprotonation times the enolate formed from racemizes quickly at -100°C, and improved enantioselectivity could not be achieved at this temperature. In order to achieve excellent enantioselectivity it was necessary to run these reactions at -109°C (THF/N_2) (scheme-51).[41]



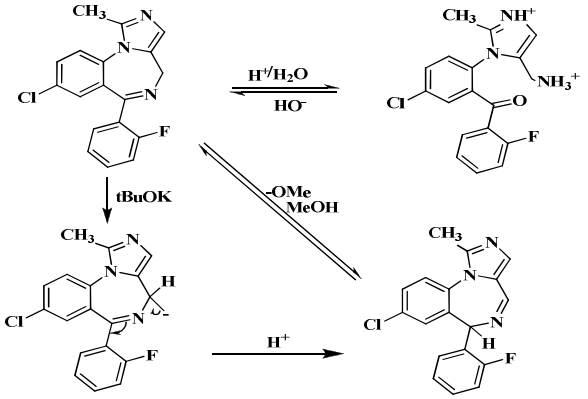
Scheme-51

Iodination: 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one with an alternative iodide-oxidant, copper(II) acetate, in the presence of potassium iodide and potassium acetate in glacial acetic acid, expected 3-acetoxy-1,4-benzodiazepine was obtained (scheme-52). This indicates that this conversion also involves the combined iodination reaction and subsequent substitution of transient iodo-intermediate with acetic acid or acetate ion to furnish 3-acetoxy derivative.[42]



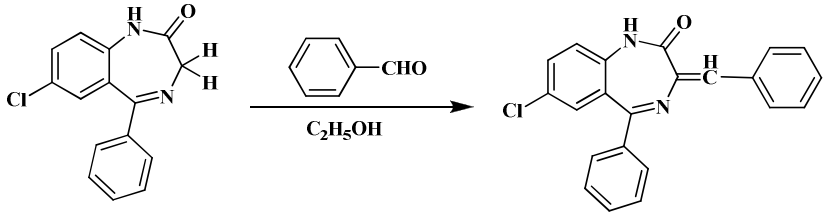
Scheme-52

Ionization: In aqueous solution, midazolam ionizes in steps (scheme-53). The first ionization step, due to the nitrogen atom in position 2 on the imidazolic ring, is characterized by a protolysis constant $K_p = 6.31 \times 10^{-7}$, and the second, $K_p = 2 \times 10^{-2}$, is due to the nitrogen atom in position 5 in the benzodiazepinic ring.[43]



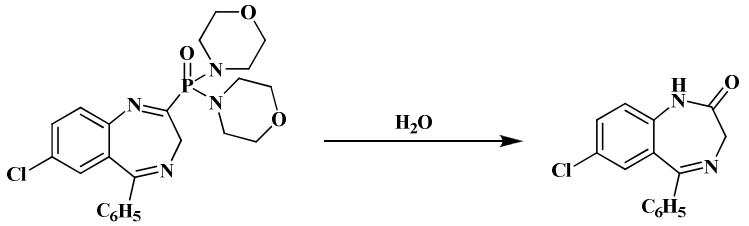
Scheme-53

Knoevenagel Condensation: Doebner Modification;[44] (scheme-54) Condensation of aldehydes or ketones with active methylene compounds in the presence of base.



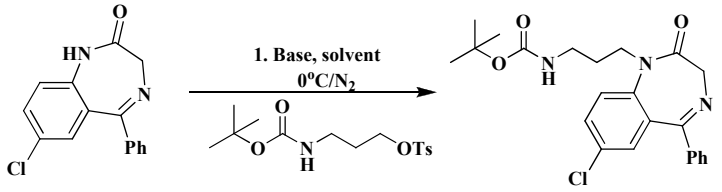
Scheme-54

Lactam synthesis: Hydrolysis of 7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3H-1,4-benzodiazepine (aqueous THF, room temperature, 7 days) led to lactam (scheme-55).[45]



