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A novel and sustainable method for the synthesis of 2-chloro-3-[*trans*-4-(4-chlorophenyl) cyclohexyl]-1,4-naphthoquinone, accomplished by systematic process development studies - *trans*-chloro naphthoquinone synthesis

Sanjay Sukumar Saralaya*, Shashiprabha†,
Shridhara Kanakamajalu‡, Kuppuswamy Nagarajan§, & Koottungalmadhom Ramaswamy Ranganathan**

Abstract

Present work reports a novel and commercially viable method for the synthesis of 2-chloro-3-[*trans*-4-(4-chlorophenyl)cyclohexyl]-1,4-naphthoquinone1, a renowned intermediate of Atovaquone (an antimalarial drug). The majority of the prior arts disclose the synthesis of this intermediate from the expensive starting material 2-chloro-1,4-naphthoquinone2, in relatively low yield. In

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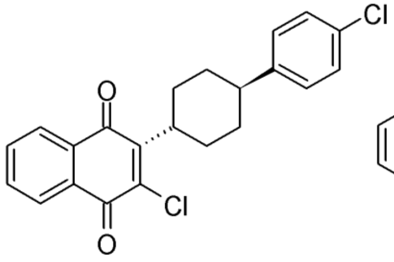
* Department of Chemistry, Sri Dharmasthala Manjunatheshwara Institute of Technology, SDM IT (Affiliated to Visvesvaraya Technological University, Belagavi), Ujire, Karnataka, India; sanjayss@sdmit.in
† PG Department of Chemistry, Sri Dharmasthala Manjunatheshwara College (Autonomous), Ujire, Karnataka, India; shashi-sudha@sdmcujire.in
‡ Technical Coordinator, ArkGen Pharma Private Limited, Peenya Industrial Area, Bangalore, Karnataka, India; shridharabhat@yahoo.co.in
§ Independent Researcher & Consultant, Bangalore, Karantaka, India; dknb69@yahoo.com
** Independent Researcher & Consultant, Bangalore, Karantaka, India; dr.krrangan@gmail.com

this regard, it was considered worthwhile to synthesize 1 by a novel route using cheaper starting material 2,3-dichloro-1,4-naphtoquinone 5, in high yield and purity. In the present study, emphasis was given for selecting the reagents and solvents, optimizing the reaction conditions, recovery and reuse of solvents and silver salt. This optimized novel process is cost-effective and would generate less effluent.

Keywords: 2-Chloro-3-[*trans*-4-(4-chlorophenyl) cyclohexyl]-1, 4-naphthoquinone, 2,3-Dichloro-1,4-naphthoquinone, Synthesis, Characterization, Process development

1. Introduction

2-Chloro-3-[*trans*-4-(4-chlorophenyl)cyclohexyl]-1,4-naphthoquinone 1, is an important intermediate for the synthesis of Atovaquone (a popular antimalarial drug). The intermediate 1 was predominantly prepared by the decarboxylative coupling of 2-chloro-1,4-naphthoquinone 2 with *trans*-4-(4-chlorophenyl) cyclohexane carboxylic acid 6. Alkylations of quinones were reported by the decarboxylation of carboxylic acids with silver ions and peroxodisulphate in early 1970s [1-4]. Numerous routes were disclosed in prior arts for the synthesis of 1, in which 2 was widely used as the key starting material. Synthesis of 1 using 2 was reported by the free radical decarboxylative coupling mechanism in low yields (6.5%) [5-8]. A method with improved yield (14%) was reported for the coupling of 2 with 4-(4-chlorophenyl) cyclohexane carboxylic acid in using silver nitrate in 10 mol% in the presence of ammonium persulfate, dichloromethane, acetonitrile, and water. Use of phase transfer catalyst (Adogen 464) for the radical coupling of 2 with trans-1,4-substituted cyclohexyl oxalate acid resulted in a significantly high yield (43%,) with 1.3 to 1.0 ratio of *trans/cis* -isomers [9]. Decarboxyative coupling of 3 and 6 in significantly lower yields (7-8%) was reported using silver nitrate in 30-50 mol% along with ammonium persulfate, acetonitrile, and water [10]. A decarboxylative coupling was reported using 4 and 6 with relatively better yield (20%) and subjected to chlorination and dehydrohalogenation to isolate 1 [11].



