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REVIEW article

A collective review of the synthetic approaches disclosed in prior patents to synthesize the renowned drug, Lamotrigine

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***Keywords*:** Lamotrigine, synthesis, cyanation, condensation, cyclization, recrystallization

Abstract: In this review work, we have extracted the essential details from prior patents about the synthesis of popular drug Lamotrigine. This initiative will provide a platform for the global researchers to invent new or innovate over the existing synthetic routes to isolate Lamotrigine with good yield and purity. The details of patents were sourced from "Google patents" search tool and the process specific details were elaborated with reaction schemes. In this context, twenty-four reactions schemes were tabulated for the better understanding of the disclosed ventures. The entire chronological exfoliation of details on the synthesis of Lamotrigine provides a clear evolutional vision of its synthetic flourish towards drug commercialization.

Introduction

Lamotrigine **1** is a popular drug molecule (**Table 1**) preferably used for the treatment of disorders related to central nervous system (CNS), specifically epilepsy [1-3]. It is a class-II drug molecule of the Biopharmaceutical Classification System (BCS), exhibits poor solubility in aqueous media (0.17 mg/mL) at ambient temperature and does not vary significantly with pH. Thus, the sparingly soluble nature of **1** in water would necessitate the administration of large volume of drug solution to achieve the intended therapeutic efficacy [4].

Initially, a few 3,5-diamino-triazine derivatives were prepared and their anti-malarial activity against *Plasmodium berghei* was tested. Most of the compounds were found to be toxic at curative doses and hence they are not investigated further because their low therapeutic ratio [5]. Under the context, a few fluoro/fluoro-alkyl/phenyl-alkyl-1,2,4-triazines were synthesized and tested their efficacy against malaria. Most of the compounds were found to be useful in the treatment of malaria [6]. In another study, anti-malarial drugs like quinacrine, chloroquine and hydroxychloroquine were tested as anti-convulsants. Among them, only hydroxychloroquine had exhibited relatively good activity profile [7]. These repurposing investigations had led to the emergence of some novel 3,5-diamino-6-(substituted phenyl)-1,2,4-triazines to treat CNS disorders, as anticonvulsants. Additionally, these triazine derivatives are non-depressants and hence are superior to phenobarbitone [8].

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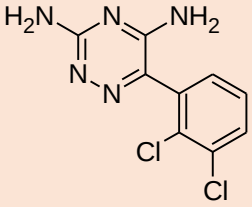
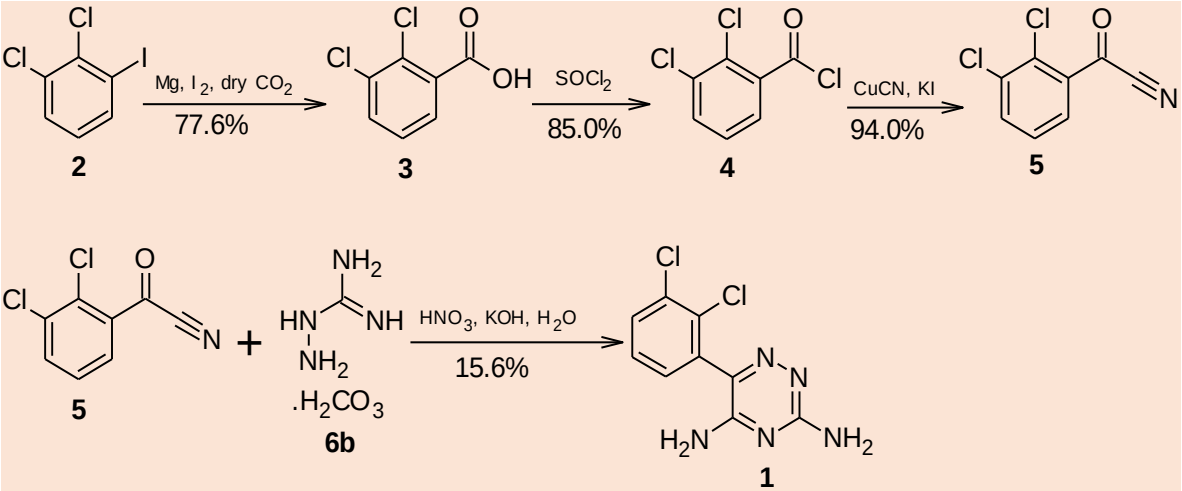
Table 1: Essential details of Lamotrigine **1**

Drug name	Lamotrigine
Trade name	Lamictal, Subvenite
Other names	BW-430C; BW430C; 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
IUPAC name	6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine
Drug class	Phenyltriazine
Drug purpose	Anti-convulsant/Anti-epileptic drug, effectively used to treat some types of epilepsy and bipolar type-I disorder
CAS number	84057-84-1
Drug-Bank number	DB00555
Molecular formula	$C_9H_7Cl_2N_5$
Molar mass	256.09 g/mol
Pharmacokinetic data	Bioavailability (98%), Protein binding (55%), Elimination half-life (29 h) and Metabolism (Liver-mediated by UGT1A4)
Melting point	177-181°C
Water solubility	0.17 mg/L
Chemical structure	 **1**

Exfoliation of synthetic approaches: Miller and others [8] had reported the synthesis of some novel 3,5-diamino-6-(substituted phenyl)-1,2,4-triazines and their use to treat psychiatric and neurological disorders (as anticonvulsants, to treat epilepsy). The work reports the synthesis of **1** (**Scheme 1**) starting from 2,3-dichloroiodobenzene **2**, which was converted to 2,3-dichlorobenzoic acid **3** in the presence of Mg turnings, iodine and solid carbon dioxide. 2,3-Dichlorobenzoyl chloride **4** was obtained by treating **3** with thionyl chloride. It was converted to 2,3-dichlorobenzoyl cyanide **5** by the use of cuprous cyanide and potassium iodide in xylene. The condensation of aminoguanidine bicarbonate **6b** with **5** was done by the use of nitric acid and the cyclization was imposed by aqueous potassium hydroxide to form **1** (mp. 216-218°C) with relatively low yield [8, 9]. In line to this, synthesis and biological activity studies of a few structurally related compounds were reported earlier [5, 6].



Scheme 1: Synthesis of **1** starting from **2** as per Miller et al. [8].

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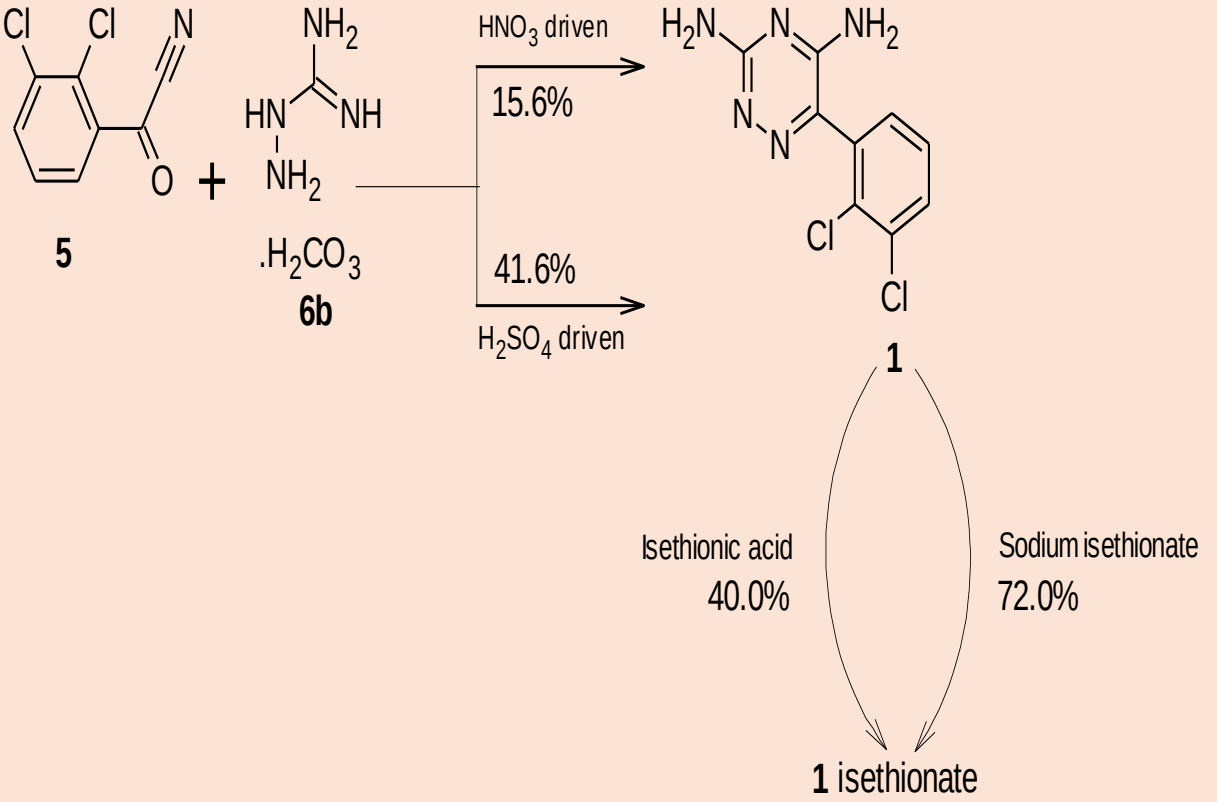
Sawyer and others [10] had illustrated the synthesis and formulation methodology of novel **1** isethionate (**Scheme 2**), a salt of parent drug **1**. The salt formed is highly water soluble and hence facilitates parenteral administration in the form of a sterile aqueous solution suitable for injection. The condensation of **5** with **6b** in the presence of nitric acid gave **1** (mp. 216-218^{o}C), but the same reaction driven by concentrated sulphuric acid gave **1** (mp. 216-218^{o}C) with relatively high yield. It was converted to isethionate (mp. 242-243^{o}C) either by the use of sodium isethionate or isethionic acid [10].



Scheme 2: Synthesis of **1** and its isethionate salt from **5** as per Sawyer et al. [10].

Winter et al. [11] had demonstrated a novel photo-chemical process to synthesize **1** and its pharmaceutically acceptable acid addition salts (**Scheme 3a-c**). 2-(2,3-Dichlorophenyl)-2-oxoacetamide **7** was condensed with **6h** in the presence of ethanolic hydrochloric acid to isolate (2*E*)-2-[(diaminomethylidene)hydrazinylidene]-2-(2,3-dichlorophenyl)acetamide **8** *(E)*. It was cyclized by the use of aqueous potassium hydroxide under varied photochemical mediations to form **1** in moderate yields (mp. 218-222°C). In another example, (2*E*,*Z*)-1-(2,3-dichlorophenyl)-2-(hydroxyimino)ethanone **11** *(E,Z)* was condensed with **6** under the influence of hydrochloric acid to isolate *N*''-[(2*E*)-1-(2,3-dichlorophenyl)-2-(hydroxyimino)ethylidene]carbonohydrazonic diamide **9** *(E)*. It was treated with thionyl chloride in toluene to achieve the dehydration to generate *N*''-[(*E*)-cyano(2,3-dichlorophenyl)methylidene]carbonohydrazonic diamide **10** *(E)*. It was cyclized by the use of 1-propanol under varied photochemical mediations to isolate **1** in good yields (mp. 218-220°C). Furthermore, **1** was treated with isethionic acid to form **1** isethionate (mp. 242-243°C) (**Scheme 3a**). The work had demonstrated the condensation of 1-(2,3-dichlorophenyl)ethanone **12** with 3-methylbutyl nitrite **13** either by HCl purge or butoxide pathway to isolate **11** ***(E,Z)***. Additionally, synthesis of **12** was achieved by the use of distinct key starting materials like **2** or 1,2-dichlorobenzene **14** or 2,3-dichlorobenzaldehyde **15** in reasonably good yields (**Scheme 3b**). The work had provided a few illustrations to condense **14** with ethyl amino (oxo) acetate **17** under the mediation of *n*-BuLi to isolate **7** in moderate yields (**Scheme 3c**) [11].