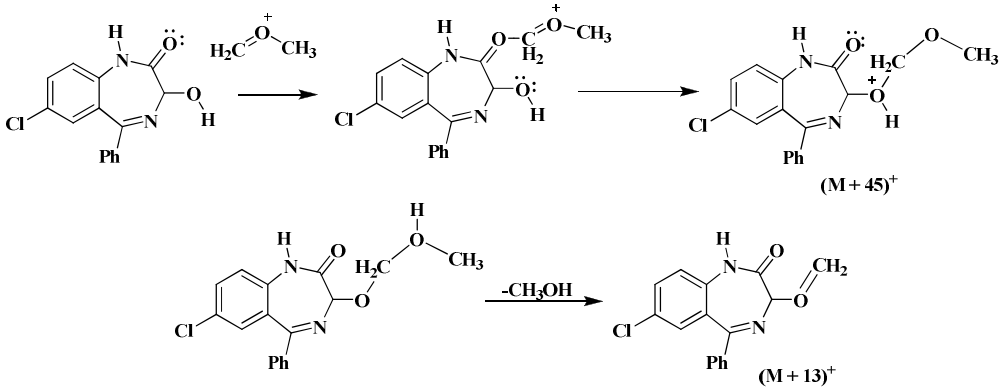
Scheme-55

Linker formation: Installation of the linker at the N_1 position of had been carried out by using a variety of different reaction conditions. Switching to sodium methoxide in methanol/DMF afforded product (scheme-56).[46]



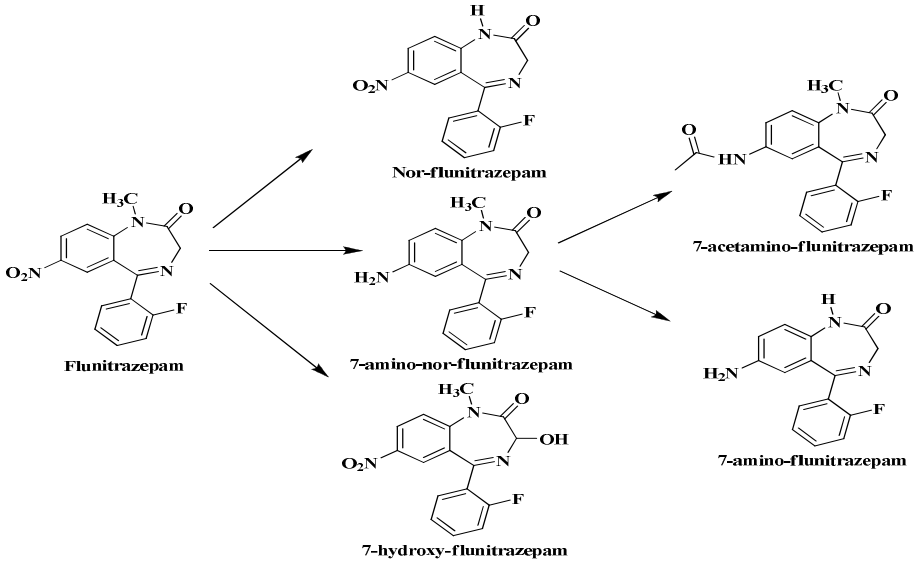
Scheme-56

Mass fragmentation: The ion-molecule reactions of various l,4-benzodiazepines and dimethyl ether ions were studied with a quadrupole ion trap mass spectrometer. The methoxy methylene ions of dimethyl ether selectively react with 3-hydroxy-l,4-benzodiazepines to form $(M+13)^+$ adducts by methylene substitution, and they react with 1,4-benzodiazepines that do not have hydroxyl substituents (diazepam, nordiazepam, nitrazepam) to form $(M+15)^+$ adduct by a simple methyl cation transfer (scheme-57).[47]



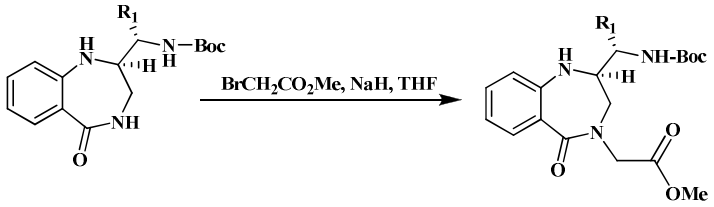
Scheme-57

Metabolism: The most important ways in flunitrazepam metabolism are N-demethylation, 3-hydroxilation and glucurono conjugation, as well as reducing nitro moiety to amino, followed by acetylation (scheme-58).[48]



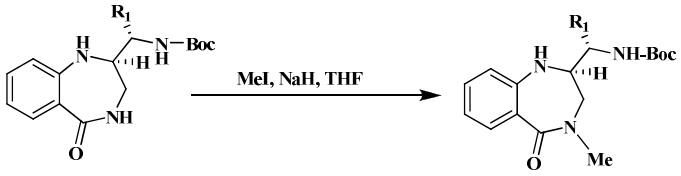
Scheme-58

Methoxylation: The reaction with methyl bromoacetate in the presence of NaH led to the 4-methoxycarbonyl methyl derivatives (scheme-59).[21]