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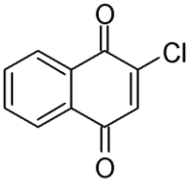

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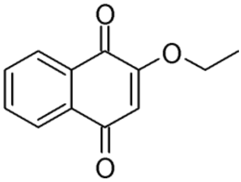

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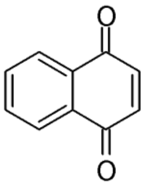

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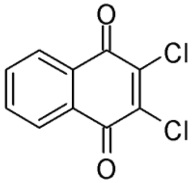

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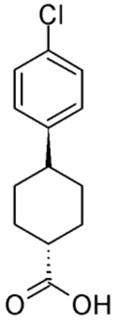

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Numerous acids, diacids, and N-Boc-protected amino acids were coupled with substituted quinones in 10-76% yields through a free radical decarboxylative coupling reaction using silver nitrate and ammonium persulfate [12]. The use of silver nitrate in 20 mol% and ammonium persulfate was reported for the synthesis of γ-carbonyl quinones by the interaction of cyclopropanols with quinones using dichloromethane and water in good yields (30-80%) [13]. A few 1,4-dihydropyridines and sodium persulfate were used for the free radical alkylation of quinones in the presence of TFA, acetonitrile, and water. By this method, a few 1,4-naphthoquinones like Co-enzyme Q0, Vitamin K3 and Lawsone were successfully alkylated in good yields (55-65%). This method avoids using an expensive reagent, silver nitrate [14]. Alkylation of N-heteroarenes and quinones with alkylcarboxylic acids in better yields (25-85%), was reported by the use of ammonium persulfate, dimethylsulphoxide and water under mild conditions [15]. Synthesis of mono-arylated benzoquinones was reported by the homolytic cleavage of aryl boronic acids or phenyltrifluoroborate in good yields (90-95%), using silver nitrate in 20 mol% with potassium persulfate under mild conditions at ambient temperature [16]. Direct coupling of N,N′-dialkyluracils and quinones was reported with moderate to good yields (32-86%) using palladium acetate and silver nitrate in ethyl acetate, as the solvent [17]. A review work summarizes the direct functionalization of quinones by free radical coupling, in presence/absence of metal catalysts [18]. A few reactions of menadione with α-keto-aromatic acids in the presence of silver nitrate in 20 mol%, ammonium persulfate, acetonitrile and water were reported for the synthesis of 3-benzoylmenadione derivatives, in moderate yields (41-45%) [19]. Some of the napthoquinones were directly alkylated with variety of aminoacids through the silver mediated decarboxylative coupling in moderate yields (16-61%) [20]. Cyanoalkylation of heteroarenes and quinones were reported using silver nitrate in 20 mol%, sodium persulfate, dichloromethane/dichloroethane, and water in good yields (40-75%) [21]. Free radical acylation and carbamoylation of quinones was reported in moderate yields (49-53%), while the reaction was carried out using ammonium persulfate, dimethylsulphoxide, and water in the absence of metal catalysts [22]. Selectfluor-mediated mono alkylation of 1,4-benzoquinones was reported with the use of silver nitrate in 20 mo% dichloroethane and water, reaction was performed by avoiding the use of strong oxidizing agent ammonium persulfate at ambient temperature in moderate yields (45-54%) [23]. Same research work was reported with the use of Hünig's base, which led to lower yields (20-38%) [24]. Selectfluor-mediated decarboxylative coupling of 4 with difluroacetic acids was reported in good yields (56-80%), wherein the conventional use of silver nitrate and ammonium persulfate combination had failed to generate the target products [25]. The direct radical alkylation of 1,4-quinones had gathered a lot of synthetic interest over the last decade. Direct alkylation involves the addition of carbon centered radicals, generated either by decarboxylation, hydrogen abstraction, or cleavage of carbon-halogen bond [26].

