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REDUCTION AND DEHYDROGENATION OF DIHYDROPYRIDAZINONES: AN OVERVIEW

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Abstract
The dihydropyridazine ring and its related derivatives are very important because these have a wide range of biological activities and comprise many specific chemical or physical properties. Synthesis and reactivity of this ring system is pretty numerous and diverse. In this review, we summarized several reductive and dehydrogenative methods for the transformation of the various substituted 4,5-dihydropyridazinones. These procedures result in further intermediates or several important products by chemoselective and easily accessible reagents under simple and mild conditions.

Keywords 4,5-Dihydropyridazinones, biological effects, PDE III inhibitors, dehydrogenation, reduction, reagents.

Introduction

During the past few decades, increasing interest of pyridazines and pyridazinones has been observed concerning the synthesis and properties of these ring systems, moreover several reviews were reported in this field[i-iii]. These compounds (**Figure 1**) have remarkable biological activities, such as positive inotropic effect (**1**-**3**) combined with vasodilation (selective phosphodiesterase PDE III inhibitors)[iv-vi] and α_1-adrenoceptor antagonist **4**[vii], or analgesic **5**[viii] activites.

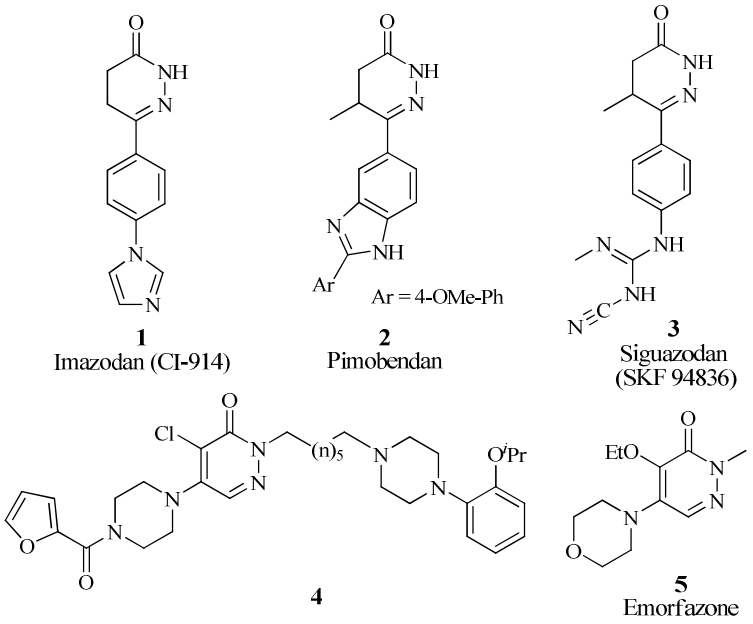


Figure 1

The sulfonylpyridazinones are selective aldose reductase inhibitors, compound **6** (**Figure 2**) is effective for the treatment of type 2 diabetes[ix,x], while the **7** irdabisant (CEP-26401) is a novel, potent histamine H_3 receptor antagonist/inverse agonist[xi] and it may have therapeutic utility in the treatment of cognitive and attentional disorders. Other derivative, such as chloridazon **8** is widely used as herbicide[xii] and the diclomezine **9** is a highly effective fugicide[xiii], it is used to treat rice sheath blight caused by *Rhizoctonia solani*.