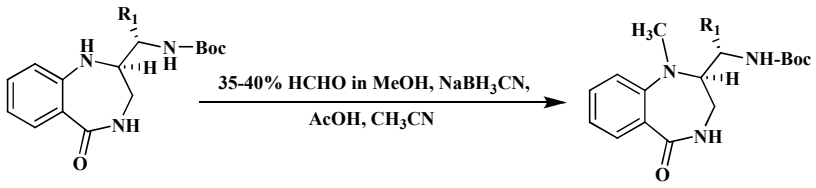
Scheme-59

Methylation: The reaction with MeI in the presence of NaH led to the corresponding 4-methyl derivatives. In the case of the tryptophan derivative some dimethylation at position 4 and at the indole NH was also observed, depending on the excess of MeI and NaH used (scheme-60).[21]



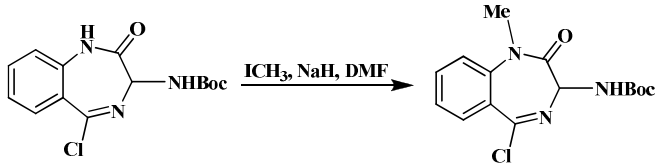
Scheme-60

Finally, as many of the biologically active 1,4-benzodiazepine derivatives are substituted at position 1, particularly with a methyl group, such as for example in Devazepide, which was satisfactorily achieved by reaction of compounds with a 35-40% methanolic solution of formaldehyde and $NaBH_3CN$ in the presence of AcOH (scheme-61).[21]



Scheme-61

A new route for the synthesis of 3-amino-1,4-benzodiazepine-based-Secretase inhibitors involved methylation using sodium hydride and methyl iodide in dimethylformamide (scheme-62).[24]



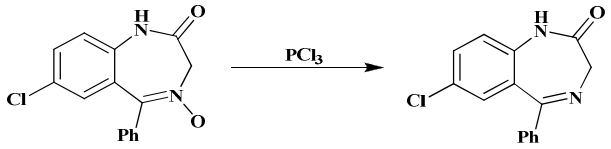
Scheme-62

N-alkylation: The *N*-alkylated benzodiazepines were synthesized from the benzodiazepine template with sodium hydride in DMF. No dialkylation products were obtained (scheme-63).[49]

Scheme-63

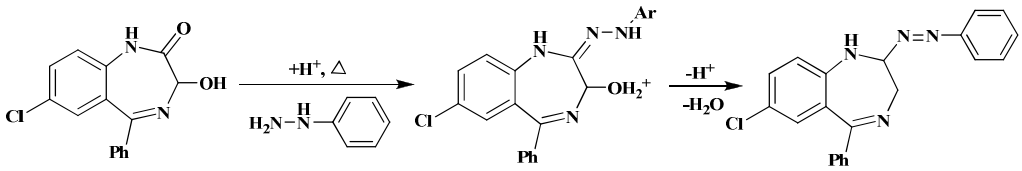
Nitration: N-Nitration of homopiperazine using 1 equiv of the new nitrating reagent, 4-chloro-5-methoxy-2-nitropyridazin-3-one, provided the mononitrated product while the use of 2 equiv resulted in nitration of both N atoms.[50]

N-oxide removal: Removing the N-oxide moiety actually enhanced the activity. The only features that all the biologically active compounds had in common were the 1,4-benzodiazepine ring with a chlorine at the 7 position and a phenyl at the 5 position.[51]



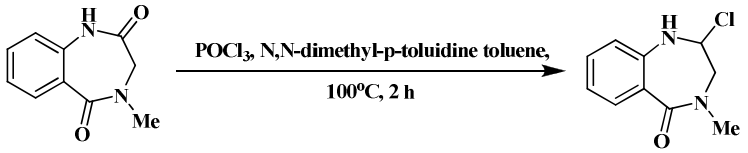
Scheme-64

Nucleophilic addition: The nucleophilic attack of the substituted phenylhydrazines formed the hydrazones and under acetic conditions the intermediate formed in a condensation reaction is the diazo derivatives (scheme-65).[34]



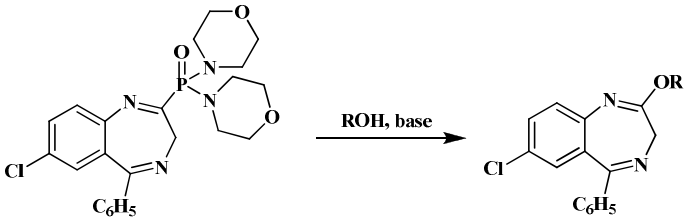
Scheme-65

Nucleophilic substitution: 1,4-benzodiazepines reacts with a variety of nucleophiles to give various 2-substituted benzodiazepines.
Iminochloride was prepared by the drop wise addition of a slight excess of $POCl_3$ to a hot toluene solution of the amine in the presence of *N*,*N*-dimethyl-*p*-toluidine (scheme-66).[49]