The prior arts disclosed for the synthesis of 1 are not commercially viable due to various collective reasons such as the use of expensive raw materials/reagents/solvents, lack of recovery/reuse of chemicals, low yield, and the generation of significantly high quantity of effluents. In this paper, we report the use of readily available and cheaper starting material 5 for the synthesis of 1 in high yield and purity [27]. The reagent/solvents recovery [28-30] and their reuse strategies employed had enormously reduced the cost and effluent load. This process is scalable and industrially adaptable.

2. Materials & Methods

Present work involves the use of key starting material 5, which was procured from DL Intrachem. Another key starting material 6 was procured from Sigma-Aldrich. Reagents like silver nitrate, red mercuric oxide, oxone, and nitric acid were procured from Rankem, ammonium persulfate, sodium molybdate, hydrogen peroxide, and sodium bicarbonate from Sd-fine chem, and solvents were procured locally in commercial grades. These key starting materials, reagents and solvents were used in the experiments without further purification. Experiments were conducted and optimized in a laboratory scale (upto 100.00g level), it could well be extrapolated to kilogram level for commercialization.
Melting points (m.p) of 1 was recorded by the open capillary method and are uncorrected. IR spectrum was recorded on FT-IR (ATR, ReactIR 702L, Mettler-Toledo). ^{1}HNMR spectra was recorded (in DMSo-d_6/$CDCl_3$) on a 300/400 MHz NMR spectrometer using TMS as internal standard. Coupling constants *J* are in Hz and multiplicities are represented as a singlet (s), doublet (d), triplet (t), broad singlet (bs), and multiplet (m). Progress of the reaction and product purity, was checked by TLC using precoated silica TLC plates (Merck $^{60}F_{254}$).

2.1. Procedure for the synthesis of 1 as per prior art disclosure

5 (5.00 g, 0.022 mol), 6 (6.06 g, 0.025 mol), silver nitrate (2.47 g, 0.0145 mol) and 60 mL acetonitrile were taken in a reactor and the mixture was heated to reflux under stirring. Solution of ammonium persulphate (14.23 g, 0.0623 mol) in 77.0 mL of DM water was added through a dropping funnel over a period of 1-2 hours. Reflux was continued for 4 hours, cooled and filtered under suction. The solid was extracted with 300 mL of dichloromethane. The organic layer was dried over anhydrous sodium sulphate and concentrated on isolating crude 1. This was further crystallized from 60 mL of acetonitrile to isolate 1. Yield: 17.64% (1.50 g).