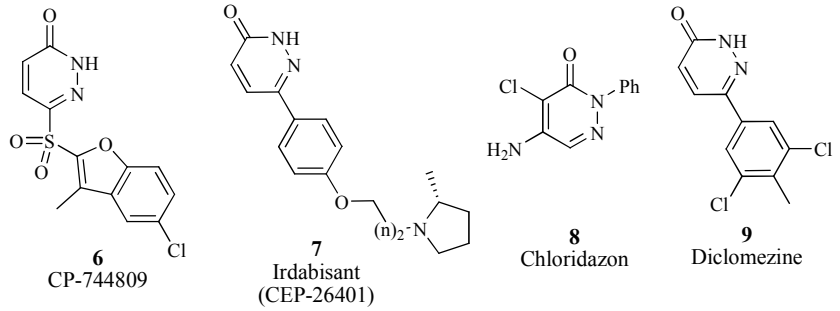


Figure 2

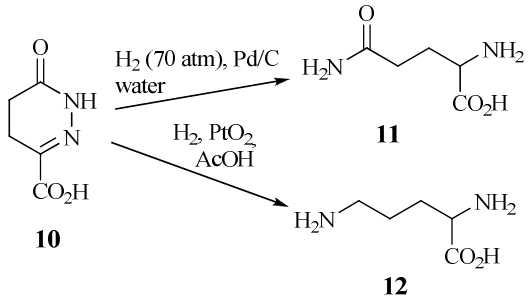
Results and Discussion

I. Reductions

1. Hydrogenation of 4,5-dihydropyridazinones

The catalytic hydrogenation of 6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic acid **10** represents a simple, convenient method for the synthesis of **11** glutamine, which plays a role in a variety of important biochemical functions. This procedure was carried out at high pressure (~ 70 atm) and room temperature over a 5% Pd/C catalyst in water to give D,L-glutamine in 63 % yield (**Scheme 1**)[xiv]. In the course of reductive ring-opening reaction an N−N bond cleavage occurred. The corresponding 5-alkyl- and arylamino derivatives were also prepared. On the other hand use of platinum oxide catalyst at low hydrogen pressure in

acetic acid as solvent **10** tetrahydropyridazine-3-carboxylic acid resulted in D,L-ornithine **12** in low yield (23%)[xv].

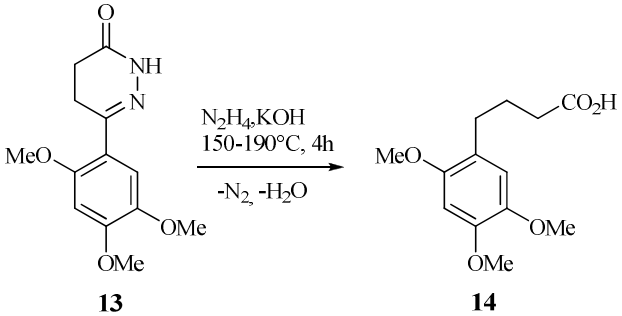


Scheme 1 Synthesis of D,L-glutamine **11** and ornithine derivatives **12**.

Hydrogenation of 6-methyl-2-phenyl-4,5-dihydropyridazin-3(2*H*)-one over Adams' catalyst (PtO_2) in glacial acetic acid at 3 atm resulted in a mixture of saturated pyridazinones[xvi].

2. Wollf-Kishner reduction

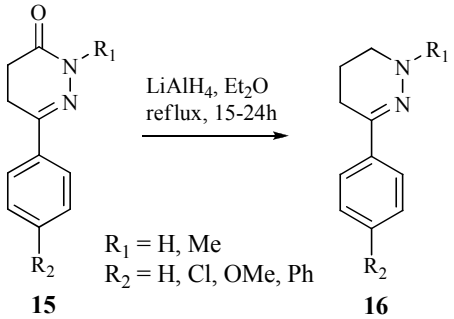
Brunner *et al.* reported the Wolff–Kishner reduction of 4,5-dihydropyridazinone[xvii] **13** with KOH and hydrazine at 150°C then 190°C, when the one-step conversion of a „hydrazone-like" intermediate **13** was transformed into 4-arylbutyric acid **14** in 86% yield (**Scheme 2**) by removal of water and with loss of N_2.



Scheme 2 Wolff–Kishner reduction of 4,5-dihydropyridazinone **13** to 4-arylbutyric acid **14**.