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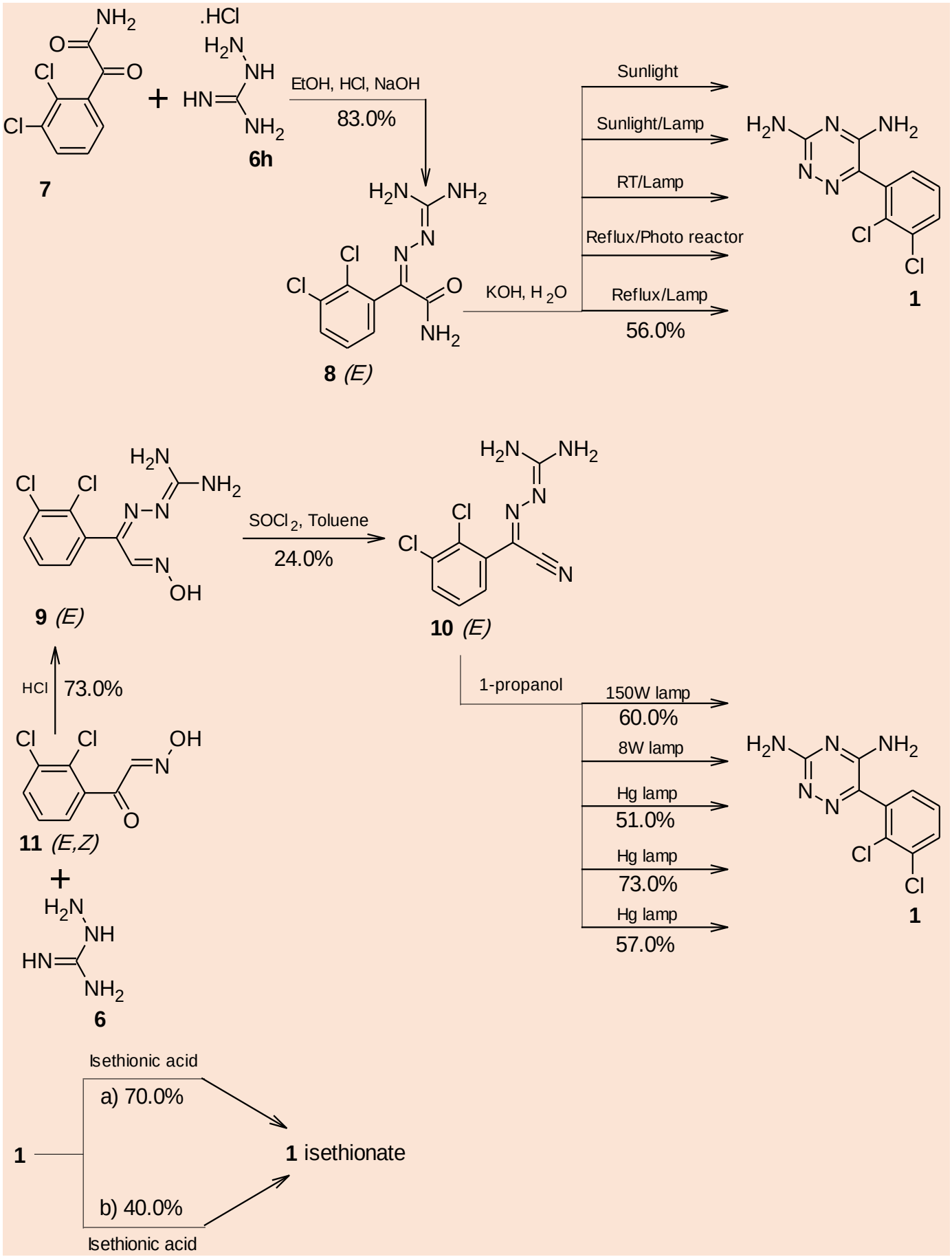

Scheme 3a: Synthesis of **1** by the photochemical pathway as per Winter et al. [11].

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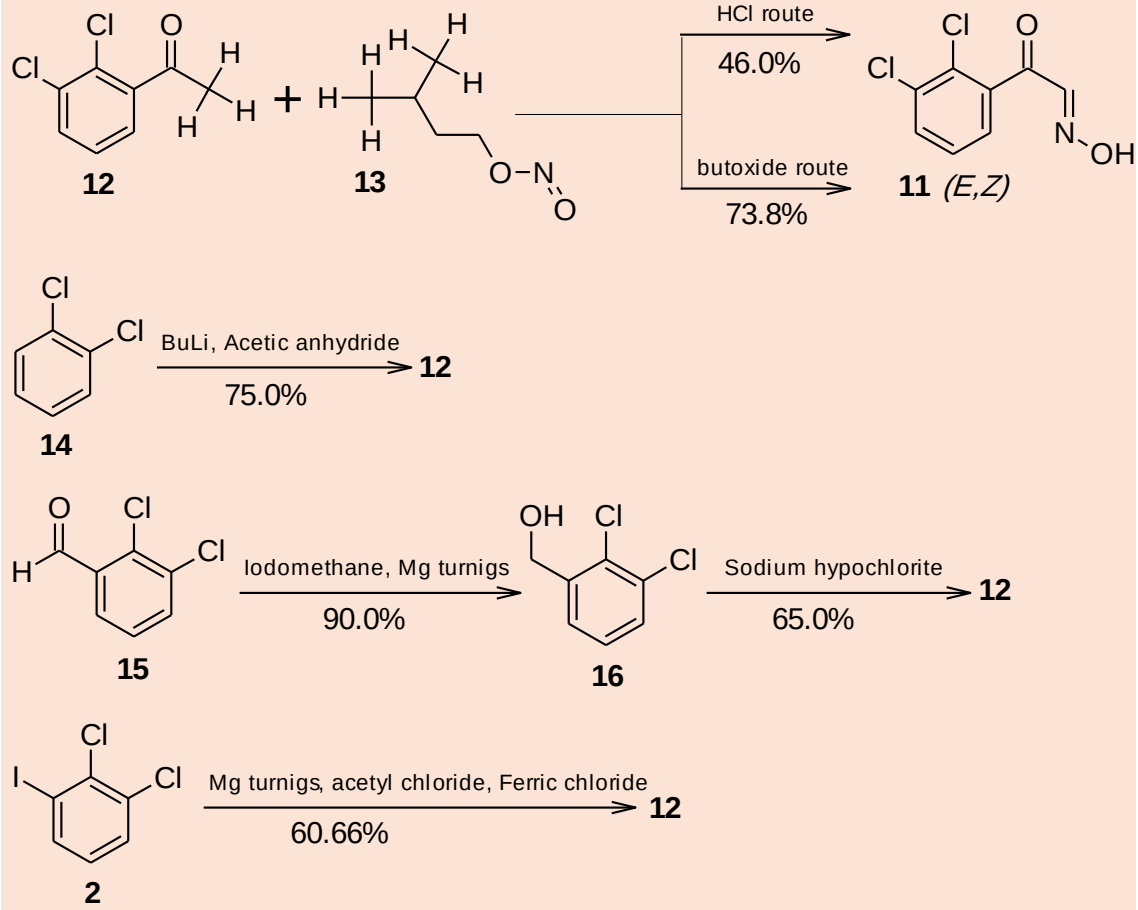
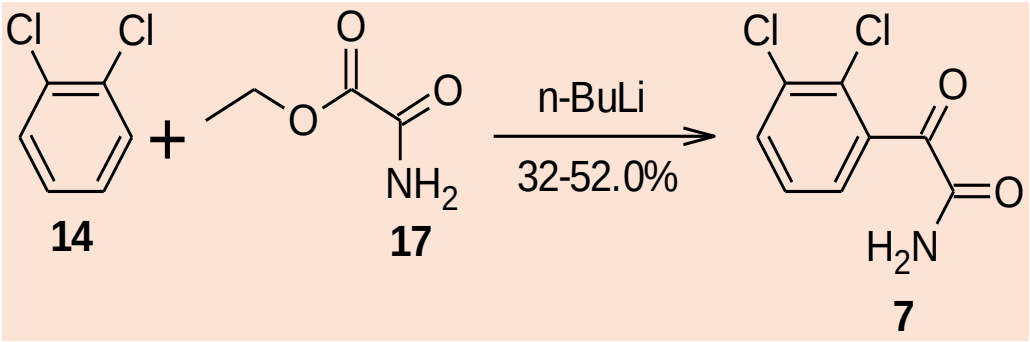


Scheme 3b: Synthesis of **11** from **14**, **15** & **16**



Scheme 3c: Synthesis of **7** from **14** and **17**.

Lee [12] had reported the synthesis of **1** and its pharmaceutically acceptable acid addition salt **1** isethionate from **12** (**Scheme 4**). In fact, **12** was prepared via past disclosed process from **2** or **14** or **15** [10]. An oxidation driven by potassium permanganate ($KMNO_4$) in alkaline medium had converted **12** to its acid derivative (2,3-dichlorophenyl)-(oxo)-acetic acid **18**. It was treated with hydrazinecarbothioamide **19** in the presence of aqueous sodium hydroxide to obtain 6-(2,3-dichlorophenyl)-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one **20**. The reaction of methyl iodide (CH_3I) with **20** in alkaline medium gave 6-(2,3-dichlorophenyl)-3-(methylsulfanyl)-1,2,4-triazin-5(4*H*)-one **21**. It was treated with phosphorous oxychloride ($POCl_3$) to isolate 5-chloro-6-(2,3-dichlorophenyl)-3-(methylsulfanyl)-5,6-dihydro-1,2,4-triazine **22**. An autoclave mediated impact of saturated ammonia (NH_3) gas in ethanol at 180^{o}C for about 72 h had converted **22** to **1** (mp. 218^{o}C). It was treated with isethionic acid via two different methods to isolate **1** isethionate (mp. 242-243^{o}C).

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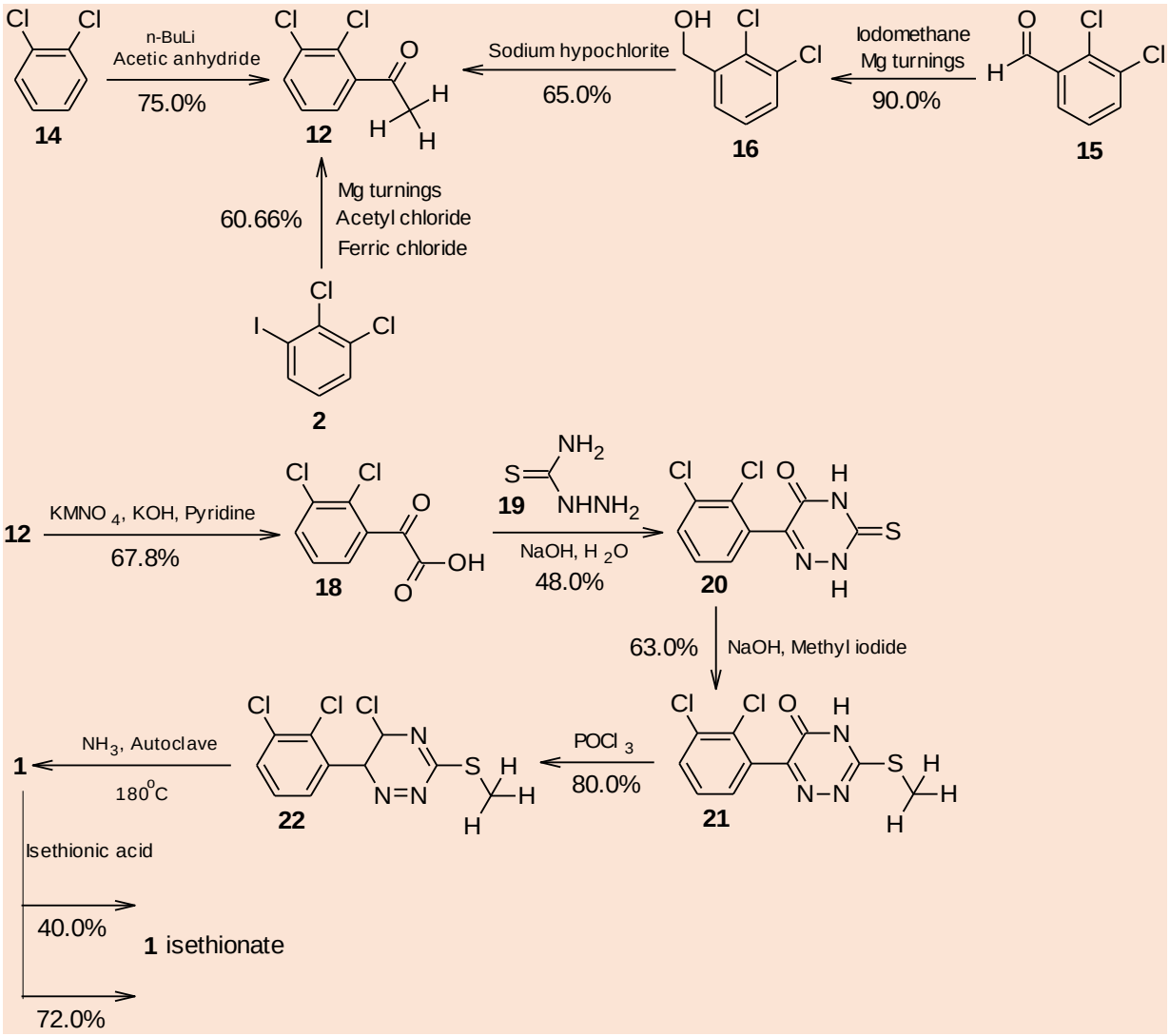
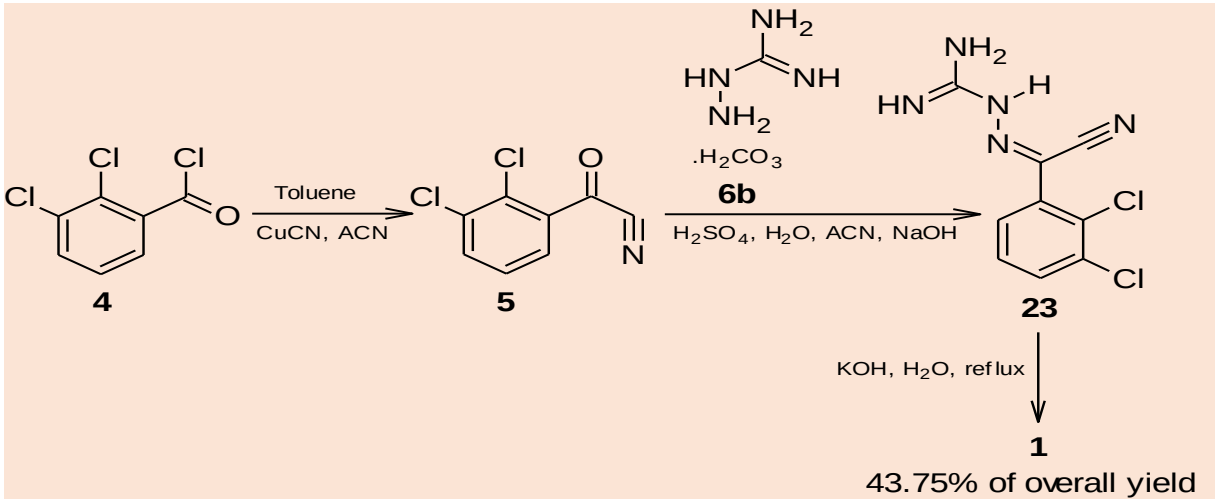


Scheme 4: Synthesis of **1** and its isethionate salt from **12** as per Lee [12].