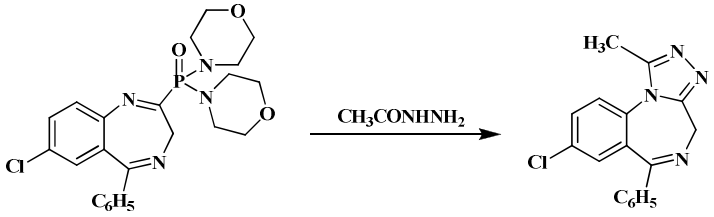
Scheme-66

Exposure of 7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3H-1,4-benzodiazepine to methanol containing sodium methoxide and to ethylene glycol containing triethylamine afforded the corresponding 2-alkoxy derivative (scheme-67).[45]



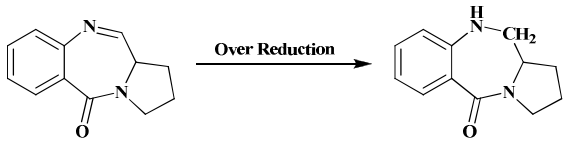
Scheme-67

The utility of 7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3H-1,4-benzodiazepine as an intermediate has been further demonstrated by its facile conversion to 1-methyl-6-phenyl-4H-striazolo[4,3-a] [1,4]benzodiazepine (scheme-68), a benzodiazepine of clinical interest.[45]



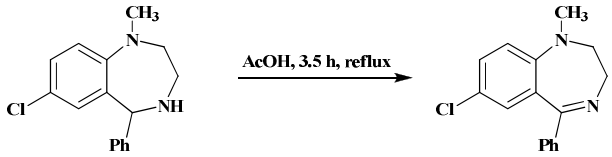
Scheme-68

Over reduction: It is notable that earlier studies by Thurston[49] led to the discovery that the balance of AcOH:THF was important for the over reduction of the newly formed imine bond of compound which would yield the undesired secondary amine as shown below:



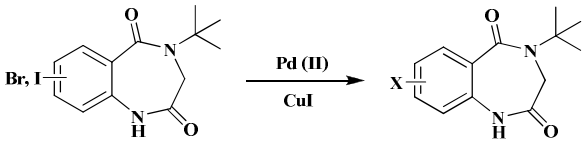
Scheme-69

Oxidation: Hexamine can be used to oxidize tetrahydro seven-membered member ring, as in the synthesis of 2,3-dihydro-1,4-benzodiazepines starting from 1,2,3,4-tetrahydro derivatives (scheme-70).[51]



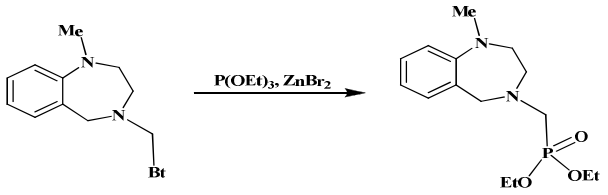
Scheme-70

Palladium-catalyzed alkynylation: The 7-, 8-, and 9-halobenzodiazepinediones prepared were subjected to palladium-mediated coupling reaction (scheme-71). One of the modifications of interest to the benzodiazepinedione moiety was the incorporation of unsaturated substrates via palladium-catalyzed alkynylation.[52]



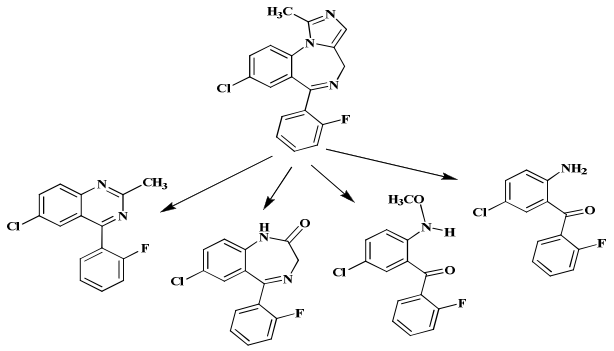
Scheme-71

Phosphorylation: Treatment of 1,4-benzodiazepine derivative with 1.2 equiv. of triethyl phosphite in the presence of $ZnBr_2$ furnished diethyl (1-methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-4-ylmethyl)phosphonate (scheme-72).[53]