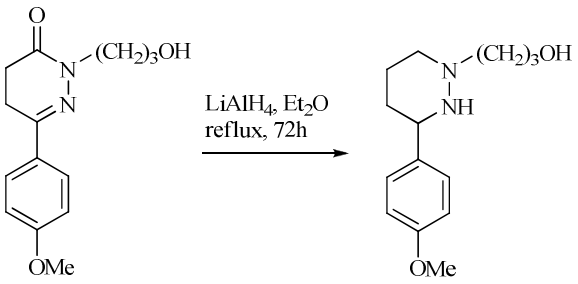
3. Reductions with lithium aluminium hydride

Application of the lithium aluminium hydride (LAH) as reducing agent was reacted with 6-aryl-4,5-dihydropyridazinones[xviii-xx] **15** in refluxing anhydrous diethyl ether or THF for 15-24 h, which resulted in 3-aryl-1,4,5,6-tetrahydro-pyridazines **16** by selective reduction of carbonyl group (**Scheme 3**) in medium to good yields (47-81%).



Scheme 3 Synthesis of 1,4,5,6-tetrahydro-pyridazines **16**.

In addition, reaction of excess reagent reduced the analogue of **15** (R_1 = Me, Ph) to a mixture of tetrahydro- and hexahydropyridazine[xxi,xxii]. Previously, Aeberli *et al* prepared[xxiii] 3-aryl-1-(3-hydroxypropyl)-hexahydropyridazine **17** successfully by lithium aluminium hydride reduction from an appropriate 4,5-dihydropyridazinone **15** on multigram scale (**Scheme 4**).

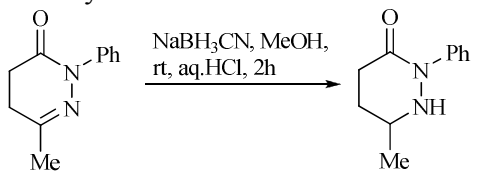


15 **17**

Scheme 4 Preparation of 1-(3-hydroxypropyl)-3-(4-methoxyphenyl)-hexahydropyridazine **17**.

4. Reductions with sodium cyanoborohydride

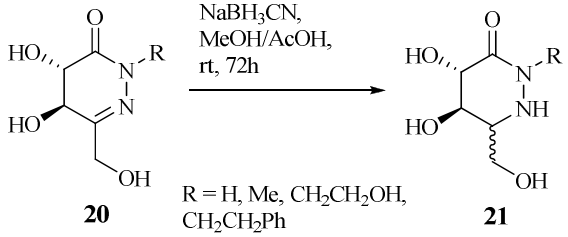
Sodium cyanoborohydride ($NaBH_3CN$) is widely used, it is a selective, mild reducing reagent for a number of functional groups such as aldehydes, ketones, acetals, epoxides and imines under moderate conditions[xxiv,xxv]. When 6-methyl-2-phenyl-4,5-dihydropyridazin-3(2*H*)-one **18** was reduced with sodium cyanoborohydride in methanol[xvi] at pH 3-4, tetrahydropyridazinone derivative **19** was obtained in 40% yield (**Scheme 5**). The reduction took place in C=N bond selectively.



18 **19**

Scheme 5 Synthesis of 6-methyl-2-phenyltetrahydropyridazin-3(2*H*)-one **19**.

The *N*-unsubstituted derivative of compound **19** as an intermediate for the preparation of 1,2-diazetidinone[xxvi] and macrocyclic dilactams[xvii] was also obtained by similar methods in excellent yields (88-96%). Sugar-derived *N*-substituted tetrahydropyridazinones **21** are weak glycosidase inhibitors[xxviii], which were obtained by reduction of the corresponding dihydro derivatives **20** with $NaBH_3CN$/MeOH in the presence of AcOH (**Scheme 6**). The procedure gave a different mixture of diastereomers (2:3-1:1-3:2) **21** in good yields (58-89%).



20 **21**

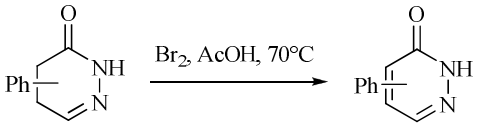
Scheme 6 Preparation of sugar-derived *N*-substituted tetrahydropyridazinones **21**.

Gardiner *et al* reported[xxix] a multistep diastereoselective synthesis of peptidic tetrahydropyridazinone from (*S*)-phenylalanine using $NaBH_3CN$ as reducing agent in a key step. Cycloalkane fused dihydropyridazinones were prepared and studied on the reduction of C=N double bond in consideration of the diastereoselectivity[xxx]. Under the usual reaction conditions in all cases, only a single diastereomer could be isolated depending on the types of anellation.