2.2. Optimized/improved procedure for the synthesis of 1

5 (100.00 g, 0.44 mol), 6 (105.14 g, 0.44 mol), silver nitrate (74.74 g, 0.44 mol), ammonium persulfate (301.23 g, 1.32 mol) and 1.0 L of acetonitrile were taken in the reactor. The reaction mixture was stirred at RT for 10-15 minutes. Added 1.3 L of DM water to the reaction mass at RT, heated to 70-75^{0}C and maintained at the same temperature for 4-5 hours. Reaction progress was monitored by TLC. After the reaction completion, cooled the reaction mixture to RT and filtered under suction to isolate the solid. The filtrate was stored for the solvent recovery process. To the solid obtained, added 4.0 L of dichloromethane and stirred for 15 minutes at RT, filtered under suction. The residue (silver chloride) isolated was dried under reduced pressure at 40-45^{0}C for 2-3 hours and stored (61.80 g) for the silver nitrate recovery process. Filtrate was washed with 3.0 L of 10% sodium bicarbonate solution and subsequently washed with 500 mL DM water. Filtrate was concentrated to isolate the residue and to recover 2.4 L of dichloromethane at vapour temperature 37-41^{0}C and stored for reuse. Added 1.0 L of acetonitrile to the residue and heated the mixture to 55-60^{0}C for 30 minutes. The mixture was gradually cooled to RT, filtered and dried at 55-60^{0}C under reduced pressure for 2-4 hours to isolate 1. Filtrate was stored for the solvent recovery process. Yield: 42% (71.27 g). m.f. $C_{22}H_{18}Cl_2O_2$, m.p. 186-188^{0}C. IR (KBr, γ max, cm^{-1}): 1667.84 (C=O), 613.73 and 708.53 for (C-Cl) group (**Fig. S1**, Supporting Information). ^{1}HNMR (400 MHz, $CDCl_3$): 8.09-8.15 (2H, m), 7.71-7.78 (2H, m), 7.28-7.32 (2H, d, *J*=8.0 Hz), 7.18-7.20 (2H, d, *J*=8.0 Hz), 3.31-3.39 (1H, m), 2.65-2.72 (1H, m), 2.29-2.39 (2H, m), 2.0-2.04 (2H, m), 1.79-1.83 (2H, m), 1.52-1.62 (2H, m) (**Fig. S2** and **S3**, Supporting Information).

2.3. Procedure for the recovery of silver nitrate

Inorganic salt, silver chloride (60.00 g, 0.42 mol), and 900 mL of ammonia solution were taken in the reactor. Zinc dust (18.12 g, 0.28 mol) was added carefully under stirring in 3 lots (1 lot: approx 6.0 g) preferentially to control the reaction exotherm. The reaction mixture was heated to 40-45^{0}C for 2-3 hours. The reaction mixture was gradually cooled to RT and kept under stirring for 18-20 hours. Filtered the reaction mixture under vacuum and the solid obtained was washed with 200 mL of 2% sulfuric acid solution to remove the traces of unreacted silver chloride. The Solid was further washed with DM water, till the filtrate becomes neutral. The recovered silver was dried at 80-85^{0}C under reduced pressure for 3-4 hours. Yield: 95% (42.89 g).

Isolated silver (42.00 g, 0.39 mol) and 126 mL of DM water were taken in the flask. To the mixture added 46.2 mL of nitric acid (65-70%) slowly through the addition funnel. After the completion of the addition, the reaction mixture was heated to 50-55^{0}C for 4-5 hours. Water was completely distilled off under reduced pressure to isolate the solid. Added 420 mL of methanol to the solid and stirred for 30 minutes at 25-30^{0}C and filtered to isolate silver nitrate as shiny crystals. It was dried under pressure at 80-85^{0}C for 4-5 hours. Yield: 92.5% (61.19 g) and purity: 98.5% (by assay).

2.4. Procedure for the recovery of acetonitrile

Stored filtrates (approx 3.2 L), obtained after the isolation of 1 were subjected to distillation. Fraction collected between 70-78^{0}C was stored and analyzed. Recovered aqueous acetonitrile had 16.2% of moisture (by KF titration), and was reused for the reaction by making it up with the required quantity of fresh acetonitrile and DM water. The recovered aqueous solvent (1.98 L) had composed of 321 mL of water and 1.66 L of acetonitrile (83% recovery) content.