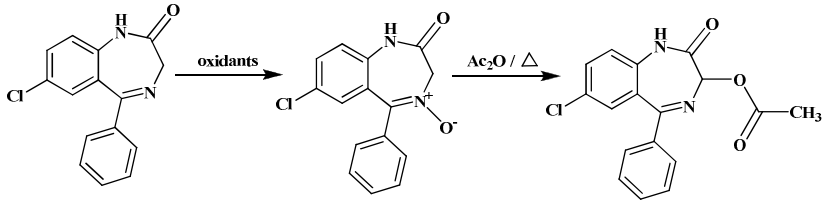
Scheme-72

Photodecomposition: It has been studied the photochemical decomposition of midazolam, in aqueous solution irradiated with a mercury lamp at high pressure. The decomposition products were isolated and identified. The midazolam photodecomposition products obtained by irradiation with a mercury lamp, at high pressure, are shown below:[43]



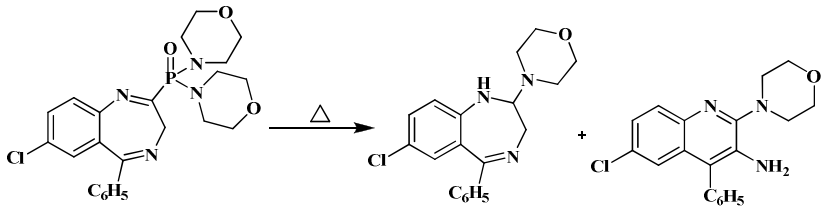
Scheme-73

Polonovsky rearrangement: 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4*N*-oxide is subjected to the Polonovsky rearrangement[54] to give the 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (scheme-74). Finally oxazepam or lorazepam are produced by controlled saponification by various methods.



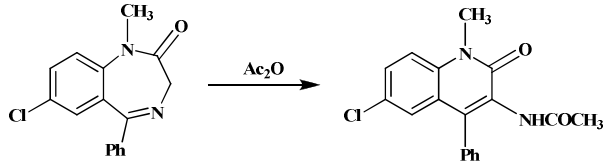
Scheme-74

Pyrolysis: Pyrolysis of 7Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3H-1,4-benzodiazepine in refluxing 1,2,4-trichlorobenzene (214^{o}C) afforded an isomeric product. The assignment of the 3-amino-2-morpholinylquinoline structure was correlated with a synthesis from 3-amino-6-chloro-2-(di-4-morpholinyl)phosphinyloxy-4-phenylquinoline and morpholine (scheme-75).[45]



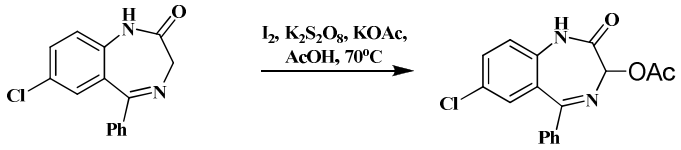
Scheme-75

Quinoline synthesis: The formation of the quinoline from the benzodiazepine has been reported (scheme-76).[39]



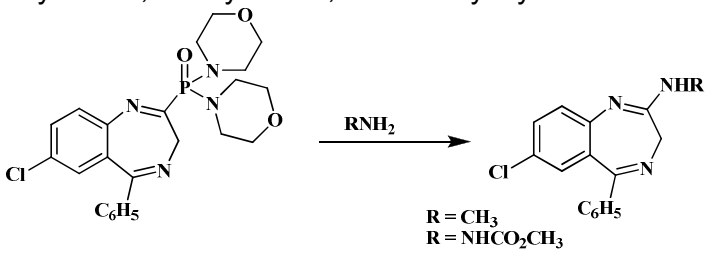
Scheme-76

Racemisation: Due to our interest to examine whether the ring expanded 1,4-benzodiazepine could have an effect on potential anti-HIV activities, 1,4-benzodiazepine compound were further transferred to compound as racemates.[55]



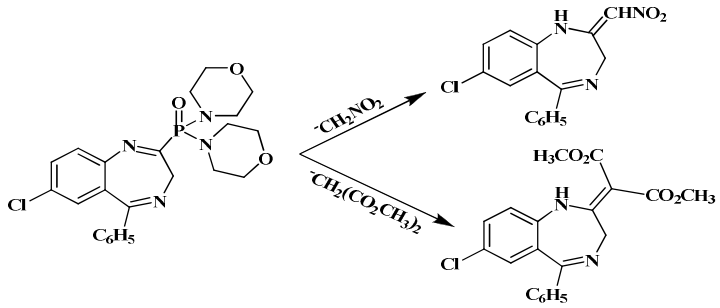
Scheme-77

Reaction with amines: The reaction of 7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3H-1,4-benzodiazepine triethylamine, methylamine, and methyl hydrazinocarboxylate is as follows:[45]



