

A novel method for the synthesis of 2-chloro-3-[trans-4-(4-chlorophenyl) cyclohexyl]-1,4-naphthoquinone: an intermediate of Atovaquone, with systematic studies towards reaction optimization, recovery and reuse aspects

SANJAY S S (✉ sanjayss@sdmit.in)

Sri Dharmasthala Manjunatheshwara Institute of Technology, Ujire <https://orcid.org/0000-0002-3932-3996>

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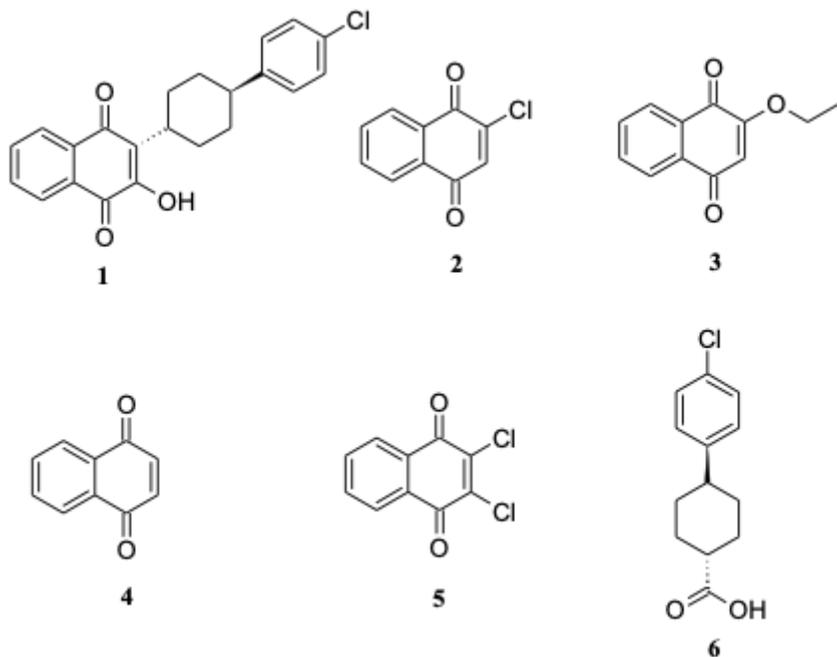
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Abstract

Present work reports a novel and commercially viable method for the synthesis of 2-chloro-3-[*trans*-4-(4-chlorophenyl) cyclohexyl]-1,4-naphthoquinone **1** (an intermediate of popular antimalarial drug, Atovaquone). Most of the prior art disclosures towards the synthesis of **1** were with low yields but involves the use of expensive raw materials and the reaction would generate lot of effluents. In this regard, it was considered worthwhile to synthesize **1** by a novel route with high yield and purity. Moreover, locally available inexpensive raw materials were used with an emphasis on recovery and reuse of essential reagent/solvents. 2,3-Dichloro-1,4-naphthoquinone **5** was selected as one of the key raw material instead of its mono-halo analogue due to its abundant availability at relatively low cost. Various experiments were performed to optimize the reaction conditions for the reliability towards consistent yield and purity. Silver metal was recovered from the inorganics, it was further converted back to silver nitrate and reused for the reaction along with recovered solvents (acetonitrile and dichloromethane).

Introduction

2-Chloro-3-[*trans*-4-(4-chlorophenyl) cyclohexyl]-1,4-naphthoquinone **1**, an important intermediate formed during the synthesis of renowned antimalarial drug Atovaquone, was predominantly prepared by the decarboxylative coupling pathway. Alkylations of quinones were reported by the decarboxylation of carboxylic acids with silver ions and peroxodisulphate from early 1970s [1–4]. Numerous synthetic methods were disclosed in prior arts for the synthesis of **1**, among them 2-chloro-1,4-naphthoquinone **2** was widely used key starting material. Synthesis of **1** using **2** was reported by the free radical decarboxylative coupling mechanism, in low yields (6.5%) [5–8]. Improved yield (14%) was reported by the use of silver nitrate in 10 mol% for the coupling reaction of **2** and 4-(4-chlorophenyl) cyclohexane carboxylic acid in 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 had resulted in significant high yield (43%,) with 1.3 to 1 ratio of *trans/cis* isomers [9]. A low yield (7–8%) decarboxyative coupling of **3** and *trans*-4-(4-chlorophenyl) cyclohexane carboxylic acid **6** was reported using silver nitrate in 30–50 mol% along with ammonium persulfate, acetonitrile and water [10]. Use of **4** was reported for the synthesis of **1**, it was decarboxylatively coupled with **6**, with better yield (20%), it was further subjected to chlorination and dehydrohalogenation to isolate **1** [11].