Vyas [13] had demonstrated the conversion of **4** to **5** by the use of copper cyanide (CuCN) in acetonitrile and toluene. The condensation of **5** with **6b** was executed in the presence of sulphuric acid and aqueous acetonitrile to isolate (2-*E*,*Z*)-2-[cyano(2,3-dichlorophenyl)methylidene]hydrazinecarboximidamide **23**. It was cyclized under reflux by the impact of potassium hydroxide solution to get **1** (mp. 216-218°C) (**Scheme 5**).



Scheme 5: Synthesis of **1** from **4** as per Vyas [13].

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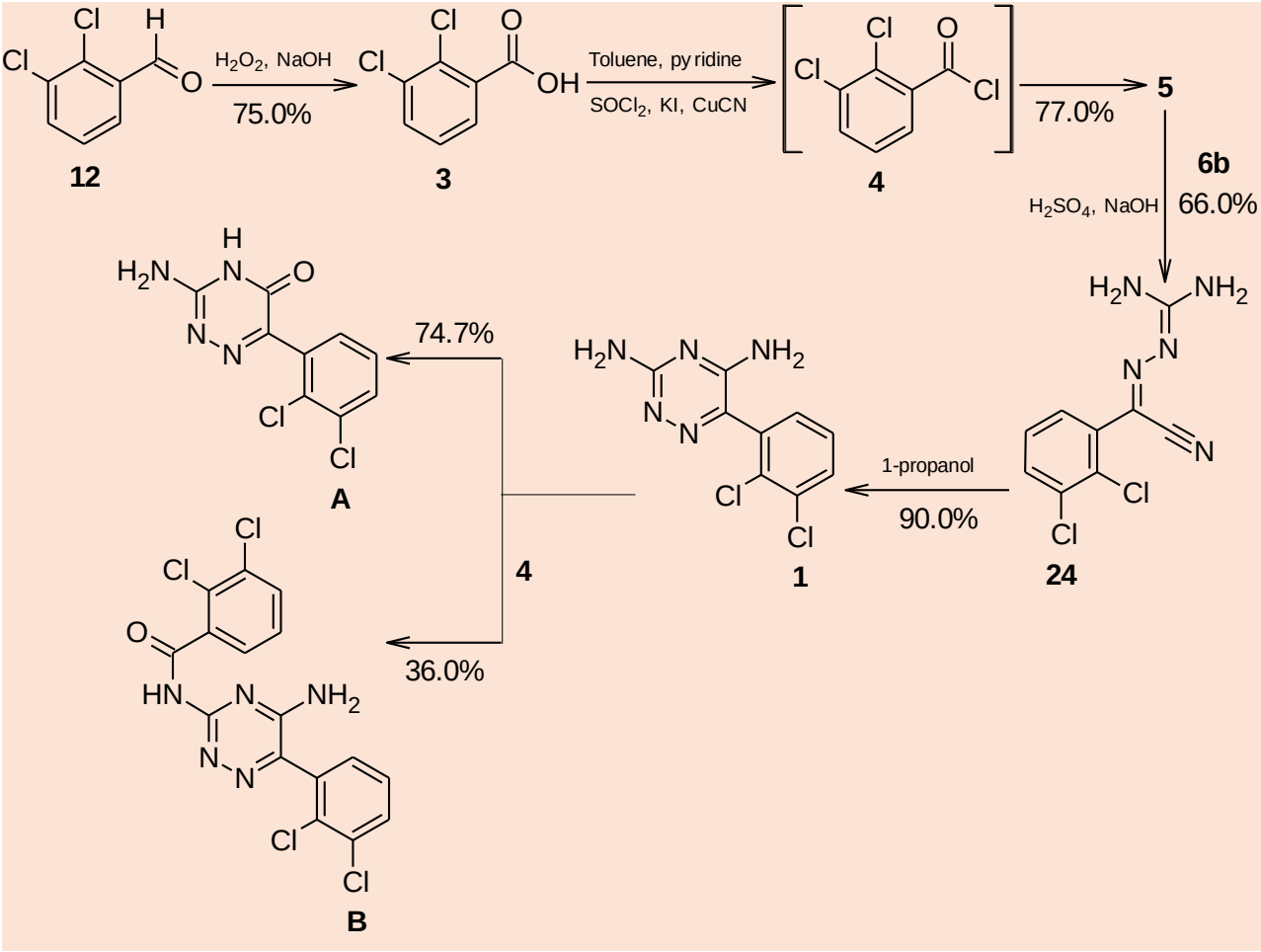
Edmeades and others [14] had reported a moderate yield process for the synthesis of **1**. Additionally, synthesis and characterization of two impurities of **1** were reported to facilitate the analysis of **1**. These impurities would act as reference standards to estimate the potential impurities in the drug (**Scheme 6**). Hydrogen peroxide (H_2O_2) mediated oxidation of **12** in the presence of sodium hydroxide and *tert*-butyl alcohol gave **3**. It was treated with thionyl chloride in the presence of pyridine in toluene to form an un-isolated **4**. An insitu addition of cuprous cyanide (CuCN) and potassium iodide to **4** had resulted in the formation of **5**. The condensation of **5** with **6b** was achieved by the use of sulphuric acid to isolate *N*"-[(*E*,*Z*)-cyano(2,3-dichlorophenyl) methylidene]carbonohydrazonic diamide **24**. It was effectively cyclized in the presence of *n*-propanol under reflux to get crude **1**, its recrystallization from *n*-propanol gave **1**. The novel potential degradation by-product 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5(4H)-one **A** was prepared by treating **1** with sodium hydroxide solution. Another novel potential contaminant *N*-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-3-yl]-2,3-dichlorobenzamide **B** was formed by the un-wanted side reactions during the drug synthesis. It was prepared by treating **1** with **4** in the presence of pyridine.



Scheme 6: Synthesis of **1** from **12** as per Edmeades et al. [14].

Nadaka and others [15] had illustrated a simple process for the synthesis of **1** from **5** (**Scheme 7**). The condensation of **5** with **6b** was achieved in the presence of polyphosphoric acid in acetonitrile to get **23**. Similarly, the reaction of **5** with aminoguanidine **6** under similar conditions with the use of polyphosphoric acid and monoglyme gave **23**. The cyclization of **23** was done by the use of *n*-propanol under reflux to isolate crude **1**, it was recrystallized from *n*-propanol or *n*-propanol and dimethyl sulphoxide mixture to obtain pure **1** (mp. 216-218^{o}C).

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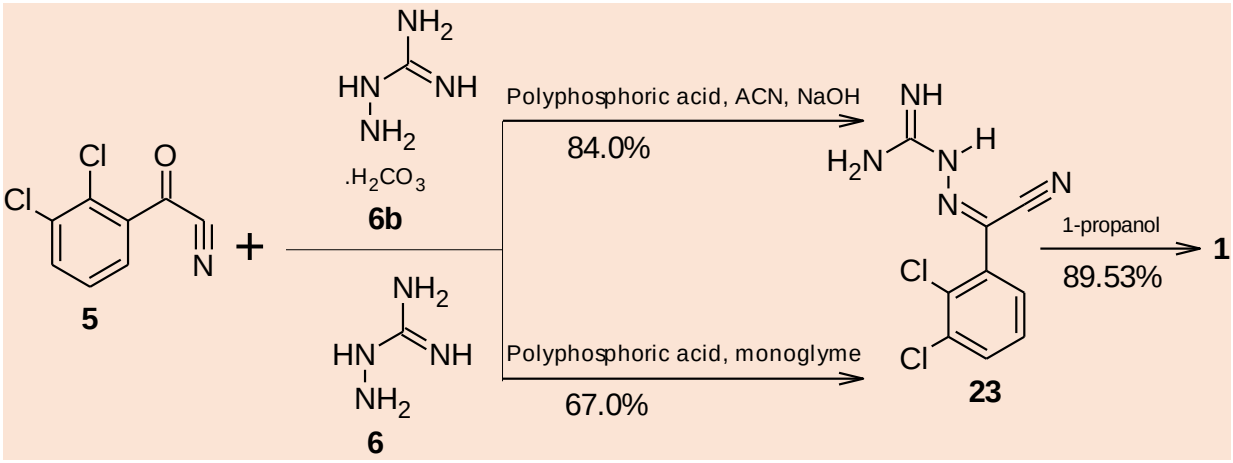
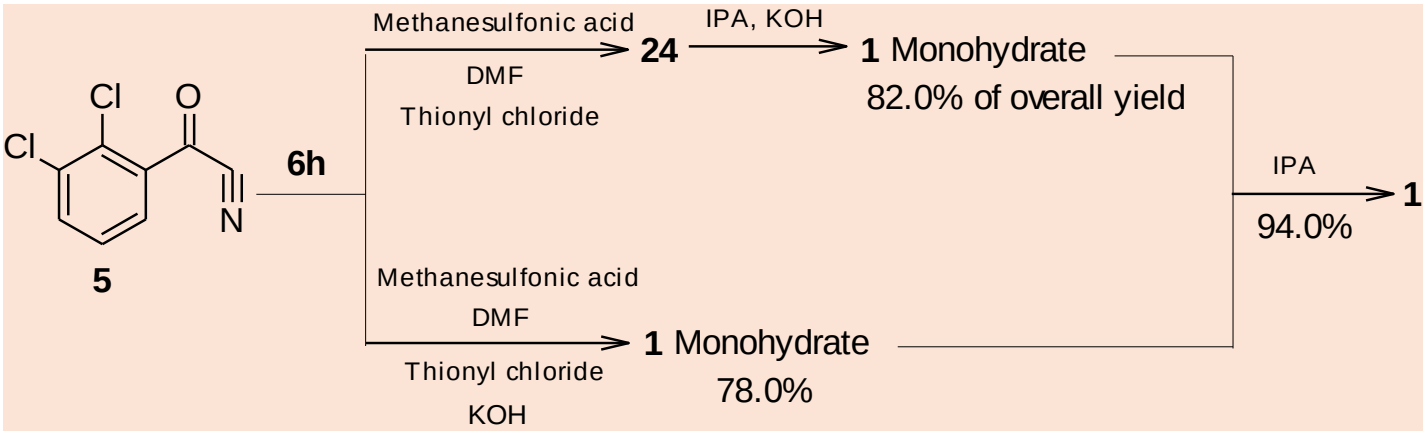


Scheme 7: Synthesis of **1** from **5** as per Nadaka et al. [15].

Guntoori and others [16] had reported an efficient novel process for the synthesis of **1** and its monohydrate form (**Scheme 8**). In an illustration, the condensation of **5** with **6h** was done in the presence of methanesulfonic acid (MSA) and dimethylformamide. To the mixture added thionyl chloride as a dehydrating agent followed by the addition of aqueous potassium hydroxide had resulted in the formation of **24**. A strong reflux of **24** in isopropyl alcohol and potassium hydroxide gave **1** monohydrate. In another example, a direct process was revealed by the condensation of **5** with **6h** in the presence of MSA and dimethylformamide. A sequential addition of thionyl chloride and potassium hydroxide had resulted in the formation of **1** monohydrate. The recrystallization of isolated monohydrate form of **1** in isopropyl alcohol gave **1** (in its anhydrous form) (216-217ºC).



Scheme 8: Synthesis of **1** and its monohydrate form from **5** as per Guntoori et al. [16].

Radhakrishnan and others [17] had illustrated an improved process for the synthesis of **1** with better yield and commercialization feasibility (**Scheme 9**). 2,3-Dichloronitrobenzene **25** in methanol was reduced in the presence of Raney nickel in an autoclave to get 2,3-dichloroaniline **26**. It was treated with sodium nitrite in acidic medium followed by the addition of sodium cyanide (NaCN) solution to isolate 2,3-dichlorobenzonitile **27**. It was refluxed in the presence of sodium hydroxide solution in methanol to get the hydrolyzed derivative **3**. It was treated with thionyl chloride to form **4** and then the addition of copper cyanide and potassium iodide in chlorobenzene had resulted in the formation of **5**. The condensation of **5** with **6b** was achieved by the use of sulphuric acid and *para*-toluene sulfonic acid (PTSA) in toluene followed by the addition of sodium methoxide (NaOMe) to get crude **1**. It was recrystallized from methanol to isolate pure **1**.