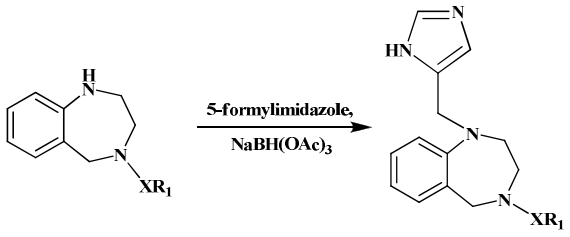
Scheme-78

Reaction with carbanions: Of particular interest is the carbon-carbon bond formation through the displacement of the dimorpholinylphosphinyloxy group with carbanions. The reaction of 7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3H-1,4-benzodiazepine with the anions of nitromethane and dimethyl malonate afforded 7-chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2H-1,4-benzodiazepine and 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2H-1,4-benzodiazepine respectively (scheme-79).[45]



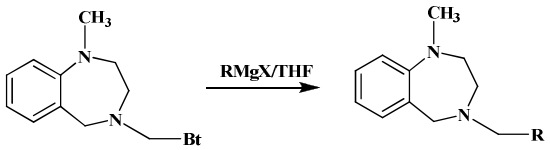
Scheme-79

Reaction with 5-formylimidazole: Reactions of 4-acyl-2,3,4,5-tetrahydro-1,4-benzodiazepines with 5-formylimidazole and $NaBH(OAc)_3$ gave 1-alkyl-4-acyl-2,3,4,5-tetrahydro-1,4-benzodiazepines (scheme-80).[56]



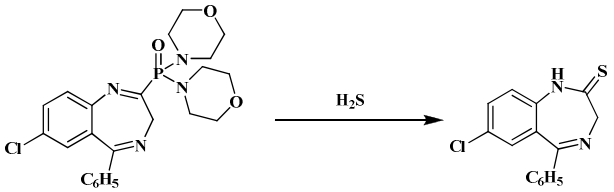
Scheme-80

Reaction with Grignard reagent: The N-4-(benzotriazolylmethyl)-tetrahydro-1,4-benzodiazepine reacted smoothly with Grignard reagents in THF to provide convenient access to substituted homologues in good yield (scheme-81). The benzotriazole moiety can be removed reductively with $NaBH_4$ to provide the simple N-methyl compound.[57]



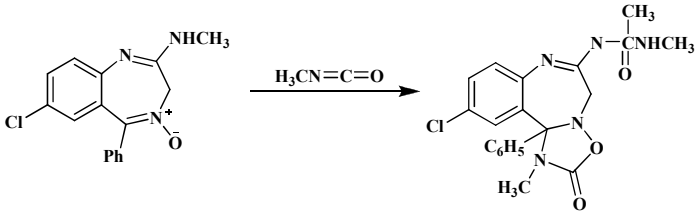
Scheme-81

Reaction with hydrogen sulphide: The displacement reaction of 7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3H-1,4-benzodiazepine is nearly instantaneous at room temperature with hydrogen sulphide (scheme-82).[45]



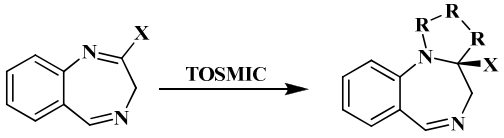
Scheme-82

Reaction with isocyanate: Treatment of chlordiazepoxide with an excess of methyl isocyanate yielded essentially two isocyanate moieties (scheme-83).[39]



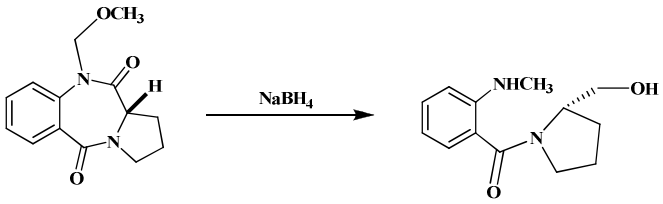
Scheme-83

Reaction with tosylmethyl isocyanide: An N-methyl-N-nitroso moiety offers a useful and chemically stable alternative leaving group to chlorine, reacting with tosylmethyl isocyanide (TOSMIC) to introduce a 2,3-fused imidazole ring (scheme-84).[58]