II. Dehydrogenation

1. Reactions of bromine in acetic acid

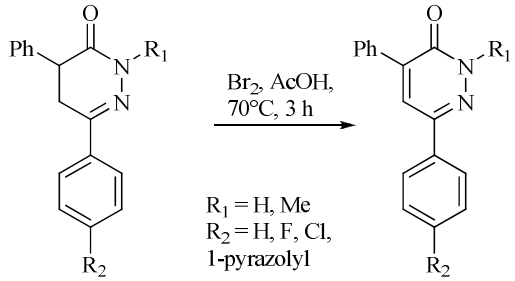
Previously, 4-, 5- and 6-phenyl substituted 4,5-dihydropyridazin-3(2*H*)-ones **22** were treated with a solution of bromine in acetic acid at 70°C (**Scheme 7**) to give the corresponding dehydrogenated derivatives **23** in good yields (75-81%)[xxxi]. An alternative method was also developed for the dehydrogenation by reaction with *N*-bromosuccinimide in dimethyl sulfoxide (DMSO) at 5°C, however this procedure was ineffective in case of 6-phenyl derivative.



22 **23**

Scheme 7 Dehydrogenation of 4-,5- and 6-phenyl-4,5-dihydropyridazinones **22**.

Sircar *et al* reported[iv] synthesis and structure-activity relationship of several 6-(4-imidazolyl)phenyl-pyridazinones as a new class of positiv inotropic agents. The use of the bromine in acetic acid under reflux at 90-95°C for 3.5h resulted in pyridazinones. Dehydrogenation of 4,6-diphenyl-dihydropyridazinone derivatives **24** (**Scheme 8**) by this method was also successful[xxxii].



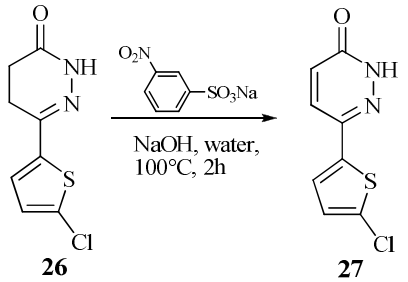
24 **25**

Scheme 8 Synthesis of diphenyl-pyridazinones **25**.

Johnston *et al* described[xxxiii] a short procedure of some 6-heteroarylpyridazinone derivatives, which are pharmacologically important compounds (FK838 and KCA-1312) and for the dehydrogenation a mixture of Br_2/AcOH was applied in good yield (73%).

2. Sodium 3-nitrobenzenesulfonate as dehydrogenation agent

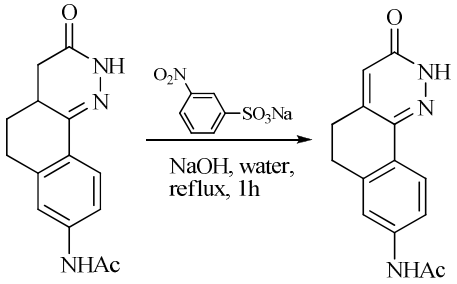
Heating of dihydropyridazinone with sodium 3-nitrobenzenesulfonate in basic medium is one commonly used method for the dehydrogenation. Sometimes, dehydrogenation with bromine was problematic because bromination occurred on the heteroaryl (e.g. thiophen) substituent as side reaction. However dehydrogenation of **26** to give pyridazinone **27** succeeded with 3-nitrobenzenesulfonate[xxxiv] in alkaline aqueous solution at 100°C in 86% yield (**Scheme 9**).



26 **27**

Scheme 9 Synthesis of 6-(5-chlorothiophen-2-yl)pyridazin-3(2*H*)-one **27**.