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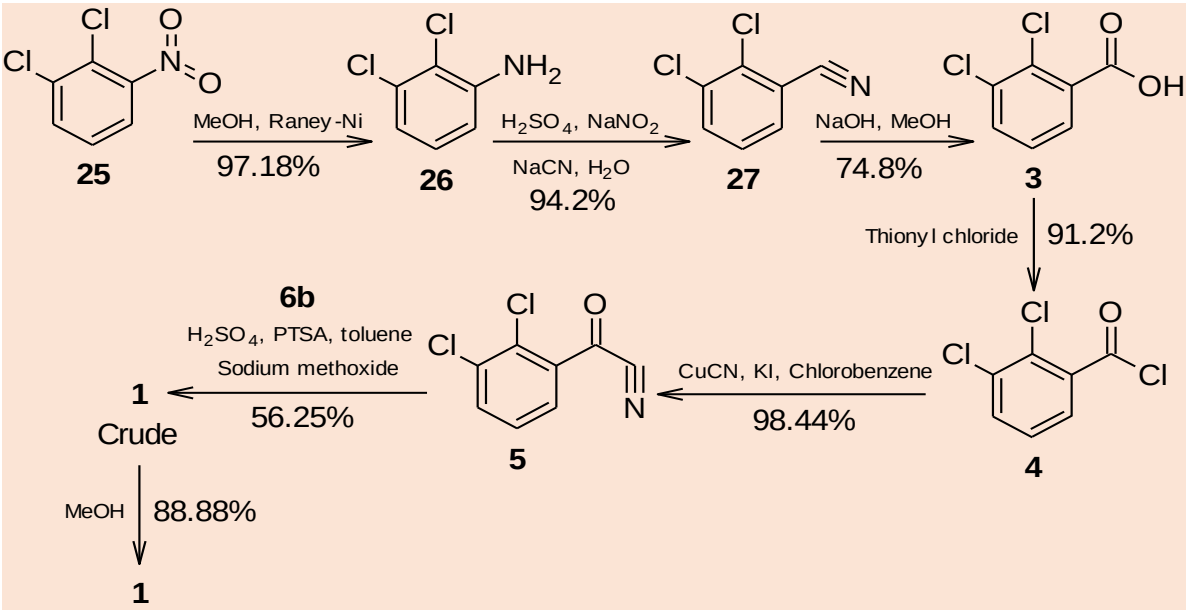
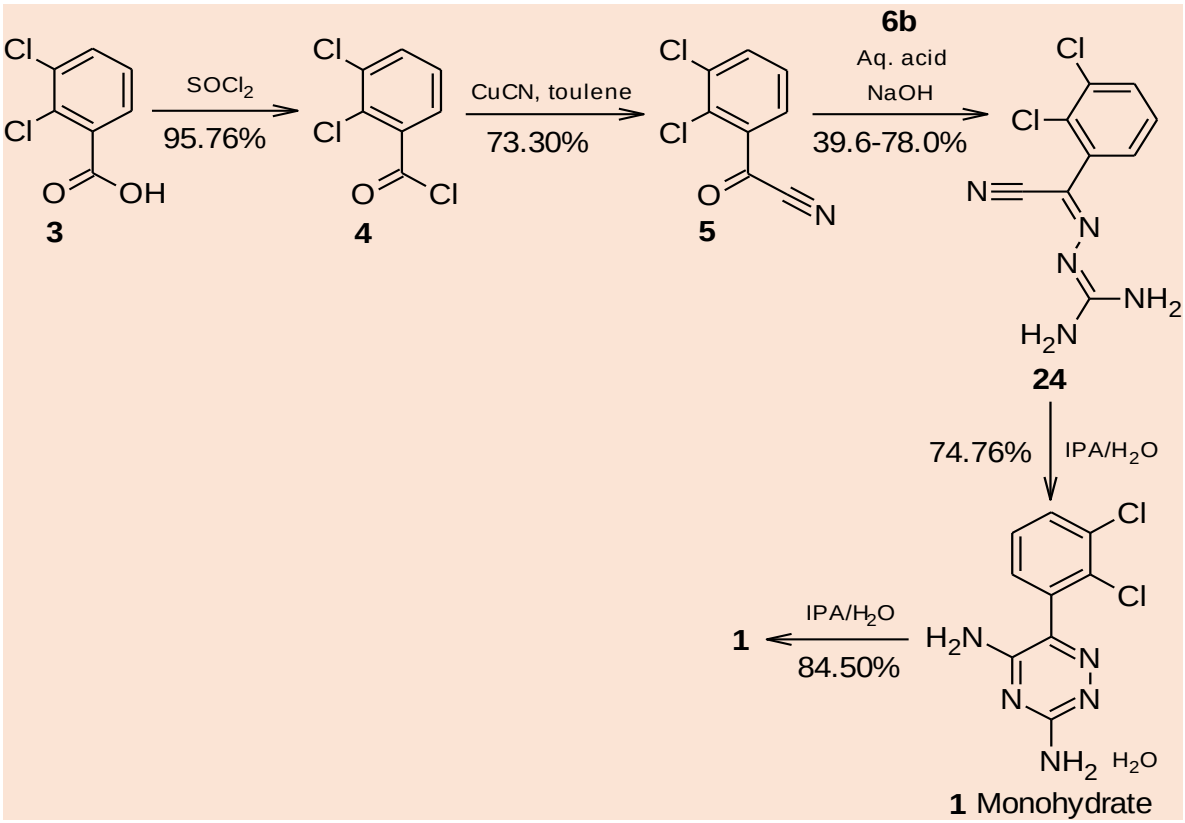


Scheme 9: Synthesis of **1** from **24** as per Radhakrishnan et al. [17].

Manjunatha and others [18] had illustrated an improved process for the synthesis of **1** and its monohydrate form (**Scheme 10**). The addition of thionyl chloride to **3** gave **4**. It was treated with copper cyanide (CuCN) in toluene at 160-165^{o}C to obtain the oily residue, and after hexane recrystallization **5** was isolated. The condensation of **5** with **6b** was performed by the use of various aqueous acids (sulphuric acid, hydrobromic acid, hydrochloric acid, nitric acid and phosphoric acid) in the presence or absence of organic solvent to get Schiff base **24** with varied yields. The mixture of **24** and aqueous isopropyl alcohol was refluxed to isolate **1** monohydrate. It was dissolved in aqueous isopropyl alcohol, clarity filtered, cooled, filtered and dried at 100^{o}C to isolate **1**.



Scheme 10: Synthesis of **1** from **3** as per Manjunatha et al. [18].

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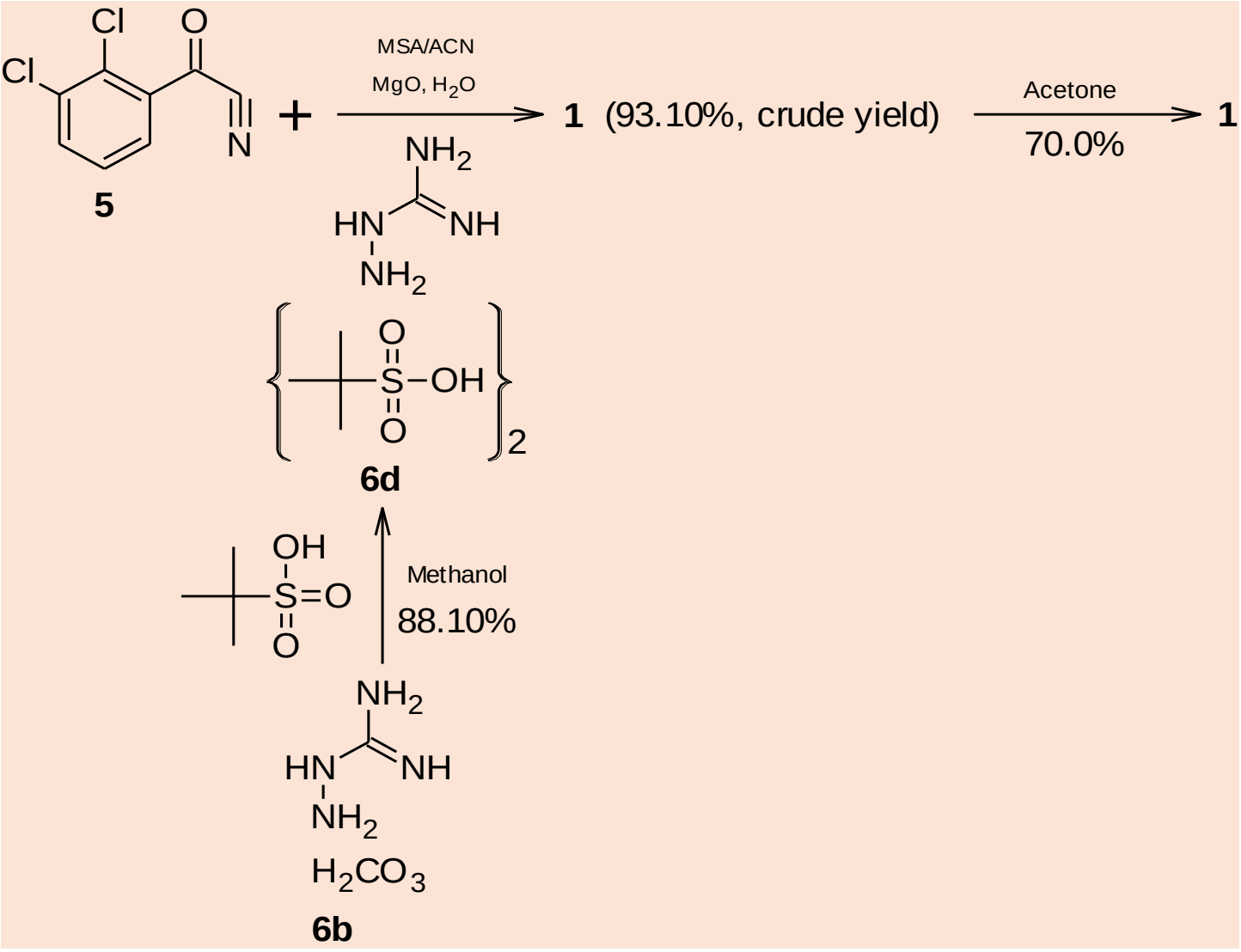
Numerous synthetic methods of **1** were disclosed in the prior arts with some disadvantages such as, formation of an aggressive reaction medium, long reaction time, multi-step pathway, low yield, release of large quantity of effluents, harmful radiation utility, use of expensive reagents, involvement of hazardous chemicals, complicated synthesis, un-economical synthetic pathway etc. To overcome these drawbacks, many researchers had started to design some novel and simple synthetic routes to isolate **1**. In this context, Jozsef and others [19] had reported a new process for the synthesis of **1** in high purity with minimum process steps (**Scheme 11**). MSA in methanol was used to convert **6b** to its dimesylate salt **6d**. The condensation of **5** with **6d** was executed under the presence of MSA in acetonitrile to form the un-isolated **23**. It was cyclized *in-situ* by the addition of magnesium oxide (MgO) in water to get crude **1** (mp. 212-216°C). Upon recrystallization from acetone gave pure **1** (mp. 215-219°C).



Scheme 11: Synthesis of **1** from **5** using MSA as per Jozsef et al. [19].

Pere et al. [20] had demonstrated a viable process to isolate **1** in good yield with shortened reaction time (**Scheme 12**). The condensation of **5** with **6b** was achieved in the presence of alone MSA or MSA and toluene to isolate **24**. It was cyclized in the under the impact of some solvents like, ethanol or ethanol (96%) or isopropyl alcohol or aqueous isopropyl alcohol etc. to isolate pure **1** (mp. 217°C) without the additional recrystallization steps [20].