Scheme-84

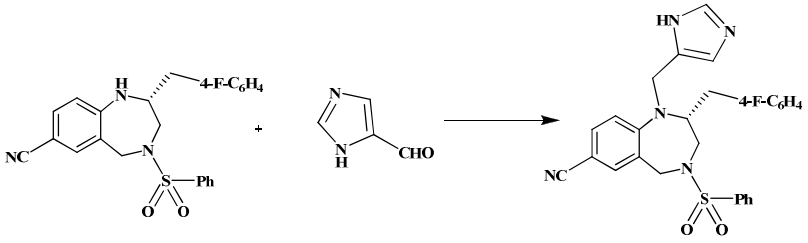
Reduction: The reduction of tertiary lactams to their respective amines has been approached with various hydrides such as lithium aluminum hydride, sodium borohydride, and lithium borohydride (scheme-85).[59]



Scheme-85

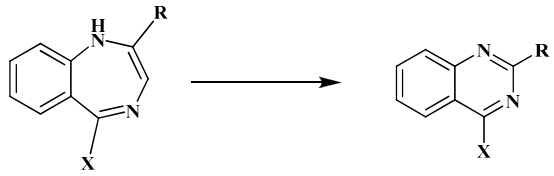
Reductive amination: The alkylation at N_1 of the 1,4-benzodiazepine with imidazole-5-carboxaldehyde is readily accomplished in excellent yield via a reductive amination process that

involves simply stirring with triethylsilane in a 1:1 mixture of CH_2Cl_2 and CF_3CO_2H at 25°C for 4 h (scheme-86).[60]



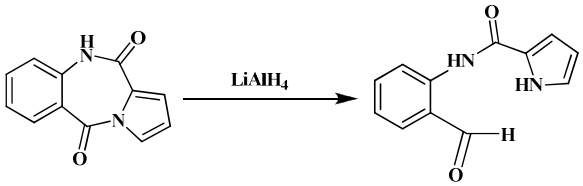
Scheme-86

Ring contraction: The thermal ring contraction conducted at 180°C, appears to be the first example of this type of reaction for unsaturated benzodiazepines (scheme-87).[61]



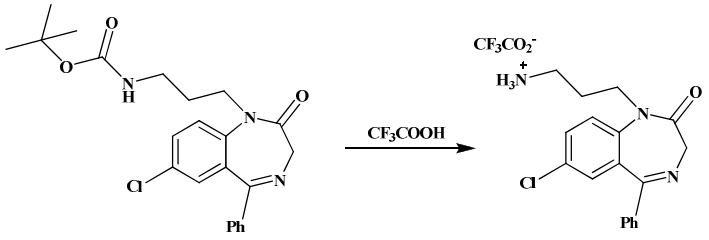
Scheme-87

Ring opening: This particular reactivity confirms the results of Carey[15] who reported the opening of the benzodiazepine ring by treatment with lithium aluminium hydride to form the aldehyde (scheme-88).



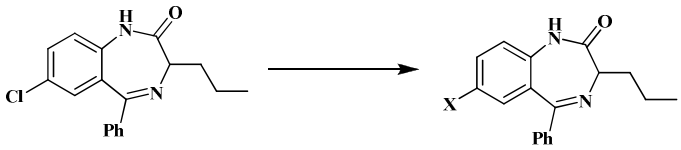
Scheme-88

Salt formation: Removal of the Boc-protecting group using trifluoroacetic acid gave the trifluoroacetic acid salt which was then ready to be coupled to the methoxy terminated poly(ethylene glycol) (MPEG) linker (scheme-89).[46]



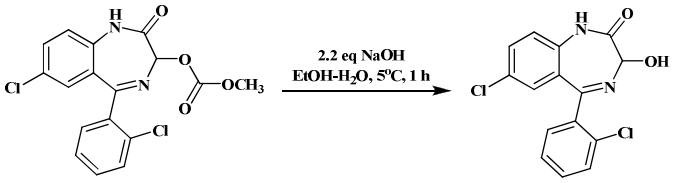
Scheme-89

Sandmeyer reaction: The nitro-benzodiazepine was reduced with a solution of Sn-(II)-chloride to the amino-benzodiazepine, which was converted into chloride in a Sandmeyer reaction (scheme-90).[49]



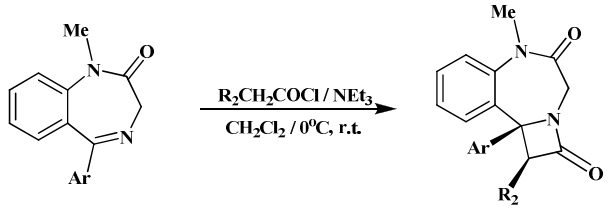
Scheme-90

Saponification: 3-acetoxy-7-chloro-1,3-dihydro-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one were converted to oxazepam and lorazepam by controlled saponification with sodium hydroxide in an ethanol-water mixture in >90% yields (scheme-91).[62]