2.5. Procedure for the synthesis of 1 using recovered reagent/solvents

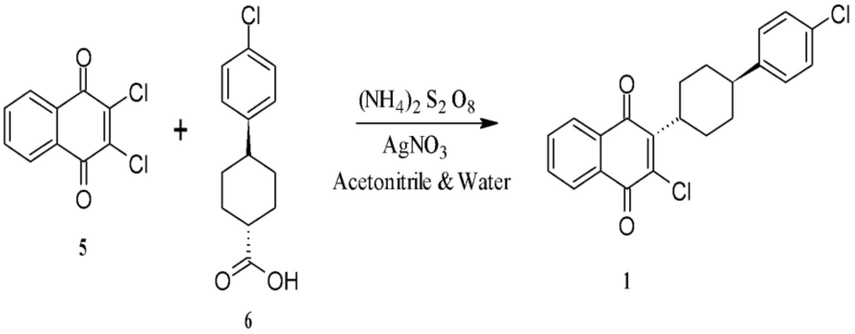
5 (100.00 g, 0.44 mol), 6 (105.14 g, 0.44 mol), silver nitrate (recovered, 60.00g + fresh, 14.74 g, 0.44 mol), ammonium persulfate (301.23 g, 1.32 mol) and 200 mL of fresh acetonitrile were taken in the reactor. The reaction mixture was stirred at RT for 10-15 minutes. Added 955 mL of recovered aqueous acetonitrile and 1.16 L of DM water to the reaction mass at RT, heated to 70-75^{0}C and maintained at the same temperature for 4-5 hours. Reaction progress was monitored by TLC. After the reaction completion, cooled the reaction mixture to RT and filtered under suction to isolate the solid. The filtrate was stored for the solvent recovery process. To the solid obtained, added 4.0 L of dichloromethane (2.4 L of recovered +1.6 L of fresh) and stirred for 15 minutes at RT.

Slurry was filtered, inorganic salt was separated and it was stored for silver nitrate recovery process. The filtrate was washed with 3.0 L of 10% sodium bicarbonate solution and subsequently washed with 500 mL DM water. The filtrate was subjected to distillation to isolate the residue, dichloromethane was recovered (2.4 L) and stored for reuse. Added 1.0 L of fresh acetonitrile to the residue and heated the mixture to 55-60^{0}C for 30 minutes. Mixture was gradually cooled to RT, filtered and dried at 55-60^{0}C under reduced pressure for 2-4 hours to isolate 1. Filtrate was stored for the solvent recovery process. Yield: 41.7% (70.76 g).

3. Results & discussion

3.1. Chemistry

Majority of disclosed routes for the synthesis of 1 involve the use of 2 as the key starting material. There were no reports on the use of 5 for the preparation of 1. Synthesis of 2 in the laboratory always resulted in the isolation of a mixture of 2 and 5. Starting material 2, procured from DL Intrachem was also found to contain almost 10-12% of 5. The preparation of pure 2 from the mixture will be a tedious process and results in loss, making it expensive. The prohibiting cost of 2 and its scarce availability had led us to explore the use of 5 instead of 2 for the decarboxylative coupling with 6 to isolate 1 (Scheme 1) in high yield and purity. In order to improve the raw material efficiency, and minimize the expenditure and effluent load, efforts were put on towards the recovery of silver nitrate from the inorganics and dichloromethane and acetonitrile from the filtrates.