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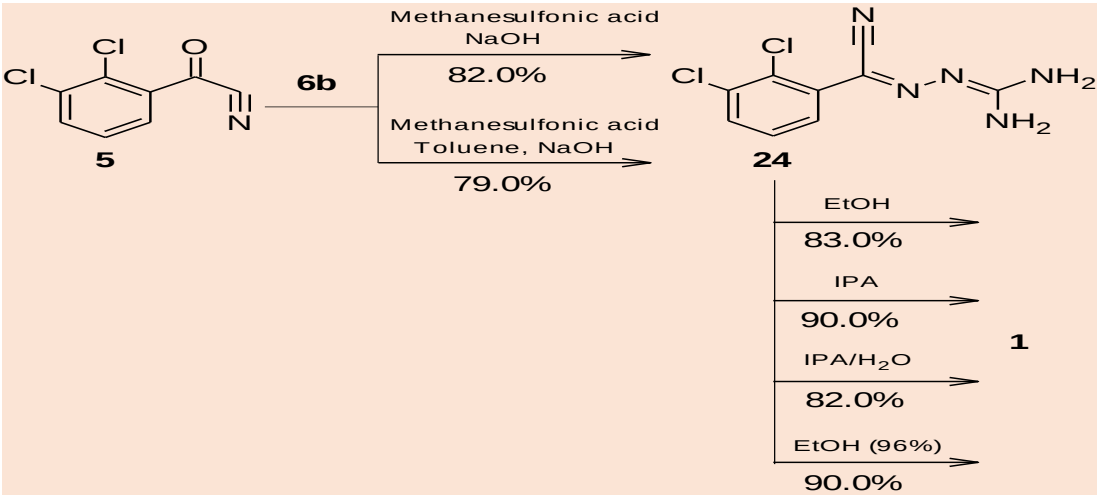
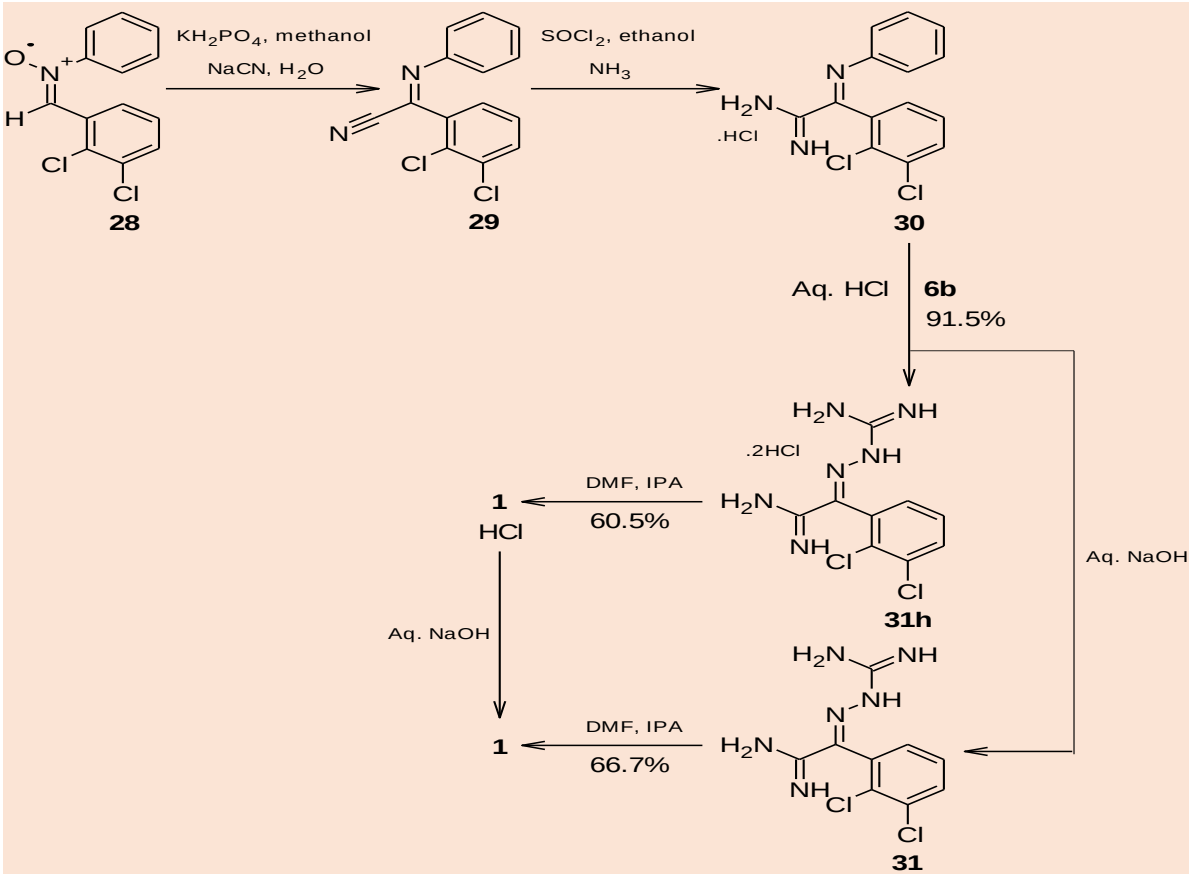


Scheme 12: Synthesis of **1** from **5** as per Pere et al. [20]

Geza and others [21] had demonstrated an impurity free and industrially viable process for the synthesis of **1** (**Scheme 13**). {[(*E*,*Z*)-(2,3-Dichlorophenyl)methylidene](phenyl)ammonio}oxidanyl **28** was treated with potassium dihydrogenphosphate and sodium cyanide in aqueous methanol to get (2*E*,*Z*)-(2,3-dichlorophenyl)(phenylimino)acetonitrile **29**. It was treated with thionyl chloride in aqueous ethanol (ethanol hydrochloric acid solution) and exposed to ethanol saturated with ammoniac to obtain the hydrochloride salt of (2*E*,*Z*)-2-(2,3-dichlorophenyl)-2-(phenylimino)ethanimidamide **30**. It was coupled with 6b in the presence of aqueous hydrocghloric acid to isolate the dihydrochloride salt of (2*E*,*Z*)-2-[2-amino-1-(2,3-dichlorophenyl)-2-iminoethylidene]hydrazinecarboximidamide **31h** or its free base **31**. The cyclization of **31h** or **31** in the presence of *N*,*N*-dimethylformamide gave **1** hydrochloride (mp. 233-235°C) or **1** (mp. 215.5-216.5°C).



Scheme 13: Synthesis of **1** from **28** as per Geza et al. [21].

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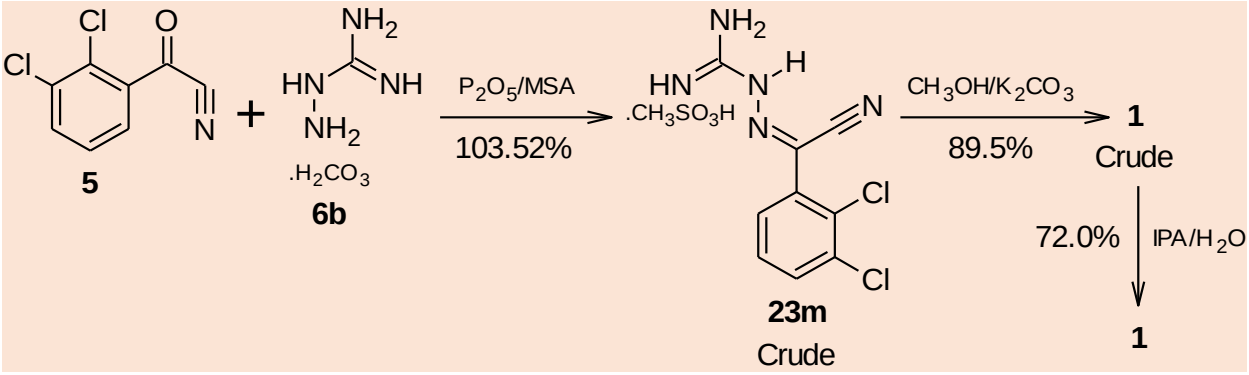
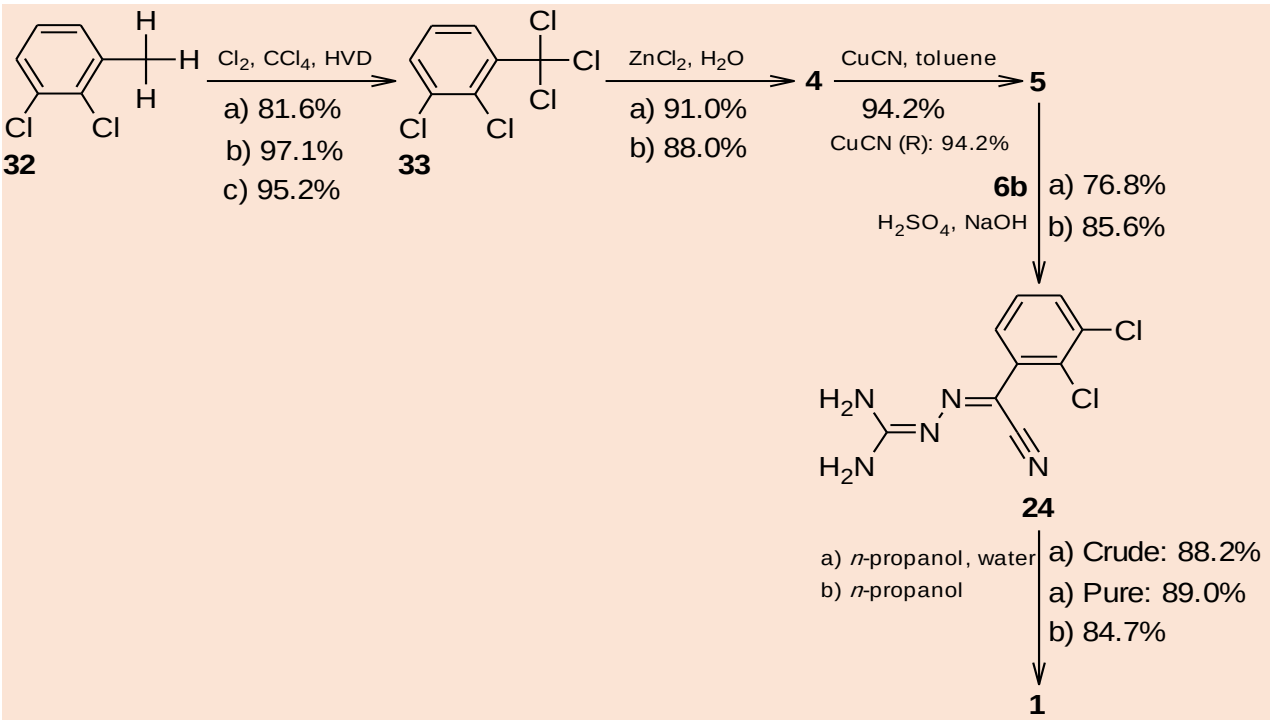
Arul and others [22] had reported an industrially feasible high yield process for the synthesis of **1** having a better flowability and satisfactory impurity profile (**Scheme 14**). The condensation of **5** with **6b** was achieved in the presence of phosphorous penta oxide (P_2O_5) and MSA to isolate the novel monomesylate salt **23m**. The cyclization of **23m** was induced by the use of methanol and potassium carbonate (K_2CO_3) to obtain crude **1**. It was recrystallized from isopropyl alcohol to isolate **1** (mp. 216-217°C).



Scheme 14: Synthesis of **1** from **5** as per Arul et al. [22].

Dirk and others [23] had demonstrated a high yield route for the synthesis of **1** from 2,3-dichloro toluene **32** (**Scheme 15**). The conversion of **32** to 2,3-dichlorobenzotrichloride **33** was achieved in the presence of chlorine gas (Cl_2) in carbon tetrachloride (CCl_4). The reduction of **33** to **4** was done by the use of zinc chloride ($ZnCl_2$). It was treated with cuprous cyanide in toluene to isolate **5**. Meanwhile, cuprous cyanide was recovered from the inorganics isolated (CuCl). The condensation of **5** with **6b** was performed in the presence of sulphuric acid and later treated with sodium hydroxide to isolate **24**. It was treated with aqueous *n*-propanol to isolate the crude **1** and the pure **1** was obtained upon recrystallization from aqueous *n*-propanol. Similarly, the cyclization in the presence of *n*-propanol was also reported to isolate pure **1**.



Scheme 15: Synthesis of **1** from **32** as per Dirk et al. [23].

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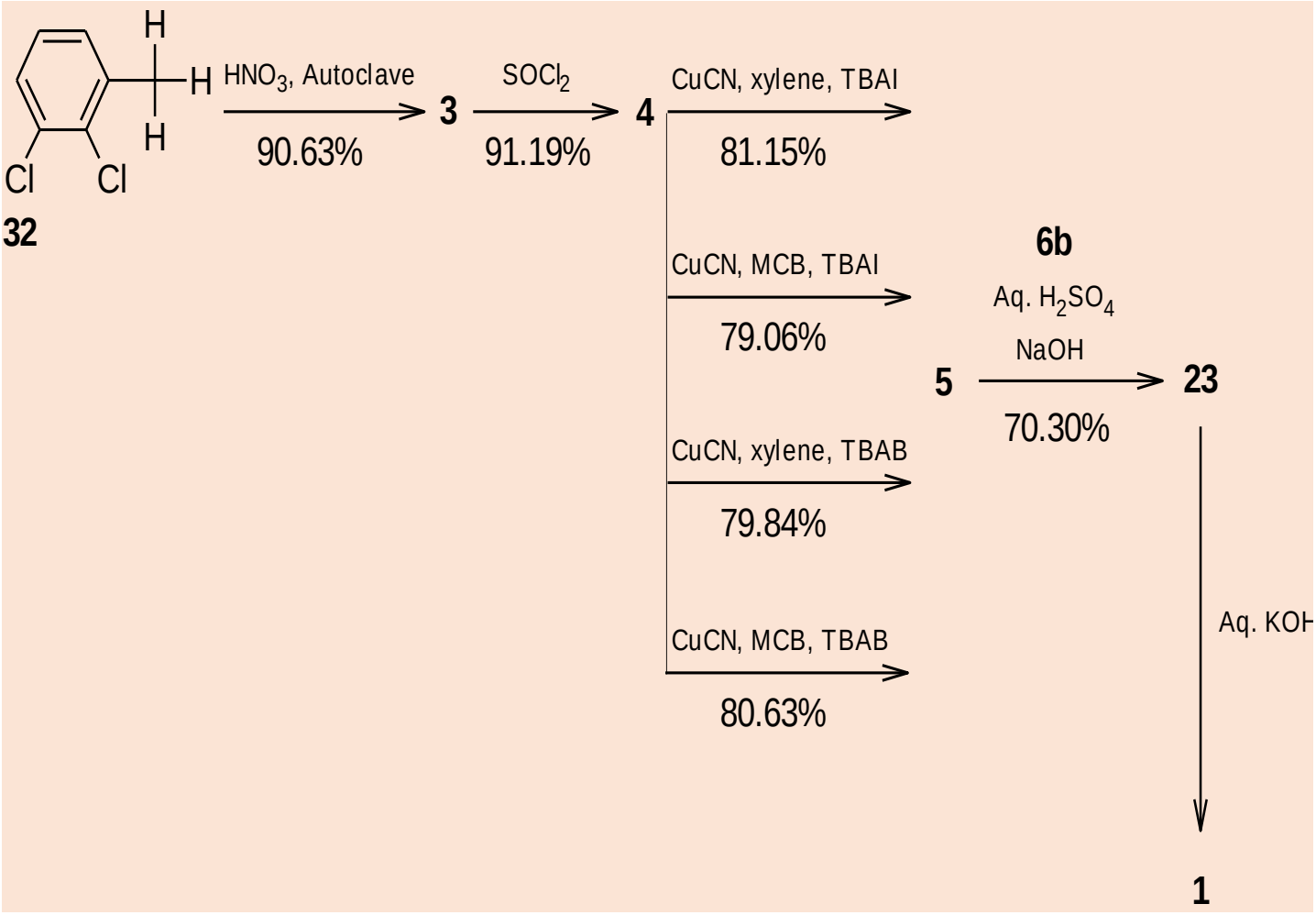
Patel and others [24] had reported the synthesis of intermediates of **1** in high yield (**Scheme 16**). Nitric acid impact on **32** at 140°C in an autoclave gave **3**. It was treated with thionyl chloride to obtain **4**. Cyano-dehalogenation of **4** in the presence of cuprous cyanide and phase transfer catalyst in xylene or mono-chloro benzene (MCB) gave **5**. The coupling of **5** with **6b** was achieved by the use of aqueous sulphuric acid, followed by the addition of sodium hydroxide solution gave **23**. It was refluxed with aqueous potassium hydroxide solution to isolate **1**.