On the other hand Ravina *et al* dehydrogenated 6-(2-thienyl)-4,5-dihydropyridazinones with both method (by Br_2/AcOH and sodium 3-nitrobenzenesulfonate) successfully[xxxv], without formation of by-product. Several tetraline fused pyridazinone derivatives (benzo[*h*]cinnolinones) were prepared and evaluated biologically and some compounds possessed potent antihypertensive activity[xxxvi]. Regioselective oxidation of dihydro derivative **28** was accomplished in a 40% yield, using sodium 3-nitrobenzenesulfonate (**Scheme 10**) in NaOH solution.



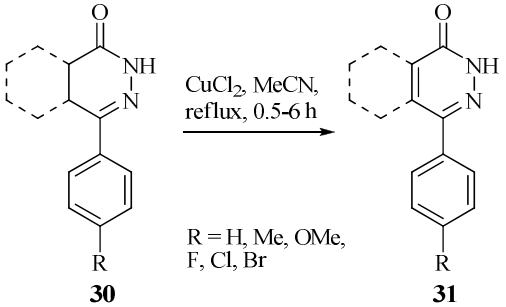
28 **29**

Scheme 10 Preparation of 8-(acetlyamino)-5,6-dihydrobenzo[*h*]cinnolin-3(*2H*)-one **29**.

Additionally, several tricyclic dihydropyridazinones were also aromatized by this method to give novel aldose reductase inhibitor and potential STAT3 inhibitor compounds[xxxvii-xxxix].

3. Dehydrogenation with copper(II) chloride

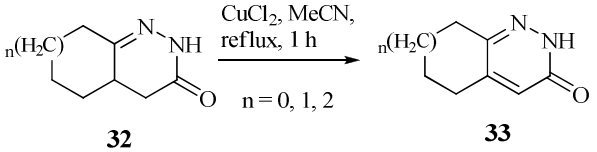
A new simple and mild procedure was developed[xl] using copper(II) chloride ($CuCl_2$) for the dehydrogenation of dihydropyridazinones and their cyclohexane fused derivatives. Thus to a solution of dihydropyridazinone **30** in acetonitrile 2 mol equivalent anhydrous $CuCl_2$ was added and the mixture refluxed for several hours (**Scheme 11**), which afforded the corresponding pyridazinone **31** in good to excellent yields (73-93%) after an easy work-up.



30 **31**

Scheme 11 Dehydrogenation of dihydropyridazinones **30** with copper(II) chloride.

This method is suitable for the synthesis of tetrahydrocinnolin-3(2*H*)-one **33** and its homologous series[xli] (**Scheme 12**) as well as for the partial aromatization of tricyclic derivatives[xlii].



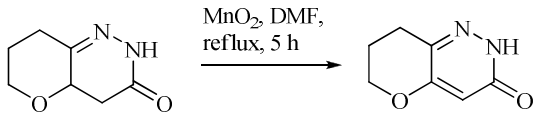
32 **33**

Scheme 12 Synthesis of tetrahydrocinnolin-3(2*H*)-one derivatives **33**.

Hudkins *et al* used also the above method for the preparation of the selective H_3 receptor inverse agonist irdabisant (CEP-26401) analogue [xi] and perfluorinated pyridazinones were obtained in this way in good yields[xliii]. Beyond that several other examples prove efficiency and practical advantage of this dehydrogenation process[xliv-xlvi].

4. Manganese(IV)oxide as a mild oxidizing agent for aromatization

Besides the bromine/acetic acid dehydrogenation method, manganese (IV) oxide (MnO_2) is a frequently applied, effective reagent for this purpose and it can be removed easily from the reaction mixture. Sircar *et al* dehydrogenated earlier some 4,5-dihydropyridazinones with MnO_2 in a mixture of dioxane and *N*,*N*-dimethylformamide (DMF) at 90°C overnight[iv]. When 6-(4-methoxyphenyl)-2-methyl-4,5-dihydro-2H-pyridazin-3-one and MnO_2 in xylene were stirred at vigorous reflux for 14 hours the corresponding dehydro derivative was obtained in good yield (75%)[xi]. Meneghetti *et al* reported[xlvii] the synthesis, conformational and biological properties of ureido-pyridazinone derivatives, which are structurally related to the known STAT3 inhibitor compound AVS-0288. For the dehydrogenation step, activated manganese (IV) dioxide was used in refluxing dry dichloromethane. Costas *et al* prepared several novel pyridazinone derivatives[xlviii] and the compounds were evaluated *in vitro* as platelet aggregation inhibitors. Tetrahydropyran fused analogue **34** was dehydrogenated (**Scheme 13**) with MnO_2 in DMF under reflux for 5 hours to afford 7,8-dihydropyrano[3,2-*c*]pyridazinone **35** in moderate yield.