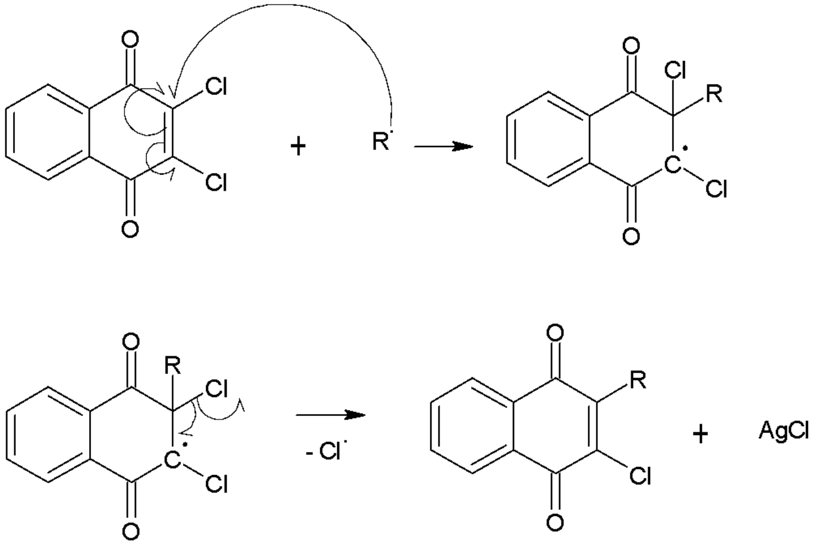


Scheme 1: Synthesis of **1** by the decarboxylative coupling reaction

The reaction mechanism for the decarboxylative coupling reaction of 6 with 5 through the free radical pathway was shown in Scheme 2. Free radical will be formed by the interaction of ammonium persulfate, silver nitrate and 6 in an aqueous acetonitrile medium. The free radical thus generated, gets coupled with 5, and chlorine radical will be expelled from compound 5 leading to the formation of 1 along with the generation of silver chloride.

$$(NH_4)_2S_2O_8 + 2AgNO_3 \longrightarrow 2SO_4^{2-} + 2Ag^{2+} + 2NH_4NO_3$$

$$RCOOH + Ag^{2+} \longrightarrow R^{\cdot} + H^{+} + CO_2 + Ag^{+}$$



Scheme 2: Reaction mechanism for the synthesis of **1**

3.2. Optimization of silver nitrate molar quantity for the reaction

Various experiments were conducted using silver nitrate and 5 in the molar ratio of 0.8:1 to 2:1 (Table 1) for the synthesis of 1. An encouraging result with respect to yield (39.6%) was obtained when 5, 6 and silver nitrate were used in equimolar ratios (Table 1, Exp. No: 2), whereas in the prior arts the molar ratio used are in the range of 0.3 to 0.7 molar equivalents of silver nitrate with respect to 5 which gave very low (less than 20%) yields. Upon using silver nitrate in higher molar ratios, there was no significant increase in the yield of 1 (Table 1, Exp. No: 3-5). All the experiments were done by the use of 5 (2.00 g, 8.81 mmol), 6 (2.10 g, 8.81 mmol), 20 mL of acetonitrile, and 26 mL of DM water with different input quantities of silver nitrate.

Table 1. Experimental results obtained by the use of silver nitrate in different molar ratios.

Exp. No.	Input quantity of silver nitrate	Molar ratio	Yield
1.	1.19 g, 7.05 mmol	0.8:1	24.1%
2.	1.49 g, 8.81 mmol	1.0:1	39.6%
3.	1.94 g, 11.45 mmol	1.3:1	39.7%
4.	2.53 g, 14.93 mmol	1.7:1	39.5%
5.	2.99 g, 17.62 mmol	2.0:1	39.6%

3.3. Selection of reagents for the decarboxylative coupling reaction

Various combinations of reagents for decarboxylative coupling reaction was tried with an intention to replace the prior art disclosed combination of silver nitrate/ammonium persulfate for the synthesis of 1. Distinct experiments (Table 2) were carried out by the use of 5 (2.00 g, 8.81 mmol), 6 (2.10 g, 8.81 mmol), 20 mL of acetonitrile and 26 mL of DM water with different reagent combinations for decarboxylative coupling, like sodium molybdate (1.81 g, 8.81 mmol)/hydrogen peroxide (0.7 mL, 26.4 mmol), sodium molybdate (1.81 g, 8.81 mmol)/ammonium persulfate (6.03 g, 26.4 mmol), red mercuric oxide (1.75 g, 8.81 mmol)/ammonium persulfate (6.03 g, 26.4 mmol), silver nitrate (1.49 g, 8.81 mmol)/oxone (10.83 g ,17.62 mmol) and silver nitrate (1.49 g, 8.81 mmol)/ammonium persulfate (6.03 g, 26.4 mmol). Experimental results clearly indicate that none of the reagent combinations gave satisfactory results as compared to silver nitrate and ammonium persulfate (Table 2, Exp. No: 5). In few experiments (Table 2, Exp. No: 1-3), the disappearance of 6 was observed by TLC but there was no formation of 1 due to free radical degradation. In an instance, (Table 2, Exp. No: 4) 1 was isolated but with too many impurities. This indicates that the free radical formed undergoes some other reaction leading to the formation of by-products.