Scheme 16: Synthesis of **1** from **32** as per Patel et al. [24].

Paul and others [25] had demonstrated an improved process for the synthesis of **1** (**Scheme 17**). The disclosure reports the conversion of **4** to **5** in the presence of copper (*I*) iodide and sodium cyanide (NaCN). The condensation of **5** and **6b** was achieved in the presence of MSA and sulphur trioxide to isolate the intermediate sulphate salt **24s**. It was subjected for cyclization by the use of sodium hydroxide solution to isolate **1** monohydrate, which upon recrystallization from aqueous isopropyl alcohol gave **1**. A similar approach was adopted to get **1** by avoiding the isolation of the intermediate salt **24s**. In another example, the condensation of **5** with **6b** was undertaken in the presence of tetrafluoroboric acid to obtain the intermediate tetrafluoroborate salt **24t**. It was cyclized in the presence of sodium hydroxide solution to obtain **1**. A similar pathway was adopted to isolate **1** by not isolating the intermediate salt **24t**. In another example, condensation of **5** with **6b** was achieved by the use of tetrafluoroboric acid and water. An azeotropic distillation of water was done to push the reaction for completion and finally alkali mediation gave **1**. The novel salts reported are highly soluble in most organic solvents, thus contributing to reaction rapidity.

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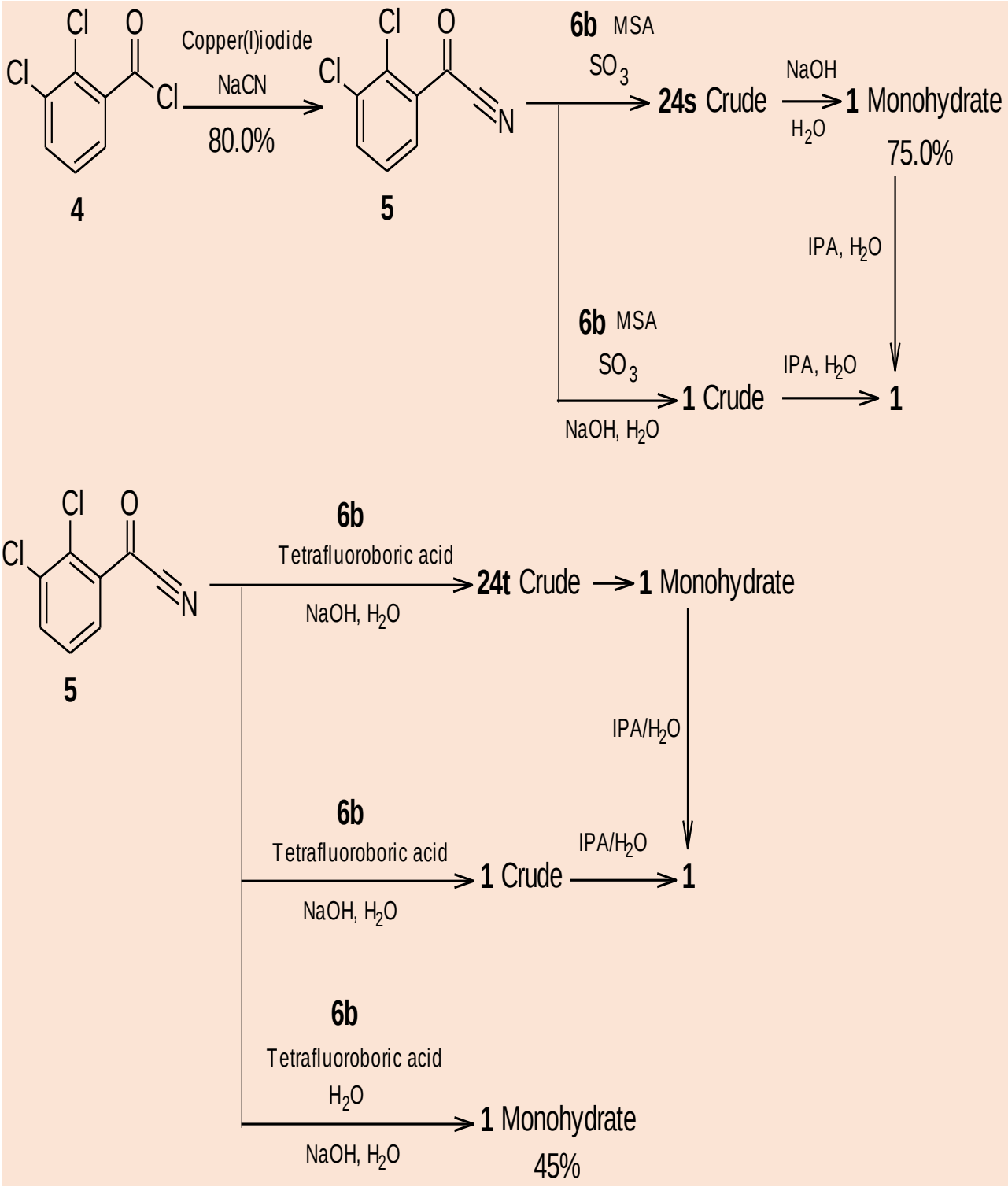

Scheme 17: Synthesis of **1** from **4** as per Paul et al. [25].

Jiang [26] had disclosed a novel one step method to synthesize **1** from **5** (**Scheme 18**). The condensation of **6b** with **5** was executed under acidic condition (sulphuric acid or phosphoric acid) to form an intermediate Schiff base **23**. It was directly heated in the presence an alkaline medium (sodium/potassium/lithium hydroxide or soium/potassium tertiary butoxide or sodium/potassium/lithium carbonate or tripotassium /trisoium phosphate) and silica gel or alumina through microwaves to induce the cyclization to get **1** (mp. 216-217^{o}C).

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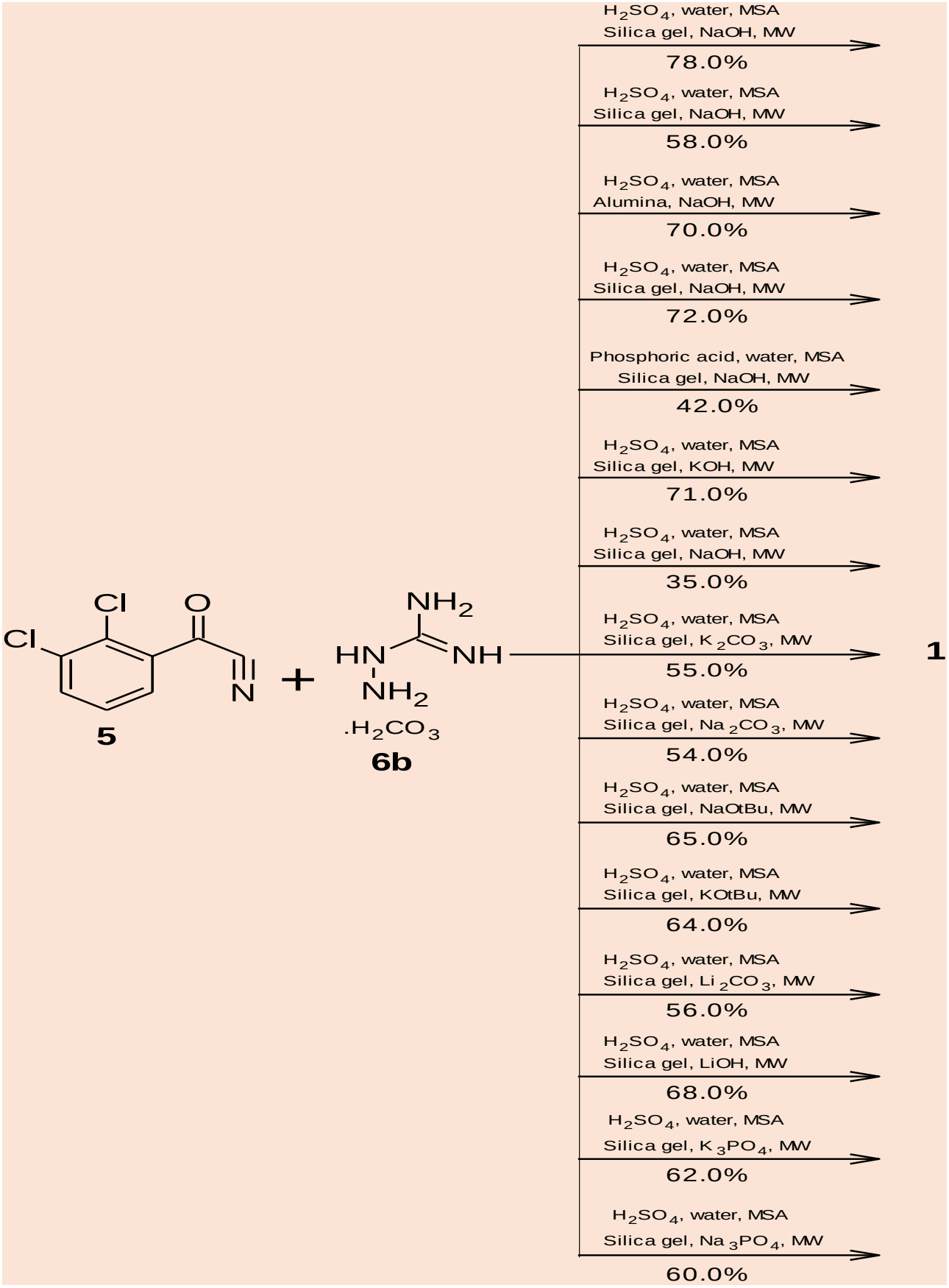

Scheme 18: Synthesis of **1** from **5** under acidic medium and microwaves impact as per Jiang [26].

To overcome the process related issues, Yang et al. [27] had demonstrated a simple one step *n*-propanol driven cyclization process to synthesize **1** from **23** (**Scheme 19**). This disclosure avoids the use of toxics and harmful chemicals with an improved yield (theoritical) of **1** [27].