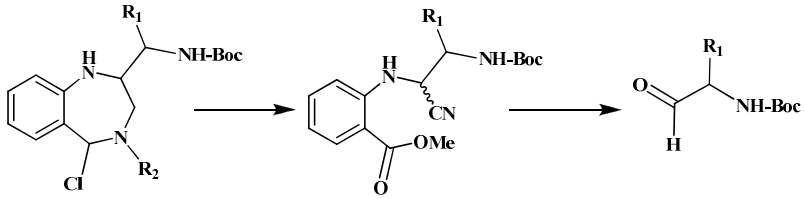
Scheme-91

Staudinger reaction: The imine moiety of 1H-1,4-benzodiazepine-2-(3H)ones reacts regio- and stereospecifically with a range of functionalized ketenes to afford substituted, fused lactam cycloaddition adducts, that constitutes one of the few examples of Staudinger-type reactions (scheme-92) involving ketimines described so far.[63]



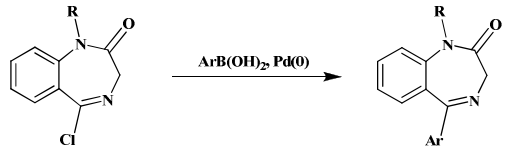
Scheme-92

Strecker reaction: The stereo controlled synthesis of phenylalanine and tryptophan derived 5-oxo-1,2,3,4-tetrahydro-5H-1,4-benzodiazepine derivatives is described, involving a modified Strecker reaction of N-Boc protected amino aldehydes and methyl anthranilate, reduction of the resulting amino nitriles and lactamization **(scheme-93)**.[21]



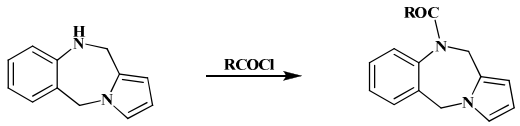
Scheme-93

Suzuki cross-coupling reaction: The imidoyl chloride moiety of 5-chloro-1-alkyl-1,4-benzodiazepin-2-ones participates in Pd-catalyzed, Suzuki cross-coupling reactions (scheme-94), reacting with a range of functionalized aromatic boronic acids provided an efficient and versatile approach to 5-aryl and 5-heteroaryl compounds.[64]



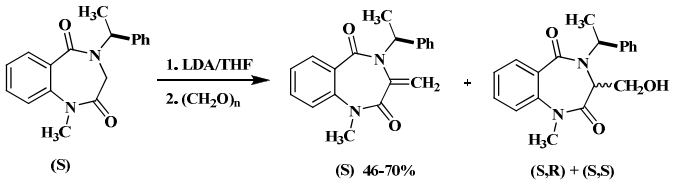
Scheme-94

Vilsmeier-Haack reaction: Pyrrolo-1,4-benzodiazepine undergoes Vilsmeier-Haack reaction (scheme-95) to give the formylated product.[64]



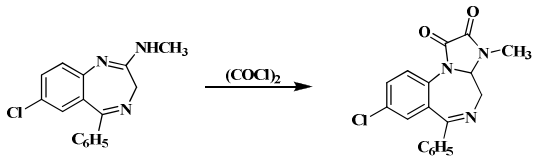
Scheme-95

Miscellaneous reactions: Benzodiazepinedione was treated with lithium diisopropylamide (LDA) in THF, followed by the addition of paraformaldehyde (scheme-96). This synthetic procedure afforded the desired *exo* methylene derivative (*S*) in 46% yield and a mixture of diastereomeric carbinols (*S*,*R*) and (*S*,*S*) (ratio 88:12) in 52% yield.[7]



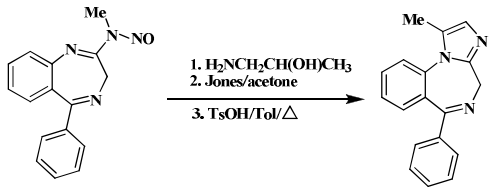
Scheme-96

Treatment with oxalyl chloride gave the expected imidazolinedione (scheme-97).[65]



Scheme-97

The *N*-nitrosoamidine functionality in compounds can also be replaced through reaction with 1-amino-2-propanol. The hydroxyl functionality present in this newly created amidine was subsequently oxidized to the corresponding methyl ketone through treatment with Jones' reagent. *p*-Toluenesulphonic acid-mediated cyclization afforded tricyclic benzodiazepines (scheme-98).[8]



Scheme-98

CONCLUSION

The chemistry of 1,4-benzodiazepines has exhibited promise on a number of fronts. The aim of this review was to demonstrate the wide variety of reactions of 1,4-benzodiazepines applicable in the organic synthesis and the production of biologically useful compounds.

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