Table 2. Experimental results obtained by the use of various decarboxylative coupling reagents for the synthesis of 1

Exp. No.	Reagents for coupling	Outcome	Inference by TLC
1.	Sodium molybdate/hydrogen peroxide [31]	discarded	no product formation
2.	Sodium molybdate/ammonium persulfate	discarded	no product formation
3.	Red mercuric oxide/ammonium persulfate [32]	discarded	5% product formation
4.	Silver nitrate/oxone [33]	purity: 53.5% yield: 84.8%	product with more impurities
5.	Silver nitrate/ammonium persulfate	purity: 98.8% yield: 39.5%	product with least impurities

3.4. Experiments for the selection of better solvent for the reaction

Prior art discloses the use of acetonitrile for the synthesis of 1 by decarboxylative coupling reaction. Various solvents like sulfolane, *N,N*-dimethylaceta*N,N*-dimethylformamide,*N*-methylpyrrolidine, tetrahydrofuran, isopropyl alcohol, acetonitrile and water were used in different experiments to select the best solvent for the reaction. Distinct experiments were done using 5 (2.00 g, 8.81 mmol), 6 (2.10 g, 8.81 mmol), silver nitrate (1.49 g, 8.81 mmol), ammoium persulfate (6.03 g, 26.4 mmol), 26 mL of DM water and 20 mL of solvent (Table 3). From the results, it was evident that none of the solvents were found to be useful alternatives to acetonitrile (Table 3, Exp. No: 8). In an experiment with the use of sulfolane (Table 3, Exp. No: 1), more impurities were formed along with 1, with a yield of 12.7%. In the majority of remaining experiments (Table 3, Exp. No: 2-7) product formation was negligible. The reaction was tried in water alone by avoiding the solvent (Table 3, Exp. No: 9), but the product formed was pasty in nature and hence got adhered to the sides of the flask.

Table 3. Results of experiments done using various solvents for the synthesis of 1

Exp. No.	Solvent used for the experiment	Outcome	Inference by TLC
1.	Sulfolane	yield: 12.7%	80-85% product purity
2.	*N,N*-dimethylacetamide	discarded	2-5% product formation
3.	Acetone	discarded	1-2% product formation
4.	*N,N*-dimethylformamide	yield: 10.4%	70-75% product purity
5.	*N*-methylpyrrolidine	discarded	1-2% product formation
6.	Tetrahydrofuran	discarded	3-5% product formation
7.	Isopropyl alcohol	discarded	2-3% product formation
8.	Acetonitrile	yield: 38.9%	95-98% product purity
9.	DM water	sticky mass	80-85% product purity

3.5. Variation in the sequence of addition of reagents and solvents for the reaction

As per the prior art disclosures, the reaction has to be carried out by the slow addition of an aqueous solution of ammonium persulphate to the mixture of 5, 6, and silver nitrate in acetonitrile at 75-80^{0}C under stirring. To enhance the yield, we varied the reagent addition sequence and the resultant outcomes were tabulated (Table 4) and examined to finalize the sequence of addition of reagents and solvents. All the experiments were carried out using 5 (5.00 g, 0.022 mol), 6 (5.25 g, 0.022 mol), silver nitrate (3.73 g, 0.022 mol), ammonium persulfate (15.10 g, 0.066 mol), 50 mL of acetonitrile and 65 mL of DM water. Reaction progress was monitored by TLC and if the conversion progress was satisfactory, reaction mixture was worked up to isolate 1. Experimental outcome indicates that the sequence of addition of reagents and solvents will decide the yield and quality of 1. Best results are obtained when all the reagents are added together and then gradually raised the reaction mixture temperature to 75-80^{0}C (Table 4, Exp. No: 4). When all the reagents are added together, as soon as the radicals of 6 are generated they immediately will react with 5 to give 1. In the remaining experiments (Table 4, Exp. No: 1, 2, 3, and 5), free radicals generated would get degraded (no product formation) or it undergoes side reactions contributing to the formation of by-products (lower yield).