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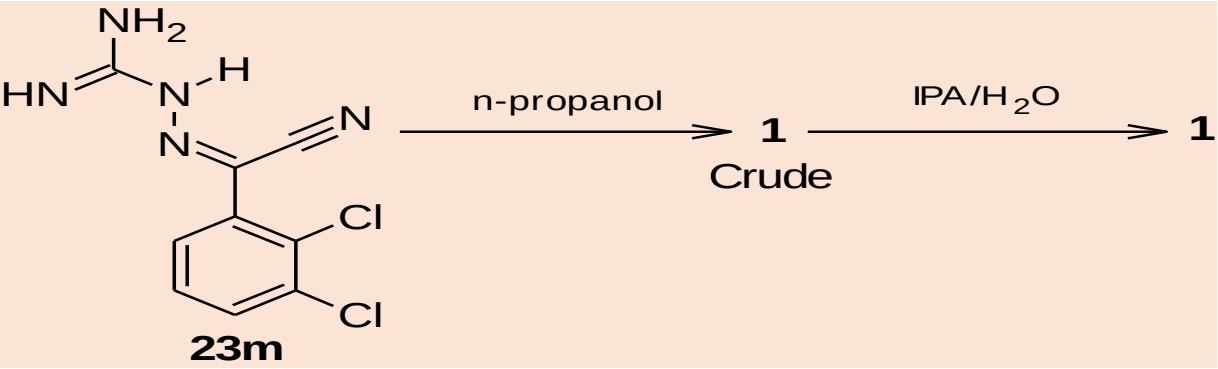
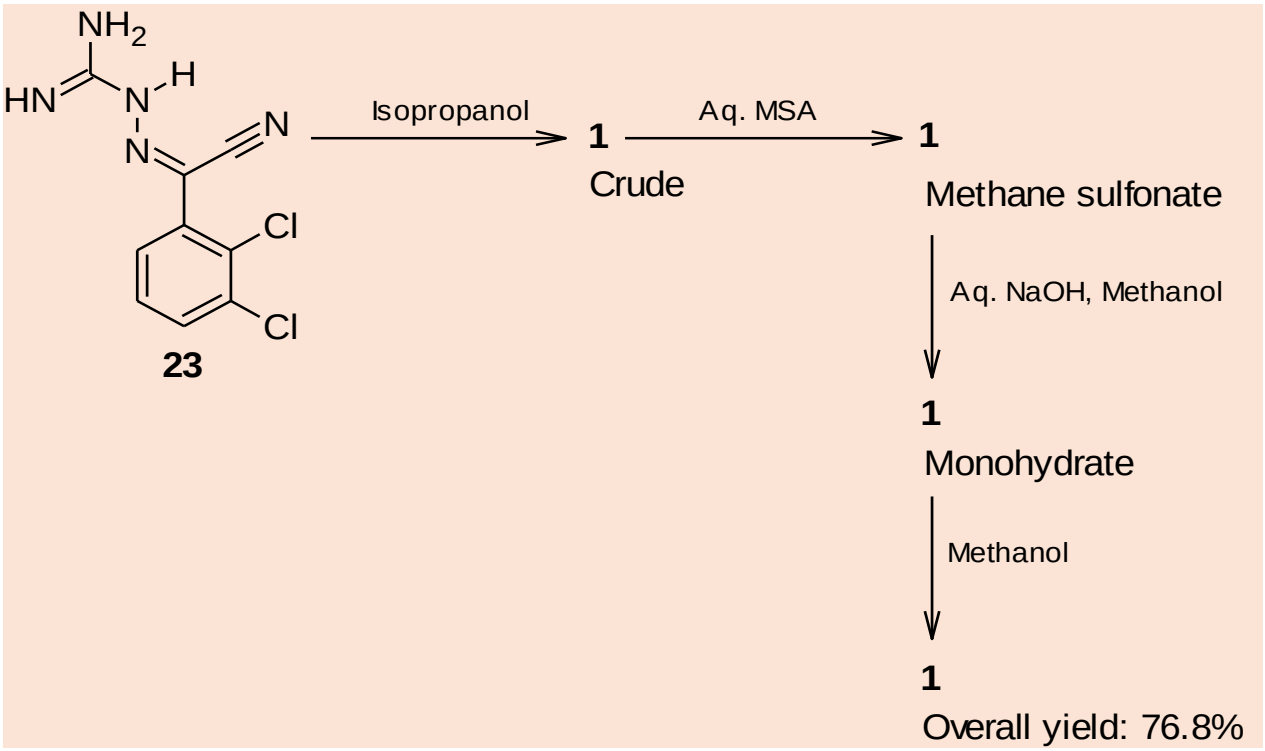


Scheme 19: Synthesis of **1** from **23** as per Yang et al. [27].

Carmen [28] had demonstrated the synthesis of **1** in high yield with least impurities starting from **23** (**Scheme 20**). The cyclization of **23** was achieved by the use of isopropanol to get crude **1**. It was treated with aqueous MSA to obtain methanesulfonate salt f **1**. It was neutralized by the addition of aqueous sodium hydroxide to isolate **1** monohydrate. It was refluxed in methanol to get **1** (mp. 216^{o}C). A similar salt formation of **1** (anhydrous) using MSA and desalting by sodium hydroxide was also illustrated to obtain **1** monohydrate.



Scheme 20: Synthesis of **1** from **23** as per Carmen [28].

Yiyue and others [29] had illustrated the synthesis of **1** (**Scheme 21**) by the controlled cyclization of Schiff base by avoiding the formation of ketone derivative (impurity). The condensation of **5** with **6b** was done by the use of sulphuric acid and water, followed by the addition of base (sodium hydroxide or potassium hydroxide or sodium carbonate) to isolate the Schiff base **23**. It was refluxed in alcohol (methanol or ethanol or isopropyl alcohol) to isolate crude **1**. Furthermore, the process of activated carbon decolorizing, recrystallization, cleaning and vacuum-drying gave **1**.

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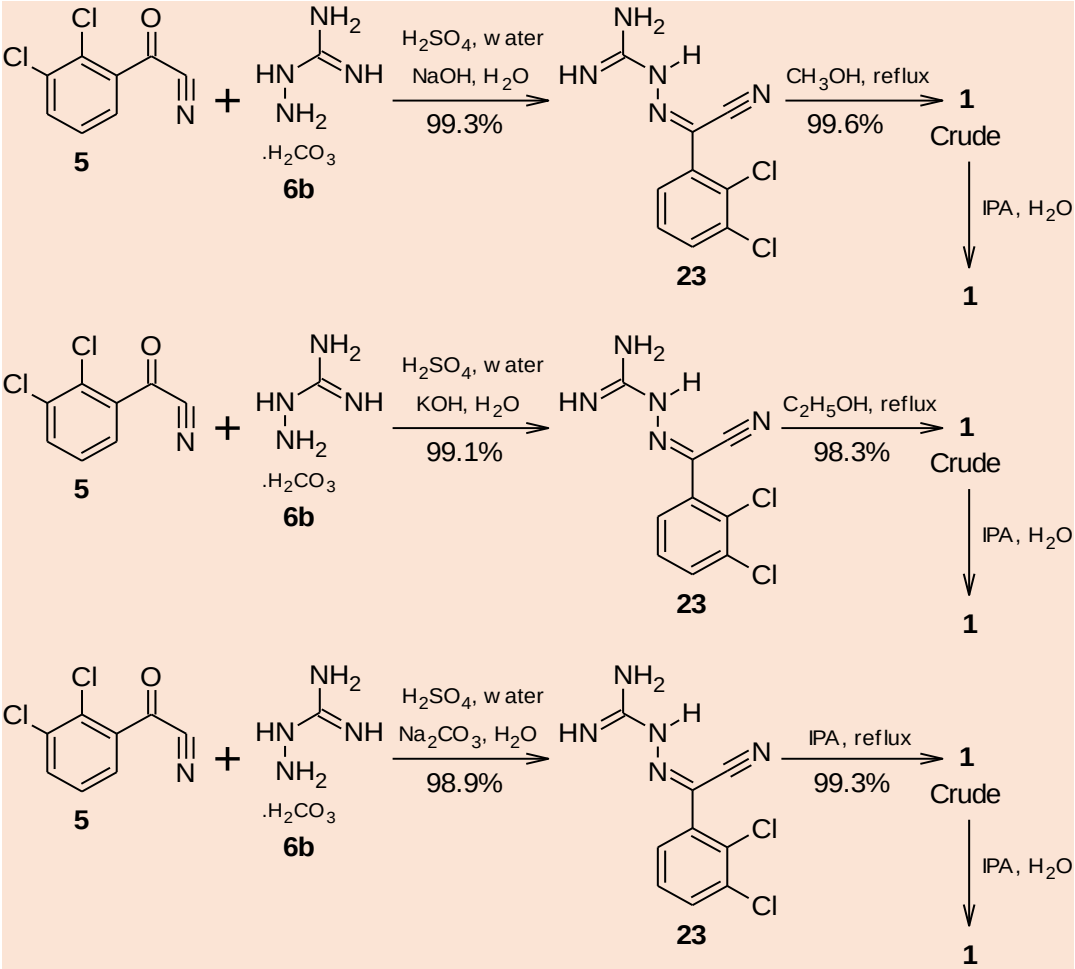
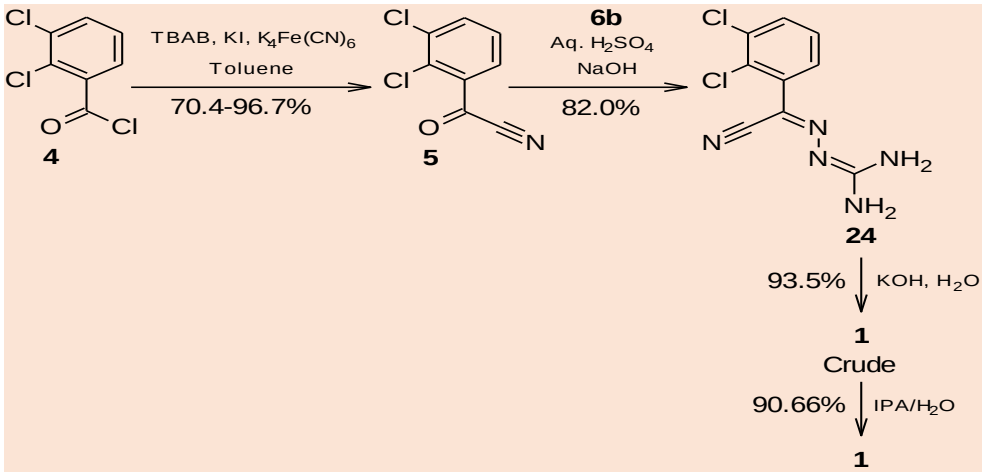


Scheme 21: Synthesis of **1** from **5** as per Yiyue et al. [29].

Luo and Li [30] had reported an improved and optimized process for the synthesis of **1** (**Scheme 22**). The disclosed process involves cyanation of **4** to get **5** using potassium hexacyanoferrate in the presence of phase transfer catalyst and potassium iodide in toluene. The condensation of **5** with **6b** was done using aqueous sulphuric acid. The cyclization of **24** was achieved by the influence of aqueous hydroxide to get **1**. A few experiments were executed to achieve catalyst screening and catalyst level ratio optimization in the cyanation step using phase-transfer catalysts like (alone/mixture) benzyltriethylammoinium chloride, *tetra*-butylammonium chloride, *tetra*-butyl ammonium bromide or 4-butyl ammonium hydrogen sulphate. Similarly, metal iodide used for the cyanation was potassium iodide or silver iodide.



Scheme 22: Synthesis of **1** from **4** as per Luo and Li [30].

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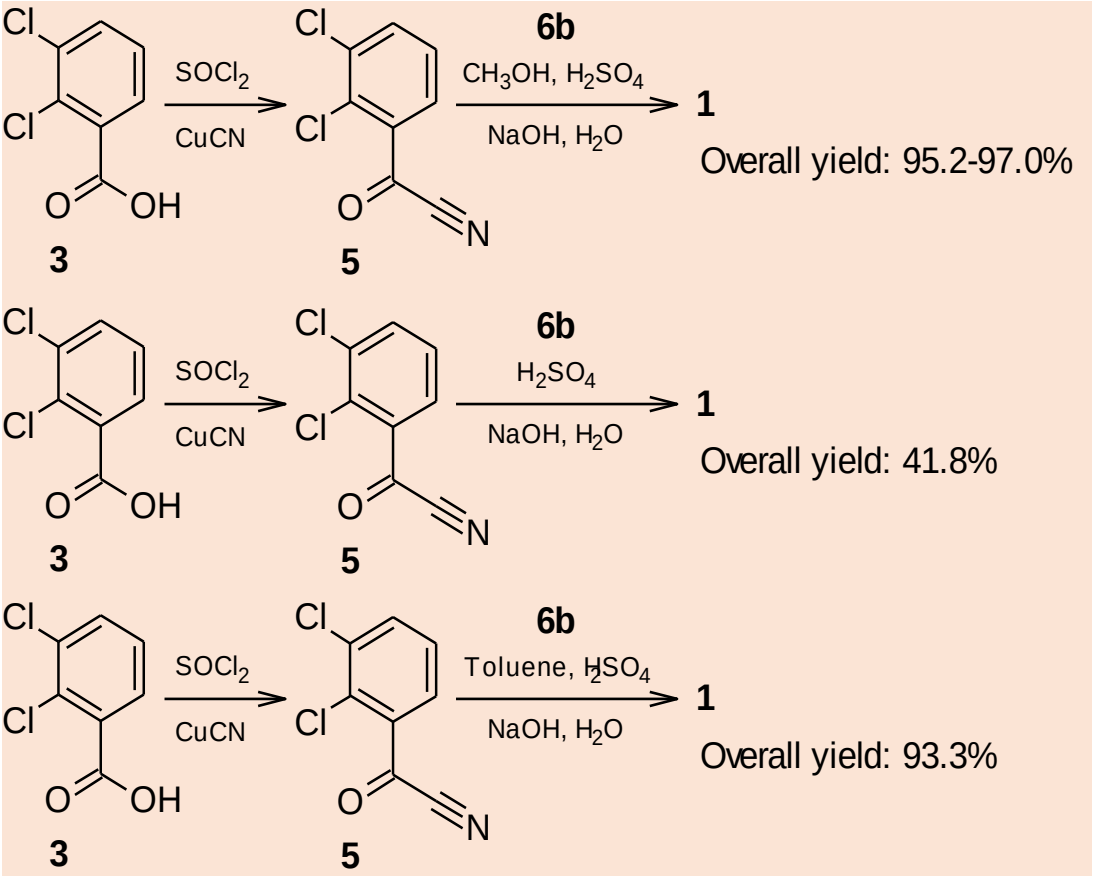
Cheng and others [31] had illustrated an improved synthesis technique of **1** (**Scheme 23**) with enhanced atom economy and better purity. The treatment of **3** with thionyl chloride followed by the addition of cuprous cyanide gave **5** (as crude liquid). The condensation of **5** with **6b** was performed in the presence of sulphuric acid and an azeotropic solvent (methanol or toluene). An *in-situ* cyclization by the addition of aqueous alkali gave **1**. A similar attempt in the absence of methanol or toluene for the condensation stage, gave poor yield of **1**. This work emphasizes the importance of water removal in the condensation stage using suitable solvents. The removal of water had increased the rate of reaction and the overall process yield to 93-97% from 40-42% [31].