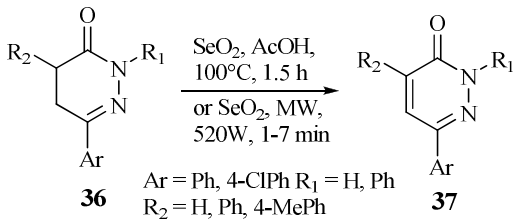


34 **35**

Scheme 13 Preparation of 7,8-dihydro-6*H*-pyrano[3,2-*c*]pyridazin-3(2*H*)-one **35**.

5. Dehydrogenation with selenium dioxide (SeO_2)

When substituted 2-methyl-6-phenyl-4,5-dihydropyridazin-3(2*H*)-ones were treated with selenium dioxide in refluxing acetic acid for 4-16 hours the aromatized products were obtained in 72-87% yields[xlv,xvix], which are key intermediate for producing selective histamin H_3 receptor antagonists. A conventional and a microwave assisted synthesis[L] of pyridazinones **37** was achieved using selenium dioxide in heating acetic acid or in a solvent free solid state reaction (**Scheme 14**) under microwave conditions (520 W, 1-7 minutes).

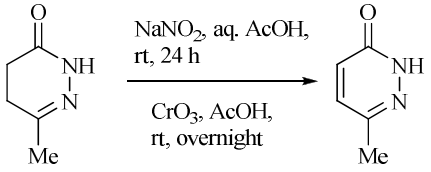


Scheme 14 Preparation of pyridazinones **37** with selenium dioxide.

6-Methyl-4,5-dihydropyridazin-3(2*H*)-one was also dehydrogenated with SeO_2 in refluxing anhydrous ethanol chemoselectively[li].

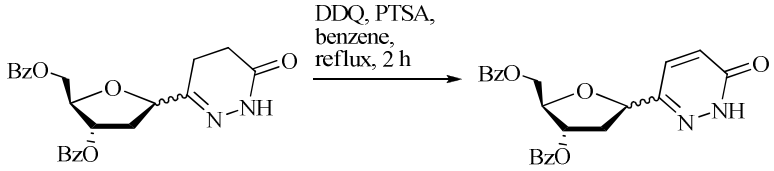
6. Miscellaneous methods for dehydrogenation of dihydropyridazinones

6-Methyl-4,5-dihydropyridazin-3(2*H*)-one was converted by two uncommon, alternative methods to pyridazinone (**Scheme 15**)[liii]. Treatment of compound **38** with sodium nitrite ($NaNO_2$) in dilute acetic acid at room temperature resulted in the aromatized derivative **39** in poor (10%) yield. Alternatively, dihydropyridazinone **38** was dehydrogenated with chromium trioxide (CrO_3) in glacial acetic acid, by letting the mixture stand overnight pyridazinone **39** was obtained in moderate yield (20%).



Scheme 15 Conversion of 6-methyl-4,5-dihydropyridazin-3(2*H*)-one **38**.

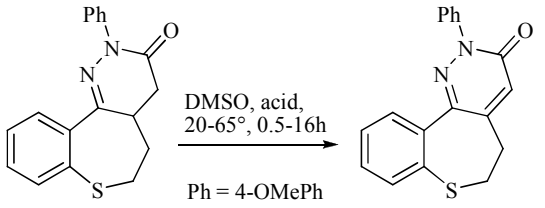
The other procedure was carried out by reaction of the 6-(dibenzoyl-2-deoxy-β- and α-D-*erythro*-pentofuranosyl)-4,5-dihydropyridzinone **40** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and *p*-toluenesulfonic acid (PTSA) (**Scheme 16**) in refluxing benzene to give pyridzinone *C*-nucleoside[liii] **41** in 87 % yield after purification.