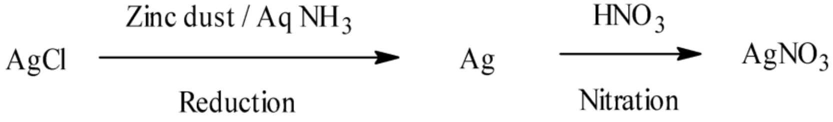
Table 4. Results of experiments done to optimize the reagent and solvent addition sequence

Exp. No.	Sequence of addition of reagents and solvents	Outcome	Inference by TLC
1.	6, silver nitrate, ammonium persulfate, DM water and acetonitrile were taken in the reactor. The reaction mixture was heated to 75-80^{0}C. 5 was added at 75-80^{0}C under stirring.	discarded	no product formation
2.	5, 6 and acetonitrile were taken in the reactor. Heated the reaction mixture to 75-80^{0}C.	discarded	only 10-15% of product

	Aqueous solution of silver nitrate and ammonium persulfate was added drop wise at 75-80^{0}C.		formation
3.	5, 6, silver nitrate and acetonitrile were taken in the reactor. Reaction mixture was heated to 75-80^{0}C. Aqueous solution of ammonium persulfate was added to the reaction at 75-80^{0}C.	purity: 97.44% yield: 28.30%	product formed with more impurities
4.	5, 6, silver nitrate, ammonium persulfate and acetonitrile were taken in the reactor. Reaction mixture was stirred at 25-30^{0}C for 15 minutes, added DM water and heated gradually to 75-80^{0}C.	purity: 97.58% yield: 39.80%	product formed with less impurities
5.	5, 6, silver nitrate, ammonium persulfate and acetonitrile were taken in the reactor. Reaction mixture was stirred at 25-30^{0}C for 15 minutes, added DM water and continued stirring at 25-30^{0}C.	discarded	only 5-10% of product formation

3.6. Recovery and reuse of silver nitrate from and for the reaction

Expensive silver nitrate will be used in considerable amounts for the decarboxylative coupling reaction. It contributes to about 30% of the cost for the synthesis of 1. Hence recovery/reuse concept was ventured into in order to increase the reagent efficiency and to reduce the process expenditure. During the reaction, silver nitrate would get converted to silver chloride and the same was converted back to silver nitrate by a series of reactions. Initially silver chloride was reduced to silver by zinc dust and ammonia solution. Free silver metal isolated was washed with dilute sulfuric acid solution to remove the unreacted silver chloride and then dried. It was later treated with nitric acid to regenerate silver nitrate with 95% yield and 98.5% purity (by assay). Regenerated silver nitrate was effectively reused for the reaction without impacting the quality and quantity of the product. The mechanism by which AgCl gets generated was shown in Scheme 2. The overall recovery pathway was schematically shown in Scheme 3.



Scheme 3: Silver nitrate recovery form silver chloride

4. Conclusion

In the present novel work, an intermediate 1 was prepared by the use of 5, isolated and characterized. Furthermore, reaction conditions were optimized by varying different limiting parameters to get better yield and purity. Various prior art disclosed routes for the synthesis of 1 had relatively low yield (upto 20%), but the novel and optimized reaction had shown a reproducible high yield (38-42%) with good purity. Recovery and reuse of solvents from the filtrates of the reaction were studied, since large quantities of solvents (acetonitrile and dichloromethane) were used at various stages of the reaction and product isolation. The study also extends towards the recovery and reuse of silver nitrate, an expensive reagent that contributes significantly to the preparation cost of 1. Recovered silver nitrate and solvents were successfully reused for the synthesis of 1 with unaltered yield and purity. Furthermore, we could be able to achieve an industrially feasible, economical and environmentally benign method for the synthesis for 1 through systematic reaction optimization, recovery and reuse studies.

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