Scheme 23: Synthesis of **1** from **3** as per Cheng et al. [31].

Zou and others [32] had disclosed an improved method for preparing **1**, which is distinct from the prior art practices. The process involves the synthesis of four major imine type ligands in different experiments by the use of benzoyl chloride **34**, 4-methylbenzoyl chloride **40**, 4-methoxybenzoyl chloride **44** to isolate ligand-1 **39**, ligand-2 **41**, ligand-3 **43** and ligand-4 **45** (**Scheme 24a**). Furthermore, 3-amino-1,2,4-triazine **46** was halogenated in the presence of *N*-bromo succinamide (NBS) in *N*,*N*-dimethylformamide to get 3-amino-6-bromo-1,2,4-triazine **47**. It was subjected to amination in the presence of $KMNO_4$ and liquid ammonia to obtain 3,5-diamino 6-bromo-1,2,4-triazine **48**. The coupling of **48** with 2,3-dichlorobenzene boric acid **49** was done by suzuki coupling pathway in *N*,*N*-dimethylformamide under the catalysis of palladium/ligand/alkali to isolate **1** through column chromatography (**Scheme 24b**). The disclosed method avoids the use of metal cyanide, and exhibited better reaction selectivity with high yield.

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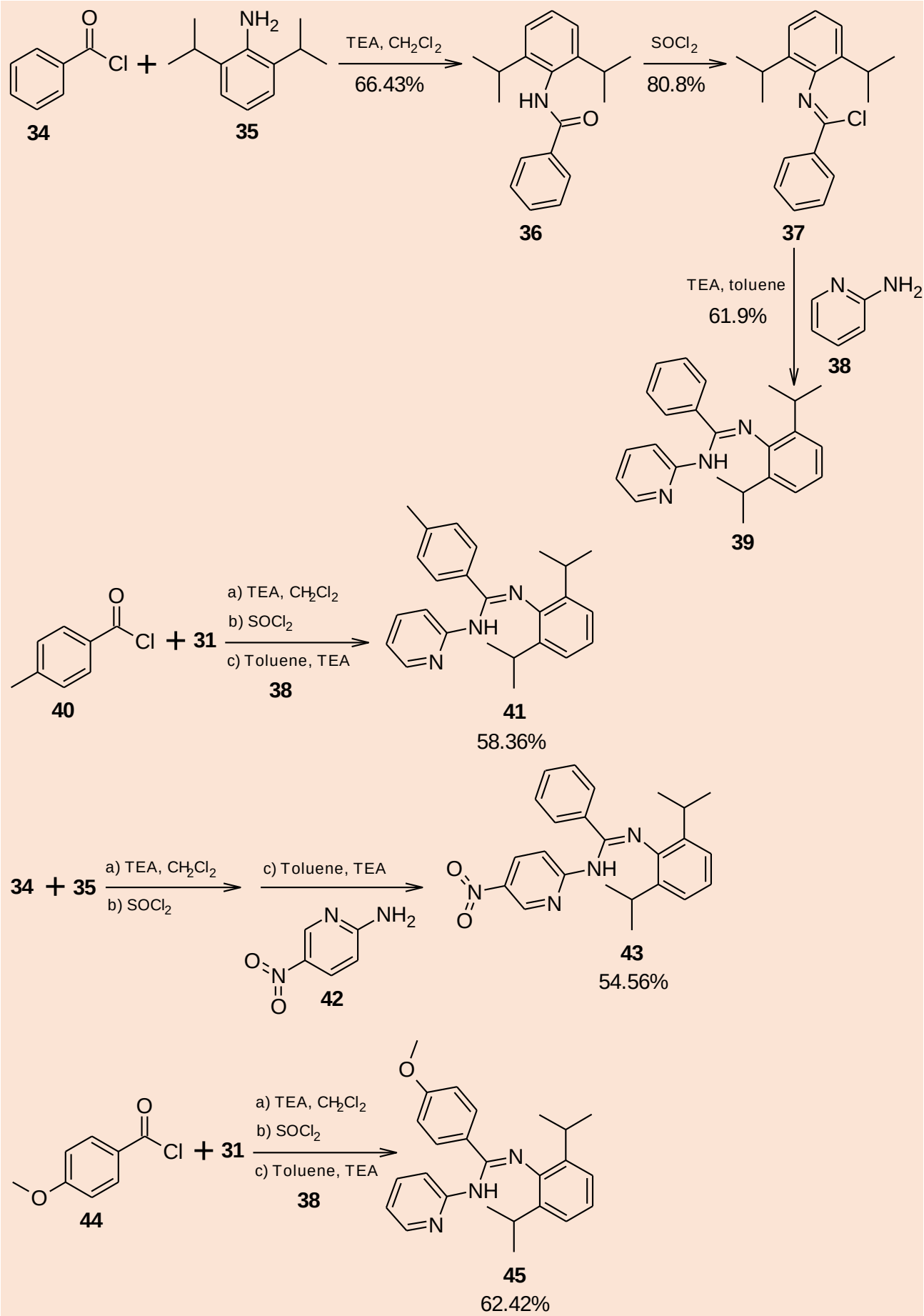

Scheme 24a: Synthesis of some ligands as per Zou et al. [32].

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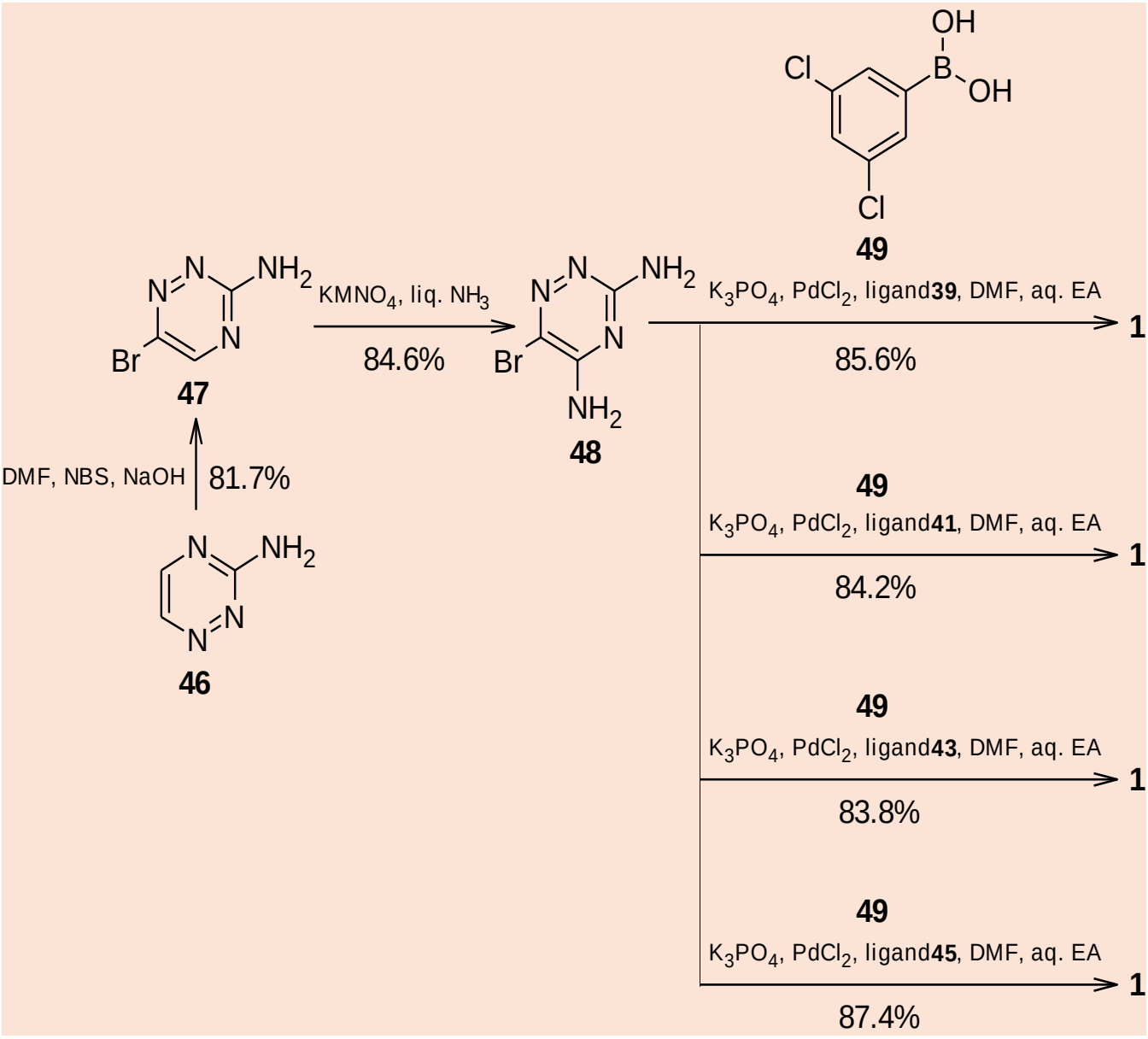

Scheme 24b: Synthesis of **1** via Suzuki coupling as per Zou et al. [32].

Li [33] had reported an invention pertaining to a crystal form of **1** hydrate (form-A). The form-A prepared had very high purity, good solubility and better chemical stability. These features will provide an essential advantage for the drug formulation.

In summary: Numerous global researchers associated to various organizations have worked on the sample preparation, process development, formulation and therapeutic studies of **1** (**Table 2**). Under the context, 24 reaction schemes were furnished for the clear understanding of prior art disclosures. A similar kind of comprehensive review effort was made by us on a few popular drugs like Atovaquone [34], Parvaquone [35], Buparvaquone [36], Zoledronic acid [37, 38] and Rasagiline [39]. Kumar R, et al., had reported a review article which outlines the pharmacological importance and general synthetic strategies of various triazines including **1**. This review contribution had covered the brief details on 1,2,3-triazines (5 drug molecules), 1,2,4-triazines (11 drug molecules) and 1,3,5-triazines (31 drug molecules) [40]. Our present review contribution is very specific to **1** and contextually particular to the synthesis pathway. For an industrial suitability, multi-step process pathways (more than 3 steps) are difficult to control with regard to achieve consistent yield and purity of the intermediates and **1**. Synthesis of **1** from **5** in minimum steps was found ideal for the commercialization and hence the same was adopted in most of the disclosed reaction schemes.

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Table 2: Patent assignee data (by an organization or an individual)

Ref. No.	Application filed by (assignee)
[6]	American home products corporation
[8]	Wellcome foundation limited
[9]	Burroughs wellcome corpotation
[10]	Wellcome foundation limited
[11]	Wellcome foundation limited
[12]	Glaxo wellcome incorporated
[13]	Sharad kumar vyas (Individual)
[14]	Glaxo wellcome incorporated
[15]	Chemagis limited
[16]	Brantford chemicals incorporated
[17]	RPG life sciences limited
[18]	Jubilant organosys limited
[19]	Richter gedeon vegyészeti gyár Rt. (Individual)
[20]	Vita cientifica, S. L.
[21]	Karl o helm AG, CF Pharma Gyogyszergyarto Kft
[22]	Unichem laboratories limited
[23]	Calaire chimie sas
[24]	Ratnamani bio-chemicals and pharmaceuticals private limited.
[25]	Lonza Ag (Individual)
[26]	Jiang yong (Individual)
[27]	Sanjin group hunan sanjin pharmaceutical company limited
[28]	Medichem, S.A.
[29]	Yancheng kaili pharmaceutical company limited
[30]	Chengdu yilukang medical technology and service company limited
[31]	Zhejiang qicai eco technology company limited
[32]	Sanjin group hunan sanjin pharmaceutical company limited
[33]	Shanghai okoda biomedical technology company limited

Conclusion: This review work indicates the sequential flourish of synthetic pathway of **1** adopted in prior patents. Moreover, every reported work highlights the prior process drawbacks and emphasizes to provide an improved process to facilitate large scale manufacturing of **1**. In this work, we have considered all the disclosed patents on the synthesis of **1** and specifically excluded the patents belonging to the same family. Under the context, we could able to tabulate 24 reaction schemes as per the disclosures in prior arts regarding the synthesis of **1**. Among them, 18 disclosures had the presence of **5** as the starting material or as an intermediate to obtain **1**. Thus, the role of **5** in the synthesis of **1** is very significant towards the yield, purity and commercial viability of the drug. This comprehensive review coverage can help the global researchers to design their novel/innovative scalable synthetic strategy to isolate **1** under the green chemistry ideology in near future.

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Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission have completely been observed by authors.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.