Scheme 16 Synthesis of 6-(dibenzoyl-2-deoxy-β- and α-D-*erythro*-pentofuranosyl)-pyridzinone **41**.

Müller patented an invention[liv] that described dehydrogenative preparation of 6-methyl- and 6-phenyl-pyridazinones by heating 4,5-dihydro derivatives in diphenyl ether, ethers of diethylene glycol and triethylene glycol (e.g. diglyme, triglyme) at high temperature (150-350°C) for about 3-5 hours in the presence of nobel metal catalysts (Pd, Pt, Ru, Rh, Ir) supported on a carrier chromia-alumina (Cr_2O_3-Al_2O_3), alumina (Al_2O_3) or silica (SiO_2).

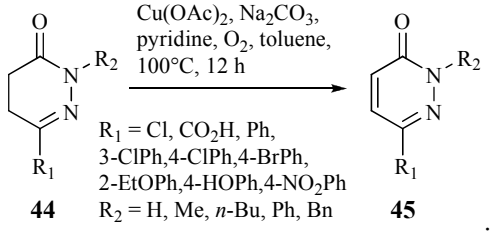
The tricyclic 4,4a,5,6-tetrahydro[1]benzothiepino[5,4-*c*]pyridazinone **42** was converted to the dehydrogenated derivative **43** regioselectively with dimethyl sulfoxide (DMSO)[lv] in a one-step reaction by acid catalysis (**Scheme 17**) in various yield (15-95%) *via* sulfoxide intermediate presumably. Different acid catalysts were tested (TFA, MSA or HBr-AcOH) and the hydrogen bromide solution (30%) in glacial acetic acid was observed as the best condition.



42 **43**

Scheme 17 Conversion of 2-(4-methoxyphenyl)-4,4a,5,6-tetrahydro[1]benzothiepino [5,4-*c*]pyridazin-3(2*H*)-one **42**.

Cyclohexane- and norbornane-fused dihydropyridazinones (4-aryl-hexahydrophthalazin-1(2*H*)-ones) were dehydrogenated by the reaction with thionyl chloride ($SOCl_2$) in refluxing benzene in moderate to good yields[lvi]. Similarly, Humne *et al* presented an efficient iodine-mediated facile aromatization[lvii] of 4,5-dihydropyridazinones, which was carried out by catalytic amount of molecular iodine with stirring in dimethyl sulfoxide (I_2/DMSO) for 8 hours at 100°C, followed by simple workup.
An easy and expeditious procedure is reported[lviii] for the preparation of both 6-substituted and 2,6-disubstituted-pyridazinones **45** through copper(II)-catalyzed dehydrogenation of C-C to C=C bonds with oxygen (**Scheme 18**). The diversity of functional groups showed good toleration under the oxidative conditions and did not influence the yields significantly. For the optimal reaction condition catalysts, effects of base, ligands, and solvents were examined. Sodium carbonate (Na_2CO_3) was the most effective inorganic base, while pyridine was identified as the most efficient ligand and after screening a series of metal salts, copper(II) acetate was selected as the catalyst. The reaction exhibited good yields (65-97%) and selectivity.



44 **45**

Scheme 18 Copper(II)-catalyzed aerobic synthesis of substituted pyridazinones **45**.

In the same way, under an aerobic condition a copper-catalyzed cascade dehydrogenative and dehalogenative reaction of 2-chloro-phenyl-dihydropyridazinones[lix] was developed. *N*-substituted substrates were also treated with copper(II) acetate ($Cu(OAc)_2$) under basic condition to afford the appropriate dehydrogenated and dehalogenated derivatives. The proposed mechanism for the aerobic cascade reaction is described. Furthermore, a simple, modified and efficient one-pot reaction was achieved for the preparation of *N*-functionalized pyridazinones by a copper(II)-salen complex catalyzed tandem dehydrogenation/dehalogenation sequential reaction[lx] in water and air atmosphere. This method includes three essential possibilities, that substitution of NH group, the dehydrogenation and the dehalogenation in the absence of organic solvents.

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