Numerous acids, diacids and N-Boc-protected amino acids were coupled with substituted quinones in 10–76% yields through free radical decarboxylative coupling reaction using silver nitrate and ammonium persulfate [12]. Silver nitrate in 20 mol% and ammonium persulfate mediated synthesis of γ -carbonyl quinones by the interaction of cyclopropanols with quinones using dichloromethane and water was reported with good yields (30–80%) [13]. 1,4-dihydropyridines and sodium persulfate were used for the free radical alkylation of quinones in the presence of trifluoroacetic acid (TFA), acetonitrile and water. By this method, 1,4-naphthoquinones, such as Co-enzyme Q₀, Vitamin K3 and Lawsone were alkylated with good yields (55–65%) by avoiding silver nitrate for the synthesis [14]. Alkylation of N-heteroarenes and quinones with alkylcarboxylic acids was reported using ammonium persulfate, dimethylsulphoxide and water with better yields (25–85%) under mild conditions [15]. Mono-arylated benzoquinones were prepared using aryl radicals formed by the homolytic cleavage of boronic acids or phenyltrifluoroborate was reported with 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, silver nitrate and ethyl acetate [17]. Direct functionalization of quinones were summarized in a review, free radical coupling in presence/absence of metal catalysts and transition metal aided cross coupling reactions were discussed with feasibility and yield [18]. Reactions of menadione with α -keto-aromatic acids in the presence of silver nitrate in 20 mol%, ammonium persulfate, acetonitrile and water was reported for the synthesis of 3-benzoylmenadione derivatives through the generation of an acyl free radical with moderate yields (41–45%) [19]. Naphthoquinones are directly alkylated with variety of aminoacids by silver mediated decarboxylative coupling with moderate yields (16–61%) [20]. A work reports the cyanoalkylation of heteroarenes and quinones 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 with moderate yields (49–53%), reaction was performed in absence of metal catalysts using ammonium persulfate, dimethylsulphoxide and water [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 strong oxidizing agent ammonium persulfate at ambient temperature with moderate yields (45–54%) [23]. Same work was reported with the use of Hünig's base, led to lower yields (20–38%) [24]. Selectfluor-mediated decarboxylative coupling of **4** with difluoroacetic acids was reported with good yields (56–80%). The conventional use of silver nitrate, ammonium persulfate combination had failed to generate the target products [25]. The direct radical alkylation of 1,4-quinones had gathered lot of synthetic interest over the last decade. The direct alkylation involves the addition of carbon centered radicals formed through decarboxylation, hydrogen abstraction or by the carbon-halogen bond reduction [26].

The procedures reported for the synthesis of **1** are not commercially viable due to the use of expensive raw materials/reagents, lack of recovery/reuse of chemicals, low yield and the generation of significantly high quantity of effluents. Hence we report the use of readily available and cheaper key starting material **5** for the synthesis of **1** with high yield and purity [27]. The reagent/solvents recovery [28–30] and reuse strategies employed in the reaction had enormously reduced the effluent load and hence the reaction got fine tuned to be more cost effective.

Materials And Methods

Present work involves the use of key starting material **5**, which was procured from DL Intrachem. Another key starting material *trans*-4-(4-chlorophenyl) cyclohexanecarboxylic acid **6** was procured from Sigma-Aldrich. Reagents like silver nitrate and nitric acid were procured from Rankem, ammonium persulfate 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.

Melting points (m.p) of **1** was recorded by the open capillary method and are uncorrected. ¹HNMR spectra was recorded (in DMSO-d₆/CDCl₃) on a 300/400 MHz NMR spectrometer using tetramethylsilane (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 thin layer chromatography (TLC) using precoated silica TLC plates (Merck ⁶⁰F₂₅₄).

Synthesis and Characterization

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 persulfate (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 to isolate crude **1**, which further was crystallized from 60 mL of acetonitrile afforded the isolation of **1**. Yield: 17.64% (1.50 g).

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. Reaction mixture was stirred at room temperature (RT) for 10–15 minutes. Added 1.3 L of DM water to the reaction mass at RT, heated to 70–75⁰C 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. 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. Residue (silver chloride) was dried under reduced pressure at 40–45⁰C for 2–3 hours and stored (61.80 g) for 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 subjected to distillation to isolate the residue, 2.4 L of dichloromethane was recovered by collecting the fraction between 37–41⁰C and stored for reuse. Added 1.0 L of acetonitrile to the residue and heated the mixture to 55–60⁰C for 30 minutes. Mixture was gradually cooled to RT, filtered and dried at 55–60⁰C under reduced pressure for 2–4 hours to isolate **1**. Filtrate was stored for the solvent recovery process. Yield: 42% (71.27 g). C₂₂H₁₈Cl₂O₂, m.p. 186–188⁰C. IR (KBr, γ max, cm⁻¹): 1667.84 (C = O), 613.73 and 708.53 for (C-Cl) group (**Fig S1**, Supplementary Information). ¹HNMR (400 MHz, CDCl₃): 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**, Supplementary Information).

Procedure for the recovery of silver nitrate and acetonitrile

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. To the stirring mixture at RT, added Zinc dust (18.12 g, 0.28 mol) carefully in 3 lots (1 lot: approx 6.0 g) to minimize the reaction exothermicity. Reaction mixture was heated to 40–45⁰C 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. Solid was further washed with DM water, till the filtrate becomes neutral. Recovered silver was dried at 80–85⁰C 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 addition, reaction mixture was heated to 50–55⁰C for 4–4.5 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 25–30⁰C

and filtered to isolate silver nitrate as shiny crystals. It was dried under pressure at 80-85⁰C for 4–5 hours. Yield: 92.5% (61.19 g) and purity: 98.5% (by assay).

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 70-78⁰C was stored and analyzed. Recovered aqueous acetonitrile had 16.2% of moisture (by KF titration), was reused for the reaction by making it up with 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.

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. Reaction mixture was stirred at room temperature (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 70-75⁰C 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. 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. Filtrate was washed with 3.0 L of 10% sodium bicarbonate solution and subsequently washed with 500 mL DM water. 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 55-60⁰C for 30 minutes. Mixture was gradually cooled to RT, filtered and dried at 55-60⁰C under reduced pressure for 2–4 hours to isolate **1**. Filtrate was stored for the solvent recovery process. Yield: 41.7% (70.76 g).

Results And Discussion

Chemistry

Majority of disclosed routes for the synthesis of **1** involves 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, 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.

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

Experimental studies towards reaction optimization for the synthesis of **1**

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**. Encouraging result with respect to yield (39.6%) was obtained when **5**, **6** and silver nitrate were used in equimolar ratios (Exp. No: 2, Table 1), 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** (Exp. No: 3–5, Table 1). 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 quantity of silver nitrate.

Table 1
Result of experiments done 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%

Selection of reagents for the decarboxylative coupling reaction

Various combination of reagents for decarboxylative coupling reaction were 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 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 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 (Exp. No: 5, Table 2). In few experiments (Exp. No: 1–3, Table 2), disappearance of **6** was observed by TLC but there was no formation of **1** due to free radical degradation. In an instance (Exp. No: 4, Table 2), **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

Results of experiments done using various decarboxylative coupling reagents for the synthesis of **1**

Exp. No.	Reagents for decarboxylative coupling reaction	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

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*-dimethylacetamide, acetone, *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), ammonium 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 the useful alternatives to acetonitrile (Exp. No: 8, Table 3). In an experiment with the use of sulfolane (Exp. No: 1, Table 3) more impurities were formed along with **1**, with a yield of 12.7%. In majority of remaining experiments (Exp. No: 2–7, Table 3) product formation was negligible. Reaction was tried in water alone by avoiding the solvent (Exp. No: 9, Table 3), 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 synthesis of **1**

Exp. No.	Solvent used for the experiment	Outcome	Inference by TLC
1.	Sulfolane	yield: 12.7%	80–85% product purity
2.	<i>N, N</i> -dimethylacetamide	discarded	2–5% product formation
3.	Acetone	discarded	1–2% product formation
4.	<i>N, N</i> -dimethylformamide	yield: 10.4%	70–75% product purity
5.	<i>N</i> -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

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 a mixture of **5**, **6** and silver nitrate in acetonitrile at 75-80⁰C 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 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 75-80⁰C (Exp. No: 4, Table 4). This indicates that 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 (Exp. No: 1, 2, 3 and 5, Table 4), 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. 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. Aqueous solution of silver nitrate and ammonium persulfate was added drop wise at 75-80 ⁰ C.	discarded	only 10–15% of product 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

Recovery and reuse of silver nitrate for the reaction

Expensive silver nitrate will be used in considerable amounts for the decarboxylative coupling reaction. It contributes to about 30% of cost for the synthesis of **1**. Hence recovery/reuse concept was ventured in order to increase the reagent efficiency, reduce the expenditure and lower the effluent load. 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 in turn treated with nitric acid to regenerate silver nitrate with 95% yield and 98.5% purity (by assay). Regenerated silver nitrate was reused for the reaction without impacting the quality and quantity of the product. Thus the concept of recovery/reuse of silver nitrate had significantly reduced the effluent load and the expenditure towards the synthesis of **1**. The mechanism by which AgCl gets generated was shown in Scheme 2. The overall recovery process was schematically shown in Scheme 3.

Conclusions

In the present novel work, an intermediate compound **1** was prepared by the use of **5** and characterized. Reaction conditions were optimized by varying different limiting parameters to get better yield and purity. Prior art disclosed routes for the synthesis of **1** had relatively low yield (upto 20%), but the optimized reaction had a reproducible high yield (38–42%). Recovery and reuse of solvents from the filtrates of the reaction was studied, since large quantities of solvents (acetonitrile and dichloromethane) were used at various stages of the reaction. The study also extends towards the recovery and reuse of silver nitrate, an expensive reagent 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 able to achieve an industrially feasible, economical and environmentally benign method for the synthesis for **1** through systematic reaction optimization, recovery and reuse studies.

Declarations

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